Diastereoselective Michael Addition of Nitrogen and Sulfur-Nucleophiles to α,β-Unsaturated δ-Thiolactams

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Received August 26, 1996

Dedicated to Professor Dr. Jürgen Fabian on the occasion of his 60th birthday

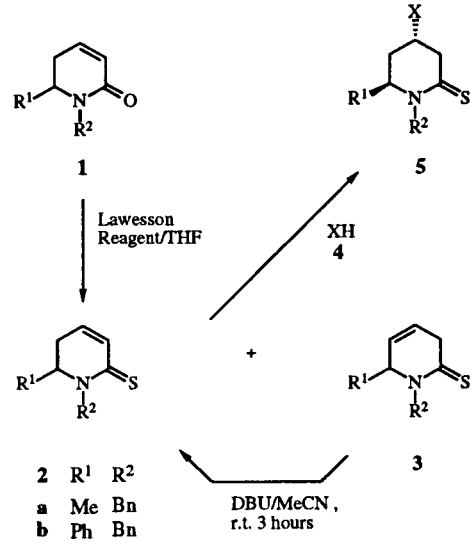
5,6-Dihydropyridine-2-thiones **2** are synthesized from 5,6-dihydropyridin-2-ones **1** and Lawesson reagent. Stereoselective Michael-like addition of amines, methylhydrazine or functionalized thiols affords *trans* piperidine-2-thiones **5** with the corresponding heterosubstituent in position 4 as major products. The configuration of the adducts **5** was determined by nmr-techniques.

J. Heterocyclic Chem., **34**, 643 (1997).

The 1,4-addition of heteronucleophiles to α,β-unsaturated lactams is known to occur with high stereoselectivity and allowed interesting ring transformations to aminoalkyl heterocycles if binucleophiles were used [1-3]. We became interested to investigate whether α,β-unsaturated thiolactams undergo corresponding nucleophilic 1,4-additions or ring transformations giving access to products with a thiocarbonyl moiety suitable for further synthetic application. We further sought to explore the stereo- and regioselectivity of such processes in order to find similarities or differences between α,β-unsaturated lactams and thiolactams. There are cases reported in the literature demonstrating different regioselectivity for α,β-unsaturated thioamides as compared with α,β-unsaturated amides. E. g. 1,6-dimethyl-5,6-dihydro-2(1*H*)-pyridinthione, the only known α,β-unsaturated thiolactam, gives 1,4-addition with *n*-butyllithium [4] or lithiated *N,N*-dimethylacetamide [5] while 1,4-addition of α,β-unsaturated lactams requires organocuprates in order to prevent 1,2-addition [6].

Surprisingly no experimental procedure for the synthesis of α,β-unsaturated thiolactams was found in the literature. Thus a suitable synthetic method had to be developed for this class of compounds. Since thionation of amides with Lawesson reagent was known to be successful in cases of α,β-unsaturated amides also [7], we applied this method to α,β-unsaturated lactams such as the 1-benzyl-substituted dihydro-2(1*H*)-pyridones **1**. After short reflux of the reactants in THF mixtures of the expected α,β-unsaturated thiolactams **2** and corresponding deconjugated thiolactams **3** were obtained in a total yield of about 50%. However, a complete isomerisation of **3** to **2** was possible by treating the crude mixture with 1,8-diazabicyclo[5.4.0]undec-7-ene in acetonitrile. It is worth mentioning that the thionation failed or gave just traces of **2**, if 6-unsubstituted 5,6-dihydropyridin-2(1*H*)-ones **1** (R^1 = H, R^2 = Et or Ts) with an ethyl or tosyl group in the 1-position were exposed to the same conditions. 5-Membered α,β-unsaturated lactams generally turned out to be reluctant to thionations with Lawesson reagent for some unknown reason.

The α,β-unsaturated thiolactams **2** were further submitted to reactions with several *N*- and *S*-nucleophiles **4**. In all cases a regioselective 1,4-addition was observed. Products **5** were usually formed in high yields and with high diastereoselectivity (see Table 1). In order to achieve complete conversion with amines, the latter had to be used in 6-fold excess. The diastereomeric ratios (Table 1) were determined by ^{13}C nmr spectroscopy from the crude reaction mixture. Further purification by column chromatography gave pure major isomers for **5c-5f** and **5h**. For the other compounds **5a**, **5b**, **5g**, **5i-5k** spectral analysis



was established with the crude mixture of diastereomers. The determination of the relative configuration of adducts **5**, *i.e. trans* for the major isomers, was performed by con-

firmational analysis using DEPT, ^{1}H, ^{1}H COSY, and ^{1}H, ^{13}C COSY nmr techniques. Spectrum simulation [8] allowed us to confirm the resolved spin systems. Since compound **5k** gave good peak separation of the major and the minor isomer in the ^{1}H nmr spectrum this compound was investigated in detail. The *cis* structure **I** and the two *trans* structures **IIa** and **IIb** were taken into consideration while the improbable α,α-*cis* isomer was neglected. The benzylic proton H-6_{eq} of the major isomer of **5k** was found at 4.76 ppm as a doublet of doublets, the two small coupling constants (J = 5.5 and 3.4 Hz) confirm an equatorial position. Starting from this assignment the neighboring protons were identified in the ^{1}H, ^{1}H COSY spectrum using the ^{3}J and ^{2}J coupling constants. Distinct cross peaks found between H-4 and H-3_{ax} as well as between H-4 and H-5_{ax} confirm an axial position for H-4.

Table 1
Synthesis of Adducts **5a-5k** (R^2 = Bn)

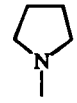
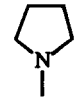
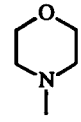
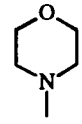
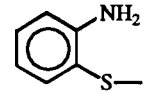
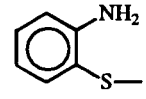
Entry	Product	R^1	X	Solvent Time Equivalents of **4**	Yield/%	Diastereomeric Ratio
1	**5a**	Me		MeOH 3 h 6	73	85:15
2	**5b**	Ph		MeOH 2 h 6	70	>95:5
3	**5c**	Me		MeOH 72 h 6	85	92:8
4	**5d**	Ph		MeOH 20 h 6	73	>95:5
5	**5e**	Me		DMF 20 h 1	52	78:22
6	**5f**	Ph		DMF 20 h 1	77	>95:5
7	**5g**	Me	-SCH_2COOEt	DMF/Et_3N 1.5 h 1	88	84:16
8	**5h**	Ph	-SCH_2COOEt	DMF/Et_3N 1.5 h 1	96	91:9
9	**5i**	Me	-SCH_2CH_2COOMe	DMF/DBU 1.5 h 1	68	71:29
10	**5j**	Ph	-SCH_2CH_2COOMe	DMF/DBU 1.5 h 1	88	73:27
11	**5k**	Ph	$N(CH_3)$-NH_2	MeOH 8 h 6	44	86:14

Table 2

^{3}J Coupling Constants and Dihedral Angles of Major *trans*, **IIb** and Minor Diastereomer *cis*, **I** of **5k**

vicinal protons	Major *trans*-adduct **IIb**		Minor *cis*-adduct **I**	
	^{3}J(Hz)	ρ(deg)	^{3}J(Hz)	ρ(deg)
$H\text{-}3_{ax}$-$H\text{-}4_{ax}$	9.1	-151	11.4	-170
$H\text{-}3_{eq}$-$H\text{-}4_{ax}$	5 4	-48	3.7	-60
$H\text{-}4_{ax}$-$H\text{-}5_{ax}$	10.9	164	11.6	173
$H\text{-}4_{ax}$-$H\text{-}5_{eq}$	3.6	60	3.7	-60
$H\text{-}5_{ax}$-$H\text{-}6_{eq}$	5.7	-45	-	-
$H\text{-}5_{eq}$-$H\text{-}6_{eq}$	3.6	53	-	-
$H\text{-}5_{ax}$-$H\text{-}6_{ax}$	-	-	10.6	-156
$H\text{-}5_{eq}$-$H\text{-}6_{ax}$	-	-	6.3	-37

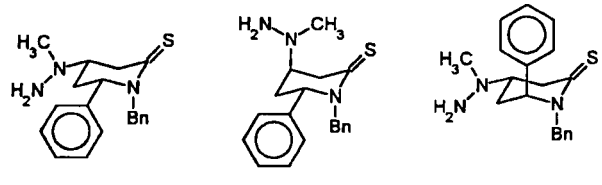
Additional small ^{4}J coupling constant between $H\text{-}3_{eq}$ and $H\text{-}5_{eq}$ (W-shape) obtained by the simulation could not be found in the COSY spectrum. As a further part of the confirmational analysis the dihedral angles were calculated from the observed coupling constants for the major and minor isomer of compound **5k** using the Haasnoot equation [9] confirming the assigned structures **II** and **I**. In the case of the major *trans* isomer the molecule preferably adopts configuration **IIb** with the phenyl and hydrazino substituents in axial and equatorial positions respectively. The preference of conformer **IIb** can be rationalized in terms of circumventing $A^{1,2}$-strain between the phenyl substituent and the benzyl group. The 2D NOESY spectrum gave further evidence for the assignment of structure **IIb** as the major isomer and also proves the regiochemistry of the addition of methylhydrazine, *i.e.* the methyl substituent being found at the nitrogen atom directly attached to the ring. Since all other adducts **5** showed similar coupling constants of the major isomers like compound **5k** (see Table 3) it can be assumed that Michael-like addition of *S*- and *N*-nucleophiles **4** to α,β-unsaturated thiolactams **3** occur *trans* to the substituent R^1 in position 6. Because no stereochemistry was reported in the case of the addition of amines to α,β-unsaturated 6-ring lactams [10] the stereochemical course of the addition of heteronucleophiles **4** to thiolactams **2** is to be compared with analogous reactions of α,β-unsaturated lactones, where a similar anti-addition was observed [11]. Some of the piperidinethiones **5** obtained possess an exocyclic nucleophilic center **5e-5k** that should be suitable for further ring transformation similar to cases found in the lactone and lactam series [1,2]. However, no ring transformation could be obtained under similar reaction conditions.

Table 3

^{3}J Coupling Constants of Major Diastereomers of Compounds **5a-5j**

vicinal protons	Coupling constants ^{3}J (Hz)									
	5a	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**	**5h**	**5i**	**5j**
$H\text{-}3_{ax}$-$H\text{-}4_{ax}$	8.1	8.1	7.8	8.3	9.4	9.9	9.8	[a]	9.8	10.4
$H\text{-}3_{eq}$-$H\text{-}4_{ax}$	5.3	4.9	5.5	4.7	5.5	[a]	5.5	[a]	5.6	~5.2
$H\text{-}4_{ax}$-$H\text{-}5_{ax}$	[a]	[a]	[a]	[a]	11.1	11.2	11.8	11.7	11.6	11.8
$H\text{-}4_{ax}$-$H\text{-}5_{eq}$	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]
$H\text{-}5_{ax}$-$H\text{-}6_{eq}$	~5.6	5.4	~5.3	5.3	5.4	5.7	5.4	5.3	5.4	5.4
$H\text{-}5_{eq}$-$H\text{-}6_{eq}$	~5.6	5.4	~5.3	5.3	3.3	3.6	3.2	3.0	3.2	3.0

[a] Difficult to assign.



I **IIa** **IIb**

cis *trans*

Figure 1. Conformations of *cis* adduct **I** and *trans* adducts **IIa** and **IIb** of compound **5k**.

EXPERIMENTAL

General.

The 1D and 2D ^{1}H nmr and ^{13}C nmr spectra were recorded with Bruker DPX 400 apparatus in deuteriochloroform solution using TMS as the internal standard. For compounds **5a-5k** (Table 1, entry 1-10) only the spectra of the major isomer (*trans* adducts) are reported. Mass spectra (70 eV) were recorded with a HP 5995 A Hewlett-Packard spectrometer. Melting points were observed on a Boetius hot stage apparatus and are uncorrected. Starting materials **1** (R^1 = Me, R^2 = Bn) [12] and **1** (R = Ph, R^2 = Bn) [13] were synthesized according to known procedures. All products were obtained as racemates.

General Procedure for the Preparation of Thiolactams **2**.

A solution of 1-benzyl-5,6-dihydro-2(1*H*)-pyridinone **1** (3.6 mmoles) in dry THF (50 ml) was added to a hot solution of Lawesson reagent (1.77 g, 4.4 mmoles) in dry THF (100 ml).

The mixture was refluxed for 10 minutes. After evaporation of the solvent (rotary evaporator) the resulting product was diluted with water and then extracted twice with 100 ml portions of diethyl ether. The combined organic layers were dried over sodium sulfate, filtered and the solvent was distilled off under vacuum. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.6 ml) was added to the crude material dissolved in acetonitrile (150 ml). After stirring for 3 hours the solvent was evaporated and the residue purified by column chromatography on silica gel (*n*-hexane:ethyl acetate 7:3) yielding yellow product **2**.

1-Benzyl-5,6-dihydro-6-methyl-2(1*H*)-pyridinthione (**2a**).

After recrystallization from *n*-hexane 374 mg (48%) of the product was obtained, mp 48-50°; ^{1}H nmr (deuteriochloroform): δ 1.23 (d, J = 6.7 Hz, 3H, CH_3), 2.11 (ddd, J = 18.2, 6.5, 0.9 Hz, 1H, 5-C*H*H), 2.55 (ddt, J_1 = 18.2 Hz, J_2 = 7.2 Hz, J_{3-4} = 2.7 Hz, 1H, 5-CH*H*), 3.74 (br quintet, J ~ 6.9 Hz, 1H, H-6), 4.30 (d, J = 14.8 Hz, 1H, PhC*H*HN), 6.07-6.14 (m, 1H, H-4), 6.25 (d, J = 14.8 Hz, 1H, PhCH*H*N), 6.60 (dd, J = 9.5 Hz, J = 2.9 Hz, 1H, H-3), 7.35-7.26 (m, 5H, Ph); ^{13}C nmr (deuteriochloroform): δ = 16.7 (CH_3), 30.4 (C-5), 51.3 (C-6), 54.6 (Ph*C*H_2N), 127.7, 127.8, 128.7, 136.7 (Ph), 127.8 (C-4), 131.9 (C-3), 189.5 (C-2); ms: m/z *(%)* 217 ($M^{+\bullet}$, 32), 184 (M^+-SH, 38), 126 (16), 97 (38), 91 (Bn^+, 100), 77 (56), 65 (51).

Anal. Calcd. for $C_{13}H_{15}NS$ (217.3): C, 71.85; H, 6.96; S, 14.75. Found: C, 71.62; H, 6.76; S, 14.69.

1-Benzyl-5,6-dihydro-6-phenyl-2(1*H*)-pyridinthione (**2b**).

This compound was obtained as an oil in 525 mg (52%) yield; ^{1}H nmr (deuteriochloroform): δ = 2.49 (ddd, J = 18.2 Hz, 6.5 Hz, 1.1 Hz, 1H, 5-C*H*H), 2.91 (ddt, J_1 = 18.2 Hz, J_2 = 8.2 Hz, J_{3-4} = 2.8 Hz, 1H, 5-CH*H*), 3.89 (d, J = 14.9 Hz, 1H, PhC*H*HN), 4.76 (d, J = 8.0 Hz, 1H, H-6), 5.93-5.00 (m, 1H, H-4), 6.57 (d, J = 14.9 Hz, 1H, PhCH*H*N), 6.70 (dd, J = 9.5 Hz, 2.9 Hz, lH, H-3), 7.12-7.15 (m, 2H, PhH), 7.28-7.36 (m, 8H, PhH); ^{13}C nmr (deuteriochloroform): δ = 32.2 (C-5), 55.1 (C-6), 58.2 (Ph*C*H_2N), 126.3, 127.8, 127.9, 128.0, 128.8, 128.9, 136.5, 138.7 (Ph, PhCH_2N), 126.9 (C-4), 132.7 (C-3), 191.4 (C-2); ms: m/z (%) 279 (M^+, 58), 246 (29), 188 (49), 128 (25), 115 (25), 91 (100), 65 (25).

Anal. Calcd. for $C_{18}H_{17}NS$ (279.4): C, 77.38; H, 6.13; S, 11.47. Found: C, 77.53; H, 6.27; S, 11.32.

General Procedure for the Preparation of Adducts **5a-5d** and **5k**.

A solution of the thiolactam **2** (1.7 mmoles) and excess of the appropriate amine **4** (10.2 mmoles) or methylhydrazine in dry methanol (5 ml) was stirred at room temperature for the appropriate time (see Table 1). After evaporation of the solvent under vacuum the product was purified by column chromatography on silica gel (chloroform:methanol 96:4).

trans (Major) and *cis* (Minor) 1-Benzyl-4-(pyrrolidino)-6-methylpiperidine-2-thione (**5a**).

The mixture of these diastereomeric compounds was obtained as oil. Spectra were obtained from a mixture of diastereomers; ^{1}H nmr (deuteriochloroform): δ = 1.31 (d, J = 6.7 Hz, 3H, CH_3), 1.78 (br s, 4H, 2CH_2), 1.85-1.98 (m, 2H, H-5_{ax}, H-5_{eq}), 2.49-2.67 (m, 5H, 2CH_2N, H-4_{ax}), 3.17 (dd, J = 18.5 Hz, 8.1, 1H, H-3_{ax}), 3.40 (dd, J = 18.5 Hz, 5.3 Hz, 1H, H-3_{eq}), 3.74 (br sex, J = 5.6 Hz, 1H, H-6_{eq}), 4.43 (d, J = 15.1 Hz, 1H, PhC*H*HN), 6.43 (d, J = 15.1 Hz, 1H, PhCH*H*N), 7.21-7.36 (m, 5H, Ph); ^{13}C nmr (deuteriochloroform): δ = 19.9 (CH_3), 23.3 (2CH_2), 35.6 (C-5), 47.6 (C-3), 51.4 (2CH_2N), 53.3 (C-4), 54.0 (C-6), 54.4 (Ph*C*H_2), 127.3, 127.5, 128.6, 135.4, (Ph), 199.4 (C-2); ms: m/z (%) 288 ($M^{+\bullet}$, 21), 255 ($M^{+\bullet}$-HS, 13), 217 ($M^{+\bullet}$-C_4H_5N, 44), 184 (42), 124 (100), 91 (Bn^+, 100), 65 (29).

Anal. Calcd. for $C_{17}H_{24}N_2S$ (288.4): C, 70.79; H, 8.39; S, 11.11. Found: C, 70.91; H, 8.45; S, 11.01.

trans (Major) and *cis* (Minor) 1-Benzyl-4-(pyrrolidino)-6-phenylpiperidine-2-thione (**5b**).

The mixture of these diastereomeric compounds was obtained as a solid, mp 119-125°. Spectra were obtained from this mixture of diastereomers; ^{1}H nmr (deuteriochloroform): δ 1.61-1.71 (m, 4H, 2CH_2), 2.02-2.16 (m, 2H, H-5_{ax}, H-5_{eq}), 2.35-2.48 (m, 5H, H-4_{ax}, 2CH_2N), 3.32 (dd, J = 18.5 Hz, 8.1 Hz, 1H, H-3_{ax}), 3.44 (dd, J = 18.5 Hz, 4.9 Hz, 1H, H-3_{eq}), 3.78 (d, J = 15.0 Hz, 1H, PhC*H*HN), 4.67 (t, J = 5.4 Hz, 1H, H-6_{eq}), 6.56 (d, J = 15.0 Hz, 1H, PhCH*H*N), 7.02 (d, J = 7.0 Hz, 2H, ArH), 7.12-7.33 (m, 8H, ArH); ^{13}C nmr (deuteriochloroform): δ 23.3 (2CH_2), 37.3 (C-5), 47.7 (C-3), 51.2 (2CH_2N), 53.5 (C-4), 55.0 (Ph*C*H_2N), 61.8 (C-6), 126.5, 126.9, 127.5, 128.0, 128.6, 129.1, 135.2, 140.2 (PhCH_2, Ph), 200.7 (C-2); ms: m/z (%) 350 (M^+, 7), 279 (12), 188 (20), 186 (39), 129 (11), 128 (14), 116 (15), 115 (20), 106 (13), 104 (13), 103 (13), 97 (17), 96 (50), 91 (100), 65 (25).

Anal. Calcd. for $C_{22}H_{26}N_2S$ (350.5): C, 75.39; H, 7.48; S, 9.15. Found: C, 75.41; H, 7.26; S, 8.93.

trans (Major) 1-Benzyl-4-(morpholino)-6-methylpiperidine-2-thione (**5c**).

This compound was obtained as a crystalline solid (hexane/ethyl acetate), mp 138-141°; ^{1}H nmr (deuteriochloroform): δ 1.24 (d, J = 6.7 Hz, 3H, CH_3), 1.75-1.86 (m, 2H, H-5_{ax}, H-5_{eq}), 2.40-2.51 (m, 4H, 2CH_2N), 2.65-2.73 (m, 1H, H-4_{ax}), 3.14 (dd, J = 18.4 Hz, 7.8 Hz, 1H, H-3_{ax}), 3.26 (dd, J = 18.4 Hz, 5.5 Hz, 1H, H-3_{eq}), 3.63 (t, J = 4.7 Hz, 4H, 2CH_2O), 3.69 (br sex, J ~ 5.3 Hz, 1H, H-6_{eq}), 4.31 (d, J = 15.0 Hz, 1H, PhC*H*HN), 6.39 (d, J = 15.0 Hz, 1H, PhCH*H*N), 7.13-7.29 (m, 5H, Ph); ^{13}C nmr (deuteriochloroform): δ 19.6 (CH_3), 32.8 (C-5), 44.8 (C-3), 49.9 (2CH_2N), 53.1 (C-6), 54.1 (C-4), 54.3 (Ph*C*H_2), 67.0 (2CH_2O), 127.5, 127.6, 128.7, 135.4 (Ph), 199.4 (C-2); ms: m/z (%) 304 ($M^{+\bullet}$, 7), 218 ($M^{+\bullet}$-C_4H_8NO), 140 (70), 91 (Bn^+, 100), 65 (31), 55 (38), 45 (29).

Anal. Calcd. for $C_{17}H_{24}N_2OS$ (304.4): C, 67.07; H, 7.95; S, 10.53. Found: C, 66.88; H, 8.13; S, 10.79.

trans (Major) 1-Benzyl-4-(morpholino)-6-phenylpiperidine-2-thione (**5d**).

This compound was obtained as a crystalline solid, mp 142-144°; ^{1}H nmr (deuteriochloroform): δ 2.06 (pseudo t, J = 5.7 Hz, 2H, H-5_{ax}, H-5_{eq}), 2.31-2.47 (m, 4H, 2CH_2N), 2.52 (pseudo quintet, J = 6.5 Hz, 1H, H-4_{ax}), 3.25 (dd, J = 18.4, 8.3 Hz, 1H, H-3_{ax}), 3.36 (dd, J = 18.4, 4.7 Hz, 1H, H-3_{eq}), 3.53-3.65 (m, 4H, 2CH_2O), 3.75 (d, J = 14.8 Hz, 1H, PhC*H*HN), 4.67 (t, J = 5.3 Hz, 1H, H-6_{eq}), 6.57 (d, J = 14.8 Hz, 1H, PhCH*H*N), 6.99-7.06 (d, J = 7.1 Hz, 2H, ArH), 7.15-7.35 (m, 8H, ArH); ^{13}C nmr (deuteriochloroform): δ 33.7 (C-5), 43.9 (C-3), 48.8 (2CH_2N), 52.6 (C-4), 53.92 (Ph*C*H_2N), 60.6 (C-6), 66.0 (2CH_2O), 125.4, 126.7, 127.7, 138.8 (Ph), 126.8, 127.1, 128.2, 134.2 (*Ph*CH_2), 199.7 (C-2); ms: m/z (%): 366 ($M^{+\bullet}$, 11), 202 (51), 112 (60), 91 (Bn^+, 100), 77 (12), 65 (21).

Anal. Calcd. for $C_{22}H_{26}N_2OS$ (366.5): C, 72.09; H, 7.15; S, 8.75. Found: C, 72.16; H, 7.22; S, 8.76.

General Procedure for the Preparation of Adducts **5e-5j**.

A solution of thiolactam **2** (0.9 mmole), of the appropriate mercapto-compound **4** (1.1 mmoles) and triethylamine (in case of ethyl thiohydroxyacetate, Table 1, entry 7 and 8) (0.11 g, 1.1 mmoles) or DBU (in case of methyl 3-thiohydroxypropionate, Table 1, entry 9 and 10) (0.167 g, 1.1 mmoles) in dry DMF (4 ml) was stirred at room temperature for 1.5 hours. After evaporation of the solvent under vacuum the product was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate 7:3).

trans (Major) 4-(2-Aminophenylthio)-l-benzyl-6-methylpiperidine-2-thione (**5e**).

This compound was obtained as an oil; ^{1}H nmr (deuteriochloroform): δ 1.24 (d, J = 6.4 Hz, 3H, CH_3), 1.87 (ddd, J = 13.5, 11.1, 5.4 Hz, 1H, H-5_{ax}), 1.97 (dm, J = 13.4 Hz, 1H, H-5_{eq}) 3.11 (dd, J = 18.4, 9.4 Hz, H-3_{ax}), 3.38-3.48 (m, 1H, H-4_{ax}), 3.52 (dd, J = 18.4, 5.5 Hz, 1H, H-3_{eq}), 3.73 (ddq, J_{1-3} = 6.4 Hz, J_4 = 5.4 Hz, J_5 = 3.3 Hz, 1H, H-6_{eq}), 4.15 (br s, 2H, NH_2), 4.36 (d, J = 14.9 Hz, 1H, PhC*H*HN), 6.39 (d, J = 14.9 Hz, 1H, PhCH*H*N), 6.00 (td, J = 7.4, 0.9 Hz, 1H, ArH), 6.71 (dd, J = 8.0 Hz, 1.2, 1H, ArH), 7.13 (td, J = 7.4, 1.2 Hz, 1H, ArH), 7.24-7.35 (m, 6H, ArH); ^{13}C nmr (deuteriochloroform): δ 19.4 (CH_3), 36.2 (C-5), 36.5 (C-4), 47.8 (C-3), 53.7 (C-6), 54.5 (Ph*C*H_2), 114.1, 115.1, 118.4, 130.7, 137.5, 149.2 (*o*-$SC_6H_4NH_2$), 127.5, 127.6, 128.7, 135.4 (Ph), 198.6 (C-2); ms: m/z (%) 342 ($M^{+\bullet}$, 2), 218 ($M^{+\bullet}$-*o*-$NH_2C_6H_4S^\bullet$, 46), 184 (6), 124 (11), 91 (Bn^+, 100), 80 (16), 65 (16).

Anal. Calcd. for $C_{19}H_{22}N_2S_2$ (344.5): C, 66.63; H, 6.47; S, 18.72. Found: C, 66.82; H, 6.76; S, 18.49.

trans (Major) 4-(2-Aminophenylthio)-1-benzyl-6-phenylpiperidine-2-thione (**5f**).

This compound was obtained as an oil; ^{1}H nmr (deuteriochloroform): δ 2.00 (ddd, J = 13.5, 11.2, 5.7 Hz, 1H, H-5_{ax}), 2.12 (dm, J ~ 13.5 Hz, 1H, H-5_{eq}), 3.12 (dd, J = 18.0, 9.9 Hz, 1H, H-3_{ax}), 3.11-3.21 (m, 1H, H-4_{ax}), 3.55 (br d, J ~ 17.5 Hz, 1H, H-3_{eq}), 3.71 (d, J = 14.7 Hz, 1H, PhC*H*HN), 4.19 (br s, 2H, NH_2), 4.69 (dd, J = 5.4, 3.6 Hz, 1H, H-6_{eq}), 6.53 (tt, J = 7.6, 1.2 Hz, 1H, ArH), 6.57 (d, J = 14.5 Hz, 1H, PhCH*H*N), 6.58 (dd, J = 8.2, 1.2 Hz, 1H, ArH), 6.93-7.32 (m, 12H, ArH); ^{13}C nmr (deuteriochloroform): δ 34.7 (C-4), 36.6 (C-5), 47.1 (C-3), 54.1 (Ph*C*H_2), 60.9 (C-6), 112.3, 114.1, 117.7, 129.7, 136.5, 148.4 (*o*-$SC_6H_4NH_2$), 125.4, 126.8, 127.0, 127.1, 127.7, 128.1, 135.8, 138.4 (*Ph*CH_2, Ph), 199.2 (C-2); ms: m/z (%): 404 ($M^{+\bullet}$, 2), 280 ($M^{+\bullet}$-$NH_2C_6H_4S^\bullet$, 45), 124 (59), 91 (Bn^+, 100), 80 (56), 77 (9), 65 (25).

Anal Calcd. for $C_{24}H_{24}N_2S_2$ (404.6): C, 71.25; H, 5.98; S, 15.85. Found: C, 71.42; H, 6.06; S, 15.69.

trans (Major) and *cis* (Minor) 1-Benzyl-4-(ethoxycarbonylmethylthio)-6-methylpiperidine-2-thione (**5g**).

This mixture of compounds was isolated as an oil. Spectra were obtained from this mixture of diastereomers; ^{1}H nmr (deuteriochloroform) δ 1.28 (t, J = 7.1 Hz, 3H, CH_3), 1.32 (d, J = 6.7 Hz, 3H, CH_3), 1.86 (ddd, J = 13.2, 11.8, 5.4 Hz, 1H, H-5_{ax}), 2.07 (dm, J = 13.4 Hz, 1H, H-5_{eq}), 3.08 (dd, J = 18.6, 9.8 Hz, 1H, H-3_{ax}), 3.25 (d, J = 14.8 Hz, 1H, S-C*H*H), 3.30 (d, J = 14.8 Hz, 1H, S-CH*H*), 3.47-3.38 (m, 1H, H-4_{ax}), 3.64 (dd, J = 18.7, 5.5 Hz, 1H, H-3_{eq}), 3.76 (ddq, J_{1-3} = 6.6 Hz, J_4 = 5.4 Hz, J_5 = 3.2 Hz, 1H, H-6_{eq}), 4.19 (q, J = 7.1 Hz, 2H, CH_2-O), 4.39 (d, J = 14.9 Hz, 1H, PhC*H*HN), 6.40 (d, J = 14.9 Hz, 1H, PhCH*H*N), 7.38-7.24 (m, 5H, Ph); ^{13}C nmr (deuteriochloro-form): δ 14.2 (CH_3CH_2), 19.3 (CH_3), 32.0 (S-CH_2), 33.8 (C-4), 35.9 (C-5), 47.6 (C-3), 53.7 (C-6), 54.6 (PhCH_2N), 61.5 (CH_2O), 127.5, 127.7, 128.8, 135.3 (Ph), 170.1 (C=O), 198.0 (C-2); ms: m/z, (%) 337 ($M^{+\bullet}$, 10), 218 ($M^{+\bullet}$-$^\bullet SCH_2COOEt$, 12), 184 (12), 126 (12), 106 (15), 91 (Bn^+, 100), 65 (19).

Anal. Calcd. for $C_{17}H_{23}NO_2S_2$ (337.5): C, 60.50; H, 6.88; S, 18.97. Found: C, 60.43; H, 6.85; S, 18.88.

trans (Major) 1-Benzyl-4-(ethoxycarbonylmethylthio)-6-phenylpiperidine-2-thione (**5h**).

This compound was obtained as an oil; ^{1}H nmr (deuteriochloroform): δ 1.14 (t, J = 7.1 Hz, 3H, CH_3), 2.17 (ddd, J = 12.0, 11.7, 5.5 Hz, 1H, H-5_{ax}), 2.26 (dm, J ~ 12.0 Hz, 1H, H-5_{eq}), 3.10-3.21 (m, 4H, S-CH_2, H-3_{ax}, H-4_{ax}), 3.71-3.85 (m, 2H, PhC*H*HN, H-3_{eq}), 4.02 (qd, J = 7.1, 1.8 Hz, 2H, CH_2O), 4.8 (dd, J = 5.3, 3.0 Hz, 1H, H-6_{eq}), 6.66 (d, J = 14.7 Hz, 1H, PhCH*H*N), 7.08 (d, J = 7.1 Hz, 2H, ArH), 7.43-7.25 (m, 8H, ArH); ^{13}C nmr (deuteriochloroform): δ 14.0 (CH_3), 31.9 (S-CH_2), 33.1 (C-4), 37.3 (C-5), 47.9 (C-3), 55.2 (PhCH_2), 61.4 (OCH_2), 61.9 (C-6), 126.4, 127.8, 128.2, 128.8, 129.2, 135.1, 139.1 (*Ph*CH_2, Ph), 169.8 (C=O), 199.4 (C-2); ms: m/z (%) 399 (M^+, 13), 280 (M^+-SCH_2COOEt, 9), 246 (12), 149 (13), 148 (15), 131 (13), 123 (13), 115 (20), 106 (21), 91 (100), 65 (15), 59 (20).

Anal. Calcd. for $C_{22}H_{25}NO_2S_2$ (399.6): C, 66.13; H, 6.31; S, 16.05. Found: C, 65.79; H, 6.55; S, 16.29.

trans (Major) and *cis* (Minor) 1-Benzyl-4-(methoxycarbonylethylthio)-6-methylpiperidine-2-thione (**5i**).

This mixture of compounds was isolated as an oil. The spectra were obtained from this diastereomeric mixture; ^{1}H nmr (deuteriochloroform): δ 1.33 (d, J = 6.7 Hz, 3H, CH_3), 1.87 (ddd, J = 13.4, 11.6, 5.4 Hz, 1H, H-5_{ax}), 2.02 (dm, J = 13.4 Hz, 1H, H-5_{eq}), 2.62 (t, J = 7.3 Hz, 2H, S-CH_2), 2.85 (t, J = 7.3 Hz, 2H, CH_2CO), 3.08 (dd, J = 18.5, 9.8 Hz, 1H, H-3_{ax}), 3.20-3.30 (m, 1H, H-4_{ax}), 3.62 (br dd, J = 18.7, 5.6 Hz, 1H, H-3_{eq}), 3.70 (s, 3H, OCH_3), 3.76 (ddq, J_{1-3} = 6.6 Hz, J_4 = 6.0 Hz, J_5 = 3.2 Hz, 1H, H-6_{eq}), 4.38 (d, J = 14.9 Hz, 1H, PhC*H*HN), 6.42 (d, J = 14.9 Hz, 1H, PhCH*H*N), 7.20-7.32 (m, 5H, Ph); ^{13}C nmr (deuteriochloroform): δ 19.4 (CH_3), 25.1 (SCH_2), 33.7 (C-4), 34.7 (CH_2C=O), 36.3 (C-5), 48.3 (C-3), 51.9 (OCH_3), 53.6 (C-6), 55.3 (PhCH_2), 127.5, 127.5, 128.8, 135.4 (Ph), 172.1 (C=O), 198.4 (C-2); ms: m/z (%) 337 (M^+, 12), 219 (22), 218 ($M^{+\bullet}$-$^\bullet SCH_2CH_2COOMe$, 13), 184 (11), 126 (11), 106 (19), 91 (Bn^+, 100), 65 (20).

Anal. Calcd. for$C_{17}H_{23}NO_2S_2$ (337.5): C, 60.50; H, 6.87; S, 19.00. Found: C, 60.41; H, 6.98; S, 19.13.

trans (Major) and *cis* (Minor) 1-Benzyl-4-(methoxycarbonylethylthio)-6-phenylpiperidine-2-thione (**5j**).

This mixture of compounds was isolated as an oil. The spectra were obtained from the mixture of diastereomers; ^{1}H nmr (deuteriochloroform): δ 2.15 (ddd, J = 13.3, 11.8, 5.5 Hz, 1H, H-5_{ax}), 2.25 (d pseudo q, J = 13.3, 3.2 Hz, 1H, H-5_{eq}), 2.51 (t, J = 7.3 Hz, 2H, SCH_2), 2.78 (t, J = 7.3 Hz, 2H, CH_2CO), 2.98-3.09 (m, 1H, H-4_{ax}), 3.18 (dd, J = 18.6, 10.4 Hz, 1H, H-3_{ax}), 3.67 (s, 3H, OCH_3), 3.78 (br dd, J ~ 18.4, 5.2 Hz, 1H, H-3_{eq}), 3.85 (d, J = 14.7 Hz, PhC*H*HN), 4.83 (dd, J = 5.4, 3.0 Hz, 1H, H-6_{eq}), 6.70 (d, J = 14.7 Hz, 1H, PhCH*H*N), 7.12 (d, J = 7.1 Hz, 2H, ArH), 7.24-7.48 (m, 8H, ArH); ^{13}C nmr (deuteriochloroform): δ

25.0 (SCH_2), 32.8 (C-4), 34.5 (CH_2C=O), 37.7 (C-5), 48.5 (C-3), 51.8 (OCH_3), 55.3 (PhCH_2), 61.9 (C-6), 126.4, 127.9, 128.8, 129.3, 135.2, 139 2, (*Ph*CH_2, Ph), 171.9 (C=O), 199.7 (C-2); ms: m/z (%) 399 ($M^{+\cdot}$, 7), 280 ($M^{+\cdot}$-$^{\cdot}SCH_2CH_2COOMe$, 11), 148 (14), 115 (21), 106 (16), 91 (Bn^+, 100), 77 (12), 65 (20), 45 (35).

Anal. Calcd. for $C_{22}H_{25}NO_2S_2$ (399.6): C, 66.13; H, 6.31; S, 16.05: Found: C, 66.33; H, 6.53; S, 16.33.

trans (Major) and *cis* (Minor) 1-Benzyl-4-(1-methylhydrazino)-6-phenylpiperidine-2-thione (**5k**).

This mixture of compunds was isolated as an oil. The spectra were obtained from this mixture of diastereomers.

The *trans*-isomer had ^{1}H nmr (deuteriochloroform): δ 2.06 (ddd, J = 13.2, 10.9, 5.7 Hz, 1H, H-5_{ax}), 2.16 (ddt, J_1 = 13.2 Hz, $J_{2\text{-}3}$ = 3.6 Hz, J_4 = 1.8 Hz, 1H, H-5_{eq}), 2.36 (s, 3H, NCH_3), 2.47-2.56 (m, 1H, H-4_{ax}), 2.80 (br s, 2H, NH_2), 3.17 (dd, J = 18.6, 9.1 Hz, 1H, H-3_{ax}), 3.42 (br dd, J = 18.6, 5.3 Hz, 1H, H-3_{eq}), 3.80 (d, J = 14.7 Hz, 1H, PhC*H*HN), 4.76 (dd, J = 5.5, 3.4 Hz, 1H, H-6_{eq}), 6.58 (d, J = 14.7 Hz, 1H, PhCH*H*N), 7.00 (d, J = 7.0 Hz, 2H, ArH), 7.12-7.33 (m, 8H, ArH); ^{13}C nmr (deuteriochloroform): δ 33.5 (C-5), 43.4 (C-3), 46.0 (NCH_3), 54.3 (PhCH_2), 55.0 (C-4), 61.1 (C-6), 125.3, 126.6, 127.0, 127.7, 128.2, 134.3, 138.8 (Ph, *Ph*CH_2), 200.1 (C-2); ms: m/z (%) 326 ($M^{+\cdot}$, 1), 280 (34), 106 (10), 103 (9), 91 (Bn^+, 100), 77 (100), 65 (17).

Anal. Calcd. for $C_{19}H_{23}N_3S$ (325.5): C, 70.12; H, 7.12; S, 9.85. Found C, 69.96; H, 6.97; S, 9.68.

The *cis*-isomer had ^{1}H nmr (deuteriochloroform): δ 1.85 (ddd, J = 11.9, 11.6, 10.6 Hz, 1H, H-5_{ax}), 2.38-2.43 (m, 1H, H-5_{eq}), 2.44 (s, 3H, NCH_3), 2.59 (tt, J = 11.6, 3.7 Hz, 1H, H-4_{ax}), 2.80 (br s, 2H, NH_2), 3.00 (dd, J = 17.4, 11.4 Hz, 1H, H-3_{ax}), 3.64 (dt, J = 17.4, 3.7 Hz, 1H, H-3_{eq}), 3.76 (d, J ~ 13.8 Hz, 1H, PhC*H*HN), 4.40 (dd, J = 10.6, 6.3 Hz, 1H, H-6_{ax}), 6.54 (d, J ~13.8 Hz, 1H, PhCH*H*N), 7.01-7.06 (m, 2H, ArH), 7.12-7.33 (m, 8H, ArH); ^{13}C nmr (deuteriochloroform): δ 36.0 (C-5), 44.8 (C-3), 45.8 (N-CH_3), 52.8 (PhCH_2), 58.2 (C-4), 62.9 (C-6), 125.8, 126.6, 126.7, 127.3, 127.6, 128.2, 134.4, 130.7 (*Ph*CH_2, Ph), 200.2 (C-2).

Acknowledgement.

We gratefully acknowledge financial support from Deutscher Akademischer Austauschdienst (DAAD) and from Fonds der Chemischen Industrie.

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