Pergamon

Tetrahedron Vol. 50, No. 10, pp. 3123-3138, 1994

0040-4020/94 $6.00+0.00

0040-4020(94)E0049-Y

FUNCTIONALIZED CHLOROENAMINES IN AMINOCYCLOPROPANE SYNTHESIS - XV.[1] SYNTHESIS OF CONFORMATIONALLY RIGID ANALOGUES OF [1,4'-BIPIPERIDINE]-4'-CARBOXAMIDE - A COMMON PHARMACOPHORIC GROUP

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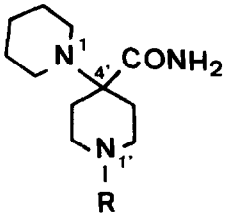
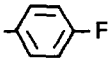
Abstract: 6-Piperidino-3-azabicyclo[3.1.0]hexane-6-carboxamide diastereomers **5** and **7** represent conformationally rigid analogues of the pharmacophoric group **1**. Compounds **5** and **7** were synthesized with high stereoselectivity via chloroenamines **12a** and **13b**, respectively. Introduction of a 4-(4-fluorophenyl)-4-oxobutyl moiety in **5** and **7** led to derivatives **6** and **8** which correspond to rigid conformers of Pipamperone **2**, a neuroleptic drug. An X-ray structure analysis was performed for compound **6**; configuration and conformation of **5** - **8** were determined ^{1}H NMR spectroscopically. 3',5'-Cyclopipamperone diastereomers **6** and **8** showed different affinities to dopamine receptors D_{2L} and D_3.

[1,4'-Bipiperidine]-4'-carboxamide (**1**) is found as structural subunit of the active components of the commercial drugs **2** - **4**.



1 - 4

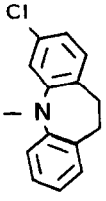
1: R = H

2: **PIPAMPERONE**[2] *Dipiperon* Ⓡ *Propitan* Ⓡ *Piperonil* Ⓡ R = -$(CH_2)_3$-C(=O)- 

(Neuroleptic agent)

3: **PIRITRAMIDE**[3] *Dipidolor* Ⓡ R = -$(CH_2)_2$-C(CN)-$(C_6H_5)_2$

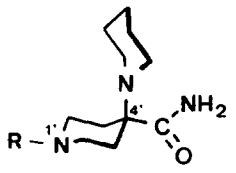
(Analgetic agent)

4: **CLOCAPRAMINE**[4] *Clofecton* Ⓡ R = -$(CH_2)_3$- 

(Antidepressive agent)

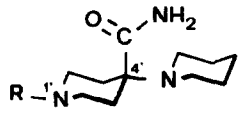
The pharmacological behaviour of these active components is mainly determined by the substituent R in **2** - **4**. [1,4'-Bipiperidine]-4'-carboxamide as pharmacophoric group, however, also influences the spectrum of activity. This was shown by structure-activity relationship studies using various amines[5] in 4'-position of **2** and **3**.

The bipiperidine pharmacophoric group in **2** - **4** is rather flexible due to ring inversion and nitrogen inversion of the piperidine rings. A t-1',r-4'-structure and a c-1',r-4'-structure should be the main conformers of these compounds. X-Ray structural analyses of Pipamperone[6] **2** and Piritramide[7] **3** showed that the c-1',r-4'-conformer is present at least in the solid state. A distance of 4.82 Å between the N(1')-atom and the 4'-carboxamide nitrogen-atom of **2** was estimated to be favourable for neuroleptic activity.[6]

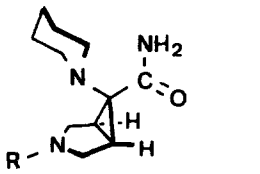


t-1',r-4'-CONFORMER

2 - 4

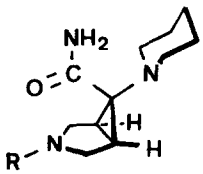


c-1',r-4'-CONFORMER



5 R = H

6 R = -$(CH_2)_3$-C(=O)-  -F



7 R = H

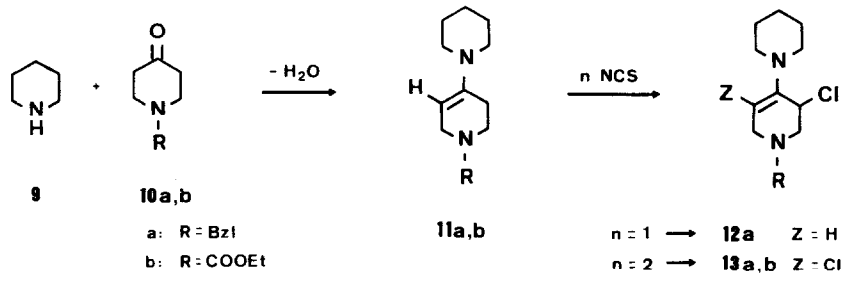
8 R = -$(CH_2)_3$-C(=O)-  -F

Bicyclic derivatives **5** and **7** can be regarded as conformationally rigid analogues of the pharmacophoric group **1**; these compounds **5** and **7** should be useful for studying conformational influences in receptor substrate interactions of the [1,4'-bipiperidine]-4'-carboxamide pharmacophoric group.

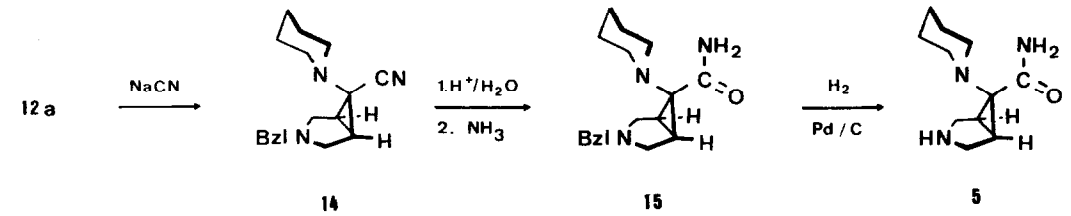
Our interest in 6-amino-3-azabicyclo[3.1.0]hexane derivatives[8-13] prompted us to synthesize the bicyclic carboxamides **5** and **7**. The compounds **6** and **8** which can be regarded as 3',5'-Cyclopipamperones were prepared additionally. They served exemplarily as target molecules in order to get a preliminary information of conformational influences of group **1** on the pharmacological activity of Pipamperone **2**.

SYNTHESIS OF DIASTEREOMERIC BICYCLIC CARBOXAMIDES 5 / 7 AND 6 / 8

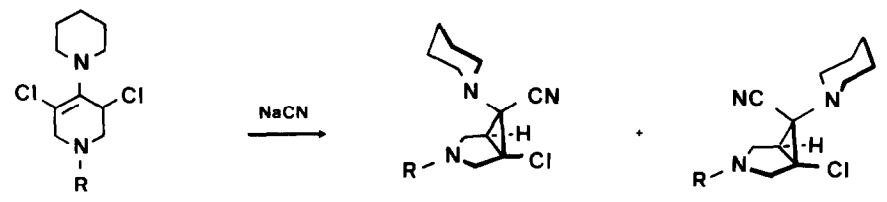
Monochloroenamine **12a** and dichloroenamines **13a,b** should be suitable starting materials for a diastereoselective access to isomeric compounds **5** and **7**, respectively.[8,14] The corresponding chloroenamines were available by reaction of enamines **11a,b** with N-chlorosuccinimide in a ratio of 1:1 (led to **12a**) or 1:2 (led to **13a,b**).



Reaction of monochloroenamine **12a** with sodium cyanide gave bicyclic nitrile **14** in 91% yield (based on enamine **11a**). **14** was hydrolyzed by acid to give amide **15** (60% yield) which was debenzylated by hydrogen leading to bicyclic carboxamide **5** (62% yield).



The analogous use of dichloroenamine **13a** instead of monochloro derivative **12a** (see ref.[8,14]) should serve as key-step on the way to diastereomer **7**. A mixture of diastereomers **16a** and **17a**, however, was obtained from this reaction of the N-benzyl compound; separation by chromatography led to pure substances **16a** (43% yield) and **17a** (37% yield). In contrast, dichloroenamine **13b** with an ester moiety at the tetrahydropyridine N-atom reacted with cyanide in the desired highly stereoselective way to give endo-nitrile **17b** in 82% yield.



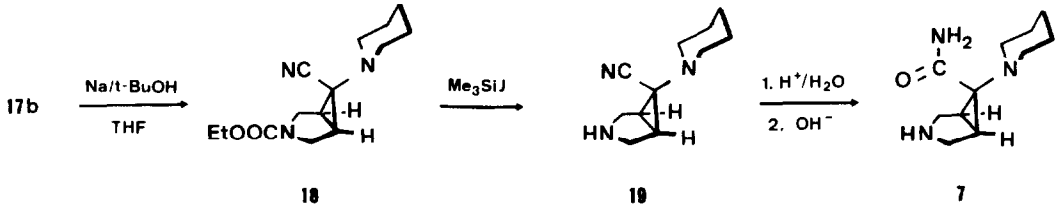
13a,b

a: R = Bzl
b: R = COOEt

16 a: 43 % b: –

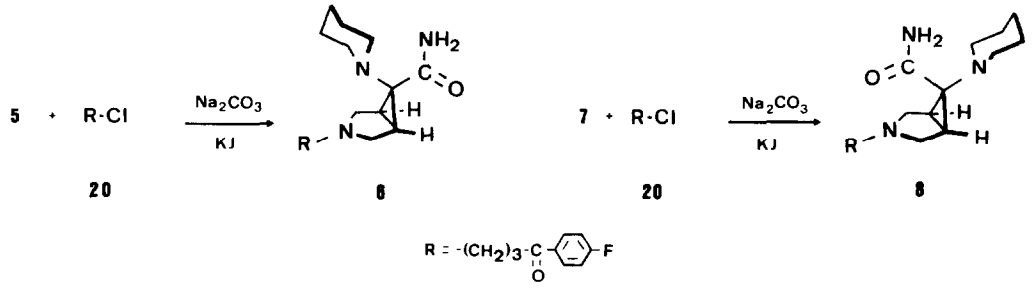
17 37 % 82 %

Dechlorination of bicyclic derivative **17b** to nitrile **18** (37% yield) could be achieved by finely powdered sodium in tetrahydrofuran/*tert*-butyl alcohol.[15] Removal of the ester moiety in urethane **18** by trimethylsilyl iodide[16] produced amine **19** (90% yield). Subsequent acidic hydrolysis of the nitrile function in **19**, finally, gave carboxamide **7** (95% yield).



18 **19** **7**

Reaction of the azabicyclohexanecarboxamides **5** and **7** with 4-chloro-1-(4-fluorophenyl)-butan-1-one in the presence of sodium carbonate and potassium iodide led to the corresponding 3',5'-Cyclopipamperones **6** (63% yield) and **8** (39% yield), respectively.



20 **6** **20** **8**

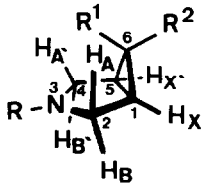
Structures of the new compounds could be established unequivocally from the ^1H and ^{13}C NMR spectra (see Experimental). Only the structural data of the target molecules **5** - **8** will be discussed subsequently more in detail.

CONFIGURATION AND CONFORMATION OF THE BICYCLIC CARBOXAMIDE DIASTEREOMERS 5 / 7 AND THE 3',5'-CYCLOPIPAMPERONE DIASTEREOMERS 6 / 8

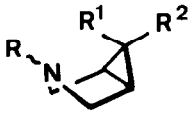
Configuration of bicyclic carboxamides **5** and **7** was deduced most easily from determination of the free activation enthalpy of the dynamics of piperidine in these compounds (e.g. see ref.[8,10]): A $\Delta G^{\ddagger}$-value of 74.3 kJ/mol clearly showed a steric hindrance of the dynamics of piperidine and indicated thus its endo-position in **5** (toluene, NCH_2-group: H_A: 2.53 ppm, H_B: 2.47 ppm, J_{AB} = 12.2 Hz, T_c = 355 K).[17] Piperidine in compound **7** gave a $\Delta G^{\ddagger}$-value of 48.0 kJ/mol (toluene, NCH_2-group: H_A: 2.34 ppm, H_B: 2.26 ppm, J_{AB} = 10.5 Hz, T_c = 234 K);[17] the absence of additional hindrance of the dynamics of piperidine is in accordance with its exo-position in **7**. Configuration of **5** and **7** could be confirmed by the basicity of these compounds. pK_a-Values of 7.68 (**7**) and 9.86 (**5**) were determined for the two isomers by potentiometric titration[18] with 0.1 M aqueous hydrochloric acid (uptake of only one proton in each case). It was found for a variety of 6-amino-3-azabicyclo[3.1.0]hexane derivatives that endo-diamines are more basic than the exo-isomers;[12,13] the stronger basicity results from intramolecular hydrogen bonding in the mono salt in the case of an endo-diamine.

The conformation of the azabicyclohexane skeleton of isomers **5** and **7** could be determined ^1H NMR spectroscopically. Only two sharp lines appeared for the $H(2)_A$ / $H(4)_{A'}$ -atoms of the azabicyclo[3.1.0]hexane system in toluene at 305 K for both compounds **5** (2.85 ppm) and **7** (2.91 ppm). The total missing of a coupling H_A/H_X and $H_{A'}/H_{X'}$ indicated the presence of a boat conformation[11] in **5** and in **7**.

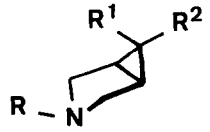
An X-ray structural analysis was performed for 3',5'-Cyclopipamperone diastereomer **6**. The Schakal-plot[19] (Fig. 1) shows clearly the endo-position of piperidine and the chair conformation of the azabicyclo[3.1.0]hexane system in **6**. Interplanar angles of 67.3° and 28.1° demonstrate a clear buckling of the bicyclic system.



Assignment of H-atoms



Boat conformation



Chair conformation

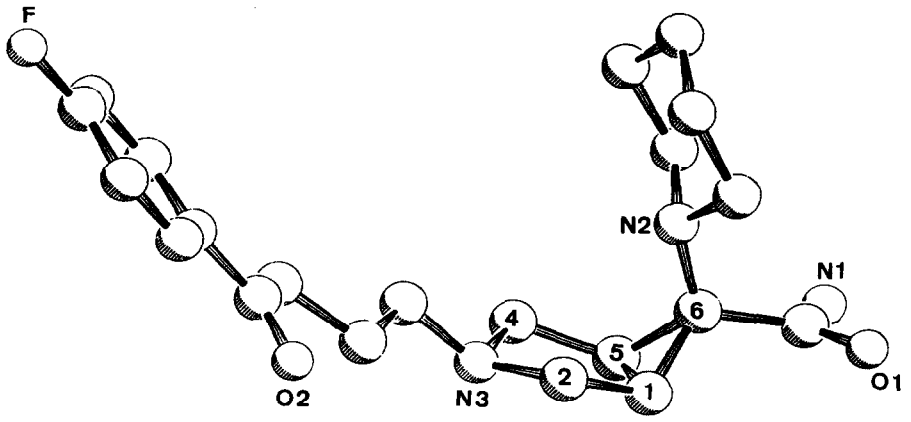


Fig. 1 Schakal-plot[19] of 3',5'-Cyclopipamperone diastereomer **6**; H-atoms are omitted for reasons of clarity

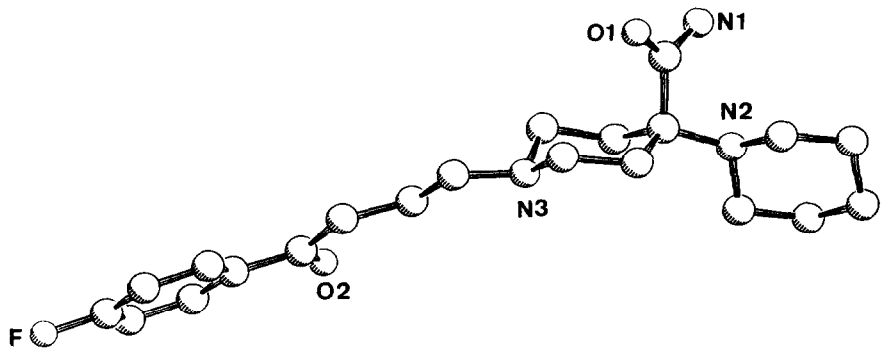


Fig. 2 Schakal-plot[19] of Pipamperone **2** (according to ref.[6])

The distances between N(3) and further heteroatoms in **6** are given in Table 1. These values are compared with the analogous distances in Pipamperone **2**. It turned out that the N(3)-piperidine and the N(3)-carboxamide distances are quite different in Pipamperone **2** in the c-1',r-4'-conformation and in Cyclopipamperone diastereomer **6**. This is shown additionally by the Schakal-plot[19] of structure **2** (Fig. 2) using the same view as in **6**. The published coordinates of the X-ray structural analysis of **2** in ref.[6] were used for drawing the Schakal-plot in this view and for the calculation of heteroatom-N(3) distances.

Table 1 Selected bond distances, torsional angles and interplanar angles of 1*α*,5*α*,6*β*-3-[4-(4-fluorophenyl)-4-oxobutyl]-6-piperidino-3-azabicyclo[3.1.0]hexane-6-carboxamide (**6**); N,N- and N,O-distances in 3',5'-Cyclopipamperone diastereomer **6** and in Pipamperone **2** (from ref.[6])

bond lengths [Å]		N,N- and N,O-distances [Å]		
	6		**6**	**2**[a]
C(1) - C(5)	1.502(5)	N(3) - N(2)	3.384(4)	4.242
C(1) - C(6)	1.492(5)	N(3) - N(1)	5.329(4)	4.823
C(5) - C(6)	1.497(4)	N(3) - O(1)	5.300(3)	3.854
		N(3) - O(2)	5.165(4)	5.136

6: torsional angles[b] [°]		**6**: interplanar angles [°]	
$H(1)_X$-C(1)-C(2)-$H(2)_A$	113.67	C(1)C(5)C(6) - C(1)C(2)C(4)C(5)	67.3(2)
$H(4)_{A'}$-C(4)-C(5)-$H(5)_{X'}$	-111.44	C(1)C(2)C(4)C(5) - C(2)N(3)C(4)	28.1(3)
$H(1)_X$-C(1)-C(2)-$H(2)_B$	- 3.82		
$H(4)_{B'}$-C(4)-C(5)-$H(5)_{X'}$	10.95		

[a] Numbering of the atoms in **2** was changed with respect to the original publication[6] for better comparison with the data of compound **6**.- [b] $H(2)_A$ / $H(4)_{A'}$ are in the endo-position and $H(2)_B$ / $H(4)_{B'}$ are in the exo-position of the 3-azabicyclo[3.1.0]hexane system.

The dihedral angles of the $H(1)_X$-C(1)-C(2)-$H(2)_A$ and $H(5)_{X'}$-C(5)-C(4)-$H(4)_{A'}$ structural units (see Table 1) are important for determination of the conformation of **6** in solution: Though a coupling of H_A with H_X (or $H_{A'}$ with $H_{X'}$) was not directly visible in the ^{1}H NMR spectrum of **6**, the strongly broadened shape of the H_A / $H_{A'}$ signal is in accordance rather with a chair than with a boat conformation. This became obvious by the ^{1}H NMR spectrum of diastereomer **8** in

which the H_A / $H_{A'}$ signal at 3.07 ppm indeed consisted of two very sharp lines excluding any J_{AX} / $J_{A'X'}$-coupling. Thus **8** is to be discribed by a boat conformation with an equatorial fluorophenyloxobutyl moiety.

RECEPTOR AFFINITY STUDIES OF 3',5'-CYCLOPIPAMPERONE DIASTEREOMERS 6 AND 8

Preliminary informations about conformational influences of the pharmacophoric group **1** on the activity of Pipamperone **2** were expected from receptor-binding studies of **2** in comparison with its cycloanalogues **6** and **8**. The affinities of these substances to cloned human dopamine receptor subtypes D_{2L} and D_3 were determined and given as K_i-values (see Table 2).[20]

Table 2 K_i-values of affinity studies of compounds **2**, **6** and **8** with the dopamine receptor subtypes D_{2L} and D_3.[a]

Compound	D_3-receptor K_i [nmol/L]	D_{2L}-receptor K_i [nmol/L]	$K_i[D_3]$ / K_i $[D_{2L}]$
2	205	56.8	3.6
6	3 197	630	5.1
8	> 10 000	> 10 000	-

[a] Number n of experiments: **2**: n = 3; **6** and **8**: n = 2.

The obtained values indicate that Pipamperone **2** has a strong affinity to the D_{2L}-dopamine receptor and a somewhat lower affinity to the D_3-dopamine receptor. In contrast, exo-piperidine derivative **8**, which is the cyclic analogue of Pipamperone **2** in the common c-1',r-4'-conformation,[6] showed no activity in these receptor-binding studies. The endo-piperidine isomer **6**, however, was active according to these studies; the activity was lowered by a factor of about 10 with respect to that of Pipamperone **2**. Cyclopipamperone diastereomer **6** and Pipamperone **2** showed similar D_3/D_{2L}-receptor selectivity.

Thus, Pipamperone **2** should interact with the dopamine D_{2L}- and D_3-receptor in the t-1',r-4'-conformation and not in the c-1',r-4'-conformation which was found by the X-ray structure

analysis[6]. The lower activity of **6** with respect to **2** may be the consequence of a conformational anchoring of the endo-piperidine ring by the bicyclic system. Such an additional conformational anchoring is not effective for **8** with piperidine in the exo-position. Conformational restrictions of the bicyclic skeleton in **6** (chair) and **8** (boat) should not be important since even at very low temperature no chair - boat inversion could be detected thus far in the ^1H NMR spectra of these bicyclic systems.

These preliminary binding studies with Cyclopipamperone diastereomers **6** and **8** show that the azabicyclohexane species **5** and **7** should be interesting analogues of the bipiperidinecarboxamide pharmacophore **1**. Further investigations, however, are necessary in order to determine the real activity of compounds such as **6** and **8** which mimic a conformationally rigid bipiperidinecarboxamide subunit.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were obtained with a Bruker AMX 400 spectrometer or otherwise if noted with a Bruker AM 200 spectrometer (TMS as internal standard). IR spectra were measured on a Perkin-Elmer 1310 Infrared Spectrophotometer. Microanalyses were performed with a Perkin-Elmer 240 or 2400 Elemental Analyzer. Tetrahydrofuran and dioxane were freshly distilled from lithium aluminum hydride, tert.-butyl alcohol was freshly distilled from sodium. A Büchi B-681 Chromatography System was used for MPLC separations, B-685 column, ϕ: 26 mm, length: 460 mm; UV/VIS Filter Photometer as detector, 254 nm. pK_a-Values were determined by titration with a Metrohm 702 SM Titrino apparatus using a Metrohm combined pH-glass electrode with Ag/AgCl/KCl (3 Mol/L). Reactions in non aqueous solvents were performed under exclusion of moisture in a nitrogen atmosphere.

Enamines 11a and 11b: The enamines were prepared according to a general procedure using a Dean-Stark apparatus.

1-Benzyl-1,2,3,6-tetrahydro-4-piperidino-pyridine[21,22] (**11a**): N-Benzyl-4-piperidone (**10a**) (54.11 g, 286 mmol), piperidine (**9**) (30.10 g, 353 mmol) and 4-toluenesulfonic acid (0,02 g) in benzene (100 mL) gave crude enamine **11a** which was distilled in a Kugelrohr apparatus. Yield: 70.96 g (97%); bp 110°C/0.001 Torr; IR (film, cm^{-1}) 1640 (C=C); ^1H NMR ($CDCl_3$) δ 1.40-1.53 (m, 2H), 1.53-1.62 (m, 4H), 2.22 (m_c, 2H), 2.57 (m_c, 2H), 2.78 (m_c, 4H), 3.06 (m_c, 2H), 3.56 (s, 2H), 4.56 (m_c, 1H), 7.20-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 144.4 (s), 138.6 (s), 129.1 (d), 128.1 (d), 126.9 (d), 97.0 (d), 62.7 (t), 53.0 (t), 50.1 (t), 48.4 (t), 28.3 (t), 25.7 (t), 24.5 (t). Anal. Calcd for $C_{17}H_{24}N_2$: C, 79.64; H, 9.44; N, 10.93. Found: C, 79.6; H, 9.3; N, 10.9.

Ethyl 1,2,3,6-tetrahydro-4-piperidino-pyridine-1-carboxylate[22,23] (**11b**): Ethyl 4-oxopiperidine-1-carboxylate (**10b**) (49.74 g, 291 mmol), piperidine (**9**) (29.70 g, 349 mmol) and 4-toluenesulfonic acid (0.02 g) in benzene (100 mL) gave crude enamine **11b** which was purified in a Kugelrohr apparatus. Yield: 67,19 g (97%); bp 95°C/0.001 Torr; IR (film, cm^{-1}) 1705 (C=O), 1655 (C=C); ^1H NMR ($CDCl_3$) δ 1.26 (t, 3H), 1.45-1.65 (m, 6H), 2.18 (m_c, 2H), 2.77 (m_c, 4H), 3.57 (m_c, 2H), 3.99 (m_c, 2H), 4.14 (q, 2H), 4.55 (broad, unsplit, 1H); ^{13}C NMR ($CDCl_3$) δ 155.1 (s), 144.6 (s), 96.2 (d), 95.5 (d), 60.8 (t), 48.4 (t), 42.4 (t), 40.3 (t), 27.2 (t), 25.4 (t), 24.1 (t), 14.5 (q). Anal. Calcd for $C_{13}H_{22}N_2O_2$: C, 65.52; H, 9.30; N, 11.75. Found: C, 65.5; H, 9.2; N, 11.8.

1α,5α,6β-3-Benzyl-6-piperidino-3-azabicyclo[3.1.0]hexane-6-carbonitrile (**14**): A solution of N-chlorosuccinimide (9.11 g, 68.25 mmol) in dichloromethane (200 mL) was dropped at -78°C within 2.5 h to a stirred solution of enamine **11a** (17.5 g, 68.25 mmol) in dichloromethane (100 mL). Stirring was continued for 0.5 h. Removal of the solvent at room temperature, extraction of the residue with pentane (4 x 40 mL) and evaporation of the combined extracts gave crude chloroenamine **12a**. The resulting yellow oil was stirred in a solution of sodium cyanide (6.69 g, 136.5 mmol) in methanol/water (1/1, 250 mL) for 140 min at 60°C. Evaporation of methanol in vacuo and extraction of the residue with ether (4 x 100 mL) gave **14** as pale yellow oil which solidified spontaneously. Yield: 17.50 g (91%); mp 83°C; IR (KBr, cm^{-1}) 2210 (C$\equiv$N); ^1H NMR ($CDCl_3$) δ 1.32 (H_Z, 1H), 1.5-1.9 (H_W, H_{X1}, H_Y, 5H), 2.46 (H_{B1}, 2H), 2.64 (H_{A1}, 2H) ($A_2B_2W_2X_2YZ$-system, $^2J_{AB}$ = 11.3 Hz), 2.25 (H_{X2}, $H_{X'2}$, 2H), 2.35 (H_{A2}, $H_{A'2}$, 2H), 3.25 (H_{B2}, $H_{B'2}$, 2H) (AA'BB'XX'-System, $^2J_{AB}$ = 9.9 Hz), 3.63 (s, 2H), 7.21-7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 139.1 (s), 128.3 (d), 128.1 (d), 126.7 (d), 117.9 (t, $^3J_{CH}$ = 4.6 Hz), 58.4 (t), 51.4 (t), 50.9 (t), 44.1 (s), 33.3 (d, $^1J_{CH}$ = 175 Hz), 25.7 (t), 23.8 (t). Anal. Calcd for $C_{18}H_{23}N_3$: C, 76.83; H, 8.24; N, 14.93. Found: C, 76.8; H, 8.5; N, 14.9.

1α,5α,6β-3-Benzyl-6-piperidino-3-azabicyclo[3.1.0]hexane-6-carboxamide (**15**): Bicyclic nitrile **14** (17.40 g, 61.83 mmol) was added to ice-cold concentrated sulfuric acid (85 mL) and stirred at 100°C for 45 min. The mixture was cooled to room temperature and poured on ice (180 g). Carboxamide **15** was precipitated by addition of aqueous ammonia solution (25%, 800 mL), filtered by suction and washed subsequently with water, ice-cold acetonitrile and ice-cold ether. Recrystallization from acetonitrile/toluene (1/1) gave pure **15**. Traces of water could be removed by sublimation at 200°C/0.001 Torr. Yield: 11.10 g (60%); mp 125°C; IR (KBr, cm^{-1}) 3390 (NH), 1660 (C=O); ^1H NMR ($CDCl_3$) δ 1.49-1.68 (m, 6H), 2.17 (H_X, $H_{X'}$, 2H), 2.78 (H_A, $H_{A'}$, 2H), 2.91 (H_B, $H_{B'}$, 2H) (AA'BB'XX'-system, $^2J_{AB}$ = 9.8 Hz), 2.86 (m_c, 4H), 3.65 (s, 2H), 5.78 (broad, 1H, NH), 6.76 (broad, 1H, NH), 7.20-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 177.2 (s), 139.0 (s), 128.9 (d), 128.0 (d), 126.9 (d), 59.5 (t), 55.2 (s), 53.3 (t), 49.9 (t), 33.9 (d, $^1J_{CH}$ = 173 Hz), 27.2 (t), 24.6 (t). Anal. Calcd for $C_{18}H_{25}N_3O$: C, 72.21; H, 8.42; N, 14.03. Found: C, 72.2; H, 8.4; N, 14.1.

1α,5α,6β-6-Piperidino-3-azabicyclo[3.1.0]hexane-6-carboxamide (5): A solution of N-benzyl compound **15** (1.00 g, 3.34 mmol) in methanol (60 mL) was saturated with hydrogen in the presence of palladium/charcoal catalyst (10% Pd, 0.20 g, 0.19 mmol) at room temperature. Hydrogenolysis was stopped when 85 mL of hydrogen were absorbed; then the catalyst was removed by filtration and the solvent was evaporated in vacuo. Recrystallization of the residue from acetonitrile gave pure **5**. Yield: 0.43 g (62%); mp 175°C (decomp.); IR (KBr, cm^{-1}) 3430, 3380, 3320, 3150 (NH), 1670, 1625, 1585 ($CONH_2$); ^1H NMR (CD_3OD) δ 1.27 (H_Z, 1H), 1.39 (H_{X1}, 2H), 1.65 (H_W, 2H), 1.73 (H_Y, 1H), 2.80 (H_{B1}, 2H), 2.87 (H_{A1}, 2H) ($A_2B_2W_2X_2YZ$-system), 2.01 (H_{X2}, $H_{X'2}$, 2H), 3.00 (H_{B2}, $H_{B'2}$, 2H), 3.10 (H_{A2}, $H_{A'2}$, 2H) (AA'BB'XX'-system); ^{13}C NMR (CD_3OD) δ 174.6 (t, $^3J_{CH}$ = 3.4 Hz), 55.1 (s), 52.6 (t), 48.9 (t), 33.1 (d, $^1J_{CH}$ = 170 Hz), 28.4 (t), 25.7 (t). Anal. Calcd for $C_{11}H_{19}N_3O$: C, 63.13; H, 9.15; N, 20.08. Found: C, 63.1; H, 9.2; N, 20.2.

1α,5α,6β-3-[4-(4-Fluorophenyl)-4-oxobutyl]-6-piperidino-3-azabicyclo[3.1.0]hexane-6-carboxamide (6): A mixture of carboxamide **5** (1.00 g, 4.78 mmol), 4-chloro-1-(4-fluorophenyl)-butan-1-one (**20**) (1.44 g, 7.18 mmol), sodium carbonate (1.65 g, 15.57 mmol) and potassium iodide (0.12 g, 0.72 mmol) in toluene (40 mL) was refluxed for 50 h. Water (20 mL) was added to the cooled mixture. Stirring for 10 min, filtration of the precipitate by suction and washing with water and toluene gave crude Cyclopipamperone **6** which was recrystallized from acetonitrile/toluene (2/1). Yield: 1.13 g (63%); mp 125°C; IR (KBr, cm^{-1}) 3390 (N-H), 1655 ($CONH_2$); ^1H NMR ($CDCl_3$) δ 1.37-1.60 (H_{X1}, $H_{X'1}$, H_Y, $H_{Y'}$, 6H), 2.85 (H_{A1}, $H_{A'1}$, 4H) ($A_2A'_2X_2X'_2YY'$-system), 1.89 (m_c, 2H), 2.17 (H_{X2}, $H_{X'2}$, 2H), 2.69 (H_{A2}, $H_{A'2}$, 2H), 2.93 (H_B, $H_{B'}$, 2H) (AA'BB'XX'-system, $^2J_{AB}$ = 9.5 Hz), 2.56 (t, 2H), 3.04 (t, 2H), 6.44 (broad, 1H, NH), 6.53 (broad,1H, NH), 7.13 (m_c, 2H), 8.00 (m_c, 2H); ^{13}C NMR ($CDCl_3$) δ 198.3 (s), 177.0 (t, $^3J_{CH}$ = 3.1 Hz), 165.5 (d, $^1J_{CF}$ = 255 Hz), 133.6 (s), 130.5 (ddd, $^3J_{CF}$ = 9 Hz), 115.5 (ddd, $^2J_{CF}$ = 21 Hz), 55.4 (s), 54.5 (t), 53.3 (t), 50.3 (t), 36.3 (t), 34.1 (d, $^1J_{CH}$ = 169 Hz), 27.1 (t), 24.6 (t), 23.6 (t). Anal. Calcd for $C_{21}H_{28}FN_3O_2$: C, 67.54; H, 7.56; N, 11.25. Found: C, 67.3; H, 7.4; N, 11.2.

1-Benzyl-3,5-dichloro-1,2,3,6-tetrahydro-4-piperidino-pyridine (13a): A solution of N-chlorosuccinimide (3.23 g, 24.2 mmol) in dichloromethane (70 mL) was dropped within 45 min at -78°C to a stirred solution of enamine **11a** (3.10 g, 12.1 mmol) in dichloromethane (25 mL). Then the solvent was evaporated in vacuo at room temperature. Extraction of the residue with pentane in a Soxhlet-apparatus (19 h) and cooling of the extract to -30°C gave dichloroenamine **13a** as white solid which was recrystallized from ether/pentane (15 mL/10 mL). Yield: 2.70 g (69%); mp 138°C (decomp.); IR (KBr, cm^{-1}) 1640 (C=C); ^1H NMR (CD_3CN, 75°C, 200 MHz) δ 1.39-1.75 (m, 6H), 2.69-2.80 (m, 1H), 2.80-2.94 (m, 2H), 2.98-3.18 (m, 4H), 3.36-3.44 (m, 1H), 3.59 (H_A, 1H), 3.72 (H_B, 1H) (AB-system, $^2J_{AB}$ = 13.4 Hz), 4.85 (m_c, 1H), 7.20-7.43 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 140.6 (s), 137.0 (s), 128.8 (d), 128.3 (d), 127.3 (d), 119.9 (s), 60.9 (t), 58.2 (t), 57.3 (t), 55.7 (d), 50.4 (t), 26.3 (t), 24.3 (t). Anal. Calcd for $C_{17}H_{22}Cl_2N_2$: C, 62.77; H, 6.82; N, 8.61. Found: C, 62.8; H, 6.7; N, 8.7.

Ethyl 3,5-dichloro-1,2,3,6-tetrahydro-4-piperidino-pyridine-1-carboxylate (13b): A solution of N-chlorosuccinimide (25.60 g, 192 mmol) in dichloromethane (700 mL) was dropped at -78°C within 3 h to a stirred solution of enamine **11b** (22.85 g, 96 mmol) in dichloromethane (120 mL). The solvent was evaporated in vacuo at room temperature. The residue was triturated with pentane (30 mL) and then extracted with pentane in a Soxhlet-apparatus (3 d). White crystals of dichloroenamine **13b** were obtained from the extract upon cooling to -30°C. Yield: 26.11 g (89%); mp 123°C (decomp.); IR (KBr, cm^{-1}) 1700 (C=O), 1645 (C=C); ^1H NMR (CD_3CN, 75°C, 200 MHz) δ 1.24 (t, 3H), 1.44-1.72 (m, 6H), 2.79-2.97 (m, 2H), 2.97-3.14 (m, 2H), 3.44 (H_{X1}, 1H), 4,33 (H_M, 1H), 4.90 (H_{A1}, 1H) (AMX-system, $^2J_{MX}$ = 14.7 Hz, $^3J_{AX}$ = 2.4 Hz), 3.80 (H_{X2}, 1H), 4,49 (H_{A2}, 1H) (AX-system, $2J_{AX}$ = 17.6 Hz), 4.13 (q, 2H); ^{13}C NMR ($CDCl_3$) δ 155.1 (s), 141.2 (s), 140.9 (s), 118.3 (s), 117.5 (s), 61.7 (t), 54.0 (d), 53.6 (d), 50.4 (t), 48.5 (t), 48.2 (t), 47.9 (t), 26.2 (t), 24.1 (t), 14.5 (q). Anal. Calcd for $C_{13}H_{20}Cl_2N_2O_2$: C, 50.83; H, 6.56; N, 9.12. Found: C, 51.0; H, 6.6; N, 9.1.

Reaction of Dichloroenamine 13a with Sodium Cyanide: Dichloroenamine **13a** (0.40 g, 1.23 mmol) was added to a solution of sodium cyanide (0.12 g, 2.45 mmol) in methanol/water (4/1, 20 mL) and stirred at room temperature until a clear solution resulted (63 h). The mixture was concentrated in vacuo to 5 mL and extracted with ether (5 x 10 mL). The ethereal extracts gave a yellow oil (0.39 g) which was purified in two portions (0.19 g each) by chromatography [17 cm x 2.6 cm column, silica gel, ether/pentane (1/4)]. Thereby, exo-amine **17a** was faster eluted than endo-amine **16a**.

1α,5a,6β-3-Benzyl-1-chloro-6-piperidino-3-azabicyclo[3.1.0]hexane-6-carbonitrile (**16a**): Yield: 0.16 g (43%); mp 76°C; IR (KBr, cm^{-1}) 2215 (C≡N); ^1H NMR ($CDCl_3$) δ 1.20-1.40 (m, 1H), 1.40-1.65 (m, 2H), 1.65-1.85 (m, 3H), 2.40 (H_X, 1H), 2.43 (H_{A1}, 1H), 3.44 (H_{B1}, 1H) (ABX-system, $^2J_{AB}$ = 10.7 Hz, $^3J_{AX}$ = 2.0 Hz, $^3J_{BX}$ = 6.6 Hz), 2.93 (H_{A2}, 1H), 3.46 (H_{B2}, 1H) (AB-system, $^2J_{AB}$ = 10.6 Hz), 2.44-2.72 (m, 4H), 3.65 (s, 2H), 7.20-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 138.4 (s), 128.5 (d), 128.4 (d), 127.2 (d), 114.7 (d, $^3J_{CH}$ = 5.3 Hz), 60.1 (t), 58.5 (t), 54.5 (s), 52.1 (s), 52.0 (t), 51.2 (t), 50.9 (t), 41.3 (d, $^1J_{CH}$ = 176 Hz), 25.6 (t), 23.7 (t). Anal. Calcd for $C_{18}H_{22}ClN_3$: C, 68.45; H, 7.02; N, 13.30. Found: C, 68.2; H, 6.9; N, 13.2.

1α,5a,6α-3-Benzyl-1-chloro-6-piperidino-3-azabicyclo[3.1.0]hexane-6-carbonitrile (**17a**): Yield: 0.14 g (37%); mp 94°C; IR (KBr, cm^{-1}) 2210 (C≡N); ^1H NMR ($CDCl_3$) δ 1.40-1.70 (m, 6H), 1.97 (H_X, 1H), 2.82 (H_{B1}, 1H), 3.11 (H_{A1}, 1H) (ABX-system, $^2J_{AB}$ = 9.8 Hz, $^3J_{AX}$ = 0 Hz, $^3J_{BX}$ = 3.5 Hz), 2.92 (H_{B2}, 1H), 3.44 (H_{A2}, 1H) (AB-system, $^2J_{AB}$ = 9.5 Hz), 2.50-2.80 (m, 4H), 3.67 (s, 2H), 7.22-7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 138.0 (s), 128.6 (d), 128.3 (d), 127.2 (d), 113.8 (s), 59.8 (t), 58.3 (t), 55.4 (s), 52.2 (t), 51.2 (t), 47.2 (s), 37.9 (d, $^1J_{CH}$ = 176 Hz), 25.6 (t), 23.8 (t). Anal. Calcd for $C_{18}H_{22}ClN_3$: C, 68.45; H, 7.02; N, 13.30. Found: C, 68.7; H, 7.1; N, 13.5.

Reaction of Dichloroenamine 13b with Sodium Cyanide - Ethyl 1α,5α,6α-1-Chloro-6-cyano-6-piperidino-3-azabicyclo[3.1.0]hexane-3-carboxylate (17b): Dichloroenamine **13b** (11.35 g, 37 mmol) was added to a solution of sodium cyanide (3.60 g, 73 mmol) in methanol/water (1/1, 500 mL) and stirred at 50°C until a clear solution resulted (8 h). The solution was concentrated in vacuo to 20 mL and extracted with ether (60 mL and 3 x 20 mL). The combined ethereal extracts gave crude **17b** as pale yellow oil which crystallized in pentane at -30°C. Yield: 8.99 g (82%); mp 58°C; IR (KBr, cm^{-1}) 2210 (C ≡ N), 1700 (C=O); ^1H NMR ($CDCl_3$) δ 1.247 (t), 1.253 (t) (together 3H), 1.40-1.55 (m, 2H), 1.55-1.68 (m, 4H), 2.10-2.15 (m, 1H), 2.55-2.67 (m, 2H), 2.67-2.80 (m, 2H), 3.72-3.85 (m, 3H), 4.09-4.22 (m, 1H), 4.14 (m_c, 2H); ^{13}C NMR ($CDCl_3$) δ 153.6 (s), 153.5 (s), 111.5 (s), 61.51 (t), 61.46 (t), 54.4 (s), 53.9 (s), 53.7 (t), 53.3 (t), 51.3 (t), 48.7 (s), 48.6 (s), 46.4 (t), 46.2 (t), 37.4 (d, $^1J_{CH}$ = 177 Hz), 36.8 (d, $^1J_{CH}$ = 177 Hz), 25.4 (t), 23.5 (t), 14.5 (q). Anal. Calcd for $C_{14}H_{20}ClN_3O_2$: C, 56.47; H, 6.77; N, 14.11. Found: C, 56.3; H, 6.7; N, 14.1.

Ethyl 1α,5α,6α-6-Cyano-6-piperidino-3-azabicyclo[3.1.0]hexane-3-carboxylate (18): Chloro-azabicyclohexanecarbonitrile **17b** (5.00 g, 17 mmol) was added at 0°C to a suspension of powdered sodium[15] (1.16 g, 50 mmol) in tetrahydrofuran (100 mL). The mixture was stirred for 20 min at room temperature. Then a solution of *tert*-butyl alcohol (3.73 g, 50 mmol) in tetrahydrofuran (25 mL) was dropped within 70 min to the mixture. Stirring was continued for 5 h. Filtration, washing the residue with tetrahydrofuran (20 mL) and removing the solvent by evaporation gave a brown oil. Addition of water (20 mL) and extraction with ether (7 x 25 mL) led to crude **18** which was purified by chromatography (1.5 cm x 8 cm column, basic Al_2O_3, ether) and recrystallization from ether/pentane (1/1). Yield: 1.64 g (37%); mp 98°C; IR (KBr, cm^{-1}) 2225 (C ≡ N), 1705 (C=O); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.24 (t, 3H), 2.05 (H_X, H_Y, 2H), 3.63 (H_D, 1H), 3.66 (H_B, 1H), 3.74 (H_C, 1H), 3.79 (H_A, 1H), (ABCDXY-system, $^2J_{AB}$ = 11.4 Hz, $^2J_{CD}$ = 11.8 Hz), 1.33-1.64 (m, 6H), 2.62 (m_c, 4H), 4.13 (q, 2H); ^{13}C NMR ($CDCl_3$) δ 154.3 (s), 113.4 (s), 61.3 (t), 51.5 (t), 46.9 (s), 46.5 (t), 46.1 (t), 32.2 (d, $^1J_{CH}$ = 176 Hz), 31.5 (d, $^1J_{CH}$ = 177 Hz), 25.7 (t), 23.8 (t), 14.7 (q). Anal. Calcd for $C_{14}H_{21}N_3O_2$: C, 63.85; H, 8.04; N, 15.96. Found: C, 63.9; H, 8.0; N, 16.0.

1α,5α,6α-6-Piperidino-3-azabicyclo[3.1.0]hexane-6-carbonitrile (19): A solution of ethyl carboxylate **18** (4.63 g, 17.6 mmol) and trimethylsilyl iodide (4.57 g, 22.8 mmol) in chloroform (9 mL) was stirred at 60°C for 6.5 h. Then a concentrated methanolic solution of hydrogen chloride (2.90 mL) was added at room temperature and the mixture was stirred for 10 min. Evaporation in vacuo, trituration of the residue with 25% aqueous KOH solution (55 mL) and extraction with ether (5 x 30 mL) gave crude nitrile **19**. Traces of starting material **18** could be removed by dissolving the product in 1 M aqueous hydrogen chloride (21 mL) at 0°C and extraction with ether (3 x 25 mL). Pure **19** was reisolated by basification of the acidic aqueous layer with 10% aqueous KOH solution (50 mL) and extraction with ether (5 x 25 mL). Evaporation of the solvent gave white crystals of **19** which were sublimated at 65°C/0,001 Torr. Yield: 3.02 g (90%); mp 61°C; IR (KBr, cm^{-1}) 3300 (N-H), 2200 (C ≡ N); ^1H NMR ($CDCl_3$)

δ 1.45 (H_Y, $H_{Y'}$, 2H), 1.55 (H_{X1}, $H_{X'1}$, 4H), 2.60 (H_{A1}, $H_{A'1}$, 4H) ($A_2A'_2X_2X'_2YY'$-system), 1.67 (broad, 1H, NH), 1.97 (H_{X2}, $H_{X'2}$, 2H), 3.12 (H_B, $H_{B'}$, 2H), 3.23 (H_{A2}, $H_{A'2}$, 2H) (AA'BB'XX'-system, $^2J_{AB}$ = 12.4 Hz); ^{13}C NMR ($CDCl_3$) δ 115.4 (s), 51.3 (t), 47.4 (t), 44.4 (s), 34.7 (d, $^1J_{CH}$ = 173 Hz), 25.5 (t), 23.7 (t). Anal. Calcd for $C_{11}H_{17}N_3$: C, 69.07; H, 8.96; N, 21.97. Found: C, 68.9; H, 8.9; N, 21.9.

1α,5α,6α-6-Piperidino-3-azabicyclo[3.1.0]hexane-6-carboxamide (7): Carbonitrile **19** (1.46 g, 7.63 mmol) was stirred in concentrated sulfuric acid (10 mL) for 1 h at 100°C. The cold mixture was poured on ice (30 g), basificated with aqueous NaOH solution (22%, 52 mL) and extracted with ether in a Kutscher-Steudel apparatus for 4 d. Pure carboxamide **7** was obtained from cooling the extract to -30°C and filtration by suction. Yield: 1.52 g (95%); mp 196°C (decomp.); IR (KBr, cm^{-1}) 3390, 3130 (N-H), 1640 (C=O); ^1H NMR (CD_3OD) δ 1.43 (H_Y, $H_{Y'}$, 2H), 1.52 (H_{X1}, $H_{X'1}$, 4H), 2.64 (H_{A1}, $H_{A'1}$, 4H) ($A_2A'_2X_2X'_2YY'$-system), 1.75 (H_{X2}, $H_{X'2}$, 2H), 2.90 (H_B, $H_{B'}$, 2H), 3.19 (H_{A2}, $H_{A'2}$, 2H) (AA'BB'XX'-system, $^2J_{AB}$ = 12.2 Hz); ^{13}C NMR (CD_3OD) δ 168.8 (s), 55.1 (s), 52.3 (t), 48.3 (t), 33.8 (d, $^1J_{CH}$ = 171 Hz), 27.6 (t), 25.6 (t). Anal. Calcd for $C_{11}H_{19}N_3O$: C, 63.13; H, 9.15; N, 20.08. Found: C, 63.2; H, 9.1; N, 20.2.

1α,5α,6α-3-[4-(4-Fluorophenyl)-4-oxobutyl]-6-piperidino-3-azabicyclo[3.1.0]hexane-6-carboxamide (8): A mixture of carboxamide **7** (0.290 g, 1.39 mmol), 4-chloro-1-(4-fluorophenyl)-butan-1-one (**20**) (0.420 g, 2.09 mmol), sodium carbonate (0.494 g, 4.66 mmol) and potassium iodide (0.058 g, 0,35 mmol) in toluene (25 mL) was refluxed for 72 h. The hot mixture was filtered by suction and the precipitate was washed with hot toluene (2 x 20 mL). The filtrate was evaporated in vacuo and the resulting yellow oil was purified by MPLC (silica gel, gradient beginning with ether, then addition of methanol). 4-Chloro-1-(4-fluorophenyl)-butan-1-one (**20**) was first eluted; then Cyclopipamperone diastereomer **8** was obtained as colorless oil which crystallized upon trituration with ether/pentane (1/1). Yield: 0.20 g (39%); mp 155°C (decomp.); IR (KBr, cm^{-1}) 3440 (N-H), 1680, 1630 ($CONH_2$); ^1H NMR ($CDCl_3$) δ 1.62 (H_X, $H_{X'}$, 2H), 2.38 (H_B, $H_{B'}$, 2H), 3.07 (H_A, $H_{A'}$, 2H) (AA'BB'XX'-system, $^2J_{AB}$ = 9.0 Hz, $^3J_{AX}$ = 0 Hz), 1.35-1.60 (m, 6H), 1.79 (qui, 2H), 2.47 (t, 2H), 2.65 (m_c, 4H), 2.99 (t, 2H), 5.13 (broad, 2H, NH), 7.14 (m_c, 2H), 8.08 (m_c, 2H); ^{13}C NMR ($CDCl_3$) δ 199.4 (s), 165.9 (s), 165.6 (d, $^1J_{CF}$ = 255 Hz), 133.8 (s), 130.8 (ddd, $^3J_{CF}$ = 9 Hz), 115.6 (ddd, $^2J_{CF}$ = 21 Hz), 53.9 (s), 52.8 (t), 52.7 (t), 51.2 (t), 35.1 (t), 29.7 (d, $^1J_{CH}$ = 179 Hz), 26.7 (t), 24.4 (t), 22.7 (t). Anal. Calcd for $C_{21}H_{28}FN_3O_2$: C, 67.54; H, 7.56; N, 11.25. Found: C, 67.5; H, 7.6; N, 11.2.

X-Ray Crystal Structure Analysis of 6.[24,25] Single crystals of **6** were obtained by crystallization from toluene/acetonitrile (3/1).

Crystal data: $C_{21}H_{28}FN_3O_2$, F.W. = 373.5; monoclinic, space group $P2_1/n$; a = 14.353(13), b = 9.198(1), c = 15.277(16) Å; $\alpha = \gamma = 90$, β = 100.10(5)°; V = 1985.6(2.9) $Å^3$; 4 molecules per unit cell; D_x = 1.249 $g \cdot cm^{-3}$; crystal size 0.35 x 0.30 x 0.50 mm.

Data collection: Diffractometer Enraf-Nonius-CAD 4, monochromatized Mo-K_α radiation; 3297 independent reflexions with $4.00 < 2\Theta < 48.00°$ [$\omega/2\Theta$ scan, scan width $(0.90 + 0.35 \tan\Theta)°$, scan speed $1.3 - 3.2°\cdot min^{-1}$], no absorption correction.
Structure solution and refinement: Full matrix least-squares method; H-atoms refined isotropically, 1798 reflections with $I_{obs} < 2.0\ \sigma(I_{obs})$; 328 variables, unit weights, weighting scheme $w = 4 \cdot F_{obs}^2/[\sigma(I)^2 + (P \cdot F_{obs}^2)^2]$, $P = 0.02$; maximum shift/error ratio 0.01, $R = 0.050$, $R_w = 0.041$.

Acknowledgments: We want to thank Boehringer Ingelheim for sponsoring our work and for performing the biological tests. This work was supported additionally by the Fonds der Chemischen Industrie. We thank Dipl.-Chem. Ute Kolb, Institut für Anorganische und Analytische Chemie der Universität Mainz, for a plot and for determination of some atomic distances of Pipamperone **2** on the basis of the published data.[6]

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(*Received in Germany* 29 *November* 1993; *accepted* 7 *January* 1994)