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A New Access to Piperidino-cyclopiperidinecarboxamides – Constrained Analogues of a Pharmaceutical used Diaminic Building Block

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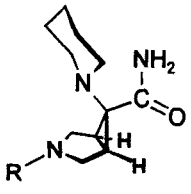
Abstract. 6-Piperidino-3-azabicyclo[3.1.0]hexane-6-carboxamide diastereomers **1a** and **2a** represent conformationally rigid analogues of **3a** which is a building block in some pharmaceutical compounds. A new access to these compounds **1a** and **2a** was found *via* the cleavage of bicyclic *N,N*-acetal **6** with hydrocyanic acid as the stereodetermining step. Reaction of derivatives **1a** and **2a** with bromodiphenyl-butyronitrile **14** gave cyclopiritramide isomers **1c** and **2c**, respectively. Qualitative preliminary investigations showed different affinities of **1c** and **2c** to the opiate-μ receptor. These results were discussed on the basis of an X-ray structural analysis of cyclopiritramide isomer **2c**. 1-Benzylcyclopiperidine derivatives **1d** and **2d** were used as model systems for studying the conformation of cyclopiritramide isomer **1c** and **2c**, respectively.

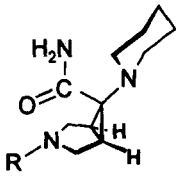
Dipiperidinecarboxamide **3a** is used as building block in some pharmaceutical drugs [1–4]. Especially Pipamperone **3b** as neuroleptic agent [1] and Piritramide **3c** as strong analgesic compound [2] should be mentioned in this context. Cyclopiperidine diastereomers **1a** and **2a** can be regarded as conformationally constrained analogues of **3a**. Receptor binding assays of Cyclopipamperone derivatives **1b** and **2b** were used for information about the required conformation of the diaminic component in **3b** for the interaction with the dopamine receptor [5].

Compounds **1a** and **2a** were synthesized from chloroenamines **4** and **5** by multistep sequences, respectively [5]. A highly sensitive reductive dechlorination on the way from **5** to **2a**, however, represents a crucial point in the synthetic pathway causing a distinct decrease of the yield of target molecule **2a**.

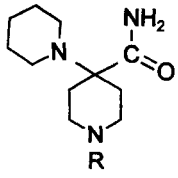
Continuation of the work in this area led us to a new access to compounds **1a** and **2a**. The new method turned out to be a clearly improved synthesis of cyclopiperidine isomer **2a**. Constrained Piritramide analogues **1c** and **2c** were prepared subsequently and used for a further investigation of conformational influences of building block **3** on the interaction with a receptor. The results of these studies are reported in this paper.



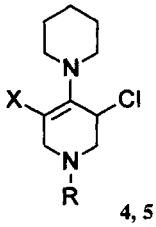
1a-d



2a-d



3a-d



4, 5

	R	X
1a	H	
1b	CH_2-CH_2-CH_2-CO-C_6H_4-F(p)	
1c	CH_2-CH_2-C(CN)(C_6H_5)$_2$	
1d	CH_2-Ph	
4	Bn	H
5	COOEt	Cl

Results and Discussion

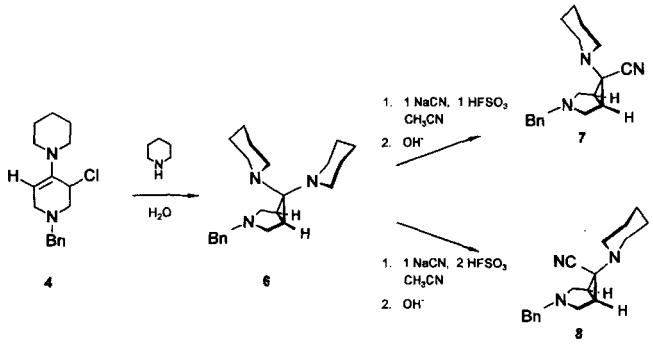
Cyclopiperidinecarboxamides 1a and 2a from N,N-Acetal 6

The new approach to diastereomeric cyclopiperidinecarboxamides **1a** and **2a** was found on the basis of a cleavage of cyclopiperidinone-*N,N*-acetal **6** by hydrocyanic acid. The conditions of these reactions strongly

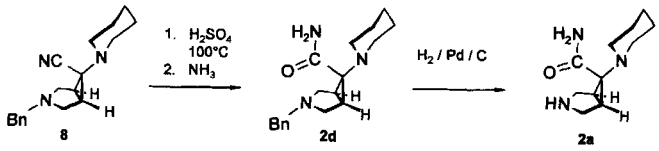
determined the stereochemical result leading to a highly selective formation of either isomer **7** or **8**. *N,N*-Acetal **6** as starting material was accessible in 71% yield by the reaction of chloroenamine **4** with excess piperidine in water. Hydrocyanic acid for the subsequent cleavage of **6** was generated from a mixture of sodium cyanide and fluorosulfonic acid in acetonitrile. Equimolar amounts of sodium cyanide, fluorosulfonic acid and *N,N*-acetal **6** gave the expected exo-nitrile **7** upon working up in 70% yield. Pure diastereomeric nitrile **8**, however, was obtained in 76% yield if excess fluorosulfonic acid (two mole equivalents) was used. ^{1}H-NMR spectroscopic investigation of the crude reaction products indicated a diastereomeric excess of more than 90% for **7** and **8**, respectively.

exo-Nitrile **7** represents an intermediate product in the already described synthesis of cyclopiperidinecarboxamide **1a** [5]. Analogous steps could be used for the preparation of endo-carboxamide **2a** from endo-nitrile **8**: Saponification of **8** generated *N*-benzylcyclopiperidinecarboxamide **2d** (59% yield) which was debenzylated whith hydrogen to give the target molecule **2a** in 64% yield.

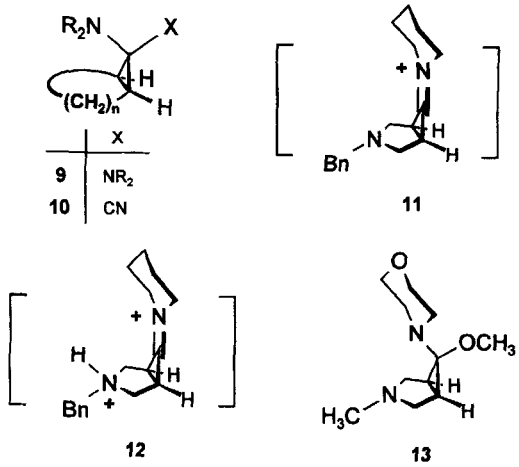
The presence of a cyclopiperidine unit in compounds **6**, **8** and **2d** follows from the ^{13}C-NMR spectra with characteristic doublets for C(3)/C(5) and a singlet for C(4). The exo-position of piperidine and thus C(4)-configuration of **8** and **2d** is indicated by the signal type of piperidine in the ^{1}H-NMR spectrum (no hindrance of dynamics at room temperature, see ref. [5–8]) and by chemical correlation based on compound **2a** with known configuration.



Cleavage of annulated cyclopropanone-*N,N*-acetals **9** by hydrocyanic acid is known as a simple approach to aminobicyclo[n.1.0]alkanecarbonitriles **10** [9–11]. Only exo-nitriles **10** were obtained thus far by the reaction of **9** [9–11]. This corresponds to the formation of exo-nitrile **7** from *N,N*-acetal **6** by the usual exo-attack of cyanide as nucleophile to iminium ion **11** as intermediate. A protonated iminium ion **12**, however, should be the intermediate in the presence of excess fluorosulfonic acid. Transfer of the smaller cyanide instead of



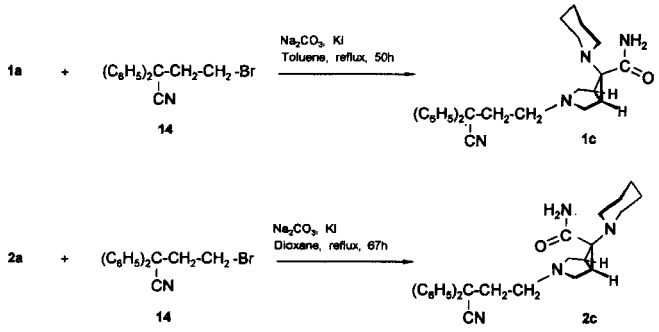
the bigger fluorosulfate as counterion to the inside of the bicyclic species **12** could explain the formation of endo-nitrile **8** under the changed reaction conditions. This observation corresponds quite well to the reaction of *N,O*-acetal **13** with Grignard reagents [12]: A complexation of the Grignard reagent to *N*(1) led to a substitution of methoxide in **13** by the carbanion with inversion of configuration at C(4). Prevention of the inside complexation caused the analogous substitution with retention of C(4)-configuration. No change of configuration of exo-nitrile **7** was observed upon its treatment with hydrocyanic acid and fluorosulfonic acid under the conditions described above.



Cyclopiritramide Diastereomers **1c** *and* **2c**

Alkylation of cyclopiperidinecarboxamides **1a** and **2a** with 4-bromo-2,2-diphenylbutyronitrile (**14**) provided the Cyclopiritramide diastereomers **1c** and **2c**, respectively. The structure of both isomers **1c** and **2c** can be clearly deduced from the ^{13}C-NMR data. The configuration at C(4) follows from the chemical shifts for the carboxamide signal (low field shifting for **1c**: δ 176,4 ppm; high field shifting for **2c**: δ 166.0 ppm; determination of configuration of cyclopiperidines by this method see [13]). Differences in the ^{1}H-NMR signals of the piperidine NCH_2-group (see above) are less marked in **1c** and **2c**: The expected typical signal pattern is observed only in the case of **2c**; **1c** gave a coalescing signal type which could not be used for determination of the more expressive free activation enthalpy due to interference with dynamics of the cyanodiphenylpropyl moiety. An X-ray structural analysis of **2c**, finally, confirmed these spectroscopic assignments.

Preliminary, qualitative biological tests of Cyclopiritramide isomers **1c** and **2c** showed different activities in a binding assay to the opiate-μ receptor (rat-forebrain, fentanyl as ligand). Isomer **1c** gave 73% binding at 10^{-7} M and 23% binding at 10^{-8} M whilst no binding



was observed for **2c** at these concentrations. An IC_{50} value of about $5.1 \cdot 10^{-8}$ M thus can be estimated for **1c**. This value is comparable to piritramide **3c** itself (pIC_{50} = 7.62 [14]). These screening data indicate that there is a difference in activity of at least one log value between **1c** and **2c**. Both isomers gave no binding to the opiate-δ or the opiate-κ receptor (recent literature concerning opiate receptors [15–17]).

Conformation of the Cyclopiperidine units in **1c, d** *and* **2c, d**

The presence of a boat conformation of the cyclopiperidine unit in Cyclopiritramide isomer **2c** is indicated by X-ray structural analysis. Inclusion of one molecul methanol from recrystallization should not influence the conformation: Hydrogen bonding of the methanolic hydroxyl group is directed towards the carboxamide group and not to the cyclopiperidine *N*-atom as shown by a packing diagram. Selected data of the X-ray structure of compound **2c** · CH_3OH are given in Table 1. Analogous values of Piritramide **3c** for comparison are taken from ref. [18]. Isomer **1c** should adopt a chair conformation as established by X-ray structural analysis of Cyclopipamperone **1b** as model substance [5]. The conformation of the cyclopiperidine unit of compounds **1c** and **2c** in solution should be identical with that of derivatives **1d** and **2d**. The latter compounds were used as model substances due to the more simple ^{1}H-NMR data. An AA'BB'XX'-system is found in the ^{1}H-NMR spectra for cyclopiperidine in **1c/d** and **2c/d**. The corresponding data of the benzyl derivatives **1d** and **2d** are listed in Table 2. The spectra were simulated by the Calm program [20]; the given coupling constants are based on the simulated spectra. Typical values [21] indicate the presence of a boat conformation for **2d** ($\delta_{A,A'} > \delta_{B,B'}$; $J_{AX} = J_{A'X'} \approx 0$ Hz) and of a chair conformation for **1d** ($\delta_{A,A'} < \delta_{B,B'}$; $J_{AX} = J_{A'X'} \approx 2$–3 Hz). The absence of a detectable coupling J_{AX} and $J_{A'X'}$ in the case of **2d** or **2c** is in accordance with the observed values of the dihedral angles $H(2)_AC(2)C(3)H(3)_X$ and $H(5)_{A'}C(5)C(6)H(6)_{X'}$ for **2c** in the crystal (X-ray structural data, Table 1).

Isomer **2c** imitates the preferred solid state conformation of Piritramide **3c** with respect to the C(4)-area but not for the *N*(1)-area. Ring inversion of cyclopiperidine of **2c** which would be necessary for a complete adaption of the molecular shape of **2c** to that of **3c** could not be observed spectroscopically, thus far. Ab initio calculations predict a difference of 1 kcal/mol between the more stable chair conformer **15C** and the boat ana-

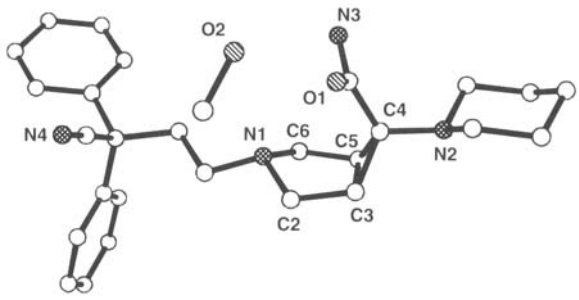


Fig. 1 X-Ray structure of Cyclopiritramide isomer **2c**; one mole methanol was included upon crystallization from this solvent.

Table 1 Selected bond distances, torsional angles and interplanar angles of 3α,4α,5α-4-(3-cyano-3,3-diphenylpropyl)-4-piperidino-cyclopiperidine-4-carboxamide (**2c**); N,N- and N,O-distances in 3,5-Cyclopiritramide diastereomer **2c** and in Piritramide **3c** (from ref. [18]).

bond lengths [Å]		*N,N*- and *N,O*-distances [Å]			torsional angles [b]) [°]		interplanar angles [°]		
	2c		**2c**	**3c**[a])		**2c**		**2c**	**3c**[a])
C(3)-C(4)	1.481(4)	N(1)-N(2)	4.207	4.257	$H(2)_A$-C(2)-C(3)-$H(3)_X$	81.5	C(3)C(4)C(5)-C(2)C(3)C(5)C(6)	64.9	45.7
C(3)-C(5)	1.488(5)	N(1)-N(3)	3.302	4.270	$H(5)_{X'}$-C(5)-$H(6)_{A'}$-C(6)	−79.1	C(2)C(3)C(5)C(6)-C(2)N(1)C(6)	33.5	55.0
C(4)-C(5)	1.487(5)	N(1)-O(1)	3.345	4.490	$H(3)_X$-C(3)-C(2)-$H(2)_B$	−39.4			
					$H(5)_{X'}$-C(5)-C(6)-$H(6)_{B'}$	42.2			

[a]) Numbering of the atoms in **3c** was changed with respect to the original publication [18] for better comparison with the data of compound **2c**. – [b]) $H(2)_A/H(6)_{A'}$ are in the endo-position and $H(2)_B/H(6)_{B'}$ are in the *exo*-position of the cyclopiperidine system.

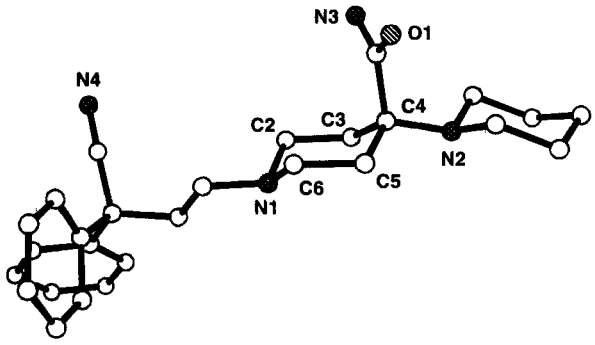
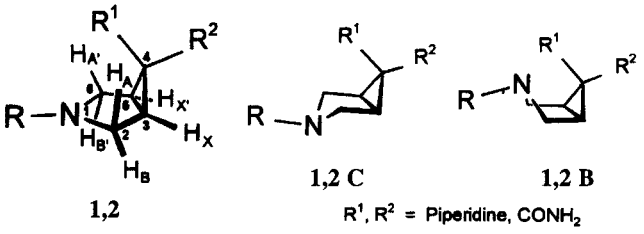


Fig. 2 X-Ray structure of Piritramide **3c** (from ref. [18] [a]). [a]) Numbering of the atoms in **3c** was changed with respect to the original publication [18] for better comparison with the data of compound **2c**



logue **15B** [22]. Extension of these calculations to the interconversion of **15C** and **15B** indicated a energetic maximum for this process of 3.1 and 2.1 kcal/mol above conformers **15C** and **15B**, respectively (Fig. 3) [23]. The optimized structure of the energetic maximum was characterized by diagonalization of the HF/6–31G* force constant matrix, and it was confirmed to be the transition state of the ring inversion of the pyrrolidine subunit in **15**. At this point, the pyrrolidine ring showed a small outside puckering of 8.3°.

It is to be expected from these values that the preference of a boat or chair conformation in a 4-aminocyclopiperidine system is no important factor for its activity. The different activities of Cyclopiritramide isomers **1c** and **2c**, consequently, should be an indicator for the adoption of an "equatorial 4-piperidine conformation" of the piperidinecarboxamide unit of Piritramide **3c** upon interaction with the opiate-μ receptor. The

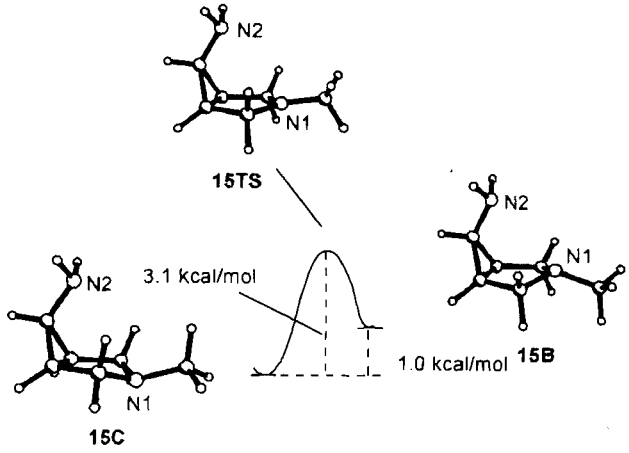


Fig. 3 Energies of boat and chair conformers **15B** and **15C** of 4-amino-1-methylcyclopiperidine and of the transition state **15TS** (almost planar pyrrolidine subunit) of ring inversion

protonation behaviour of the piperidinecarboxamide unit and of the cyclopiperidine analogues is investigated presently. These results will be necessary for a final evaluation of the utility of cyclopiperidine compounds as models for receptor studies with derivatives containing a 4-amino-piperidine building block.

This work was supported by the Fonds der Chemischen Industrie. We want to thank Dr. M. Janssen, Janssen Research Foundation, for performing the biological tests.

Experimental

^{1}H- and ^{13}C-NMR spectra were obtained with a Bruker AMX 400 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.

1-Benzyl-4,4-dipiperidino-3,5-cyclopiperidine (**6**)

A mixture of piperidine (7.23 g, 85 mmol) and water (40 ml) was added to chloroenamine **4** (7.27 g, 25 mmol) [5] and stirred for 2 h. Then water and excess piperidine were removed in vacuo (40 °C/12 Torr). The residue was extracted with

Table 2 ^{1}H-NMR data of the cyclopiperidine unit of N-benzylcyclopiperidinecarboxamides **1d** and **2d** (400 MHz, CD_3OD, δ-values, J[Hz] from the simulated spectra [20])[a])

Compound	$H_{A,A'}$	$H_{B,B'}$	$H_{X,X'}$	J_{AB} $J_{A'B'}$	$J_{AB'}$ $J_{A'B}$	$J_{AA'}$	J_{AX} $J_{A'X'}$	$J_{AX'}$ $J_{A'X}$	J_{BX} $J_{B'X'}$	$J_{BX'}$ $J_{B'X}$	$J_{BB'}$	$J_{XX'}$
1d	2.48	3.13	2.19	10.2	0.25	–0,5	2.9	–0,2	6.8	–0,25	–	8.8
2d	3.14	2.40	1.63	9.0	–0.1	–	–	–	3.7	–0,25	0.3	7.8

[a]) Coupling constants J < | 0.1 | Hz were not considered.

pentane (3×25 ml); concentration of the pentane solution (35 ml) gave crude *N,N*-acetal **6** upon cooling to –30 °C which was recrystallized from pentane. Yield: 6.03 g (71%); m.p. 55 °C. – ^{1}H-NMR ($CDCl_3$): δ = 1.88 (H_X, $H_{X'}$, 2H), 2.26 (H_A, $H_{A'}$, 2H), 3.07 (H_B, $H_{B'}$, 2H) (AA'BB'XX'-System, $^2J_{AB}$ = 9.4 Hz), 1.31 (m_c, 1H), 1.43 (m_c, 7H), 1.57 (m_c, 2H), 1.71 (m_c, 1H), 1.83 (m_c, 1H), 2.62 (m_c, 4H), 2.69 (m_c, 4H) (piperidine systems), 3.63 (s, 2H), 7.20–7.39 (m, 5H). – ^{13}C-NMR ($CDCl_3$): δ = 139.9 (s), 128.7 (d), 128.1 (d), 126.6 (d), 72.8 (s), 59.4 (t), 53.6 (t), 52.0 (t), 50.5 (t)., 33.9 (d, $^1J_{CH}$ = 169 Hz), 27.0 (t), 26.7 (t), 25.1 (t), 25.0 (t). Anal. Calcd for $C_{22}H_{33}N_3$ (339.5): C, 77.83; H, 9.80; N, 12.38. Found: C 77.7 H 9.7 N 12.3.

Reaction of *N,N*-Acetal 6 with Hydrocyanic Acid:

Fluorosulfonic acid was added slowly at –20 °C to a mixture of sodium cyanide (0.25 g, 20 mmol, dried in vacuo) and acetonitrile (20 ml, distilled from calcium hydride). The mixture was stirred for 10 min at –20 °C, then N,N-acetal 6 (1.69 g, 5.0 mmol) was added and the mixture was refluxed for 2 h. Addition of aqueous sodium hydroxide (50%, 10 ml) at –20 °C and extraction with ether (4×20 ml) gave crude nitrile **7** or **8** which was recrystallized from ether/pentane (1:1).

3α,4β,5α-1-Benzyl-4-piperidino-3,5-cyclopiperidine-4-carbonitrile (**7**)

0.29 ml (5 mmol) fluorosulfonic acid; yield: 0.98 g (70%); m.p. 82 °C (lit. [5] 83 °C). The ^{1}H-NMR spectrum was identical with the published data (lit. [5]).

3α,4α,5α-1-Benzyl-4-piperidino-3,5-cyclopiperidine-4-carbonitrile (**8**)

0.58 ml (10 mmol) fluorosulfonic acid; yield: 1.06 g (76%); m.p. 87 °C; IR (KBr, cm^{-1}): ν = 2215 (C≡N). – ^{1}H-NMR ($CDCl_3$) δ 1.88 (H_X, $H_{X'}$, 2H), 2.62 (H_B, $H_{B'}$, m_c, 6H), 3.12 (H_A, $H_{A'}$, 2H) (AA'BB'XX'-System, $^2J_{AB}$ = 9.6 Hz, $^3J_{BX}$ = 3.2 Hz, $^3J_{AX}$ < 0.6 Hz), 1.45 (m_c, 2H), 1.54 (m_c, 4H), 3.66 (s, 2H), 7.21–7.39 (m, 5H). – ^{13}C-NMR ($CDCl_3$): δ = 138.9 (s), 128.4 (d), 128.1 (d), 126.7 (d), 115.7 (s), 58.4 (t), 52.3 (t), 51.1 (t), 45.0 (s), 32.3 (d, $^1J_{CH}$ = 175 Hz), 25.7 (t), 23.8 (t). Anal. Calcd for $C_{18}H_{23}N_3$ (281.4): C, 76.83; H, 8.24; N, 14.93. Found: C 77.0 H 8.2 N 15.0.

3α,4α,5α-1-Benzyl-4-piperidino-3,5-cyclopiperidine-4-carboxamide (**2d**)

Bicyclic nitrile **8** (1.20 g, 4.26 mmol) was added to ice-cold concentrated sulfuric acid (6 ml) and stirred at 100 °C for 45 min. The mixture was cooled to room temperature and poured on ice (13 g). Carboxamide **2d** was precipitated by addition of aqueous ammonia solution (25%, 45 ml), filtered by suction and washed subsequently with water, ice-cold acetonitrile and ice-cold ether. Recrystallization from acetonitrile/toluene (1/1) gave pure **2d**. Yield: 0.82 g (64%); m.p. 111°C. – IR (KBr, cm^{-1}): ν = 3410 (NH), 1630 (C=O). – ^{1}H-NMR ($CDCl_3$): δ = 1.41 (m_c, 2H), 1.49 (m_c, 4H), 2.66 (m_c, 4H) (piperidine), 1.63 (H_X, $H_{X'}$, 2H), 2.45 (H_B, $H_{B'}$, 2H), 3.07 (H_A, $H_{A'}$, 2H), (AA'BB'XX'-system), 3.58 (s, 2H), 5.10–5.40 (broad, 2H, NH), 7.17–7.30 (m, 5H). – ^{13}C-NMR ($CDCl_3$): δ = 166.2 (s), 139.2 (s), 128.3 (d), 128.0 (d), 126.6 (d), 58.6 (t), 55.0 (s), 52.0 (t), 50.4 (t), 32.9 (d, $^1J_{CH}$ = 170 Hz), 27.0 (t), 25.0 (t). Anal. Calcd for $C_{18}H_{25}N_3O$ (299.4): C, 72.21; H, 8.42; N, 14.03. Found: C 72.4 H, 8.4 N, 14.1.

3α,4α,5α-4-Piperidino-3,5-cyclopiperidine-4-carboxamide (**2a**)

A solution of N-benzyl compound **2d** (0.44 g, 1.47 mmol) in methanol (25 ml) was saturated with hydrogen in the presence of palladium/charcoal catalyst (10% Pd, 0.09 g, 0.09 mmol) at room temperature. Hydrogenolysis was stopped when 37 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 **2a**. Yield: 0.18 g (59%); m.p. 188 °C (lit. [5] 196 °C); the ^{1}H-NMR spectrum was identical with the data published for **2a** (lit. [5]).

3α,4β,5α-1-(3-Cyano-3,3-diphenylpropyl)-6-piperidino-3,5-cyclopiperidine-4-carboxamide (**1c**)

A mixture of carboxamide **1a** (1.00 g, 4.78 mmol) [5], 4-bromo-2,2-diphenylbutyronitrile (**14**) (2.15 g, 7.17 mmol), sodium carbonate (1.65 g, 15.5 mmol) and potassium iodide (0.12 g, 0.72 mmol) in toluene (40 ml) was refluxed for 50 h. Water (20 ml) and toluene (10 ml) were added to the cooled mixture. Stirring for 15 min, filtration of the precipitate by suction and washing with water (10 ml) and toluene (2×5 ml) gave crude Cyclopiritramide **1c** which was recrystallized from toluene. Yield: 1.28 g (62%); m.p. 164 °C; IR (KBr, cm^{-1}): ν = 3500–3000 (N–H), 2230 (C≡N), 1650 ($CONH_2$). – ^{1}H-NMR ($CDCl_3$): δ = 1.28–1.60 (m, 6H), 2.70–2.85 (broad, unsplit, 4H) (piperidine), 2.18 (H_X, $H_{X'}$, 2H), 2.55 (H_A, $H_{A'}$, 2H), 3.05 (H_B, $H_{B'}$, 2H) (AA'BB'XX'-system, $^2J_{AB}$ = 8.9 Hz), 2.59 (m_c, 4H), 6.20 (broad, 2H, NH), 7.26–7.42 (m, 10H). – ^{13}C-NMR ($CDCl_3$): δ = 176.4 (t), 140.0 (s), 128.9 (d), 127.9 (d), 126.7 (d), 122.0 (s), 55.4 (s), 53.2 (t), 51.1 (t), 50.5 (t), 50.0 (s), 38.5 (t), 34.4 (d, $^1J_{CH}$ = 173 Hz), 27.0 (t), 24.6 (t). Anal. Calcd for $C_{27}H_{32}N_4O$ (428.6): C, 75.67; H, 7.53; N, 13.07. Found: C 75.6 H, 7.5 N, 13.0.

3α,4α,5α-1-(3-Cyano-3,3-diphenylpropyl)-6-piperidino-3,5-cyclopiperidine-4-carboxamide (**2c**)

A mixture of carboxamide **2a** (0.230 g, 1.10 mmol), 4-bromo-2,2-diphenylbutyronitrile (**14**) (0.495 g, 1.65 mmol), sodium carbonate (0.385 g, 3.63 mmol) and potassium iodide (0.052 g, 0,31 mmol) in dioxane (12 ml, freshly distilled from lithium aluminum hydride) was refluxed for 67 h. The hot mixture was filtered by suction, and the precipitate was washed with hot 2-propanol (2×5 ml). The filtrate was concentrated and treated by chromatography (2×18 cm column, silicagel 0.063 – 0.2 mm). Unreacted bromo compound **14** was eluted with ether; cyclopiperidine **2c** was obtained by subsequent elution with ether/acetone (1/1). Yield: 0.208 g (44%); m.p. 173 °C; IR (KBr, cm^{-1}): ν = 3500–3000 (N–H), 2220 (C≡N), 1665 ($CONH_2$). – ^{1}H-NMR ($CDCl_3$): δ = 1.40 (m_c, 2H), 1.48 (m_c, 4H), 2.65 (m_c, 4H) (piperidine), 1.60 (H_X, $H_{X'}$, 2H), 2.42 (H_A, $H_{A'}$, 2H), 3.11 (H_B, $H_{B'}$, 2H) (AA'BB'XX'-system, $^2J_{AB}$ = 9.0 Hz), 2.49 (m_c, 4H), 5.23 (broad, 1H, NH), 5.52 (broad, 1H,

NH), 7.25–7.40 (m, 10H). – ^{13}C-NMR ($CDCl_3$): δ = 166.0 (s), 139.9 (s), 128.8 (d), 127.8 (d), 126.7 (d), 122.1 (s), 54.0 (s), 52.8 (t), 51.2 (t), 50.6 (t), 50.1 (s), 37.6 (t), 29.7 (d, $^1J_{CH}$ = 172 Hz), 26.8 (t), 24.4 (t). Anal. Calcd. for $C_{27}H_{32}N_4O$ (428.6): C, 75.67; H, 7.53; N, 13.07. Found: C 75.5 H, 7.5 N 13.0.

X-Ray Crystal Structure Analysis of 2c · CH_3OH [24]

Single crystals of **2c** · CH_3OH were obtained by crystallization from methanol. Crystal data: $C_{28}H_{36}N_4O_2$, F.W. = 460.6; triclinic, space group P1; a = 9.305(2), b = 9.863(2), c = 14.418(3) Å; α = 72.94(3)°, β = 75.84(3)°, γ = 79.42(3)°; V = 1217.6(4) Å^3; 2 molecules per unit cell; D_x = 1.256 g·cm^{-3}; crystal size 0.30×0.25×0.35 mm. Data Collection: Diffractometer Siemens P4, temperature: 293(2) K; monochromatized Mo-Kα radiation; 4473 measured reflections, 3346 independent reflections with 1.51° < Θ < 28.99°, $R_{(int)}$ = 0.0598 and 2003 observed reflections with I > 2σ(I); no absorption correction. Structure solution and refinement: The structure was solved by the direct method using SHELXS-86 [25] and refined by full matrix least-squares method on F^2 using SHELXL-93 [26] All non-hydrogen atoms were refined anisotropically and hydrogen atoms were located in calculated positions and refined using a riding model with isotropic displacement parameters. 358 parameters; weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.05\,P)^2 + 0.11\,P]$ where $P = (F_o^2 + 2F_c^2)/3$; $R1[F^2 > 4\sigma(F^2)] = 0.0537$, $wR2[F^2] = 0.1078$.

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