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FUNCTIONALIZED CHLOROENAMINES IN AMINOCYCLOPROPANE SYNTHESIS - XVII.[1] 3,5-CYCLOPIPERIDINE-4-CARBOXAMIDES WITH AN UNSUBSTITUTED 4-AMINO MOIETY - A SYNTHETIC AND A CONFORMATIONAL STUDY

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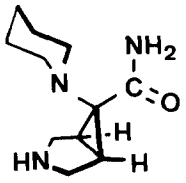
Abstract: 4-Amino-3,5-cyclopiperidine compounds **4a**, **4b** and **11** with unsubstituted amino moieties in 1- and/or 4-position were prepared via tribenzyl derivative **10** by selective removal of the protecting groups. The preference of a cyclopiperidine boat conformation of diamines **4a**, **4b** and **11** in solution was indicated by ^{1}H NMR spectroscopy. X-Ray structural analysis of carboxamide **4a** established the presence of both a chair and a boat cyclopiperidine molecule in the solid state. Some selected conformations of 1-methyl-4-amino-3,5-cyclopiperidine **16** were studied by HF/6-31 G* calculations.

Diastereomeric cyclopiperidinecarboxamides[2] **1** and **2** represent constrained analogues of bipiperidinecarboxamide **3** which is part of the structural unit of the commercially pharmaceutical drugs Pipamperone,[3] Piritramide,[4] Carpipramine[5] and Clocapramine.[6] In this context, compounds **4** and **5** should be of interest since the free amino moiety in 4-position allows the introduction of further groups which are important from a pharmacological point of view.



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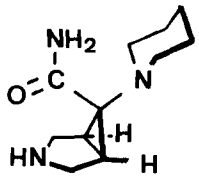

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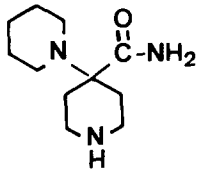

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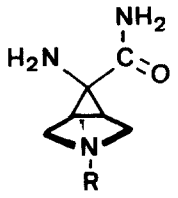


4: endo-NH_2

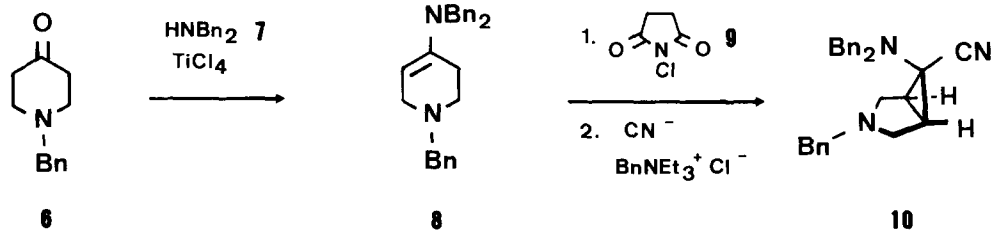
5: exo -NH_2

a: R = Bn **b**: R = H

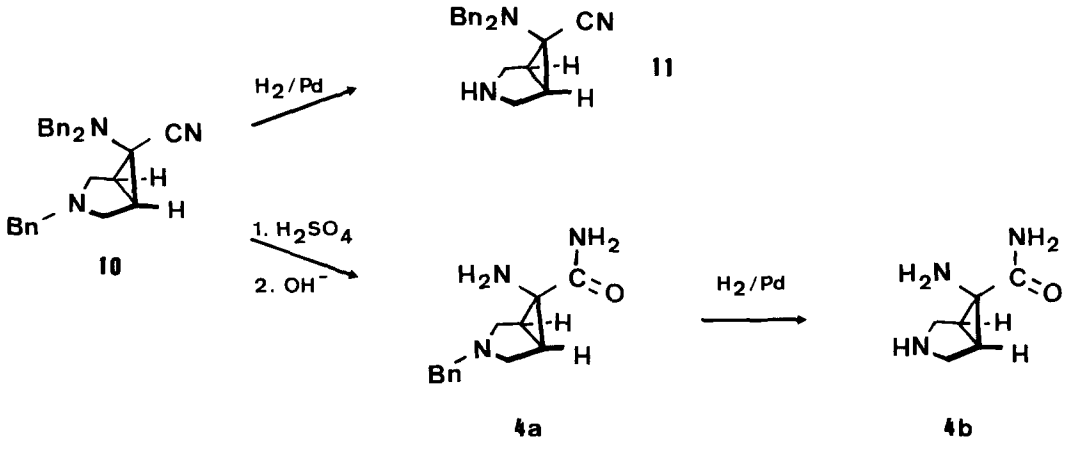
We found, that endo-amino derivatives **4** can be prepared via tribenzyl cyclopiperidine **10**. The results of these synthetic and structural investigations are reported in this paper.

SYNTHESIS AND CONFIGURATION OF 4-AMINO-3,5-CYCLOPIPERIDINE DERIVATIVES 4a, 4b, 10 AND 11

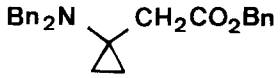
Tribenzyl cyclopiperidine **10** could be obtained from enamine **8** by monochlorination with N-chlorosuccinimide (**9**) and subsequent reaction with cyanide in the presence of benzyltriethylammonium chloride as phase-transfer-catalyst (60% yield). Enamine **8** as starting material was easily accessible (60% yield) from N-benzylpiperidone (**6**) and dibenzylamine (**7**) by the Weingarten-method.[7]



Only the N(1)-benzyl group could be removed by hydrogenolysis of tribenzyl derivative **10** with a palladium/charcoal catalyst to give dibenzylcyclopiperidinecarbonitrile **11** (78% yield).



Deactivation[8] of the C(4)-amino moiety by the cyano group obviously prohibits the removal of the corresponding benzyl moieties in **10**. This becomes evident by the unproblematic debenzylation of dibenzylaminocylopropane compounds such as **12**[9] or **13**[10] by hydrogen. Transformation of the nitrile group in **10** to a less deactivating carboxamide moiety, therefore, was provided for allowing a subsequent debenzylation of the C(4)-amino group. Interaction of nitrile **10** with sulfuric acid under smooth conditions (neat concentrated sulfuric acid at 20°C or sulfuric acid in dichloromethane at 5°C[11]) caused no saponification. Carboxamide formation, however, occurred upon heating both reagents to 100°C for 1 h. Saponification of nitrile **10** was surprisingly accompanied by a specific debenzylation of the C(4)-amino group leading to aminocarboxamide **4a** (48% yield). Subsequent hydrogenolysis of N(1)-benzyl compound **4a** finally provided N-unprotected cyclopiperidine **4b** in 69% yield. Hydrogenolysis and acidic hydrolysis thus represent two complementary methods for specific removal of the different benzyl protecting groups in **10**.



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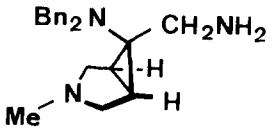

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CONFIGURATION AND CONFORMATION OF 4-AMINO-3,5-CYCLOPIPERIDINE DERIVATIVES 4a, 4b, 10 AND 11

The cyclopiperidine unit of **4a**, **4b**, **10** and **11** followed unequivocally from the ^{13}C NMR data (see Expt. Part). Constitution **11** with the connection of both benzyl moieties to the C(4)-N-nitrogen atom could be deduced from the ^{1}H NMR spectrum: One AB-system for both benzylic methylene signals in toluene at -43°C indicated the presence of two chemical equivalent N-benzyl groups with anisochronic H-atoms (H_A: 3.34 ppm, H_B: 3.38 ppm, J_{AB} = 12.7 Hz) [anisochronism of the benzylic H-atoms due to steric hindrance in the endo position, ref.[12]].

Titration of **4a** with 0.1 M aqueous hydrochloric acid showed that only one proton was taken up (**4a**: pK_a = 9.1; determined via the half neutralization point[13]). Similar ^{1}H NMR signal shifting of the benzylic and the cyclopiperidine methylene H-atoms (0.83, 0.64 and 0.72 ppm) upon protonation of **4a** indicated the location of the proton and of the benzyl moiety both at N(1) and thus constitution **4a** for the corresponding amine.

Endo-amine configuration of **4a**, **4b**, **10** and **11** could be established ^{13}C NMR spectroscopically by the magnitude of the $^{3}J_{CH}$ coupling between the cyano- or carboxamide group and the bridge-head hydrogen atoms (see ref.[14,15]; $^{3}J_{CH}$: cyano group: **10**: 4.6 Hz; **11**: 4.8 Hz; carboxamide group: **4a**: 3.6 Hz; **4b**: 3.2 Hz). The cyclopiperidine system of **4a**, **4b**, **10**

and **11** appeared as AA'BB'XX'-signal pattern in the ^1H NMR spectrum. Sharp lines were found for $H_A/H_{A'}$ and small values were obtained for J_{BX} / $J_{B'X'}$-coupling in the case of **4a** ($J_{AX'}$, $J_{A'X'}$ < 0.7 Hz; $J_{BX} = J_{B'X'} = 3.8$ Hz), **4b** ($J_{AX'}$, $J_{A'X'}$ < 0.9 Hz; $J_{BX} = J_{B'X'} = 3.3$ Hz) and **11** ($J_{AX'}$, $J_{A'X'}$ < 0.7 Hz; $J_{BX'}$, $J_{B'X'}$ < 2.3 Hz). These values are characteristic of the presence of a boat conformation for these species (see ref.[16,17]). Analogous ^1H NMR data of compound **10** ($J_{AX} = J_{A'X'} = 0.9$ Hz; $J_{BX} = J_{B'X'} = 5.1$ Hz) should be interpreted in terms of an existing chair - boat equilibrium.

STRUCTURE OF 4-AMINO-1-BENZYL-3,5-CYCLOPIPERIDINE-4-CARBOXAMIDE 4a

X-Ray structural analysis of carboxamide **4a** confirmed the location of the benzyl rest at N(1) and the 4-endo-amino configuration. Two different molecules, a boat and a chair cyclopiperidine, were found in the unit cell (Fig. 1). Bond lengths of the cyclopiperidine skeleton are not significantly influenced by its conformation (Table 1). Boat and chair conformation show a clear buckling of the bicyclic system. A weak intramolecular hydrogen bonding was indicated for N(2)-H ··· N(1) (2.415 Å) in the boat molecule (Fig 1). This H-atom at N(2) is located 0.306 Å outside of the plane C(7)N(1)N(2) leading to N(2)-lone pair in a skew geometry. Contrarily, N(2)-lone pair is directed outside in the chair conformation; this allows intramolecular hydrogen bonding N(2) ··· H-N(3) [amido-N - H ···· N(2): 2.171 Å] (Fig. 1).

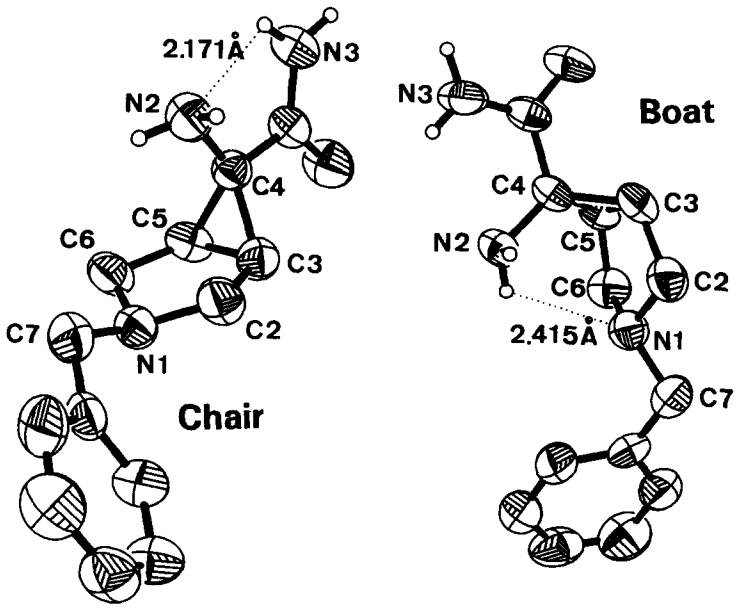


Fig. 1 Thermal ellipsoid plot of **4a** with the atom-labelling scheme. Ellipsoids are scaled to enclose 50% of the electron density.

Table 1 Selected bond distances, N,N-distances, torsional angles and interplanar angles of 1-benzyl-4-amino-3,5-cyclopiperidine-4-carboxamide[a] **4a**

bond lengths [Å]			bond lengths [Å]		
	boat	**chair**		**boat**	**chair**
C(3) - C(4)	1.534(6)	1.531(5)	C(2) - C(3)	1.486(8)	1.512(6)
C(4) - C(5)	1.533(6)	1.526(7)	C(5) - C(6)	1.505(7)	1.490(7)
C(3) - C(5)	1.491(7)	1.498(7)	N(1) - C(2)	1.467(6)	1.465(7)
C(4) - N(2)	1.448(5)	1.437(6)	N(1) - C(6)	1.463(7)	1.461(5)

N,N-distances [Å]

	boat	**chair**
N(1) - N(2)	2.92	3.43
N(1) - N(3)	5.20	5.51
N(2) - N(3)	2.72	2.68

torsional angles [°][b]

	boat	**chair**
H(3)-C(3)-C(2)-H(2)$_A$	80.9	102.0
H(6)$_A$-C(6)-C(5)-H(5)	-81.8	-109.7
H(3)-C(3)-C(2)-H(2)$_B$	-40.3	-19.3
H(6)$_B$-C(6)-C(5)-H(5)	39.6	11.4

interplanar angles [°]

	boat	**chair**
C(3)C(4)C(5) - C(2)C(3)C(5)C(6)	66.2	68.7
C(2)C(3)C(5)C(6) - C(2)N(1)C(6)	27.1	23.7

[a] The designation of some atoms in Fig. 1, Fig. 2, Fig. 3 and Table 1 in this paper was partially changed with respect to the designation in the deposited data.- [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 3,5-cyclopiperidine system.

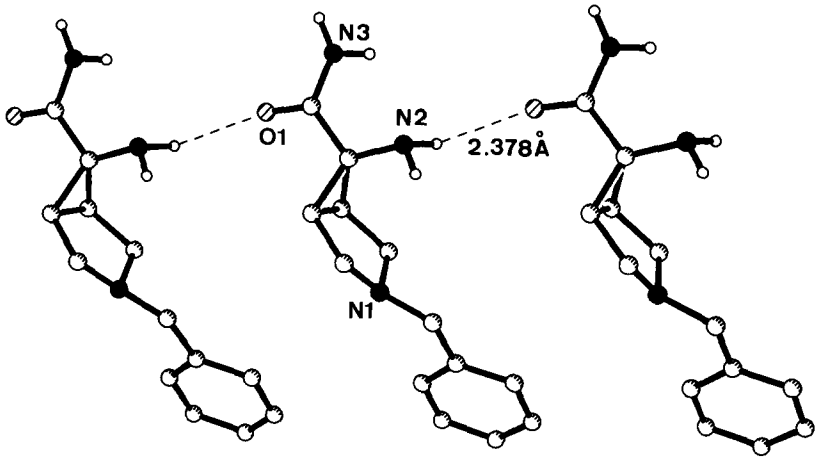


Fig. 2 Schakal[18] plot of the hydrogen bonding within the layer of the chair molecules of **4a**.

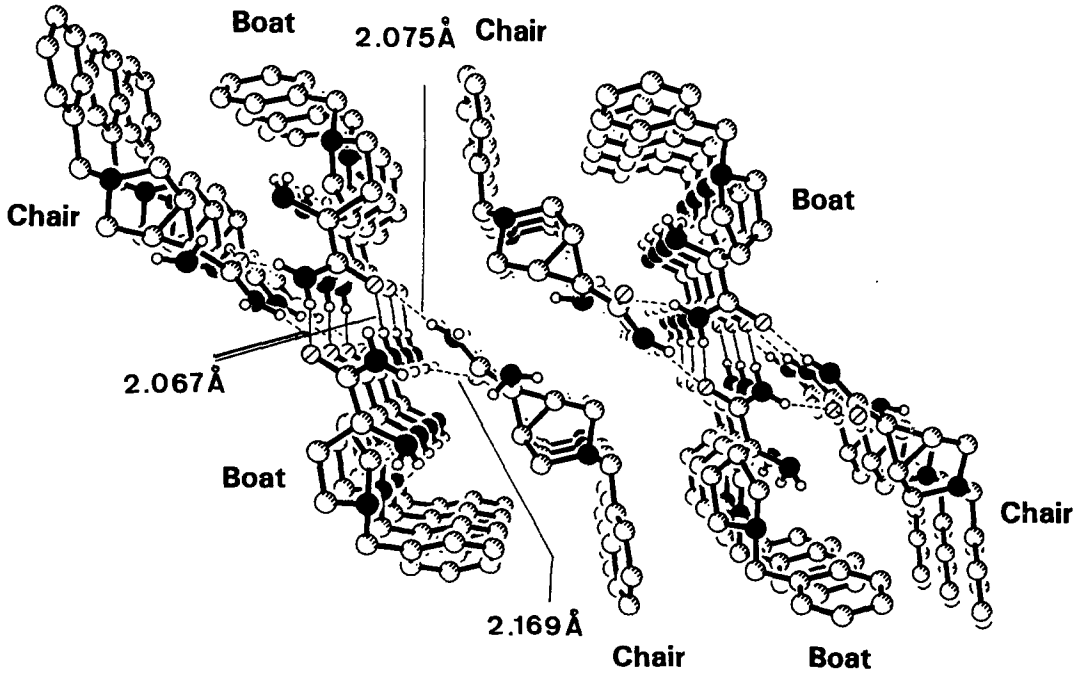


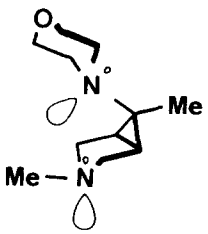
Fig. 3 Arrangement of the boat and the chair shaped molecules of **4a** in the crystal.

The arrangement of the cyclopiperidine molecules **4a** in the crystal leading to hydrophilic and lipophilic spaces is depicted in Fig. 3. The crystal structure is strongly determined by intermolecular carboxamide hydrogen bonding. Two stocks of multifold layers of boat cyclopiperidines are orientated by facing the carboxamide groups. The resulting N(3)-H ··· O -bonds (2.067 Å) are arranged in a helical manner connecting continuously the layers of the two different stocks. The chair cyclopiperidine molecules also form multifold layers. In contrast to the former, the linking of the chair layers is mainly realized by hydrogen bonding with the carboxamide helix of the boat cyclopiperidines [(chair) N(3)-H ··· O (boat) 2.075 Å; (boat) N(3)-H ··· O (chair) 2.169 Å]. Neighboured chair molecules are connected additionally by a carbonyl-O ··· H-N(2)-aminogroup bonding (carbonyl-O ··· H-N(2): 2.378 Å (Fig. 2).

HF/6-31G* CALCULATIONS OF 4-AMINO-1-METHYL-3,5-CYCLOPIPERIDINE 16

A chair conformation was found by X-ray structural analysis for cyclopiperidines **14** and **15** with an endo-morpholine[16] or piperazine[15] group. The atypical chair conformation should be the consequence of steric anchoring of the heterocyclic N-lone pair to the inside of the cyclopiperidine and its repulsive effect to the N(1)-lone pair. The conformations of compounds of type **4** with an unsubstituted and rotationally mobile amino moiety at C(4) should be of interest from this point of view. Derivative **4a**, with its strong tendency for carboxamide hydrogen bonding, and the packing influence of the benzyl moieties is obviously not an appropriate model compound for information about conformational properties of the cyclopiperidine skeleton possessing an unsubstituted amino moiety in 4-position.

This conformational problem, therefore, was studied by *ab initio* calculations. Parent compound **16** was selected for these calculations, which were performed with the Convex, HP and Cray versions of the Gaussian 92 program package.[19] The 6-31G* basis set[20] was chosen for geometry optimizations.



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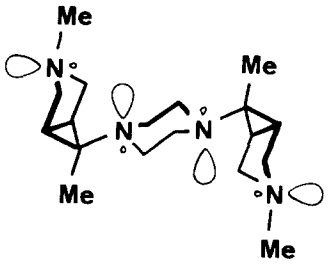

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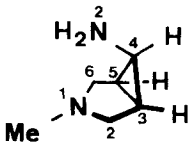

16

Four different conformations of **16** were fully optimized in C_s symmetry and characterized by diagonalization of the HF/6-31G* force matrix [boat conformation with inside or outside N(2)-lone pair (**16B$_{in}$** and **16B$_{out}$**), chair conformation with inside or outside N(2)-lone pair (**16C$_{in}$** and **16C$_{out}$**)]. Optimization of all geometric parameters led to a boat structure with C_1 geometry with a skew N(2)-lone pair (**16B$_{sk}$**). Only conformations with an equatorial N(1)-methyl group were considered in accord with the results of former *ab initio* calculations for the parent compound 1-methyl-3,5-cyclopiperidine.[16]

HF-6-31G* total energies [au], relative energies including ZPE correction [kcal/mol], NN-distances [Å] and the ring buckle [°] of these selected conformations of cyclopiperidine **16** are given in Tab. 2.; the corresponding structures are shown in Fig. 4. **16B$_{sk}$** proved to be the favoured conformation for **16**. The skew orientation of the N(2) lone pair is a consequence of hydrogen bonding between (N2)-H ··· N(1); this hydrogen atom is located only 0.14° outside the C(4)N(1)C(7)-plane. Hydrogen bonding of this type has been found experimentally in amines (e.g. ammonia[21], primary amines[22]) and by calculations (e.g. ammonia[23-25]).

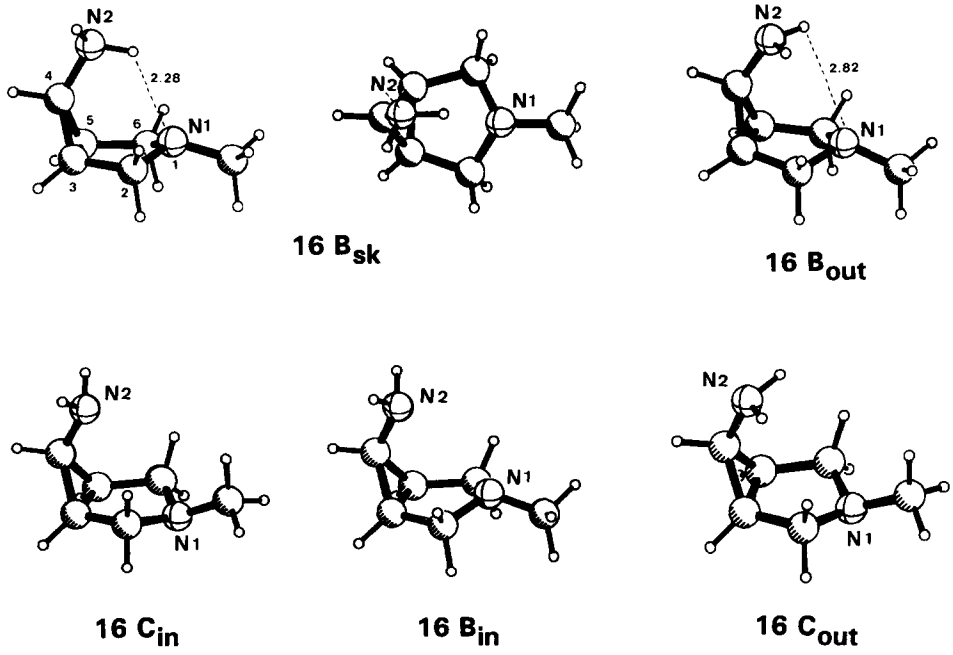

Fig. 4 HF/6-31G* Optimized geometries of 4-amino-3,5-cyclopiperidine **16**

Table 2 HF-6-31G* total energies [au], relative energies including ZPE correction [kcal/mol], NN-distances [Å] and ring buckle [°] of selected conformations of 1-methyl-4-amino-3,5-cyclopiperidine **16**

Conformation	HF [au]	E_{rel}[a] [kcal/mol]	ZPE [kcal/mol]	NN-distance [Å]	ring buckle[b] [°]
16B$_{sk}$	- 343.03353	0	122.1	2.95	32.0
16B$_{out}$	- 343.03042	1.5	121.6	2.98	30.4
16C$_{in}$	- 343.02988	2.2	122.0	3.36	23.1
16B$_{in}$	- 343.02754	3.2	121.5	3.00	23.4
16C$_{out}$	- 343.02498	4.8	121.5	3.51	22.0

[a] Including ZPE correction.- [b] Interplanar angle between C(6)N(1)C(2) and C(2)C(3)C(5)C(6).-

The lowest energy within the family of conformations with C_s-symmetry was found for the boat-shaped molecule **16B$_{out}$**. Repulsive effects between the hydrogen atoms at N(2) and C(2)/C(6) (distance: 2.54 Å) destabilize the generally more favourable boat conformation in cyclopiperidine systems in order to avoid the eclipsed arrangement of H(exo)C(2)-C(3)H and H(exo)C(6)-C(5)H. Through space H,H-repulsive effects increase strongly for conformation **16C$_{out}$** (distance of hydrogen atoms of N(2) and C(2)/C(6): 2.17 Å); **16C$_{out}$**, therefore, proved not to be a minimum on the energy hypersurface. H,H-repulsions of this type are not present in the conformations **16C$_{in}$** and **16B$_{in}$**, in the latter case, however, lone pair-lone-pair repulsion becomes important.

Conformations of 4-aminocyclopiperidines thus are determined by minimization of ecliptic arrangements H(exo)C(2)-C(3)H and H(exo)C(6)-C(5)H, of N(1)-lone-pair - N(2)-lone-pair repulsion and of steric interaction of endo-hydrogen atoms at C(2)/C(6) with hydrogen atoms at the nitrogen atom N(2). Hydrogen bonding between N(1) and the unsubstituted amino moiety in the 4-position is also important.

EXPERIMENTAL

^1H NMR 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 397 Infrared Spectrophotometer. Microanalyses were performed with a Perkin-Elmer 2400 Elemental Analyzer. Amine **4a** was titrated with a Metrohm Titrino SM 702 apparatus using Metrohm electrodes [combined pH-glass electrode with Ag/AgCl/KCl (3 N) as inner reference electrode]. Ab initio calculations were done with Convex C220, HP-735 and Cray YMP computers.

1-Benzyl-4-(dibenzylamino)-1,2,3,6-tetrahydropyridine (8): A solution of titanium tetrachloride (3 mL, 27 mmol) in toluene (10 mL) was dropped slowly to a vigorously stirred solution of piperidinone **6** (10.0 g, 53 mmol) and dibenzylamine (**7**) (41.7 g, 210 mmol) in toluene (200 mL) at 0°C. Stirring was continued for 15 h at room temperature. Removal of the precipitate by filtration and evaporation of the toluene gave crude enamine which was purified by distillation in a Kugelrohr apparatus. Yield: 11.6 g (60%), bp 225°C/0.005 Torr; IR (KBr, cm^{-1}) 1650 (C=C); ^1H NMR ($CDCl_3$) δ 2.53-2.56 (m, 2H), 2.73-2.76 (m, 2H), 3.17-3.18 (m, 2H), 3.70 (s, 2H), 4.33 (s, 4H), 4.55 (t, 1H), 7.32-7.47 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 141.4 (s), 139.3 (s), 138.4 (s), 129.0 (d), 128.2 (d), 128.0 (d), 127.1 (d), 126.8 (d), 126.5 (d), 94.2 (d), 62.4 (t), 52.7 (t), 52.3 (t), 49.9 (t), 27.6 (t). Anal. Calcd for $C_{26}H_{28}N_2$: C, 84.81; H, 7.66; N, 7.61. Found: C, 84.5; H, 7.6; N, 7.7.

3*α*,4*β*,5*α*-1-Benzyl-4-(dibenzylamino)-3,5-cyclopiperidine-4-carbonitrile (10): A solution of N-chlorosuccinimide (**9**) in dichloromethane (100 mL) was dropped within 1 h at -78°C to a stirred solution of enamine **8** (11.6 g, 32 mmol) in dichloromethane (100 mL). Then the cooling bath was removed and stirring was continued for 1 h. Removal of the solvent and extraction of the residue with pentane (3 x 50 mL) gave crude chloroenamine (11.6 g) which was dissolved in acetonitrile (150 mL). Sodium cyanide (2.8 g, 58 mmol), benzyltriethylammonium chloride (3.3 g, 15 mmol) and water (15 mL) were added to this solution. Stirring for 2 d at room temperature, evaporation of the solvent, addition of water (50 mL) and extraction with ether (3 x 50 mL) led to crude nitrile **10** which was purified by recrystallization from ether to give colorless crystals. Yield: 7.4 g (60%), mp 102°C; IR (KBr, cm^{-1}) 2190 (C≡N); ^1H NMR ($CDCl_3$) δ 2.09 (H_X, $H_{X'}$, 2H), 2.28 (H_A, $H_{A'}$, $J_{AX} = J_{A'X'} = 0.9$ Hz, 2H), 2.60 (H_B, $H_{B'}$, $J_{BX} = J_{B'X'} =$ 5.1 Hz, 2H) (AA'BB'XX'-system), 3.51 (s, 2H), 3.74 (s, 4H), 7.23-7.41 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 138.9 (s), 137.4 (s), 129.6 (d), 128.9 (d), 128.17 (d), 128,14 (d), 127.4 (d), 127.0 (d), 118.6 (t, $^3J_{CH} = 4.6$ Hz), 59.8 (t), 58.0 (t), 52.2 (t), 44.2 (s), 33.2 (d, $^1J_{CH} = 174.5$ Hz). Anal. Calcd for $C_{27}H_{27}N_3$: C, 82.41; H, 6.92; N, 10.68. Found: C, 82.2; H, 7.0; N, 10.7.

3*α*,4*β*,5*α*-4-(Dibenzylamino)-3,5-cyclopiperidine-4-carbonitrile (11): A solution of tribenzyl derivative **10** (2.0 g, 5.1 mmol) in methanol (150 mL) was saturated with hydrogen in the presence of palladium/charcoal catalyst (10% Pd, 1.52 g, 1.44 mmol). Hydrogenolysis was

stopped, when 300 mL of hydrogen were absorbed. The catalyst was removed by filtration and the solvent was evaporated in vacuo. Recrystallization of the residue from ether gave pure **11**. Yield: 1.2 g (78%), mp 98°C; IR (KBr, cm^{-1}) 3300 (N-H), 2190 (C≡N); ^1H NMR ($CDCl_3$) δ 1.83 (s, broad, 1H, NH), 2.02 (H_X, $H_{X'}$, 2H), 2.30 (H_A, $H_{A'}$, J_{AX}, $J_{A'X'}$ < 0.7 Hz, 2H), 2.73 (H_B, $H_{B'}$, J_{BX} , $J_{B'X'}$ < 2.3 Hz, 2H) (AA'BB'XX'-system), 3.71 (s, 4H), 7.23-7.38 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 137.2 (s), 129.5 (d), 128.7 (d), 127.9 (d), 117.2 (t, $^3J_{CH}$ = 4.8 Hz), 58.4 (t), 48.3 (t), 41.8 (s), 33.6 (d, $^1J_{CH}$ = 173 Hz). Anal. Calcd for $C_{20}H_{21}N_3$: C, 79.17; H, 6.98; N, 13.85. Found: C, 78.8; H, 7.0; N, 13.8.

3α,4β,5α-4-Amino-1-benzyl-3,5-cyclopiperidine-4-carboxamide (**4a**): Tribenzyl derivative **10** (1.0 g, 2.5 mmol) was added to sulfuric acid (95-97%, 5 mL) at 0°C. The solution was heated to 100°C for 1 h, cooled to room temperature and poured into a mixture of ice (50 g) and ether (50 mL). Aqueous sodium hydroxide (5 M) was added till pH = 10.5. Separation of the ethereal layer, extraction of the aqueous solution with ether (3 x 30 mL) and concentration of the ether solution gave crude **4a** which was recrystallized from ether. Yield: 0.28 g (48%), mp 112°C; IR (KBr, cm^{-1}) 3420 (N-H), 1660 (C=O); ^1H NMR ($CDCl_3$) δ 2.06 (H_X, $H_{X'}$, 2H), 2.77 (H_B, $H_{B'}$, J_{BX} = $J_{B'X'}$ = 3.8 Hz, 2H), 3.02 (H_A, $H_{A'}$, J_{AX}, $J_{A'X'}$ < 0.7 Hz, 2H) (AA'BB'XX'-system), 2.11 (s, 2H, NH_2), 3.60 (s, 2H), 6.14 (s, 1H) and 7.35 (s, 1H, $CONH_2$), 7.21-7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 176.8 (t, $^3J_{CH}$ = 3.6 Hz), 139.1 (s), 128.23 (d), 128.18 (d), 127.0 (d), 59.5 (t), 52.4 (t), 43.2 (s), 29.5 (d, $^1J_{CH}$ = 174 Hz). Anal. Calcd for $C_{13}H_{17}N_3O$: C, 67.51; H, 7.41; N, 18.17. Found: C, 67.5; H, 7.3; N, 18.2.

3α,4β,5α-4-Amino-3,5-cyclopiperidine-4-carboxamide (**4b**): A solution of N-benzyl derivative **4a** (0.46 g, 2.0 mmol) in methanol (100 mL) was saturated with hydrogen in the presence of palladium/charcoal catalyst (10% Pd, 0.6 g, 0.57 mmol). Hydrogenolysis was stopped, when 60 mL of hydrogen were absorbed. The catalyst was removed by filtration and the solvent was evaporated in vacuo. Recrystallization of the residue from methanol gave pure **4b**. Yield: 0.21 g (69%), mp 130°C (decomp.); IR (KBr, cm^{-1}) 3400 (N-H), 1660 (C=O); ^1H NMR (D_2O/CD_3CN 1/1) δ 2.10 (H_X, $H_{X'}$, 2H), 3.05 (H_A, $H_{A'}$, J_{AX}, $J_{A'X'}$ < 0.9 Hz, 2H), 3.12 (H_B, $H_{B'}$, J_{BX} = $J_{B'X'}$ = 3.3 Hz, 2H) (AA'BB'XX'-system); ^{13}C NMR (D_2O/CD_3CN 1/1) δ 182.8 (t, $^3J_{CH}$ = 3.2 Hz), 48.1 (t), 43.9 (s), 35.4 (d, $^1J_{CH}$ = 175 Hz). Anal. Calcd for $C_6H_{11}N_3O$: C, 51.05; H, 7.85; N, 29.77. Found: C, 50.5; H, 7.7; N, 29.5.

3α,4β,5α-4-Amino-1-benzyl-4-carbamoyl-3,5-cyclopiperidinium Trifluoromethanesulfonate (**4a · TFA**): A solution of trifluoromethanesulfonic acid in propan-2-ol (0.1 M, 2.0 mL) was added to cyclopiperidinecarboxamide **4a** (46.2 mg, 0.20 mmol) in water (40 mL). Stirring for 10 min and complete removal of the solvent in vacuo gave ammonium salt **4a · TFA** in quantitative yield; mp 158-160°C; IR (KBr, cm^{-1}) 3390 (N-H), 1680 (C=O); ^1H NMR (D_2O) δ 2.37 (H_X, $H_{X'}$, 2H), 3.60 (H_A, $H_{A'}$, 2H), 3.66 (H_B, $H_{B'}$, 2H) (AA'BB'XX'-system), 4.32 (s, 2H), 7.46-7.50 (m, 5H); ^{13}C NMR (D_2O) δ 179.4 (s), 133.3 (s), 133.1 (d), 132.9 (d), 132.3 (d), 59.2 (t), 55.0 (t), 42.3 (s), 30.6 (d, $^1J_{CH}$ = 180 Hz). Anal. Calcd for $C_{14}H_{18}F_3N_3O_4S$: C, 44.09; H, 4.76; N, 11.02.

Found: C, 44.0; H, 5.0; N, 10.8.

X-Ray Crystal Structure Analysis[26] **of 4a**. Single crystals of **4a** were obtained by crystallization from ether.

Crystal data: $C_{13}H_{17}N_3O$, F.W. = 231.3; monoclinic, space group $P2_1/n$; a = 18.939(4), b = 6.277(2), c = 22.643(5) Å; β = 113.44(3)°; V = 2469.7(11) Å^3; 8 molecules per unit cell; D_x = 1.244 g · cm^{-3}; crystal size 0.30 x 0.25 x 0.40 mm.

Data collection: Diffractometer Siemens P4, monochromatized Mo-K_α radiation; 3791 independent reflections with 2.0° < 2Θ < 60.0° [ω scan, scan speed 5.00 - 45.00 ° · min^{-1}], no absorption correction.

Structure solution and refinement: The structure was solved by direct methods using SHELXS-86[27]. Refinement was performed by a full-matrix least-squares method using SHELXTL-PLUS[28]. H atoms were refined as riding on their bond neighbours with isotropic thermal displacement factors, 2116 reflections with F > 4.0 σ(F); 320 variables, unit weights, weighting scheme $w^{-1} = \sigma^2(F) + 0.0064\ F^2$; maximum shift/error ratio 0.077, R = 0.0551, R_w = 0.0858.

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