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Plyers-shaped diamines I. 3-endo-Amino-2,4-cyclotropane- and 3-endo-amino-2,4-cyclogranatanecarbonitriles

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Abstract

3-endo-Amino-2,4-cyclotropane- and 3-endo-amino-2,4-cyclogranatanecarbonitriles could be synthesized from the enamines of tropinone or pseudopelletierines by subsequent reactions with N-chlorosuccinimide and cyanide. Configuration and conformation of the tricyclic unit in the new compounds were determined by ^{1}H NMR spectroscopy. The plyers-like shape of the diamine unit was confirmed by an X-ray structural analysis.

Keywords: Polycyclic heterocyclic compounds; Diamines; Configuration; Conformation

1. Introduction

4β-Amino-3,5-cyclopiperidines **1** originally represent the type of a chelating diamine. The optimum plyers-like arrangement of the two N-lone pairs in **1B**, however, is unfavorable; it is avoided by switching off the interaction of N(1) and 4-amino-N lone pair by one of two ways: The first way - N(1) lone pair inversion and adaption of a chair conformation **1C** - is realized if a sterically inside anchored 4-amino-N lone pair is present (e. g. NR^1_2 = morpholine [1], piperidine [2], piperazine [3,4], pyrrolidine [5], dimethyl [5] - or dibenzylamine [6]). The second possibility is observed in the case of an unsubstituted 4-amino group [6] which rotates outside in order to create the energetically favored cyclopiperidine boat conformation **1B** (Figure 1). Really plyers-like shaped N-lone pairs, therefore, are expected if the 4-amino lone pair in compound **1** is anchored inside and the boat conformation **1B** is constrained simultaneously by a 2,6-bridge.

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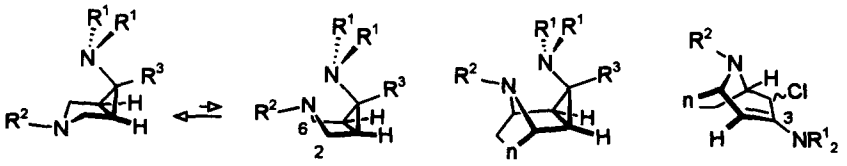
Figure 1



1C C: CHAIR **1B** B: BOAT **2:** n = CH_2 **3:** n = $(CH_2)_2$ **4**

2,4-Cyclotropane- and 2,4-cyclogranatane derivatives **2** and **3** with a piperidino, morpholino or dibenzylamino unit in 3-endo-position should be applicable as simple target molecules for this structural principle (Figure 1). The synthesis of diamines of type **2** and **3** was planned by introduction of the "zero-bridge" via reaction of a chlorenamine precursor **4** with a nucleophile [2-10]. The possibility of such an access and the sterical requirements of the chloroenamine (e. g. ref. [11,12]) were studied first with cyanide as nucleophile since less strong lone pair - lone pair interaction is predicted for diamines **2** and **3** if R^3 represents a nitrile function[1]. The results of these investigations are reported in this paper.

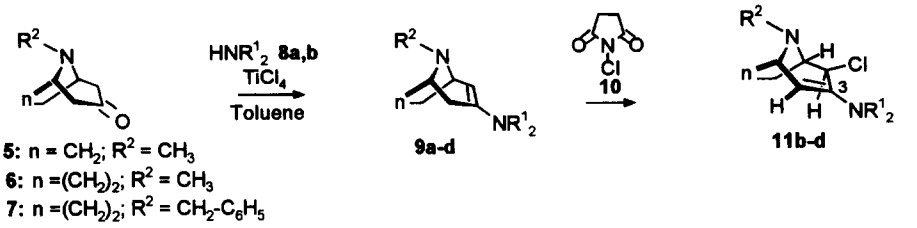
2. Synthesis of 3-amino-2,4-cyclotropane- and 3-amino-2,4-cyclogranatane derivatives

Enamines **9a-d** were obtained from tropinone **5** or pseudopelletierines **6/7** and amines **8a,b** by the Weingarten method [13] using titanium tetrachloride as catalyst. Highly selective mono chlorination could be performed with N-chlorosuccinimide (NCS) **10** at -78°C for enamines **9b-d**. Analogous chlorination of piperidino derivative **9a** gave a mixture of monochloro- and dichloroenamines **11a** and **12a** (ratio 4 : 1) which was used for the cyclopropanation reaction without further purification. Dichloroenamine **12a** was accessible as pure compound by chlorination of enamine **9a** with two equivalents of NCS **10** (Scheme 1).

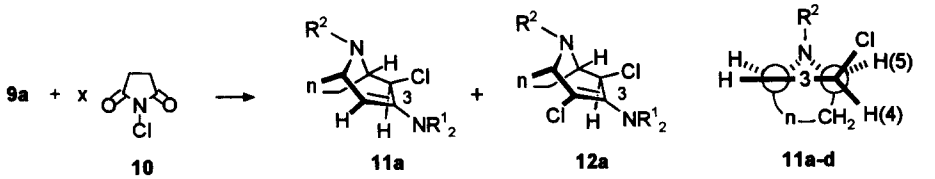
The structures of compounds **11a-d** and **12a** were established by the ^{13}C and ^{1}H NMR data. The absence of a considerable coupling of ClC-H(4) with H(5) in the ^{1}H NMR spectra indicates the exo-position of the chloro atom at C(4) in all chloro derivatives (no detectable coupling for **11a-c** and **12a**; $^{3}J_{HH}$ = 1.8 Hz for **11d**). The small coupling in the latter case can be explained by increasing of the H(5)C(5)C(4)H(4) dihedral angle by the pyrrolidine unit in **11d** with respect to a piperidine unit in **11a-c** or **12a**.-

[1] The influence of a nitrile group on the N-lone pair of an adjacent aminomethyl moiety is demonstrated by strong decrease of basicity, e.g. pK_a Me_2N-CH_3: 9.7, Me_2N-CH_2-CN: 4.2 [14]

Scheme 1



5: n = CH_2; R^2 = CH_3
6: n =$(CH_2)_2$; R^2 = CH_3
7: n =$(CH_2)_2$; R^2 = CH_2-C_6H_5



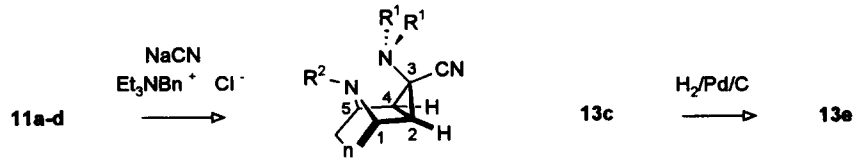
	x = 1:	x = 2:
11a	80	-
12a	20	100

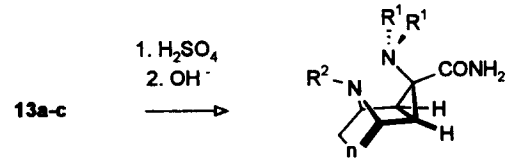
8	NR_2
a	N
b	N O

9 11-14	n	NR^1_2	R^2
a	$(CH_2)_2$	N	CH_3
b	$(CH_2)_2$	N O	CH_3

9 11-14	n	NR^1_2	R^2
c	$(CH_2)_2$	N O	CH_2-C_6H_5
d	CH_2	N O	CH_3

Scheme 2





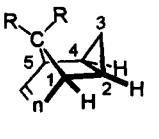
13	n	NR^1_2	R^2
e	$(CH_2)_2$	N O	H

Reaction of chloroenamines **11a-d** with cyanide in acetonitrile - water (9:1) in the presence of benzyltriethylammonium chloride led to tricyclic carbonitriles **13a-d** in 41-75% yield. Each of the isolated compounds **13a-d** proved to be a single stereoisomer (Scheme 2). Saponifaction of the nitrile function in derivatives **13a-c** provided carboxamides **14a-c**. The N-benzyl moiety in nitrile **13c** could be removed hydrogenolytically to give the diaminonitrile **13e** in 92% yield. The presence of a 2,4-cyclotropane unit in **13d** and of a 2,4-cyclogranatane skeleton in the obtained derivatives **13a-c,e** can be established clearly by the ^{13}C NMR data (indication of a plane of symmetry by the number of signals; doubletts for C(2)/C(4) with characteristic $^{1}J_{CH}$ coupling of 170-175 Hz).

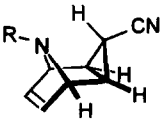
3. Configuration of the synthesized 3-amino-2,4-cyclotropane- and 3-amino-2,4-cyclogranatane derivatives

2α,4α-Configuration of products **13a-e** and **14a-c** is deduced from the ^{1}H NMR spectra by the absence of a detectable coupling between the hydrogen atoms H(1)/H(5) and H(2)/H(4). This argument was used for establishing of the α-configuration at C(2) and C(4) for compounds **15** [R, R = -$(CH_2)_2$-] [15], **16** [16], and **17** [17]. Derivative **18** [R, R = -$(CH_2)_2$-] [15], on the other hand, showed a clearly detectable coupling of $^{3}J_{HH}$ = 2.8 Hz for the analogous bridge head hydrogen atoms.

Figure 2



15: n = CH
16: n = CH - CH_2



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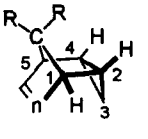
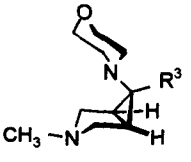


18: n = CH



19: R^3 = CN
20: R^3 = CH_3

The location of the C(3)-amino group in endo-position, and thus *3β-configuration* of products **13a-d** and **14a-c** was determined via the $^{3}J_{CH}$ coupling of the C(3)-carbon substituent with the C(2)-H and C(4)-H hydrogen atoms. The observed values of 4.6-5.0 Hz for **13** and 3.2-3.8 Hz for **14** are typical for syn-standing moieties (e. g. ref. [2,6,8,18]). Partially contradictory predictions concerning the configuration at C(3) were obtained by using the "dynamic ^{1}H NMR method" for the morpholino derivatives **13b-e** and **14b** (Table 1): Quite different activation enthalpies are generally found for the dynamics of an N-heterocyclus which is connected to the C_1-bridge of an [n.1.0]bicyclic system depending on its location in α- or β-position [1-3,7,8,10,11,18-22]. The free activation enthalpies $\Delta G^{\ddagger}$ of the dynamics of morpholine in **13b-e** and **14b** were determined by the usual approximation formula [23] for coupled systems.

Table 1
Free activation enthalpy $\Delta G^{\ddagger}$ of the dynamics of morpholine in tricyclic compounds **13b-e** and **14b**

	Topomerizing H_AH_B	H_A [ppm]	H_B [ppm]	J_{AB} [Hz]	T[a] [K]	T_c[b] [K]	Solvent	$\Delta G^{\ddagger}$ [kJ/mol]
13b	OCH_2[c]	3.48	3.71	9.6	223	255	C_7D_8	50.7[d]
13c	NCH_2[c]	2.11	2.84	10.9	213	294	C_7D_8	56.1[d]
13d	NCH_2[e]	2.64	2.80	10.7	183	233	CD_2Cl_2	47.8[d]
13e	NCH_2[c]	2.00	2.64	11.2	300	375	C_7D_8	72.9[d]
14b	OCH_2[c]	3.25	3.56	9.6	296	353	C_7D_8	70.4[d]

[a] Temperature for determination of H_A, H_B and J_{AB}.
[b] Coalescence temperature.
[c] 400 MHz.
[d] Calculation of $\Delta G^{\ddagger}$ according to the approximation formula [23] for coupled H_A and H_B.
[e] 200 MHz.

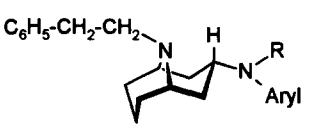
An easy topomerization was found for the methylene hydrogen atoms of morpholine in carbonitriles **13b** ($\Delta G^{\ddagger}$ = 50.7 kJ/mol), and **13d** ($\Delta G^{\ddagger}$ = 47.8 kJ/mol). Especially the last value seems to be more typical for an exo-morpholine than for the endo-morpholine being present. The resulting problems for determination of configuration of compounds of type **13** by the "dynamic ^{1}H NMR method", however, are indicated already by the cyclopiperidine derivatives **19** ($\Delta G^{\ddagger}$ = 58.5, 58.6 kJ/mol [8]) and **20** ($\Delta G^{\ddagger}$ = 58.6, 59.9 kJ/mol [7]). The observed low $\Delta G^{\ddagger}$-values (**19**: about 16 kJ/mol lower than for the bicyclohexyl analogue [18]) should be the consequence of increasing ground state energy of the endo-heterocyclus due to repulsion of its sterically inside anchored N lone pair and the cyclopiperidine N(1) lone pair. Constraining of such a system in a boat conformation by bridging should intensify this effect and lead to the very small $\Delta G^{\ddagger}$ -values as determined for **13b,d**. This argumentation is underlined by the distinctly higher $\Delta G^{\ddagger}$-value for the dynamics of morpholine in N(9)-unsubstituted nitrile **13e** (**13b/13e**: $\Delta\Delta G^{\ddagger}$ = 22.2 kJ/mol). In this case the lone pair - lone pair repulsion can be avoided by outside location of the N(9) lone pair. The increased hindrance of the dynamics of morpholine in the corresponding carboxamide **14b** ($\Delta G^{\ddagger}$ = 70.4, 70.5 kJ/mol) is unexpected. This behaviour requires further investigation.

4. Conformation of the synthesized 3-amino-2,4-cyclogranatane derivatives

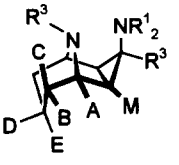
^{1}H NMR studies of compounds **21** [24] and **22** [25] can be used for assignment of conformation of cyclogranatane species **13a-c,e** and **14a-c**. A chair and a boat piperidine unit are

present in **21** and **22** (Figure 3). Both units differ strongly in the coupling of the bridge-head hydrogen [C(1)-H, C(5)-H] with the vicinal methylene hydrogen atoms (chair piperidine: $^3J_{HH}$ = 3.8-4.1 Hz and $^3J_{HH} \approx 0$ Hz; boat piperidine: $^3J_{HH}$ = 11.5-12.3 Hz and $^3J_{HH}$ = 2.6-3.3 Hz) [24,25]. The piperidine moiety in the 9-aza-tricyclo[3.3.1.$0^{2,4}$]nonane skeleton of **13a-c,e** and **14a-c** appears as AA'BB'CC'DE-system (Figure 3; chemical equivalent hydrogen atoms which are indicated by a prime are not shown in the drawn formulae). The Calm-program [26] was used for simulation of the corresponding spectra and for refinement of the coupling constants. The cyclopropane hydrogen atoms H_M, $H_{M'}$ were excluded from the simulation due to no visible coupling with the neighbouring bridge-head hydrogen atoms H_A, $H_{A'}$. Sufficient adaption of the calculated to the experimental ^{1}H NMR signals requires the inclusion of $^4J_{HH}$ -coupling of the equatorial hydrogen atoms of the piperidine part of the cyclogranatane skeleton ($^4J_{HH} \approx$ 1-2 Hz, $H_A/H_{A'}$; H_A/H_D; $H_{A'}/H_D$; $H_B/H_{B'}$). The detection of coupling for H_A/H_B ($H_{A'}/H_{B'}$) and H_A/H_C ($H_{A'}/H_{C'}$) in a magnitude of 2 - 3 Hz clearly establishes the presence of a chair conformation of the piperidine unit in the tricyclic system. This is also observed for the norcyclogranatane derivative **13e** with the outside N(9) lone pair; slightly changed coupling values especially for H_D and H_E indicate a less bent chair of the piperidine unit.

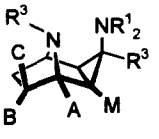
Figure 3



21: R = H
22: R = COR'



13a-c,e; 14a-c



13d

The cyclotropinone unit in **13d** was simulated with the Calm program, too. In this case the AA'BB'CC'MM'-system was analyzed including the cyclopropane hydrogen atoms (for data see experimental part).

5. Crystal structure of 3-morpholino-2,4-cyclogranatanecarbonitrile 13b

The correct assignment of configuration and conformation of the new type of compounds is confirmed by an X-ray structural analysis of tricyclic carbonitrile **13b**. Selected bond distances, atomic distances and dihedral angles are listed in Table 2. The molecular plot and the numbering of atoms are depicted in Figure 4 and Figure 5.

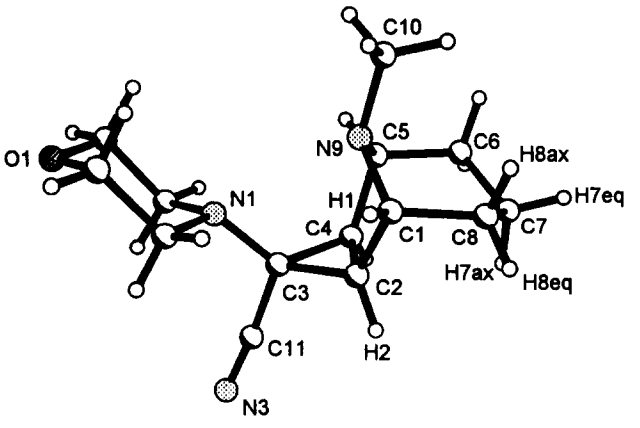


Figure 4 X-Ray structure[2] and numbering of atoms of **13b**.

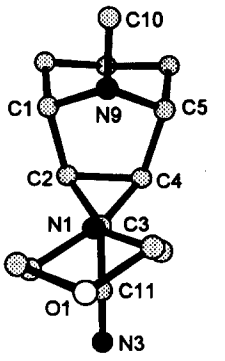


Figure 5 Arrangement of the N(1) and N(9) lone pairs in **13b**.[2]

Table 2
Selected bond distances [Å], atomic distances [Å] and interplanar angles [°] of 3-morpholino-2,4-cyclogranatane-3-carbonitrile **13b**. [a]

C(1) - C(2)	1.520(2)	C(4) - C(5)	1.521(2)
C(2) - C(3)	1.525(2)	C(3) - C(4)	1.513(2)
C(2) - C(4)	1.505(2)	N(9) - C(11)	1.450(2)
N(9) - C(1)	1.458(2)	N(9) - C(5)	1.466(2)
C(3) - N(1)	1.435(2)	N(1) · · · N(9)	2.88

H(2)-C(2)-C(1)-H(1)	- 74.7	H(5)-C(5)-C(4)-H(4)	77.4
H(1)-C(1)-C(8)-H(8ax)	- 57.1	H(1)-C(1)-C(8)-H(8ax)	59.5
H(1)-C(1)-C(8)-H(8eq)	57.9	H(1)-C(1)-C(8)-H(8eq)	- 57.3
H(8ax)-C(8)-C(7)-H(7ax)	158.6	H(6ax)-C(6)-C(7)-H(7ax)	- 159.0
H(8ax)-C(8)-C(7)-H(7eq)	43.7	H(6ax)-C(6)-C(7)-H(7eq)	- 42.6
H(8eq)-C(8)-C(7)-H(7ax)	40.7	H(6eq)-C(6)-C(7)-H(7ax)	- 39.7
H(8eq)-C(8)-C(7)-H(7eq)	- 74.2	H(6eq)-C(6)-C(7)-H(7eq)	76.6

C(2)C(3)C(4)	C(1)C(2)C(4)C(5)	63.4°
C(1)C(2)C(4)C(5)	C(1)N(9)C(5)	44.6°
C(3)N(1)O(1)	C(11)N(9)C(3)	9.2°

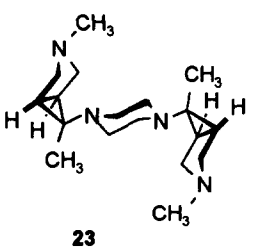
[a] Numbering of the atoms in Table 2, Figure 4 and Figure 5 was changed with respect to the deposited data.

[2] XP-Plots, Molecular Graphics from SHELXTL-Plus [27] Software Package; hydrogen atoms were omitted in Figure 5 for reasons of clarity.

The plot in Figure 4 clearly points out that the nitrogen atoms N(9) and N(1) are of trigonal pyramidal geometry with the two lone pairs directed towards each other leading to a plyers-like shape. The N ··· N distance of 2.88 Å and a ring buckle $\alpha = 44.6°$ for **13b** are remarkable in this context. Interaction of the lone pairs of N(1) and N(9) is slightly decreased by a small distortion of the molecule. The magnitude of distortion is shown by Figure 5, it is expressed exactly by the angle of the planes C(3)N(1)O(1) and C(10)N(9)C(3) which correspond to the direction of the lone pairs (Table 2). Different lenghts of oppositely located bonds (e.g. C(2)-C(3) and C(3)-C(4) or N(9)-C(1) and N(9)-C(5), Table 2) are close to significant; they may be the consequence of the observed minimization of lone pair - lone pair repulsion.

The plyers-like shape is indeed the consequence of twofold constraining of the aminopiperidine which remains in a chair conformation if only one bridge is used for constraining [e.g compounds **20** [1] or **23** [3] (3,5-C_0-bridge) or the tropanamine derivatives **24**

Figure 6



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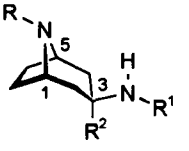

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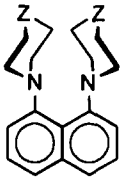
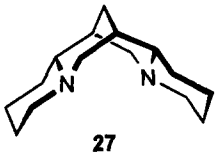
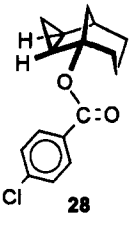


25: Z = O
26: Z = CH_2



27



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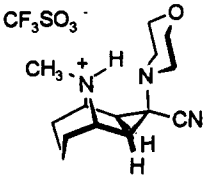

29

[28-31] (1,5-C_2-bridge)]. In the latter case a slight C(3)-flattening of the chair was found due to potential hydrogen bonding. The N lone pair arrangement of the new compounds **13** and **14** can be compared with that of the wellknown proton sponges [32] (e. g. NN-distances of 2.86 Å and 2.89 Å in diamines [33] **25** and **26**, respectively) or of additionally constrained bispidines [34] (e. g. NN-distances of 3.01 Å in α-isosparteine [35] **27**) (Figure 6). The relative rigidity of the tricyclic system in **13b** can be recognized by contrasting it with the carbocyclic analogue **28**, for which an almost identical ring buckling was found (**13b**: 63.4° and 44.6°; **28** [36]: 64° and 43°).

6. Basicity of aminocyclogranatane compounds 13b,e and 14a,b, aminocyclotropane derivative 13d and reference substance 19

Aminocyclogranatane compounds **13b,e** and **14a,b**, aminocyclotropane derivative **13d** and reference substance **19** were titrated as aqueous 0.001 molar solutions (nitrogen saturated, bidistilled water) with 0.1 molar aqueous hydrochloric acid. The pH of the aqueous solution was measured with a combined glass electrode. Titration curves showed that all endo-diamines were only monoprotonated in the aqueous system. pK_a values were determined by application of the Henderson-Hasselbalch equation [37] at the corresponding half-neutralization points ($pH = pK_a$). The pK_a-values are given in Table 3. Diaminonitriles **13b**, **13d** and diaminocarboxamides **14a,b** represent relatively strong bases. The chelating influence of the two N lone pairs is indicated by the increase of basicity of **13b** with respect to reference substance **19** by about 1.9 units.

Table 3
pK_a-Values of the diamines **13b,d,e**, **14a,b** and **19** in water (c_o = 1 mmol)[a]

Compound	13b	13d	13e	14a	14b	19
pK_a	10.73	10.18	8.85	10.50	10.07	8.82

[a] Limit of error: ± 0.08

The lower pK_a-value of norcyclogranatane nitrile **13e** can be discussed in terms of a decrease of the inductive effect and of the buttressing effect by the missing methyl group. The main location of the proton can be recognized by the change of the $^1J_{CH}$-coupling upon protonation of the amine [4,5]. This was studied exemplarily with compound **13b** and its monoprotonated species **29**. Strong increase of $^1J_{CH}$-coupling for the bridge head C-H-unit (ΔJ = 13.8 Hz) and the N-methyl group (ΔJ = 11.6 Hz) and only slight increase of $^1J_{CH}$-coupling for the morpholine N-methylene group (ΔJ = 3.6 Hz) establish clearly the protonation of **13b** at N(9) to give ammonium salt **29**.

7. Conclusion

Easily available chloroenamine precursors **11** indeed allow an access to tricyclic diaminocarbonitriles **13** with a configuration corresponding to a plyers-type arrangement of the lone pairs of the two nitrogen atoms.

8. Experimental

^{1}H NMR and ^{13}C NMR spectra were obtained with a Bruker AMX 400 spectrometer (TMS as internal standard). Microanalyses were performed using a Perkin-Elmer 2400 Elemental Analyzer. Reactions with titanium tetrachloride or N-chlorosuccinimide were run in a nitrogen atmosphere. The amines were titrated with a Metrohm Titrino SM 702 apparatus using Metrohm electrodes [combined pH-glass electrode with Ag/AgCl/KCl (3 mol·dm^{-3}) as inner reference electrode].

Enamines **9a-d** *of bicyclic azaketones* **5**, **6** *and* **7** *- general procedure*: A solution of titanium tetrachloride in toluene was dropped at -5°C with stirring within 30 min into a mixture of bicyclic azaketone **5**, **6** or **7**, secondary amine **8a,b** and toluene. Stirring was continued for 90 min at -5°C and 10 h at room temperature. Then the reaction mixture was filtered by suction and the solvent was removed in vacuo. Distillation of the residue in a Kugelrohr apparatus gave pure enamines **9a,b**; **9c** and **9d** were purified by crystallization from pentane and ether at -20°C, respectively.

9-Methyl-3-piperidino-9-azabicyclo[3.3.1]non-2-ene (**9a**): 1.32 mL (12.0 mmol) of $TiCl_4$ in 20 mL of toluene, **6**: 3.0 g (19.6 mmol); **8a**: 11.6 mL (117.5 mmol) in 150 mL of toluene. Yield: 2.93 g (68%), bp 100°C/0.001 mbar, colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.32-1.40 (m, 2H), 1.47-1.81 (m, 10H), 2.35 (s, 3H), 2.48-2.60 (m, 2H), 2.83 (m_c, 4H), 3.13 (m_c, 1H), 3.25 (m_c, 1H), 4.45 (d, $^3J_{HH}$ = 5.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 144.6 (s), 97.6 (d), 54.2 (d), 52.5 (d), 48.0 (t), 41.0 (q), 32.3 (t), 29.1 (t), 25.6 (t), 25.0 (t), 24.0 (t), 14.5 (t). Anal. Calcd for $C_{14}H_{24}N_2$: C, 76.31; H, 10.98; N, 12.71. Found: C, 76.0; H, 10.9; N, 12.6.

9-Methyl-3-morpholino-9-azabicyclo[3.3.1]non-2-ene (**9b**): 2.2 mL (20.0 mmol) of $TiCl_4$ in 25 mL of toluene, **6**: 5.0 g (32.6 mmol); **8b**: 17.76 mL (195.8 mmol) in 300 ml of toluene. Yield: 5.19 g (72%), bp 90°C/0.001 mbar, mp 34°C; ^{1}H NMR ($CDCl_3$) δ 1.28-1.39 (m, 2H), 1.42-1.50 (m, 1H), 1.51-1.86 (m, 4H), 2.33 (s, 3H), 2.40-2.49 (m, 1H), 2.82 (m_c, 4H), 3.02 (m_c, 1H), 3.24 (m_c, 1H), 3.72 (m_c, 4H), 4.44 (d, $^3J_{HH}$ = 5.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 144.9 (s), 98.8 (d), 66.8 (t), 54.8 (d), 53.0 (d), 48.2 (t), 41.7 (q), 32.8 (t), 29.5 (t), 25.8 (t), 15.2 (t). Anal. Calcd for $C_{13}H_{22}N_2O$: C, 70.23; H, 9.97; N, 12.60. Found: C, 70.3; H, 10.0; N, 12.9.

9-Benzyl-3-morpholino-9-azabicyclo[3.3.1]non-2-ene (**9c**): 2.2 mL (20.0 mmol) of $TiCl_4$ in 25 mL of toluene, **7** [38]: 7.1 g (32.6 mmol); **8b**: 17.76 mL (195.8 mmol) in 300 mL of toluene. Yield: 6.59 g (68%), bp 145°C/0.05 mbar, mp 60°C; ^{1}H NMR ($CDCl_3$) δ 1.36-1.51 (m, 3H), 1.63-1.95 (m, 4H), 2.45-2.53 (m, 1H), 2.89 (m_c, 4H), 3.12 (m_c, 1H), 3.32 (m_c, 1H), 3.64 (H_A), 3.71 (H_B) (AB-system, J_{AB} = 13.6 Hz, 2H), 3.78 (m_c, 4H), 4.50 (d, $^3J_{HH}$ = 5.4 Hz, 1H), 7.21-7.41 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 145.4 (s), 139.8 (s), 128.6 (d), 127.9 (d), 126.5 (d), 99.3 (d), 66.8 (t), 57.6 (t), 52.7 (d), 51.1 (d), 48.3 (t), 33.1 (t), 29.8 (t), 26.1 (t), 15.8 (t). Anal. Calcd for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.5; H, 8.6; N, 8.9.

8-Methyl-3-morpholino-8-azabicyclo[3.2.1]oct-2-ene (**9d**): 5.12 mL (46.6 mmol) of $TiCl_4$ in 50 mL of toluene, **5**: 11.0 g (79 mmol); **8b**: 43 mL (474 mmol) in 700 mL of toluene. Yield: 13.28 g (81%), mp 37°C; ^{1}H NMR ($CDCl_3$) δ 1.54 (m_c, 1H), 1.65 (d, 1H), 1.77 (tt, 1H), 2.05 (m_c, 2H), 2.31 (s, 3H), 2.60 (dd, 1H), 2.72 (H_A, 2H), 2.79 (H_B, 2H), 3.70 (H_X, H_Y, 4H) (ABXY-system, morpholine), 3.28 (m_c, 2H), 4.68 (d, $^3J_{HH}$ = 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 141.3 (s), 101.8 (d), 66.2 (t), 58.3 (d), 57.5 (d), 47.2 (t), 36.5 (q), 33.8 (t), 32.3 (t), 28.4 (t). Anal. Calcd for $C_{12}H_{20}N_2O$: C, 69.19; H, 9.68; N, 13.45. Found: C, 68.9; H, 9.8.; N, 13.2.

Chlorination of enamines **9a-d** *with N-chlorosuccinimide* (**10**) - *general procedure*: A solution of N-chlorosuccinimide (**10**) (0.53 g, 4.0 mmol) in dichloromethane (60 mL) was dropped at -78°C within 3 h into a solution of enamine **9** (4.0 mmol, **9a**: 0.88 g; **9b**: 0.89 g; **9c**: 1.19 g **9d**: 0.83 g) in dichloromethane (70 mL). Stirring was continued for 1 h at -78°C and then without cooling till room temperature was reached (3 h). Removal of the solvent and extraction of the residue with pentane (100 mL) gave crude chloroenamines **11a-d**. **11b** was distilled in a Kugelrohr apparatus for purification; **11c,d** were purified by recrystallization from pentane. **11a** could not be obtained as pure compound, distillation of the reaction product in a Kugelrohr apparatus at 90°C/0.001 mbar gave a mixture of **11a** and dichloroenamine **12a** (**11a** : **12a** ≈ 4 : 1). Pure dichloroenamine **12a** was obtained in an anologous way by using two equivalents of NCS (**10**) (1.06 g, 8.0 mmol) and running the chlorination at 0°C instead of -78°C.

4-Chloro-9-methyl-3-piperidino-9-azabicyclo[3.3.1]non-2-ene (**11a**) (accompanied by about 20% of dichloroenamine **12a**): Yield: 0.85 g, yellow oil; ^{1}H NMR ($CDCl_3$) characteristic signals: δ 2.59 (s, 3H), 4.30 (s, 1H), 4.45 (d, $^3J_{HH}$ = 5.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 145.0 (s), 103.9 (d), 63.5 (d), 55.2 (d), 54.0 (d), 49.0 (t), 42.6 (q), 29.5 (t), 26.2 (t), 25.6 (t), 24.5 (t), 15.2 (t).

4-Chloro-9-methyl-3-morpholino-9-azabicyclo[3.3.1]non-2-ene (**11b**): Yield: 0.77 g (75%), bp 115°C/0.01 mbar, colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.28-1.36 (m, 1H), 1.38-1.50 (m, 2H), 1.52-1.55 (m, 1H), 1.72-1.88 (m, 2H), 2.60 (s, 3H), 2.76-2.84 (m, 2H), 3.02-3.09 (m, 2H), 3.48 (m_c, 1H), 3.51 (m_c, 1H), 3.80 (m_c, 4H), 4.24 (s, 1H), 4.76 (d, $^3J_{HH}$ = 5.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 144.6 (s), 104.6 (d), 66.6 (t), 63.3 (d), 54.9 (d), 53.2 (d), 48.3 (t), 42.5 (q), 29.8 (t), 26.4 (t), 15.1 (t). Anal. Calcd for $C_{13}H_{21}ClN_2O$: C, 60.81; H, 8.24; N, 10.91. Found: C, 60.5; H, 8.2; N, 10.8.

9-Benzyl-4-chloro-3-morpholino-9-azabicyclo[3.3.1]non-2-ene (**11c**): Yield: 1.24 g (94%), mp 69°C; ^{1}H NMR ($CDCl_3$) δ 1.25-1.30 (m, 1H), 1.41-1.50 (m, 2H), 1.53-1.59 (m, 1H), 1.70-1.90 (m, 2H), 2.81 (m_c, 2H), 3.07 (m_c, 2H), 3.44 (m_c, 1H), 3.57 (m_c, 1H), 3.82 (m_c, 4H), 3.91 (H_A), 4.01 (H_B) (AB-system, J_{AB} = 14.1 Hz, 2H), 4.28 (s, 1H), 4.77 (d, $^3J_{HH}$ = 5.5 Hz, 1H), 7.20-7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 145.0 (s), 139.9 (s), 128.3 (d), 127.9 (d), 126.5 (d), 105.0 (d), 66.6 (t), 61.8 (d), 57.6 (t), 53.7 (d), 52.4 (d), 48.3 (t), 30.5 (t), 27.0 (t), 15.6 (t). Anal. Calcd for $C_{19}H_{25}ClN_2O$: C, 68.64; H, 7.59; N, 8.43. Found: C, 68.7; H, 7.5; N, 8.6.

4-Chloro-8-methyl-3-morpholino-8-azabicyclo[3.2.1]oct-2-ene (**11d**): Yield: 0.65 g (67%), colorless crystals; ^{1}H NMR (CD_3CN) δ 1.31-1.40 (m, 1H), 1.49 (m_c, 1H), 1.90-2.08 (m, 2H),

2.24 (s, 3H), 3.38-3.41 (m, 2H), 2.59-2.66 (m, 2H), 2.83-2.90 (m, 2H), 3.63 (m_c, 4H), 4.35 (d, $^3J_{HH}$ = 1.8 Hz, 1H), 4.95 (d, $^3J_{HH}$ = 6.2 Hz, 1H); ^{13}C NMR (CD_3CN) δ 142.4 (s), 109.8 (d), 68.2 (d), 67.2 (t), 60.6 (d), 60.5 (d), 48.8 (t), 40.1 (q), 30.3 (t), 25.6 (t). Anal. Calcd for $C_{12}H_{19}ClN_2O$: C, 59.37; H, 7.89; N, 11.54. Found: C, 59.6; H, 7.8; N, 11.5.

2,4-Dichloro-9-methyl-3-piperidino-9-azabicyclo[3.3.1]non-2-ene (**12a**): Yield: 1.0 g (87%), bp 95°C/0.001mbar, light yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.81-1.80 (m, 12H), 2.65 (s, 3H), 2.85-2.91 (m, 2H), 3.12-3.17 (m, 2H), 3.37 (m_c, 2H), 4.48 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 141.2 (s), 122.5 (s), 63.1 (d), 61.8 (d), 58.9 (d), 50.5 (t), 42.7 (q), 29.0 (t), 26.2 (t), 24.3 (t), 24.1 (t), 15.3 (t). Anal. Calcd for $C_{14}H_{22}Cl_2N_2$: C, 58.13; H, 7.67; N, 9.68. Found: C, 58.1; H, 7.7; N, 9.8.

Tricyclic carbonitriles **13a-d** - *general procedure*: A solution of sodium cyanide (0.49 g, 10.0 mmol) in water (3 mL) was added to a solution of chloroenamine **11** [4.0 mmol, **11a**: 1.31 g (accompanied by 20% of **12a**; corresponds to 4.0 mmol of **11a**); **11b**: 1.03 g; **11c**: 1.33 g; **11d**: 0.97 g] and benzyltriethylammonium chloride (0.92 g, 4.0 mmol) in acetonitrile (30 mL) at -20°C. The mixture was stirred 2 h at 0°C and 10 h at 20°C. Filtration, evaporation of the filtrate and extraction of the residue with pentane (3 x 30 mL; in the case of **13a,b,d**) or chloroform (3 x 30 mL; in the case of **13c**) gave crude tricyclic carbonitriles **13a-d**. Purification was performed by distillation in a Kugelrohr apparatus and subsequent recrystallization in the case of **13a-c** (ether) or **13d** (ether/pentane 1:1; -20°C).

1α,2α,3β,4α,5α-9-Methyl-3-piperidino-9-azatricyclo[3.3.1.0^{2,4}]nonane-3-carbonitrile (**13a**): Yield: 0.47 g (46%); mp 91°C, bp 100°C/0.001 mbar; ^{1}H NMR (C_6D_6) δ 0.72 (H_B, $H_{B'}$, 2H), 1.20 (H_D, 1H), 1.40 (H_M, $H_{M'}$, 2H), 1.46 (H_E, 1H), 1.59 (H_C, $H_{C'}$, 2H), 2.81 (H_A, $H_{A'}$, 2H) (AA'BB'CC'DEMM'-system, $^4J_{AA'}$ = 1.0 Hz, $^3J_{AB}$ = $^3J_{A'B'}$ = 2.45 Hz, $^3J_{AC}$ = $^3J_{A'C'}$ = 3.2 Hz, $^4J_{AD}$ = $^4J_{A'D}$ = 0.9 Hz, $^4J_{BB'}$ = 2.0 Hz, $^2J_{BC}$ = $^2J_{B'C'}$ = 12.9 Hz, $^3J_{BD}$ = $^3J_{B'D}$ = 1.0 Hz, $^3J_{BE}$ = $^3J_{B'E}$ = 6.2 Hz, $^3J_{CD}$ = $^3J_{C'D}$ = 6.0 Hz, $^3J_{CE}$ = $^3J_{C'E}$ = 12.15 Hz, $^2J_{DE}$ = 13.5 Hz, $^3J_{AM}$ = $^3J_{A'M'}$ < 0.8 Hz), 2.19 (s, 3H), 1.43 (m_c, 6H), 2.57 (m_c, 4H) (piperidine); ^{13}C NMR ($CDCl_3$) δ 118.9 (t, $^3J_{CH}$ = 4.8 Hz), 57.6 (d), 51.5 (t), 44.8 (s), 33.9 (d, $^1J_{CH}$ = 171.8 Hz), 32.5 (q), 25.8 (t), 24.1 (t), 21.4 (t), 17.1 (t). Anal. Calcd for $C_{15}H_{23}N_3$: C, 73.43; H, 9.45; N, 17.12. Found: C, 73.5; H, 9.5; N, 17.1.

1α,2α,3β,4α,5α-9-Methyl-3-morpholino-9-azatricyclo[3.3.1.0^{2,4}]nonane-3-carbonitrile (**13b**): Yield: 0.42 g (42%); mp 115°C, bp 110°C/0.01 mbar; ^{1}H NMR (C_6D_6) δ 0.67 (H_B, $H_{B'}$, 2H), 1.18 (H_D, 1H), 1.34 (H_M, $H_{M'}$, 2H), 1.43 (H_E, 1H), 1.56 (H_C, $H_{C'}$, 2H), 2.72 (H_A, $H_{A'}$, 2H) (AA'BB'CC'DEMM'-system, $^4J_{AA'}$ = 0.95 Hz, $^3J_{AB}$ = $^3J_{A'B'}$ = 2.0 Hz, $^3J_{AC}$ = $^3J_{A'C'}$ = 3.25 Hz, $^4J_{AD}$ = $^4J_{A'D}$ = 0.9 Hz, $^4J_{BB'}$ = 1.8 Hz, $^2J_{BC}$ = $^2J_{B'C'}$ = 13.2 Hz, $^3J_{BD}$ = $^3J_{B'D}$ = 1.1 Hz, $^3J_{BE}$ = $^3J_{B'E}$ = 6.15 Hz, $^3J_{CD}$ = $^3J_{C'D}$ = 6.1 Hz, $^3J_{CE}$ = $^3J_{C'E}$ = 12.4 Hz, $^2J_{DE}$ = 13.5 Hz, $^3J_{AM}$ = $^3J_{A'M'}$ < 0.8 Hz), 2.11 (s, 3H), 2.50 (broad, 4H), 3.53 (m_c, 4H) (morpholine); ^{13}C NMR ($CDCl_3$) δ 118.7 (t, $^3J_{CH}$ = 4.6 Hz), 66.9 (t, $^1J_{CH}$ = 143.5 Hz), 57.3 (d, $^1J_{CH}$ = 144.3 Hz), 50.3 (t, $^1J_{CH}$ = 134.2 Hz), 44.0 (s), 33.6 (d, $^1J_{CH}$ = 172.6 Hz), 31.8 (q, $^1J_{CH}$ = 132.4 Hz), 20.3 (t), 16.9 (t). Anal. Calcd for $C_{14}H_{21}N_3O$: C, 67.98; H, 8.56; N, 16.99. Found: C, 68.2; H, 8.5; N, 17.0.

1α,2α,3β,4α,5α-9-Benzyl-3-morpholino-9-azatricyclo[3.3.1.0^{2,4}]nonane-3-carbonitrile (**13c**): Yield: 0.97 g (75%); mp 170°C, bp 170°C/0.01 mbar; ^{1}H NMR (C_6D_6) δ 0.83 (H_B, $H_{B'}$, 2H), 1.38 (H_D, 1H), 1.50 (H_M, $H_{M'}$, 2H), 1.60 (H_E, 1H), 1.79 (H_C, $H_{C'}$, 2H), 3.01 (H_A, $H_{A'}$, 2H) (AA'BB'CC'DEMM'-system, $^4J_{AA'}$ = 1.0 Hz, $^3J_{AB}$ = $^3J_{A'B'}$ = 2.2 Hz, $^3J_{AC}$ = $^3J_{A'C'}$ = 3.2 Hz, $^4J_{BB'}$ = 1.8 Hz, $^2J_{BC}$ = $^2J_{B'C'}$ = 13.8 Hz, $^3J_{BD}$ = $^3J_{B'D}$ = 1.2 Hz, $^3J_{BE}$ = $^3J_{B'E}$ = 6.8 Hz, $^3J_{CD}$ = $^3J_{C'D}$ = 6.2 Hz, $^3J_{CE}$ = $^3J_{C'E}$ = 12.65 Hz, $^2J_{DE}$ = 13.7 Hz, $^3J_{AM}$ = $^3J_{A'M'}$ < 0.8 Hz), 2.1-3.0 (broad, 4H), 3.84 (m_c, 4H) (morpholine), 3.75 (s, 2H), 7.30 (t, 1H), 7.38 (t, 2H), 7.60 (d, 2H); ^{13}C NMR ($CDCl_3$) δ 139. 6 (s), 128.4 (d), 127.9 (d), 126.7 (d), 117.8 (t, $^3J_{CH}$ = 5.0 Hz), 66.2 (t), 55.4 (d), 50.9 (t), 49.7 (t), 45.7 (s), 33.1 (d, $^1J_{CH}$ = 169.9 Hz), 20.7 (t), 16.6 (t). Anal. Calcd for $C_{20}H_{25}N_3O$: C, 74.26; H, 7.80; N, 13.0. Found: C, 74.2; H, 7.8; N, 13.0.

1α,2α,3β,4α,5α-8-Methyl-3-morpholino-8-azatricyclo[3.3.1.0^{2,4}]octane-3-carbonitrile (**13d**): Yield: 0.39 g (42%); mp 70°C, bp 110-115°C/0.01 mbar; ^{1}H NMR (C_6D_6) δ 0.80 (H_B, $H_{B'}$, 2H), 0.99 (H_M, $H_{M'}$, 2H), 1.37 (H_C, $H_{C'}$, 2H), 2.86 (H_A, $H_{A'}$, 2H) (AA'BB'CC'MM'-system, $^3J_{AB}$ = $^3J_{A'B'}$ = 0.9 Hz, $^3J_{AC}$ = $^3J_{A'C'}$ = 4.0 Hz, $^3J_{BB'}$ = 8.9 Hz, $^2J_{BC}$ = $^2J_{B'C'}$ = -12.0 Hz, $^3J_{BC'}$ = $^3J_{B'C}$ = 4.0 Hz, $^3J_{CC'}$ = 10.8 Hz, $^3J_{MM'}$ = 7.0 Hz, $^3J_{AM}$ = $^3J_{A'M'}$ < 0.8 Hz), 1.68 (s, 3H), 2.53 (m_c, 4H), 3.59 (m_c, 4H) (morpholine); ^{13}C NMR ($CDCl_3$) δ 120.5 (t, $^3J_{CH}$ = 4.6 Hz), 67.2 (t), 61.0 (d), 49.7 (t), 41.4 (s), 33.9 (d, $^1J_{CH}$ = 175.0 Hz), 33.3 (q), 25.3 (t). Anal. Calcd for $C_{13}H_{19}N_3O$: C, 66.92; H, 8.21; N, 18.01. Found: C, 66.8; H, 8.1; N, 17.9.

1α,2α,3β,4α,5α-3-Morpholino-9-azatricyclo[3.3.1.0^{2,4}]nonane-3-carbonitrile (**13e**): A solution of N-benzyl derivative **13c** (0.30 g, 0.93 mmol) in methanol (75 mL) was saturated with hydrogen in the presence of palladium charcoal catalyst (10% Pd, 0.1 g, 0.09 mmol) and stirred for 16 h at room temperature. The catalyst was removed by filtration and the solvent was evaporated in vacuo. The residue was distilled in a Kugelrohr apparatus at 95°C/0.01 mbar to give compound **13e** as colorless crystals. Yield: 0.20 g (92%); mp 136°C; ^{1}H NMR (C_6D_6) δ 1.17 (H_{B1}, $H_{B'1}$, 2H), 1.30 (H_D, 1H), 1.33 (H_E, 1H), 1.34 (H_M, $H_{M'}$, 2H), 1.69 (H_C, $H_{C'}$, 2H), 3.00 (H_{A1}, $H_{A'1}$, 2H) (AA'BB'CC'DEMM'-system, $^4J_{AA'}$ = 1.0 Hz, $^3J_{AB}$ = $^3J_{A'B'}$ = 3.0 Hz, $^3J_{AC}$ = $^3J_{A'C'}$ = 3.3 Hz, $^4J_{AD}$ = $^4J_{A'D}$ = 1.0 Hz, $^4J_{BB'}$ = 1.8 Hz, $^2J_{BC}$ = $^2J_{B'C'}$ = 12.5 Hz, $^3J_{BD}$ = $^3J_{B'D}$ = 1.2 Hz, $^3J_{BE}$ = $^3J_{B'E}$ = 5.5 Hz, $^3J_{CD}$ = $^3J_{C'D}$ = 8.7 Hz, $^3J_{CE}$ = $^3J_{C'E}$ = 9.8 Hz, $^2J_{DE}$ = 14.7 Hz, $^3J_{AM}$ = $^3J_{A'M'}$ < 0.8 Hz), 1.94 (H_{A2}, 2H), 2.60 (H_{B2}, 2H), 3.00 (H_X, 2H), 3.48 (H_Y, 2H) (ABXY-system, morpholine); ^{13}C NMR ($CDCl_3$) δ 116.1 (t, $^3J_{CH}$ = 4.7 Hz), 66.4 (t), 55.4 (d), 50.7 (t), 40.6 (s), 32.2 (d, $^1J_{CH}$ = 172.5 Hz), 28.9 (t), 17.1 (t). Anal. Calcd for $C_{13}H_{19}N_3O$: C, 66.92; H, 8.21; N, 18.01. Found: C, 66.6; H, 8.1; N, 17.6.

Tricyclic carboxamides **14a-c** *- general procedure:* Tricyclic carbonitrile **13** (0.8 mmol, **13a**: 0.20 g; **13b**: 0.20 g; **13c**: 0.26 g) was added to cooled (-20°C) concentrated sulfuric acid and heated to 100°C for 1h. The cooled solution was poured on ice (120 g). Addition of aqueous solution of sodium hydroxide (5M) till pH 12 and extraction with ether (3 x 50 mL) gave crude carboxamides **14a-c** which were purified by distillation in a Kugelrohr apparatus and crystallization from ether.

1α,2α,3β,4α,5α-9-Methyl-3-piperidino-9-azatricyclo[3.3.1.0^{2,4}]nonane-3-carboxamide (**14a**): Yield: 0.12 g (57%); mp 206°C, bp 110°C/0.001 mbar; ^{1}H NMR (C_6D_6) δ 0.87 (H_B, $H_{B'}$, 2H), 1.26 (H_D, 1H), 1.68 (H_C, $H_{C'}$, 2H), 1.96 (H_E, 1H), 2.09 (H_M, $H_{M'}$, 2H), 2.99 (H_A, $H_{A'}$, 2H) (AA'BB'CC'DEMM'-system, $^3J_{AB} = {}^3J_{A'B'} = 2.0$ Hz, $^3J_{AC} = {}^3J_{A'C'} = 3.0$ Hz, $^4J_{AD} = {}^4J_{A'D} = 0.9$ Hz, $^4J_{BB'} = 1.6$ Hz, $^2J_{BC} = {}^2J_{B'C'} = 13.8$ Hz, $^3J_{BD} = {}^3J_{B'D} = 1.0$ Hz, $^3J_{BE} = {}^3J_{B'E} = 6.4$ Hz, $^3J_{CD} = {}^3J_{C'D} = 6.4$ Hz, $^3J_{CE} = {}^3J_{C'E} = 12.5$ Hz, $^2J_{DE} = 13.4$ Hz, $^3J_{AM} = {}^3J_{A'M'} < 0.8$ Hz), 1.02 (m_c, 1H), 1.28 (m_c, 2H), 1.42 (m_c, 2H), 1.62 (m_c, 1H), 2.54 (t, 2H), 2.74 (d, 2H) (piperidine), 2.22 (s, 3H), 5.70 (broad, 1H), 7.80 (broad, 1H); ^{13}C NMR ($CDCl_3$) δ 180.3 (t, $^3J_{CH} = 3.3$ Hz), 57.3 (d), 54.6 (s), 50.3 (t), 35.5 (d, $^1J_{CH} = 172.0$ Hz), 32.2 (q), 28.0 (t), 25.0 (t), 20.2 (t), 16.8 (t). Anal. Calcd for $C_{15}H_{25}N_3O$: C, 68.40; H, 9.57; N, 15.95. Found: C, 68.2; H, 9.5; N, 15.9.

1α,2α,3β,4α,5α-9-Methyl-3-morpholino-9-azatricyclo[3.3.1.0^{2,4}]nonane-3-carboxamide (**14b**): Yield: 0.12 g (58%); mp 232°C, bp 150°C/0.01 mbar; ^{1}H NMR (C_6D_6) δ 0.86 (H_{B1}, $H_{B'1}$, 2H), 1.24 (H_D, 1H), 1.64 (H_C, $H_{C'}$, 2H), 1.92 (H_E, 1H), 2.07 (H_M, $H_{M'}$, 2H), 2.92 (H_{A1}, $H_{A'1}$, 2H) (AA'BB'CC'DEMM'-system, $^3J_{AB} = {}^3J_{A'B'} = 2.0$ Hz, $^3J_{AC} = {}^3J_{A'C'} = 3.0$ Hz, $^4J_{AD} = {}^4J_{A'D} = 0.9$ Hz, $^4J_{BB'} = 1.7$ Hz, $^2J_{BC} = {}^2J_{B'C'} = 13.8$ Hz, $^3J_{BD} = {}^3J_{B'D} = 1.0$ Hz, $^3J_{BE} = {}^3J_{B'E} = 6.4$ Hz, $^3J_{CD} = {}^3J_{C'D} = 6.4$ Hz, $^3J_{CE} = {}^3J_{C'E} = 12.5$ Hz, $^2J_{DE} = 13.4$ Hz, $^3J_{AM} = {}^3J_{A'M'} < 0.8$ Hz), 2.19 (s, 3H), 2.29 (H_{A2}, 2H), 2.80 (H_{B2}, 2H), 3.27 (H_X, 2H), 3.62 (H_Y, 2H) (ABXY-system, morpholine), 5.95 (broad, 1H), 7.70 (broad, 1H); ^{13}C NMR ($CDCl_3$) δ 179.1 (t, $^3J_{CH} = 3.2$ Hz), 68.5 (t), 57.0 (d), 53.9 (s), 49.3 (t), 35.1 (d, $^1J_{CH} = 172.9$ Hz), 32.0 (q), 19.9 (t), 16.3 (t). Anal. Calcd for $C_{14}H_{23}N_3O_2$: C, 63.37; H, 8.74; N, 15.84. Found: C, 63.6; H, 8.6; N, 15.7.

1α,2α,3β,4α,5α-9-Benzyl-3-morpholino-9-azatricyclo[3.3.1.0^{2,4}]nonane-3-carboxamide (**14c**): Yield: 0.23 g (84%); mp 173°C, bp 150°C/0.01 mbar; ^{1}H NMR ($CDCl_3$) δ 1.08 (H_{B1}, $H_{B'1}$, 2H), 1.51 (H_D, 1H), 2.22 (H_M, $H_{M'}$, 2H), 2.15 (H_E, 1H), 2.01 (H_C, $H_{C'}$, 2H), 3.20 (H_{A1}, $H_{A'1}$, 2H) (AA'BB'CC'DEMM'-system, $^3J_{AB} = {}^3J_{A'B'} = 2.1$ Hz, $^3J_{AC} = {}^3J_{A'C'} = 3.0$ Hz, $^4J_{AD} = {}^4J_{A'D} = 1.0$ Hz, $^4J_{BB'} = 1.5$ Hz, $^2J_{BC} = {}^2J_{B'C'} = 13.5$ Hz, $^3J_{BD} = {}^3J_{B'D} = 1.2$ Hz, $^3J_{BE} = {}^3J_{B'E} = 6.5$ Hz, $^3J_{CD} = {}^3J_{C'D} = 6.1$ Hz, $^3J_{CE} = {}^3J_{C'E} = 12.7$ Hz, $^2J_{DE} = 13.1$ Hz, $^3J_{AM} = {}^3J_{A'M'} < 0.8$ Hz), 2.25 (H_{A2}, 2H), 3.12 (H_{B2}, 2H), 3.40 (H_X, 2H), 3.75 (H_Y, 2H) (ABXY-system, morpholine), 3.76 (s, 2H), 7.29 (t, 1H), 7.42 (t, 2H), 7.59 (d, 2H), 6.70 (s, broad, 1H), 7.90 (s, broad, 1H); ^{13}C NMR ($CDCl_3$) δ 179.0 (t, $^3J_{CH} = 3.8$ Hz), 138.0 (s), 130.7 (d), 127.8 (d), 127.1 (d), 68.3 (t), 55.4 (d), 54.0 (s), 50.1 (t), 47.7 (t), 34.7 (d, $^1J_{CH} = 172.0$ Hz), 20.5 (t), 16.1 (t). Anal. Calcd for $C_{20}H_{27}N_3O_2$: C, 70.35; H, 7.97; N, 12.31. Found: C, 70.2; H, 7.9; N, 12.3.

1α,2α,3β,4α,5α-3-Cyano-9-methyl-3-morpholino-9-azoniatricyclo[3.3.1.0^{2,4}]nonane trifluoromethane sulfonate (**29**): A solution of trifluoromethane sulfonic acid (0.1 M in 2-propanol; 8.00 mL) was added to a solution of tricyclic carbonitrile **13b** (198 mg, 0.8 mmol) in methanol (40 mL). The solution was stirred at room temperature for 30 min. Evaporation of the solvent in vacuo, trituration of the residue with ether (5 mL) and drying led to pure ammonium salt **29**. Yield: 297 mg (93%); mp 229°C (decomp.). ^{13}C NMR (CD_3CN/D_2O 4:1) δ 121.2 (q), 115.2 (t, $^3J_{CH} = 4.6$ Hz), 66.8 (t, $^1J_{CH} = 146.0$ Hz), 60.8 (d, $^1J_{CH} = 158.1$ Hz), 51.8 (t, $^1J_{CH} = 137.8$ Hz), 42.8 (s), 30.9 (q, $^1J_{CH} = 144.0$ Hz), 29.0 (d, $^1J_{CH} = 185.7$ Hz), 20.4 (t), 14.4 (t). Anal. Calcd for $C_{15}H_{22}F_3N_3O_4S$: C, 45.33; H, 5.58; N, 10.57. Found: C, 45.3; H, 5.5; N, 10.2.

X-Ray crystal structure analysis [39] *of 1α,2α,3β,4α,5α-9-methyl-3-morpholino-9-azatricyclo[3.3.1.0^{2,4}]nonane-3-carbonitrile* (**13b**): Single crystals of **13b** were obtained by crystallization from ether.

Crystal data: $C_{14}H_{21}N_3O$, F.W. = 247.3; monoclinic, space group $P2_1/c$; a = 11.376(2), b = 8.939(2), c = 14.148(3) Å; α = γ = 90, β = 109.29(3)°; V = 1357.9(5) Å^3; Z = 4; D_x = 1.210 g · cm^{-3}; crystal size 0.30 x 0.25 x 0.15 mm; colourless prisms. Data collection: Diffractometer Siemens P4, temperature: 203(2) K; monochromatized Mo-K_α radiation; 2121 independent reflections with 1.90 < Θ < 23.99° [ω scan, scan speed 3.00 - 45.00° · min^{-1}], no absorption correction. Structure solution and refinement: The structure was solved by the direct method using SHELXS-86 [40] and refined by full matrix least squares analysis on F^2 using SHELXL-93 [41]. All non-H atoms are refined anisotropically and hydrogen atoms are located from difference electron density maps and refined isotropically. 1633 reflections with F > 4 σ(F) were used, 247 variables, weighting scheme $w^{-1} = \sigma^2(F_o^2) + (0.0676P)^2 + 0.0147P$ where $P = (F_o^2 + 2F_c^2) / 3$, goodness of fit 1.029, final R indices (obs. data) R1 = 0.0392, wR2= 0.0985.

Titration of diamines **13b,d,e, 14a,b** *and* **19** *with hydrochloric acid*: Freshly distilled diamines **13**, **14** or **19** (0.09 mmol; **13b**: 22.3 mg; **13d**: 21.0 mg; **13e**: 21.0 mg; **14a**: 23.7 mg; **14b**: 23.9 mg; **19**: 18.6 mg) were dissolved in water (90 mL, bidestilled and saturated with nitrogen) under stirring at room temperature for 24 h. Each 30 mL of the solution were titrated by aqueous 0.1 M hydrochloric acid.

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