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FUNCTIONALIZED CHLOROENAMINES IN AMINOCYCLOPROPANE SYNTHESIS - VI.[1] CHLOROTETRAHYDROPYRIDINES AS A BASIS FOR THE SYNTHESIS OF 3-AZABICYCLO[3.1.0]HEXANE DERIVATIVES

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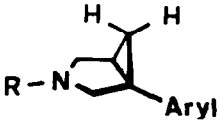
Abstract: Enamines **8a-e** could be chlorinated by equimolar amounts of N-chlorosuccinimide (**9**) generating monochloroenamines **10a-e**; **10a** and **10d** were isolated as pure substances. Two equivalents of **9** afforded the dichloroenamines **12a,c** from **8a,c**. Interaction of the chlorinated enamines **10a-e** and **12a,c** with cyanide gave morpholino-azabicyclohexane derivatives. **10a-d**, thereby, led to exo-cyano-isomers **11a-c**; **12a,c** generated endo-cyano compounds **13a,c**. In the case of the ethoxycarbonylated chloroenamine **10e** a mixture of diastereomeric products **11e** and **14e** resulted from the analogous reaction. Reduction of **11a** and **14e** with lithium aluminum hydride produced a pair of diastereomeric triamines **15** and **16**. A tricyclic diazasystem **19** was formed from the reaction of cyanide with the carbamoylated chloroenamine **18**. Monochloroenamine **10a** and dichloroenamine **12a** showed a significant mutagenic behaviour in the Ames test.

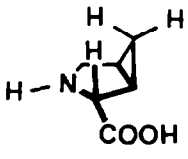
The azabicyclo[3.1.0]hexane system is reported in the literature to be the basis for some active compounds. Formula **1** - **4** represent derivatives of this type which are of interest due to their biological activities.



1

Analgetic[2] and antidepressant[3] activity

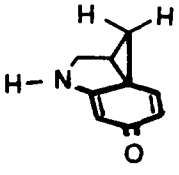
Bicifadine: Aryl= 4-Methylphenyl, R = H



2

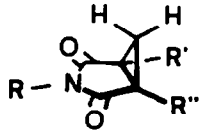
Gametocidic activity in cereals[4]

Methanoproline



3

Simplified A-unit of CC - 1065; antitumor activity[5]



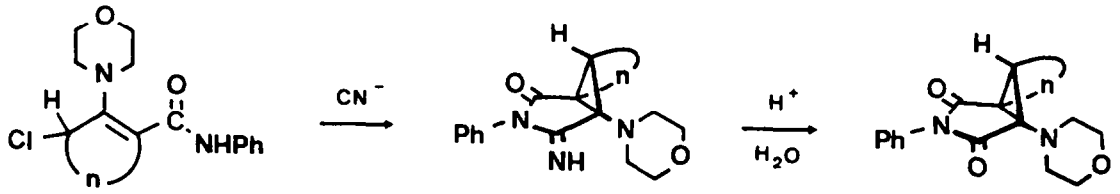
4

Fungicidic activity[6]

Procymidone: R', R'' = H, R = $C_6H_3Cl_2$

aromatase inhibitor[7], R = Bu, R' = H, R'' = H_2N-C_6H_4-

Most of these compounds have been prepared by a [2+1]-cycloaddition reaction to give a cyclopropane-1,2-dicarboxylic acid, formation of an imide and a subsequent reduction producing the pyrrolidine unit. An easy access to 1-morpholino-3-aza-bicyclo[3.1.0]hexanedione **7**, a Procymidone analogue, was found on the basis of a carbamoylated chloroenamine **5** by a two step procedure.[8,9]



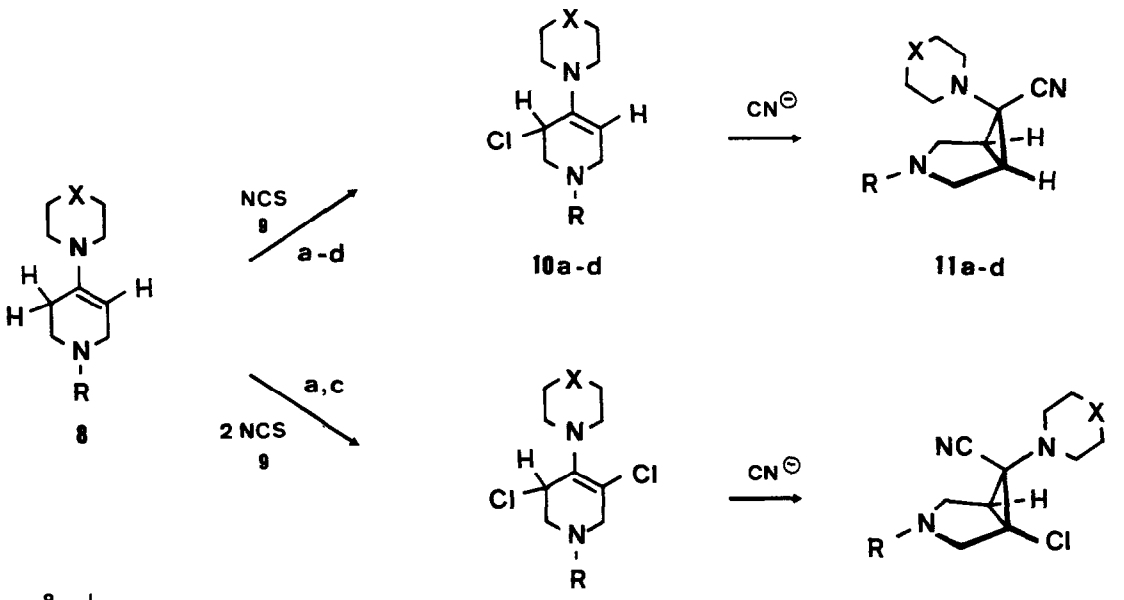
5 **6** **7**

A synthesis of the 6-amino-3-azabicyclo[3.1.0]hexane system also could be expected by the reaction of nucleophiles with suitable chlorinated 4-amino--tetrahydropyridines via a 1,3-elimination. Starting materials of this type should be obtained easily by chlorination of enamines **8** or **17**. Cyanide was used as a typical nucleophile to test the cyclopropane forming process.

6-AMINO-3-AZABICYCLO[3.1.0]HEXANE-CARBONITRILES 11, 13 AND 14

Monochlorination of enamine **8a,d** was achieved by the reaction with an equimolar amount of N-chlorosuccinimide (**9**) in dichloromethane at -20°C to give pure, crystalline **10a** in 86% yield and **10d** in 73% yield, respectively. Dichloroenamines **12a,c** were accessible in 90% and 76% yield from **8a,c** and **9** in a ratio of 1 : 2 at -15°C in the same solvent. **10a,d** and **12a,c** were characterized by the ^{13}C NMR spectra [allyl-unit: **10a**: 144.2 (s), 103.6 (d), 54.5 (d, $^{1}J_{CH}$ = 152 Hz); **10d**: 143.2 (s), 102.3 (d), 53.1 (d, $^{1}J_{CH}$ = 150 Hz); **12a**: 139.2 (s), 120.5 (s), 55.0 (d, $^{1}J_{CH}$ = 152 Hz); **12c**: 140.7 (s), 120.4 (s), 57.1 (d, $^{1}J_{CH}$ = 151 Hz)]. The ^{1}H NMR data are in accordance with the chloroenamine structure of **10a,d** and **12a,c**. Two signals (**10a**: 4.68 ppm and 4.78 ppm; **10d**: 4.55 ppm and 4.76 ppm) represent the chloroally moiety of **10a,d**. In **12a,c** only one hydrogen atom is indicated in the low field region (**12a**: 4.70 ppm, **12c**: 4.82 ppm; H_X of an ABX-system). An alternative chlorination of the 2- or 6-methylene moiety of the tetrahydropyridine system is excluded by the formation of a covalent bonded chloro compound (e.g. **10a,d** and **12a,c** are soluble in pentane; α-chloroamines are known to be ionic in structure[10]).

A 1,3-ring closure process forming a bicyclic system indeed was induced by the interaction of cyanide with the chlorinated enamines **10a**, **10d**, **12a** and **12c**, respectively. Thus bicyclic nitriles **11a** (74.5% yield) and **11d** (77%

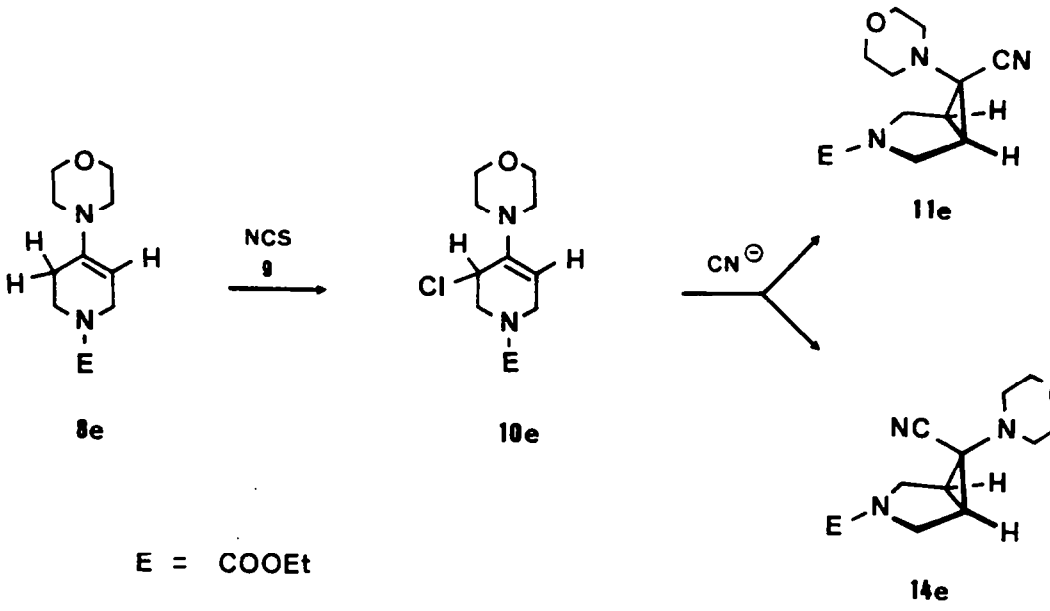


8, 10–14	a	b	c	d	e
X	O	CH_2	NMe	O	O
R	Me	Me	Me	$CH_2C_6H_5$	COOEt

yield) were obtained from chloroenamines **10a,d** and sodium cyanide in aceto-nitrile - water. Chloro-substituted bicyclic nitriles **13a,c** resulted from dichloroenamines **12a,c** and cyanide by a similar procedure (58% and 55% yield, respectively; water as a solvent). Isolation of the chloroenamines **10a,d** is not necessary for the preparation of **11a,d** as shown by a one-pot procedure starting from enamines **8a,d**. Analogously the piperidino- and the piperazino enamines **8b** and **8c** directly were converted to 3-aza-bicyclo[3.1.0]hexane compounds **11b** and **11c** (overall yields for the one-pot synthesis: **11a**: 61%, **11b**: 40%, **11c**: 53%, **11d**: 79%). All bicyclic products isolated from these reactions proved to be sterically pure compounds. In the case of **8e**, however, the same two step reaction sequence led to a mixture of two diastereomeric bicyclic nitriles **11e** and **14e**. The mixture of the two nitriles could be separated by fractionated crystallization to give pure compounds **11e** (31% yield) and **14e** (38% yield).

CONFIGURATION OF THE 6-AMINO-3-AZA-BICYCLO[3.1.0]HEXANE CARBONITRILES 11, 13 AND 14

The configuration of the bicyclic derivatives **11**, **13** and **14** was established by ^1H and ^{13}C NMR spectroscopy and in one case by chemical correlation, too.



^{1}H NMR spectroscopy was used to detect the configuration of **11a**, **11c-e**, **13a** and **14e** via observation of the dynamics of the six-membered heterocycle (see Table 1). Dynamics of an N-heterocycle which is connected to the C_1-bridge of an [n.1.0]bicyclic system are influenced by the steric environment: Strong hindrance is observed for an endo-N-heterocyclic system and less hindrance is found for an exo-N-heterocyclic system (see ref.[1,9,11-14] and references cited therein).

A typical "quasi-triplet" ^{1}H NMR signal-type of morpholine at room temperature is in accordance with less hindrance of the dynamics. Such a type of signals is found for the OCH_2 group in **13a** and **14e** and the NCH_2 unit of **14e**. **13a** is an asymmetric compound; the NCH_2 moiety, therefore, appears as an AB-system, in which each line is split into the typical room temperature morpholine "quasi-triplet". $\Delta G^{\ddagger}$-values of 47.7-48.1 kJ/mol for **13a** and 44.3-44.6 kJ/mol for **14e** were obtained from the temperature dependency of the OCH_2 ^{1}H NMR signals in dichloromethane. These values clearly are characteristic of morpholine in the exo-position of a [3.1.0]bicyclic system.[9]

In contrast to this an endo-position of the six-membered heterocycle can be assumed for **11a,c-e** from the ^{1}H NMR spectra at room temperature: Thus the morpholino moiety of **11a,d,e** appears as broad unsplit signals indicating coalescence phenomena. A similar behaviour was found for the piperazino system in **11c**. Observation of the temperature dependency of the corresponding signals gave $\Delta G^{\ddagger}$-values ranging between 58.4 and 64.6 kJ/mol. The dynamics of the endo six-membered heterocyclic system obviously are not as strongly hin-

dered as expected for a [3.1.0]bicyclic system (e. g. see ref. [9,13]). The magnitude of these values, however, should be sufficient enough to allow a correct assignment of the endo-amino configuration. Compounds **11b** and **13c** gave low temperature ^{1}H NMR spectra in which the signals of the six-membered heterocycle leading to coalescence could not be analyzed totally. In these two cases ^{1}H NMR spectroscopy is not suitable for establishing the configuration.

Table 1 $\Delta G^{\ddagger}$-Values of the Dynamics of the Six-Membered Heterocycle on the Basis of ^{1}H NMR Data (200 MHz) and Coalescence Temperatures (T_c) of the Bicyclic Compounds **11a,c-e**, **13a** and **14e**.

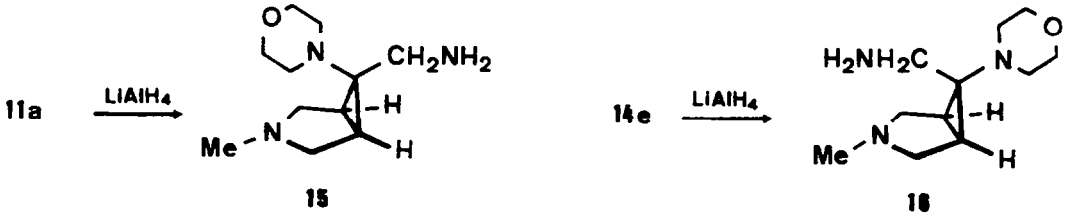
	T [°C]	Group	$H_{A1/2}$[a]	H_{B1}	H_{B2}[a]	$^2J_{HH}$ [Hz]	T_c [°C]	Solvent	$\Delta G^{\ddagger}$[b] Maximum	Minimum
11a	-30	OCH_2	3.49	3.17[c]		11.5	16	$CD_3C_6D_5$	58.5	
	-30	NCH_2	2.51[c]	1.73		11.5	25		58.4	
11c	-43	NCH_2	2.63[c]	1.95		11.2	52	$CD_3C_6D_5$	64.3	
	-43	NCH_2	2.33	1.73[c]		11.2	52		64.6	
11d	-30	OCH_2	3.52	3.25[c]		11.6	17	$CD_3C_6D_5$	59.1	
	-30	NCH_2	2.52[c]	1.73		11.6	34		60.2	
11e	-38	NCH_2	2.71[c] 2.74[c]	2.58		11.5	30	CD_2Cl_2	64.0	63.4
13a	-73	OCH_2	4.09 4.07	3.80[c] 3.75[c]		10.5	-36	CD_2Cl_2	48.1	47.7
14e	-88	OCH_2	3.76	3.34[c] 3.39[c]		10.1	-50	CD_2Cl_2	44.6	44.3

[a] For symmetric compounds **11a-d**: $H_{A1} = H_{A2}$ and $H_{B1} = H_{B2}$.– [b] Calculated for symmetric compounds **11a-d** with the approximation formula for the coupled case (ref.[15]) and for unsymmetric compounds **13a** or **11e** and **14e** (hindered rotation about the N-CO-bond) with the approximation formula for the uncoupled case (ref.[9,16]).– [c] Each line is split into a doublet with $^3J_{HH} \approx {}^2J_{HAHB}$.–

^{13}C NMR data gave further confirmation of the steric structure of the bicyclic compounds **11a,c-e**, **13a** and **14e**; they allowed additionally the detection of the configuration of **11b** and **13c**. A carbon atom and a hydrogen atom which are bond vicinally to a cyclopropane lead to different $^3J_{CH}$ coupling constants according to their steric arrangement: syn-substituents were reported to give a larger coupling constant than anti-subsituents.[17] Thus, values of $^3J_{CH}$ = 1.75 or 2.3 Hz and $^3J_{CH}$ = 4.5 or 4.6 Hz were found for the coupling between the carbon atom connected with C-7 and the hydrogen atoms at C-1 / C-6 of a norcaradiene system for the anti- and the syn-case,

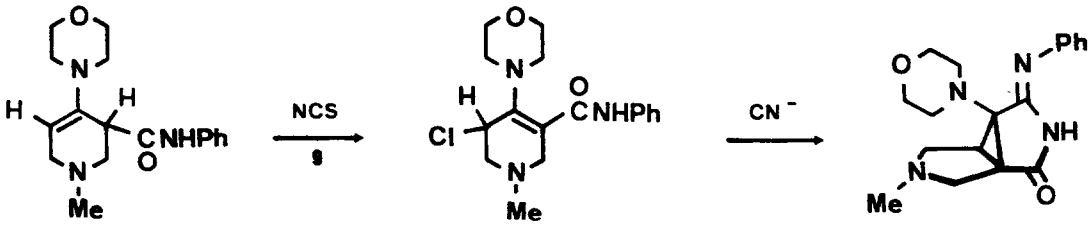
respectively.[18] The diastereomeric compounds **11e** and **14e** gave the information about the magnitude of these couplings at an 6-amino-3-azabicyclo[3.1.0]hexane carbonitrile system. A triplet with $^{3}J_{CH}$ = 4.3 Hz and a singlet ($^{3}J_{CH}$ < 1.2 Hz) were observed for the cyano group in the ^{13}C NMR spectrum of **11e** ("syn--coupling") and **14e** ("anti-coupling"). Analogously triplets with a similar coupling constant were found for the cyano signal for **11a** ($^{3}J_{CH}$ = 4.4 Hz), **11b** ($^{3}J_{CH}$ = 4.3 Hz), **11c** ($^{3}J_{CH}$ = 4.4 Hz) and **11d** ($^{3}J_{CH}$ = 4.3 Hz) establishing a uniform exo-position of the cyano group. On the other hand singlets were resulting for the cyano ^{13}C NMR signal of **13a** and **13c** requiring $^{3}J_{CH}$ < 2.5 Hz and indicating an endo-cyano configuration (all data measured in $CDCl_3$ with a resolution of at least 0.15 Hz).

The accessibility of both diastereomeric compounds **11e** and **14e** could be used for further support of the structure **11a** by chemical correlation. A second pair of diastereomeric compounds thus could be obtained by $LiAlH_4$-reduction of **11a** and **14e** leading to **15** (65% yield) and **16** (73% yield), respectively. The ^{1}H NMR signals of the morpholino moiety strongly differ for both compounds. As expected, an AA'XX'-type spectrum was observed for **16**. Contrarily, broad coalescing signals were obtained for the second isomer indicating unequivocally the endo morpholino structure of **15** and its precursor **11a**, as well.



A TRICYCLIC DIAZASYSTEM 19 FROM CYANIDE AND A CARBAMOYLATED CHLOROENAMINE 17

The reaction of **5** with cyanide led to a tricyclic system **6**.[8] A carbamoylated morpholino-tetrahydropyridine **17** could give a tricyclic diaza system in analogy to this. In order to test such an access enamine **8a** was carbamoylated with phenylisocyanate producing **17** which was isolated only as nonconjugated isomer. **17** was chlorinated by **9** at -5°C performing carbamoylated chloroenamine **18** (74% yield). The ^{13}C NMR data clearly indicate the structure of **18** (e.g. singlets at 147.7 ppm and 123.6 ppm, doublet at 54.0 ppm, $^{1}J_{CH}$ = 150 Hz). Reaction of chloroenamine **18** with cyanide indeed formed a tricyclic diaza compound in 51% yield. A rearranged product **19**, however, was obtained even when the reaction was run at room temperature. The presence of the

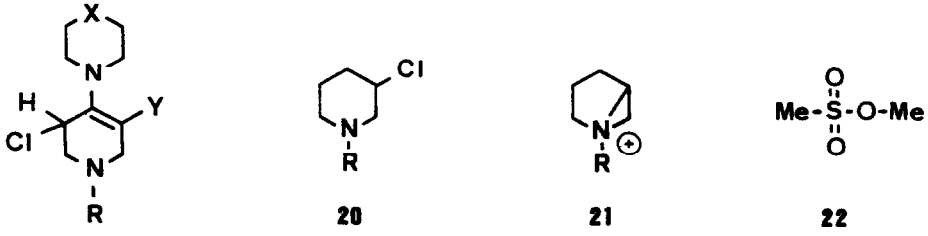


17 18 19

additional amino moiety in **18** causing a more basic medium is most presumably the origin of a very fast isomerization of the primary product of type **6** not being isolable in this case (see ref. [8]). The constitution of **19** can be deduced from the ^{13}C NMR spectrum. Especially the signal for C-1 of the N-phenyl moiety at 147.5 ppm unequivocally establishes the rearranged system **19** (see ref. [8]).

THE NEW WAY TO 6-AMINO-3-AZABICYCLO[3.1.0]HEXANE COMPOUNDS A TOXIC PROBLEM?

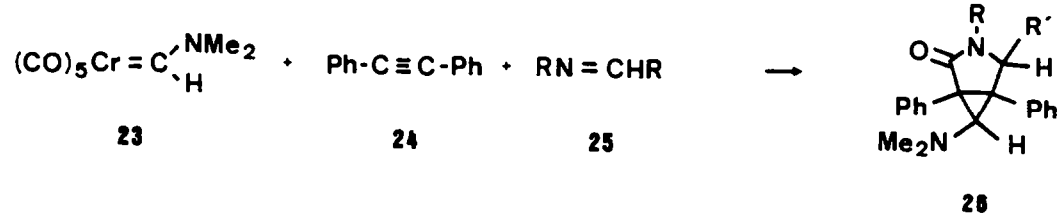
Amino-chlorotetrahydropyridines **10** and **12** proved to be starting materials for an easy access to 6-amino-3-azabicyclo[3.1.0]hexane compounds as shown here by the reaction with cyanide as a nucleophile. The additional nitrogen atom in the chloroenamines **10** and **12** originates an N-lost structural unit in these compounds. Thus, 3-chloropiperidine derivatives **20** are reported to produce an aziridinium ion **21** as intermediate in nucleophilic substitution.[19] **21** could be characterized as isolable perchlorate.[19] Ames tests,[20] therefore, were performed with monochloroenamine **10a** and dichloroenamine **12a**. Preliminary experiments showed a significant mutagenic behaviour at TA 100 bacteria for both compounds.[21] The mutagenicity turned out to be slightly lower than that of methyl methanesulfonate **22**.



10 : Y = H
12 : Y = Cl

20 21 22

A second access to the 6-amino-3-azabicyclo[3.1.0]hexane system requires no amino-chlorotetrahydropyridines as starting materials. This way, however, seems to be limited to special substituents. Thus the formation of 6-amino-3-azabicyclo[3.1.0]hexane derivatives **26** was reported from the reaction of the chromium carbene complex **23** with diphenylacetylene **24** and an imine **25**.[22] The alkyne component in this synthesis could be varied only to a very small extend: Whilst phenyl-trimethylsilyl-acetylene showed an analogous behaviour, the formation of a bicyclic species **26** was not observed with 5-decyne or phenyl-1-propyne as alkyne unit.[22]



23 **24** **25** **26**

EXPERIMENTAL

^{1}H NMR spectra were obtained with a Bruker AM 400 or, if noted, with a Bruker WP 200 spectrometer; ^{13}C NMR spectra were recorded with a Bruker AM 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.

Enamines 8c and 8e: The enamines were prepared according to a general procedure[23].

1-Methyl-4-(1,2,3,6-tetrahydro-1-methyl-pyridin-4-yl)-piperazine (**8c**): 30.1 g (266.2 mmol) of N-methyl-4-piperidone, 32 g (319.4 mmol) of N-methylpiperazine and 0.15 g (0.75 mmol) of p-toluenesulfonic acid in toluene (80 mL) gave crude enamine which was purified by fractionated distillation. Yield: 48.0 g (77%); bp 91-93°C/0.02 Torr; IR (film, cm^{-1}) 1645 (C=C); ^{1}H NMR ($CDCl_3$) δ 2.13 (H_{A1}, $H_{A1'}$, 2H) and 2.46 (H_{X1}, $H_{X1'}$, 2H) (AA'XX'-system), 2.19 (s, 3H), 2.23 (s, 3H), 2.34 (H_{A2}, $H_{A2'}$, 4H) and 2.75 (H_{X2}, $H_{X2'}$, 4H) (AA'XX'-system), 2.86 (m_c, 2H), 4.51 (m_c, 1H); ^{13}C NMR (CD_3CN) δ 144.6 (s), 97.8 (d), 55.8 (t), 55.2 (t), 53.3 (t), 48.3 (t), 46.5 (q), 46.1 (q), 28.7 (t). Anal. Calcd for $C_{11}H_{21}N_3$: C, 67.65; H, 10.84; N, 21.51. Found: C, 67.6; H, 10.7; N, 21.3.

Ethyl 1,2,3,6-tetrahydro-4-morpholino-pyridine-1-carboxylate (**8e**)[24,25] 20 g (116.8 mmol) of ethyl 4-oxopiperidine-1-carboxylate, 12.2 g (140.2 mmol) of morpholine and 0.05 g (0.25 mmol) of p-toluenesulfonic acid in 75 mL of benzene gave crude enamine which was purified by distillation in a Kugelrohr apparatus. Yield: 26.35 g (94%); bp 120°C/0.0005 Torr; IR (film, cm^{-1}) 1690 (C=O), 1650 (C=C); ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3H), 2.11-2.22 (m, 2H), 2.79 (H_X, 4H) and 3.72 (H_A, 4H) (AA'XX'-system), 3.57 (m_c, 2H), 3.98 (m_c, 2H), 4.13 (q, 2H), 4.50-4.61 (broad, unsplit, 1H); ^{13}C NMR ($CDCl_3$) δ 155.3 (s), 144.1 (s), 96.8 and 96.3 (d), 66.5 (t), 60.9 (t), 48.0 (t), 42.4 (t), 40.3 (t), 26.6 (t), 14.6 (q). Anal. Calcd for $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66. Found: C, 59.8; H, 8.3; N, 11.8.

4-(3-Chloro-1,2,3,6-tetrahydro-1-alkyl-4-pyridyl)-morpholines 10 - General Procedure: A solution of **9** (0.67 g; 5.0 mmol) in dichloromethane (25 mL) was dropped to a mixture of enamine **8** (5.0 mmol; **8a**[23,26]: 0.91 g; **8d**[27]: 1.29 g) in dichloromethane (**8a**: 2 mL, **8d**: 15 mL) at -20°C. The cooling bath was removed when the addition of **9** was finished and stirring was continued for 30 min. Then the solvent was evaporated in vacuo and the residue was extracted with pentane (100 mL) in a Soxleth apparatus. Pure chloroenamines **10** crystallized from the pentane solution; further **10** was obtained upon concentration of the solvent.

4-(3-Chloro-1,2,3,6-tetrahydro-1-methyl-4-pyridyl)-morpholine (**10a**): Yield: 0.93 g (86%); mp 97°C. IR (KBr, cm^{-1}) 1640 (C=C); ^1H NMR (CD_3CN) δ 2.29 (s, 3H), 2.66-2.76 (m, 4H), 2.86-2.94 (m, 3H), 3.19-3.25 (m, 1H), 3.65 (m_c, 4H), 4.68 (m_c, 1H), 4.78 (m_c, 1H); ^{13}C NMR δ(CD_3CN) 144.2 (s), 103.6 (d), 67.2 (t), 61.4 (t), 54.9 (t), 54.5 (d), 48.9 (t), 45.3 (q). Anal. Calcd for $C_{10}H_{17}ClN_2O$: C, 55.42; H, 7.91; N, 12.93. Found: C, 55.0; H, 8.1; N, 13.1.

4-(1-Benzyl-3-chloro-1,2,3,6-tetrahydro-4-pyridyl)-morpholine (**10d**): Yield: 1.05 g (73%); mp 90°C. IR (KBr, cm^{-1}) 1645 (C=C); ^1H NMR ($CHCl_3$) δ 2.75-2.83 (m, 3H), 2.90-3.01 (m, 4H), 3.33 (H_{A1}, 1H, part of an ABX-system), 3.55 (H_{B2}, 1H), 3.72 (H_{A2}, 1H) (AB-system, $^2J_{BB}$ = 13.0 Hz), 3.69-3.78 (m, 4H), 4.55 (m_c, 1H), 4.76 (H_{X1}, 1H); ^{13}C NMR ($CDCl_3$) δ 143.2 (s), 137.5 (s), 128.7 (d), 128.1 (d), 127.0 (d), 102.3 (d), 66.5 (t), 61.4 (t), 57.7 (t), 53.1 (d), 52.4 (t), 47.8 (t). Anal. Calcd for $C_{16}H_{21}ClN_2O$: C, 65.63; H, 7.23; N, 9.57. Found: C, 65.3; H, 7.2; N, 9.5.

1α,5α,6ß-3-Alkyl-6-morpholino-3-azabicyclo[3.1.0]hexane-6-carbonitrile 11 from Chloroenamines 10 - General Procedure: A mixture of chloroenamine **10** (5.0 mmol; **10a**: 1.08 g; **10d**: 1.46 g), sodium cyanide (0.37 g; 7.5 mmol) and acetonitrile - water (10 : 1; **10a**: 16 mL; **10d**: 32 mL) was stirred and heated to 70°C for 2.5 h. Then the solvent was removed in vacuo and 6.0 mL of aqueous NaOH solution (2.5 M) was added to the residue. **11** was extracted from the mixture with dichloromethane (**11a**: 2 x 6 mL; **11d**: 3 x 16 mL) and recrystallized (**11a**: acetonitrile; **11d**: ether) to give colorless crystals.

1α,5α,6ß-3-Methyl-6-morpholino-3-azabicyclo[3.1.0]hexane-6-carbonitrile (**11a**): Yield: 0.77 g (74.5%); mp 92°C; IR (KBr, cm^{-1}) 2220 (C≡N); ^1H NMR (CD_3CN, 200 MHz) δ 2.19 (s) and 2.20-2.30 (m) (7H), 2.50-2.59 (m, 4H), 3.10-3.25 (m, 2H), 3.40-3.85 (broad, unsplit, 4H); ^{13}C NMR ($CDCl_3$) δ 117.7 (s), 66.7 (t), 53.6 (t), 50.1 (t), 44.2 (s), 40.5 (q), 34.1 (d, $^1J_{CH}$ = 173 Hz). Anal. Calcd for $C_{11}H_{17}N_3O$: C, 63.74; H, 8.27; N, 20.27. Found: C, 63.7; H, 8.3; N, 20.2.

1α,5α,6ß-3-Benzyl-6-morpholino-3-azabicyclo[3.1.0]hexane-6-carbonitrile (**11d**): Yield: 1.07 g (77%); mp 92.9°C; IR (KBr, cm^{-1}) 2205 (C≡N); ^1H NMR ($CDCl_3$) δ 2.31 (H_X, $H_{X'}$, 2H), 2.39 (H_B, 2H), 3.25 (H_A, 2H) (ABXX'-system), 2.30-2.90 (broad, unsplit, 4H), 3.55-4.05 (broad, unsplit) and 3.66 (s) (6H), 7.13-7.44 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 138.7 (s), 128.3 (d), 128.2 (d), 126.9 (s), 117.4 (s), 66.4 (t), 58.3 (t), 51.3 (t), 50.0 (t), 43.7 (s), 33.1 (d, $^1J_{CH}$ = 175 Hz). Anal. Calcd for $C_{17}H_{21}N_3O$: C, 72.06; H, 7.47; N, 14.83. Found: C, 72.0; H, 7.6; N, 14.7.

3-Alkyl-6-amino-3-azabicyclo[3.1.0]hexane-6-carbonitriles 11a-d from Enamines 8a-d by a One-Pot Procedure: - General Procedure: A solution of **9** (0.67 g, 5.0 mmol) in dichloromethane (25 mL) was dropped to a solution of enamine **8** (5.0 mmol; **8a**[23,26]: 0.91 g, **8b**[26,28]: 0.90 g; **8c**: 0.98 g; **8d**[27]: 1.29 g) in dichloromethane (**8a-c**: 2 mL, **8d**: 15 mL) analogous to the preparation of **10a,d**. Then the solvent was removed in vacuo. Sodium cyanide (0.38 g , 7.75 mmol) and a mixture of acetonitrile - water (10 : 1; **10a-c**: 16 mL; **10d**: 32 mL) were added to the residue consisting of crude chloroenamine **10** and succinimide and treated as described above for the preparation of **11a,d**. Yields are calculated with respect to enamines **8** as starting materials.

1α,5α,6ß-3-Methyl-3-morpholino-3-azabicyclo[3.1.0]hexane-6-carbonitrile (**11a**): Yield: 0.63 g (61%); mp 92°C; ^1H NMR data identical with those described above for **11a**.

1α,5α,6ß-3-Methyl-6-piperidino-3-azabicyclo[3.1.0]hexane-6-carbonitrile (**11b**): Refluxing for 3 h; extraction with 10 mL of dichloromethane; recrystallization from pentane. Yield: 0.41 g (40%), mp 53°C; IR (KBr, cm^{-1}) 2220 (C≡N); ^1H NMR ($CDCl_3$) δ 1.21-1.33 (m, 1H), 1.45-1.88 (m, 6H), 2.19-2.30 (m) and 2.24 (s) (8H), 2.45 (H_B, $^3J_{BX}$ = 9 Hz, 2H), 2.63 (H_A, 2H), (AB-system, $^2J_{AB}$ = 10 Hz), 3.22-3.34 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 118.2 (s), 53.4 (t), 51.0 (t), 44.6 (s), 40.3 (q), 34.2 (d, $^1J_{CH}$ = 171 Hz), 25.8 (t), 24.0 (t). Anal. Calcd for $C_{12}H_{19}N_3$: C, 70.20; H, 9.33; N, 20.47. Found: C, 69.6; H, 9.4; N, 20.2.

1α,5α,6ß-3-Methyl-6-(4-methyl-piperazin-1-yl)-3-azabicyclo[3.1.0]hexane-6-carbonitrile (**11c**): Refluxing for 2 h; extraction with 15 mL of dichloromethane; recrystallization from ether. Yield: 0.58 g (53%); mp 108°C; IR (KBr, cm^{-1}) 2205 (C≡N); ^1H NMR (CD_3CN) δ 1.98-2.08 (broad, unsplit, 2H), 2.17 (s), 2.21 (s) and 2.21-2.29 (m) (8H), 2.50-2.63 (broad, unsplit, 4H), 2.65-2.82 (broad, unsplit, 2H), 3.13-3.22 (m, 2H); ^{13}C NMR (CD_3CN) δ 118.8 (s), 55.5 (t), 54.1 (t), 50.5 (t), 46.3 (q), 44.4 (s), 40.5 (q), 34.9 (d, $^1J_{CH}$ = 172 Hz). Anal. Calcd for $C_{12}H_{20}N_4$: C, 65.42; H, 9.15; N, 25.43. Found: C, 65.5; H, 9.1; N, 25.6.

1α,5α,6ß-3-Benzyl-6-morpholino-3-azabicyclo[3.1.0]hexane-6-carbonitrile (**11d**): Yield: 0.94 g (79%); mp 93°C; ^1H NMR data identical with those described above for **11d**.

Dichloroenamines 12a and 12c from 8a,c and NCS - General Procedure: Enamine **8** (5.0 mmol; **8a**[23,26]: 0.91 g; **8c**: 0.98 g) in 10 mL of dichloromethane was slowly added to a stirred suspension of **9** (1.33 g, 10 mmol) in dichloromethane (25 mL) at -15°C. Then the reaction mixture was warmed to room temperature and the solvent was evaporated. Extraction of the residue with pentane (3 x 30 mL) gave pure **12a,c** as colorless crystalline compounds.

4-(3,5-Dichloro-1,2,3,6-tetrahydro-1-methyl-4-pyridyl)-morpholine (**12a**): Yield: 1.13 g (90%); mp 92°C; IR (KBr, cm^{-1}) 1645 (C=C); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.43 (s, 3H), 2.73 (H_{B1}, 1H), 3.07 (H_{A1}, 1H), 4.70 (H_X, 1H) (ABX-system, $^2J_{A1B1}$ = 13.0 Hz), 2.93 (H_{B2}, 1H), 3.48 (H_{A2}, 1H) (AB-system, $^2J_{A2B2}$ = 15.8 Hz), 2.82-2.98 (m, 2H), 3.17-3.31 (m, 2H), 3.74 (m_C, 4H); ^{13}C NMR ($CDCl_3$) δ 139.2 (s), 120.5 (s), 67.0 (t), 60.2 (t), 59.4 (t), 55.0 (d), 49.1 (t), 44.4 (q). Anal. Calcd for $C_{10}H_{16}Cl_2N_2O$: C, 47.82; H, 6.42; N, 11.15. Found: C, 47.7; H, 6.3; N, 11.3.

1-(3,5-Dichloro-1,2,3,6-tetrahydro-1-methyl-4-pyridyl)-4-methyl-piperazine (**12c**): Yield: 1.00 g (76%); mp 87°C; IR (KBr, cm^{-1}) 1645 (C=C); ^1H NMR (CD_3CN, 200 MHz) δ 2.21 (s, 3H), 2.32 (s) and 2.25-2.51 (m) (7H), 2.69 (H_{B1}, 1H), 2.96 (H_{A1}, 1H), 4.82 (H_X, 1H) (ABX-system, $^2J_{A1B1}$ = 13.3 Hz), 2.58-2.86 (m, 4H), 2.82 (H_{B2}, 1H), 3.27 (H_{A2}, 1H) (AB-system, $^2J_{A2B2}$ = 16.0 Hz), 3.15-3.43 (m, 2H); ^{13}C NMR (CD_3CN) δ 140.7 (s), 120.4 (s), 60.8 (t), 60.5 (t), 57.1 (d), 56.1 (t), 49.6 (t), 46.5 (q), 44.6 (q). Anal. Calcd for $C_{11}H_{19}Cl_2N_3$: C, 50.01; H, 7.25; N, 15.90. Found: C, 49.8; H, 7.2; N, 15.9.

1α,5α,6α-1-Chloro-3-methyl-6-morpholino-3-azabicyclo[3.1.0]hexane-6-carbonitrile (**13a**): Dichloroenamine **12a** (1.26 g, 5.0 mmol) was added to a solution of sodium cyanide (0.49 g, 10 mmol) in water (30 mL) and stirred at room temperature for 18 h. Precipitated **13a** was filtered by suction, washed with water (20 mL) and dried. Further **13a** could be obtained from the water solution by extraction with ether (3 x 50 mL). Recrystallization from ether gave pure **13a**. Yield: 0.70 g (58%); mp 101°C; IR (KBr, cm^{-1}) 2205 (C≡N); ^1H NMR (CD_3CN) δ 2.13 (H_{X1}, 1H), 2.78 (H_{B1}, 1H), 3.04 (H_{A1}, 1H) (ABX-system, $^2J_{A1B1}$ = 9.9 Hz, $^3J_{A1X1}$ = 0 Hz, $^3J_{B1X1}$ = 3.6 Hz), 2.27 (s, 3H), 2.63 (H_Y, 2H), 2.67 (H_{X2}, 2H), 3.64 (H_{B2}, H_{A2}, 4H) (ABXY-system, $^2J_{X2Y}$ = 11.3 Hz), 2.85 (H_{B3}, 1H), 3.40 (H_{A3}, 1H) (AB-system, $^2J_{A3B3}$ = 9.5 Hz); ^{13}C NMR (CD_3CN) δ 113.9 (s), 67.2 (t), 62.6 (t), 56.5 (s), 55.0 (t), 51.0 (t), 47.4 (s), 40.3 (q), 39.0 (d, $^1J_{CH}$ = 178 Hz). Anal. Calcd for $C_{11}H_{16}ClN_3O$: C, 54.66; H, 6.67; N, 17.38. Found: C, 54.4; H, 6.6; N, 17.4.

1α,5α,6α-1-Chloro-3-methyl-6-(4-methyl-piperazin-1-yl)-3-azabicyclo[3.1.0]-hexane-6-carbonitrile (13c): Dichloroenamine **12c** (1.32 g, 5.0 mmol) was added to a mixture of sodium cyanide (0.98 g, 20 mmol) and tetrabutylammonium chloride (0.83 g, 3.0 mmol) in water (20 mL) and stirred at room temperature for 16 h. Precipitated **13c** was filtered by suction and dried. Addition of aqueous sodium carbonate solution (50 mL of Na_2CO_3, 2.5 M) and extraction with dichloromethane (3 x 15 mL) gave further **13c**; recrystallization from pentane gave pure **13c**. Yield: 0.70 g (55%); mp 74.5°C; IR (KBr, cm^{-1}) 2220 (C≡N); ^{1}H NMR ($CDCl_3$) δ 1.98 (H_{X1}, 1H), 2.82 (H_{B1}, 1H), 3.07 (H_{A1}, 1H) (ABX-system, $^2J_{A1B1}$ = 9.8 Hz, $^3J_{A1X1}$ = 0 Hz, $^3J_{B1X1}$ = 3.5 Hz), 2.28 (s, 3H), 2.32 (s, 3H), 2.36-2.54 (H_{X2}, H_Y, broad, unsplit, 4H), 2.70 (H_{B2}, 2H), 2.85 (H_{A2}, 2H) ($^2J_{A2B2}$ = 10.0 Hz), 2.91 (H_{B3}, 1H), 3.41 (H_{A3}, 1H) (AB-system, $^2J_{A3B3}$ = 9.6 Hz); ^{13}C NMR ($CDCl_3$) δ 112.9 (s), 61.8 (t), 55.6 (s), 54.5 (t), 54.2 (t), 49.5 (t), 46.3 (s), 45.9 (q), 39.8 (q), 38.2 (d, $^1J_{CH}$ = 175 Hz). Anal. Calcd for $C_{12}H_{19}ClN_4$: C, 56.57; H, 7.52; N, 21.99. Found: C, 56.4; H, 7.5; N, 22.1

Ethyl 6-cyano-6-morpholino-3-azabicyclohexane-3-carboxylates 11e and 14e from Enamine 8e, NCS and cyanide: A solution of **9** (11.31 g, 84.7 mmol) in dichloromethane (250 mL) was dropped within 1.5 h at -78°C to a solution of enamine **8e** (20.35 g, 84.7 mmol) in dichloromethane (50 mL). Removal of the solvent at room temperature, extraction of the residue with tetrachloromethane (4 x 15 mL) and evaporation of the combined tetrachloromethane extracts gave crude chloroenamine **10e**. Attempted distillation of **10e** in a Kugelrohr apparatus caused decomposition.

The yellow oil (25.16 g), thus obtained, was added to a solution of sodium cyanide (8.3 g, 169.4 mmol) and benzyltriethylammonium chloride (19.29 g, 84.7 mmol) in water (120 mL). The mixture was stirred for 14 h at 50°C and subsequently extracted with ether (300 mL) in a Kutscher-Steudel apparatus for 40 h. Pure **14e** crystallized from the ethereal solution by cooling in a refrigerator. A further portion of **14e** was obtained from the concentrated filtrate (200 mL). endo Morpholino compound **11e** could be isolated after the removal of exo derivative **14e** by subsequent crystallization. Very slow evaporation of the ether at room temperature facilitated the formation of crystals of **11e**.

Ethyl 1α,5α,6ß-6-cyano-6-morpholino-3-azabicyclo[3.1.0]hexane-3-carboxylate (**11e**): Yield: 6.98 g (31%); mp 81°C; IR (KBr, cm^{-1}) 2220 (C≡N), 1685 (C=O); ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3H), 2.28 (H_{X1}, $H_{X1'}$, 2H), 3.61 (H_{B1}, $H_{B1'}$, 2H), 3.72 (H_{A1}, $H_{A1'}$, 2H) (ABXX'A'B'-system, $^2J_{A1B1}$ = $^2J_{A1'B1'}$ = 13.0 Hz), 2.48-2.62 (H_Y, 2H), 2.70-2.86 (H_{X2}), 3.38-3.58 (H_{B2}, 2H), 3.77-3.92 (H_{A2}, 2H) (4 broad unsplit signals), 4.14 (q, 2H); ^{13}C NMR ($CDCl_3$) δ 154.3 (s), 116.6 (s), 66.6 (t), 61.4 (t), 51.1 (t), 45.8 (t), 54.2 (t), 40.8 (s), 30.7 (d, $^1J_{CH}$ = 174 Hz), 30.0 (d, $^1J_{CH}$ = 176 Hz), 14.9 (q). Anal. Calcd for $C_{13}H_{19}N_3O_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 58.7; H, 7.1; N, 15.7.

Ethyl 1α,5α,6α-6-cyano-6-morpholino-3-azabicyclo[3.1.0]hexane-3-carboxylate (**14e**) Yield: 8.61 g (38%); mp 162°C; IR (KBr, cm^{-1}) 2220 (C≡N), 1700 (C=O); ^{1}H NMR ($CDCl_3$) δ 1.23 (H_{X1}, t, 3H), 4.10 (H_{B1}, 1H), 4.15 (H_{A1}, 1H) (ABX_3-system, $^2J_{A1B1}$ = 10.8 Hz), 2.08 (H_{X2}, H_Y, 2H), 3.61 (H_{B2}, H_{B3}, 2H), 3.74 (H_{A2}, 1H), 3.79 (H_{A3}, 1H) (2 ABXY-systems, $^2J_{A2B2}$ = 11.6 Hz, $^2J_{A3B3}$ = 11.7 Hz), 2.70 (H_{X3}, $H_{X3'}$, 4H), 3.65 (H_{A4}, $H_{A4'}$, 4H) (AA'XX'-system); ^{13}C NMR ($CDCl_3$) δ 154.6 (s), 113.3 (s), 66.8 (t), 61.7 (t), 50.8 (t), 46.8 (t), 46.5 (s), 46.3 (t), 32.2 (d, $^1J_{CH}$ = 176 Hz), 31.5 (d, $^1J_{CH}$ = 177 Hz), 15.0 (q). Anal. Calcd for $C_{13}H_{19}N_3O_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 58.7; H, 7.2; N, 15.7.

$LiAlH_4$ Reduction of the Nitriles 11a and 14e – General Procedure: Bicyclic nitrile (6.0 mmol, **11a**: 1.24 g; **14e**: 1.60 g) was added to a suspension of lithium aluminum hydride (2.29 g, 60 mmol) in ether (100 mL). The mixture was refluxed for 70 h, then excess $LiAlH_4$ was destroyed by addition of aqueous sodium hydroxide solution (5 M; 30 mL). Crude bicyclic amines **15** and **16** were obtained from the ethereal solution by evaporation of the solvent. **15** and **16** were purified by distillation in a Kugelrohr apparatus.

4-(1α,5α,6β-6-Aminomethyl-3-methyl-3-azabicyclo[3.1.0]hex-6-yl)-morpholine **(15)**: Yield: 0.82 g (65%), colorless oil, bp 140-145°C/0.001 Torr; ^{1}H NMR δ 1.31 (s, broad, 2H, NH), 1.70 (H_{X1},$H_{X1'}$, 2H), 2.14 (H_{B1}, $H_{B1'}$, 2H), 3.05 (H_{A1}, $H_{A1'}$, 2H) (AA'BB'XX'-system, $^2J_{A1B1} = {}^2J_{A1'B1'} = 9.0$ Hz), 2.21 (s, 3H), 2.69 (s, 2H), 2.30-2.55 and 2.75-3.00 (broad unsplit, 4H), 3.40 - 3.80 (broad unsplit, 4H); ^{13}C NMR (CD_3CN) δ 68.2 (t), 56.0 (s), 55.0 (t), 50.7 (t), 43.7 (t), 40.6 (q), 32.7 (d, $^1J_{CH} = 168$ Hz). Anal. Calcd for $C_{11}H_{21}N_3O$: C, 62.53; H, 10.02; N, 19.89: Found: C, 62.0; H, 10.0; N, 18.8.

4-(1α,5α,6α-6-Aminomethyl-3-methyl-3-azabicyclo[3.1.0]hex-6-yl)-morpholine **(16)**: Yield: 0.93 g (73%); colorless oil, bp 85°C/0.001 Torr; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.29 (s, 2H, NH), 1.50 (H_{X1}, $H_{X1'}$, 2H), 2.51 (H_{B1}, $H_{B1'}$, 2H), 2.96 (H_{A1}, $H_{A1'}$, 2H) (ABXX'A'B'-system, $^2J_{A1B1} = {}^2J_{A1'B1'} = 9.8$ Hz), 2.45 (s, 3H), 3.10 (s, 2H), 2.65 (H_{X2}, $H_{X2'}$, 4H), 3.58 (H_{A2}, $H_{A2'}$, 4H) (AA'XX'-system); ^{13}C NMR ($CDCl_3$) δ 67.9 (t), 56.2 (t), 53.6 (s), 49.9 (t), 41.9 (q), 36.7 (t), 30.9 (d, $^1J_{CH} = 171$ Hz). Anal. Calcd for $C_{11}H_{21}N_3O$: C, 62.53; H, 10.02; N, 19.89: Found: C, 63.0; H, 9.9; N, 19.0.

1,2,3,6-Tetrahydro-1-methyl-4-morpholino-N-phenyl-3-pyridinecarboxamide (17) (ref. [23], no data given): Phenylisocyanate (11.9 g, 0.1 mol) was dropped to a solution of enamine **8a** (18.23 g, 0.1 mol) in anhydrous acetone (25 mL) within 20 min. The reaction temperature was kept below 50°C. The mixture was stirred at room temperature for 2 h; then the solvent was removed in vacuo and the residue was triturated with chloroform (20 mL). The colorless solid was filtered by suction and washed consecutively with acetone (3 x 5 mL) and pentane (3 x 25 mL). A further crop of **17** was obtained from the mother liquor by addition of pentane. Yield: 22.8 g (76%); mp 125°C; IR (KBr, cm^{-1}) 1690, 1660 (C=O, C=C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.43 (s, 3H), 2.50 (m_c, 1H), 2.73-2.87 (m, 4H), 3.05-3.20 (m, 4H), 3.24 (m_c, 1H), 3.48 (d of d, 1H), 3.70-3.77 (m, 4H), 4.75 (d of d, 1H), 7.13 (t, 1H), 7.35 (t, 2H), 7.56 (d, 2H), 10.5 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 171.7 (s), 143.2 (s), 138.8 (s), 128.9 (d), 123.5 (d), 119.6 (d), 99.6 (d), 66.7 (t), 54.7 (t), 53.8 (t), 48.2 (t), 44.7 (q), 44.3 (d). Anal. Calcd for $C_{17}H_{23}N_3O_2$: C, 67.75; H, 7.69; N, 13.94. Found: C, 67.8; H, 7.7; N, 13.8.

5-Chloro-1,2,3,6-tetrahydro-1-methyl-4-morpholino-N-phenyl-3-pyridinecarboxamide (18): A solution of **9** (2.67 g, 20 mmol) in dichloromethane (60 mL) was dropped under stirring to a mixture of carbamoylated enamine **17** (6.03 g, 20 mmol) and dichloromethane (80 mL) at -5°C. Stirring was continued for 2.5 h at 20°C. Extraction with aqueous Na_2CO_3 solution (2.5 M, 2 x 60 mL), removal of the solvent and washing of the residue with ice-cold acetonitrile (5 mL) gave pure **18**. Yield: 4.97 g (74%); IR (KBr, cm^{-1}) 1660, 1620, 1600 (C=O, C=C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.49 (s, 3H), 2.66 (H_{A1}, 1H), 3.11 (H_{B1}, 1H), 4.82 (H_X, 1H) (ABX-system, $^2J_{A1B1} = 13.0$ Hz), 2.80 (H_{A2}, 1H), 4.12 (H_{B2}, 1H) (AB-system, $^2J_{A2B2} = 17.5$ Hz), 3.13-3.32 (m, 4H), 3.73-3.95 (m, 4H), 7.11 (t, 1H), 7.35 (t, 2H), 7.63 (d, 2H), 11.25 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 162.9 (s), 147.7 (s), 138.1 (s), 129.1 (d), 123.8 (d), 123.6 (s), 119.1 (d), 66.8 (t), 60.3 (t), 54.5 (t), 54.0 (d, $^1J_{CH} = 150$ Hz), 51.4 (t), 44.8 (q). Anal. Calcd for $C_{17}H_{22}ClN_3O_2$: C, 60.80; H, 6.60; N, 12.51. Found: C, 60.3; H, 6.5; N, 12.5.

5-Morpholino-4-phenylimino-3,8-diazatricyclo[4.3.0.0^{1,8}]nonan-2-one (19): A mixture of sodium cyanide (0.25 g, 5.0 mmol) and chloroenamine **18** (1.68 g; 5.0 mmol) in methanol - water (1:1, 40 mL) was heated to 60°C under stirring for 17h. Cooling to 5°C gave **19** as a precipitate which was filtered by suction, washed consecutively with water (3 x 10 mL), ether (2 x 10 mL) and pentane (2 x 10 mL) and recrystallized from acetonitrile. Yield: 0.83 g (51%); mp 228°C; IR (KBr, cm^{-1}) 1750 (C=O), 1670 (C=N); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.45 (s, 3H), 2.48 (H_{A1}, 1H), 3.60 (H_{B1}, 1H) (AB-system, $^2J_{A1B1} = 10.0$ Hz), 2.43 (H_{A2}, 1H), 3.20 (H_{B2}, 1H), 2.63 (H_X, 1H) (ABX-system, $^2J_{A2B2} = 9.5$ Hz), 2.0-3.5 (broad, 4H), 3.5-4.0 (broad, 4H), 6.83 (d, 2H), 7.05 (t, 1H), 7.30 (t, 2H), 7.6 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 172.5 (s), 152.1 (s), 147.5 (s), 129.4 (d), 124.1 (d), 120.5 (d), 67.3 (t), 61.0 (s), 53.6 (t), 50.2 (t), 49.0 (t, broad), 46.4 (d, $^1J_{CH} = 181$ Hz), 45.5 (s), 40.8 (q). Anal. Calcd for $C_{18}H_{22}N_4O_2$: C, 66.03; H, 7.08; N, 17.11. Found: C, 66.1; H, 6.9; N, 17.3.

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