Tetrahedron Vol. 47, No 38, pp 8133-8144, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00
Pergamon Press plc

FUNCTIONALIZED CHLOROENAMINES IN AMINOCYCLOPROPANE SYNTHESIS - VIII.[1] AMINO-AZABICYCLO[3.1.0]HEXANE DIASTEREOMERS FROM CHLOROENAMINES AND -BOROHYDRIDE

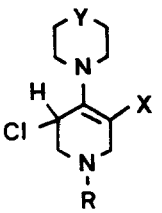
Elmar Vilsmaier*, Claus Tetzlaff, Volker Butz and Gerhard Maas

Fachbereich Chemie der Universität Kaiserslautern,
Erwin-Schroedinger-Straße, W-6750 Kaiserslautern, Germany

(*Received in Germany* 26 *June* 1991)

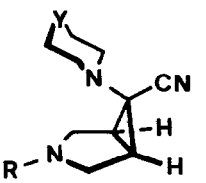
Abstract: Bicyclic endo-amines **6a,b** could be prepared in a stereospecific way from the reaction of chloroenamines **1a,b** and sodium borohydride and by deboranation of the primarily formed borane adducts **8**. An X-ray structure analysis is given for **8a**. In contrast to **1a,b**, chloroenamine **1c** and sodium borohydride preferentially produced an exo-amine **7c** besides the endo-amine **6c** (3 : 1). Subsequent $LiAlH_4$-reduction of **7c** allowed the synthesis of **7a** - the diastereoisomer of **6a**. Interaction of sodium borohydride with dichloroenamine **2a** provided diamine **12** instead of an expected bicyclic exo-amine **10**.

Amino-chloro-tetrahydropyridines **1a,b** gave isomerically pure endo-amino-azabicyclo[3.1.0]hexanes **3a,b** upon the reaction with cyanide.[2] Exo-amino-derivatives **4a,b** were obtained by an analogous reaction of cyanide with the dichloroenamines **2a,b**.[2] In the meantime the chlorine atom in **4a** could be removed by sodium in tert.-butyl alcohol yielding **5a**, the diastereomeric compound of **3a**.[1]



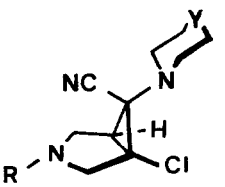
1: X = H
2: X = Cl

1a,b $\xrightarrow{CN^{\ominus}}$

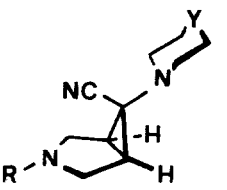


3a,b

2a,b $\xrightarrow{CN^{\ominus}}$



4a,b

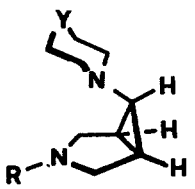


5a

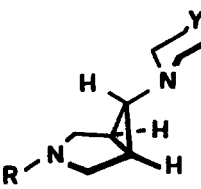
a: R = Me, Y = O ; **b**: R = Me, Y = NMe

Thus the chloroenamines **1** and **2** represent a basis for a simple diastereocomplementary approach to the isomeric nitriles **3** and **5**.

We were interested in the general applicability of this diastereocomplementary synthesis. We studied, therefore, the reaction of the chloroenamines **1** and **2** with other nucleophiles. The results of the reactions of **1** and **2** with hydride as a nucleophile are reported in this paper. Sodium borohydride was used as the hydride reagent to yield 6-amino-3-azabicyclo[3.1.0]hexane isomers **6** and **7** as the target molecules of this reaction.



6

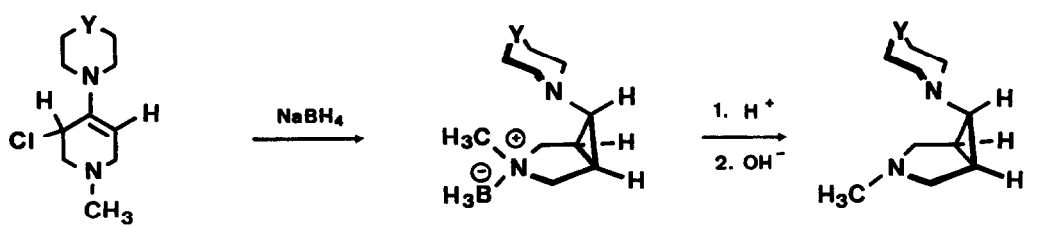


7

1-7	R	Y
a	Me	O
b	Me	NMe
c	COOEt	O

ENDO-AMINO-3-AZABICYCLO[3.1.0]HEXANE DERIVATIVES 6

Amino-3-azabicyclo[3.1.0]hexane compounds, indeed, could be synthesized as pure endo-isomers **6a** and **6b** from the reaction of monochloroenamines **1a,b** with sodium borohydride in acetonitrile and subsequent deboranation of the primarily formed borane adducts. In the case of **1a**, a monoadduct **8a** was isolated in 57% yield; its acidic hydrolysis provided deboranated endo-amine **6a** (93%). The piperazino-chloro-tetrahydropyridine **1b** led to a mixture of monoadduct **8b** and bisadduct **8d**; this mixture directly was deboranated without separation to give pure endo-amine **6b** in an overall yield of 45%. endo-Amines **6a** and **6b** were exclusively accessible by this synthesis.



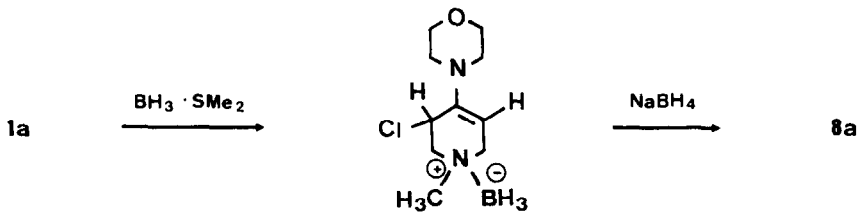
1a,b **8a, 8b/d** **6a,b**

6a,b **8a,b**

8	a	b	d
Y	O	NMe	N(Me)BH3

Transfer of a hydride from BH_4^- to the chloroenamine **1** gives borane as a byproduct which can produce borane adducts. **8a** and **8b/d** could be generated by two ways: (i) reaction of BH_3 with the bicyclic amine **6** or (ii) boranation already at the chloroenamine level prior to the cyclopropane ring closure reaction. It was shown that both ways lead to borane adducts **8**. Addition of BH_3 - $S(CH_3)_2$ to bicyclic amines **6a** and **6b** in a 1 : 1 ratio specifically produced borane monoadducts **8a,b** according to (i). This contrasts with analogous reactions of BH_3 - THF with diamines such as N,N'-dimethylpiperazine, N,N,N',N'-tetramethylethylenediamine or 1,4-diazabicyclo[2.2.2]octane in which only bisadducts could be obtained irrespective of the amine - borane ratio.[3] The accessibility of borane monoadducts from di- or triamines as **6** should be the consequence of strong differences of the two heterocyclic sytems in **6** with respect to steric hindrance and to basicity.

Way (ii) was examined using the morpholino-chlorotetrahydropyridine **1a** which could be boranated by BH_3 - $S(CH_3)_2$ to give **9** in 87% yield. The highly selective boranation of **1a** at the piperidine nitrogen atom seems to be worth mentioning: Enamines can be easily[4,5] hydroborated at the CC-double bond, a similar attack of BH_3 at the CC-double bond[6] was described for 2,5-dihydropyrroles[7] and 1,2,5,6-tetrahydropyridines[8]. Interaction of **9** with $NaBH_4$ produced **8a** (46% yield) as well. Identical products **8a** were obtained from all three reactions [**1a** and $NaBH_4$, way (i) and way (ii)].

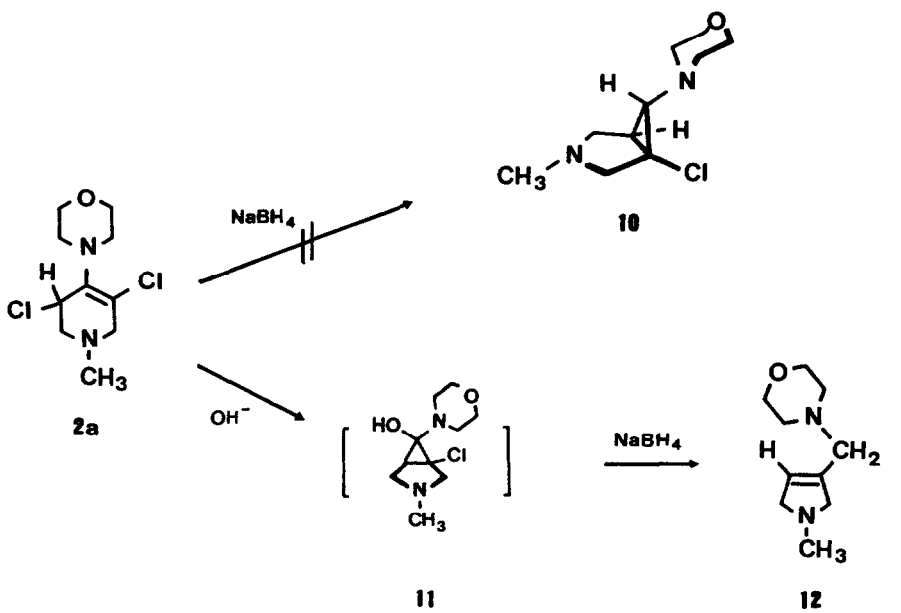


9

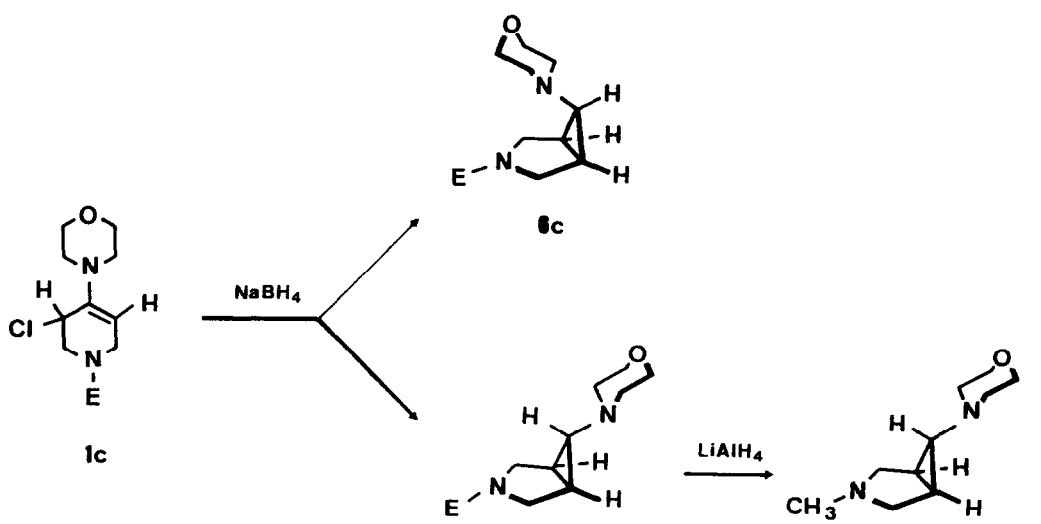
POTENTIAL WAYS TO EXO-AMINO-3-AZABICYCLO[3.1.0]HEXANE DERIVATIVES 7

The reactions of chloroenamines with cyanide pointed out that dichloroenamine **2a**[1,2] and, thus far less successful, chloroenamine **1c**[2] can serve as a basis for the synthesis of bicyclic exo-amine systems.

Dichloroenamine **2a**, therefore, first was investigated as starting material for a potential cyclopropanation reaction induced by sodium borohydride. A pyrroline derivative **12**, however, was obtained in 71% yield from **2a** and sodium borohydride instead of the expected bicyclic exo-amine **10**. The formation of **12** can be easily explained by attack of OH^- to **2a** producing semiaminal[9] **11** which should lead to **12** by a sequence of a ring opening reaction, an elimination of chloride anion and a reduction of the carbonyl group.



Chloroenamine **1c** proved to be superior in this case. Reaction of **1c** with sodium borohydride in water led to a 1 : 3 mixture of **6c** and **7c**. The two isomers were separated by MPLC to give pure **6c** in



c: R = E = COOEt
Y = O

23% yield and **7c**, as the desired compound, in 57% yield. Subsequent reduction of **7c** by lithium aluminum hydride produced exo-amine **7a** (82% yield), the diastereomer of **6a**.

Using acetonitrile instead of water as the solvent led to a mixture of several substances from which only endo-amine **6c** could be isolated as pure compound in 35% yield. The ^{1}H NMR spectrum of the crude product mixture indicated the presence of only small amounts of exo-amine **7c**. Cerium(III) chloride / sodium borohydride (Luche's reagent)[10,11] and chloroenamine **1c** (molar ratio: 1 : 10 : 1) in water gave **6c/7c** in a 1 : 3 ratio (no change of the relative quantities).

CONSTITUTION AND CONFIGURATION OF THE BICYCLIC COMPOUNDS 6 - 8

The structure **8a** for the borane adduct which was obtained from chloroenamine **1a** and $NaBH_4$ was unequivocally established by an X-ray structure analysis. The endo-position of morpholine, the exo-position of the borane moiety and the presence of a chair conformation of the [3.1.0]bicylic system are pointed out as the important details. The B-N-distance of 1.618 (8) Å of **8a** is of a similar magnitude as it was reported for the trimethylamine-borane adduct [B-N-distance: 1.609 Å (microwave)[12]; 1.638 Å (microwave)[13]; 1.656 Å (gas electron diffraction and spectroscopic data)[14]]. Selected bond lengths, bond angles, torsional angles and interplanar angles are given in Table 1.

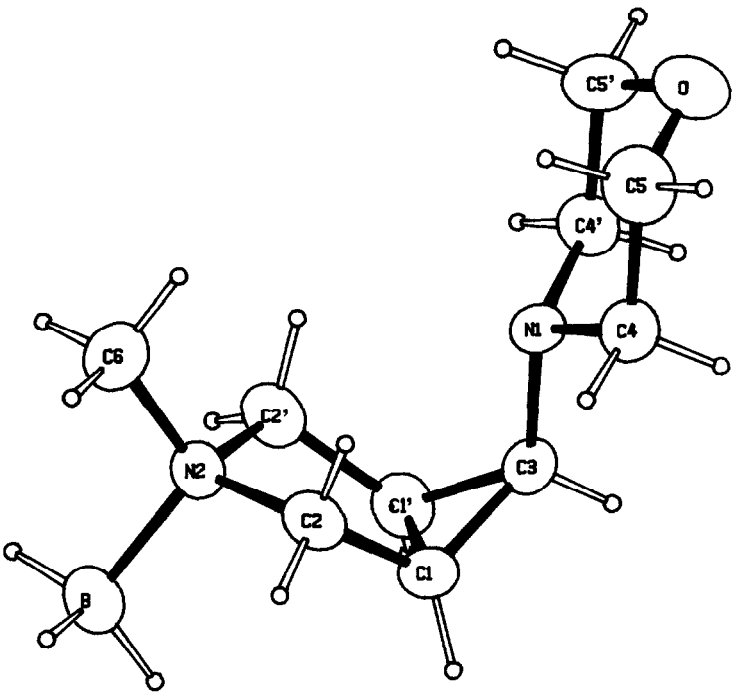
The knowledge of the structure of **8a** allowed the assignment of the constitution and the configuration of compounds **6a - c**, **7a** , **7c** and **8b** on the basis of ^{1}H and ^{13}C NMR spectroscopic data.

^{13}C NMR data clearly indicated the presence of the cyclopropane unit (two doublets with a typical coupling constant $^1J_{CH}$ = 165 - 175 Hz). The ^{13}C NMR spectra additionally gave the information that the borane moiety in **8b** is located at the pyrrolidine nitrogen atom.

Table 1 Selected Bond Lengths, Bond Angles, Torsional Angles and Interplanar Angles for **8a**

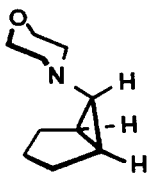
bond lengths [Å]			
C(1) - C(1')	1.500(8)	C(2) - N(2)	1.499(4)
C(1) - C(3)	1.487(5)	C(6) - N(2)	1.471(7)
C(1) - C(2)	1.493(5)	B - N(2)	1.618(8)
C(3) - N(1)	1.428(6)		
bond angles [°]			
C(1)-C(3)-C(1')	60.6(4)	C(1)-C(2)-N(2)	105.4(3)
C(3)-C(1)-C(1')	59.7(2)	C(2)-N(2)-C(2')	104.3(4)
C(1')-C(1)-C(2)	106.9(2)		
torsional angles [°]		**interplanar angles [°]**	
H(1)-C(1)-C(2)-H(2A)	- 119.7	C(1)C(1')C(3) - C(1)C(1')C(2')C(2)	112.7
H(1)-C(1)-C(2)-H(2B)	2.4	C(1)C(1')C(2')C(2) - C(2')C(2)N(2)	32.6

Fig. 1 Ortep plot of **8a**

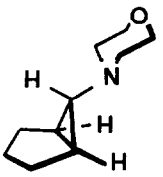


The addition of the borane moiety to an amino group is accompanied by a down-field shifting of the ^{13}C NMR signals of the directly neighboured C-atoms. This is observed for **8a,b** for the ^{13}C NMR signals of the Me-N-CH_2- unit of the pyrrolidine system (**6a** → **8a**; Me: 40.4 ppm → 49.9 ppm; CH_2: 53.8 ppm → 60.9 ppm; **6b** → **8b**: Me: 40.2 ppm → 49.5 ppm; CH_2: 53.6 ppm → 61.2 ppm) with almost no change of the morpholine and N-methylpiperazine ^{13}C NMR signals, respectively. The pyrrolidine-N-methyl moiety could be identified by a typical fine coupling (half-line-width of the corresponding signals in **6a,b** and **8a,b**: 12.2-13.1 Hz) in contrast to the piperazino-N-methyl group with no observable fine coupling (half-line-width of the corresponding signals in **6b**: 8.1 Hz and **8b**: 7.6 Hz). Indication of the pyrrolidine methylene ^{13}C NMR-signal was possible by selective ^1H-decoupling of the clearly designated H_A-proton of the pyrrolidine moiety changing the original triplet into a doublet.

Assignment of configuration of 6-aminobicyclo[3.1.0]hexane derivatives by dynamic ^{1}NMR spectroscopy proved to be difficult for parent compounds possessing a hydrogen atom at the C_1-bridge: Thus, **13** and **14** gave $\Delta G^{\ddagger}$ - values of 50.1 / 49.7 kJ/mol and 48.2 / 48.1 kJ/mol, respectively.[15] The $\Delta G^{\ddagger}$ - values of the diastereomeric diamines **6a** and **7a** are of an analogous magnitude (see Table 2.). Borane adduct of **6a** gave a coalescence for the morpholine signals, too. This is only observable for a non quaternized morpholine group, consequently the borane moiety is



13



14

connected to the pyrrolidine nitrogen atom. The higher $\Delta G^{\ddagger}$ - value (56.9 / 57.6 kJ/mol) for the borane diamine adduct **8a** clearly indicates the endo-position of the morpholine group: Addition of BH_3 leads to an increase of steric bulkiness exclusively in the endo-position of the bicyclic system.

Table 2 $\Delta G^{\ddagger}$ - Values of the Dynamics of the Morpholine Ring of the Compounds **6a**, **7a** and **8a** determined on the Basis of ^1H NMR Data (200 MHz) and Coalescence Temperatures (T_c) in $CD_3C_6D_5$

	T [°C]	group	$H_{A/X}$	$H_{B/Y}$	$^2J_{HH}$ [Hz]	T_c [°C]	$\Delta G^{\ddagger}$ [a] [kJ/mol]
6a	-73	OCH_2	3.65	3.42	10.7	-38	47.7
7a	-73	OCH_2	3.63	3.41	10.0	-38	47.0
	-73	NCH_2	2.35	2.24	12.0	-40	46.0
8a	-60	OCH_2	3.53	3.08	11.6	15	57.6
	-40	NCH_2	1.97	1.63	12.0	9	56.9

[a] Calculated with the approximation formula for the coupled case (ref. [16]).

Configuration of [n.1.0]bicyclic systems with only one substituent in the C_1-bridge generally could be deduced from the $^3J_{HH}$ coupling constant of the cyclopropane protons (e.g. **13**: $^3J_{HH}$ = 7.1 Hz; **14**: $^3J_{HH}$ = 2.0 Hz)[15]. Values of $^3J_{HH}$ = 6.6 Hz (**6c**), $^3J_{HH}$ = 2.0 Hz (**7a**) and $^3J_{HH}$ = 2.2 Hz (**7c**) thus are in agreement with the endo- and exo-amino-configuration, respectively. The cyclopropane ^1H NMR signals of **6a,b**, however, are not separated enough for determination of the coupling constant. But in these cases the formation of the borane adducts **8a,b** from **6a,b** led to a sufficient shifting of the bridge head hydrogen signals as a consequence of their syn-position of the borane unit. The resulting $^3J_{HH}$ value of 6.2 Hz in both cases indicates the endo-amino-configuration for **8a** and **8b** and their precursors **6a/b**, too.

^{11}B NMR spectroscopic data of **8a** (δ = -9.6 ppm), **8b** (δ = -10.6 ppm) and **9** (δ = -10.0 ppm) correspond quite well with values reported for amine-borane complexes in the literature.[17]

STEREOCHEMISTRY OF THE CYCLOPROPANATION REACTION

Chloro-amino-tetrahydropyridines **1** can serve as a convenient basis for a diastereocomplementary access to bicyclic amines **6** and **7**. Interpretation of the stereochemical result, however, is difficult: It is not clear whether a chloroenamine-borane-adduct **9** is involved in the formation of the bicyclic systems **8a** and **8b**. **9** obviously was isolated as a uniform, sterically pure compound; in this case the reaction of a diastereomer of **9** could give the desired insight in the course of the cyclopropane forming reaction.

Chloroenamine **7c** as starting material and water as the solvent should lead to a bicyclic iminium ion as intermediate. Inside attack of the nucleophile generating exo-amine **7c** predominately could be understood as a consequence of a borohydride - urethane moiety - interaction in this case.

EXPERIMENTAL

^1H NMR spectra were obtained with a Bruker AMX 400 or, if noted, with a Bruker WP 200 spectrometer; ^{13}C NMR spectra were recorded 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. A Büchi B-680 Chromatography System was used for the MPLC separations, B-685 column, Φ: 26 mm, length: 460 mm; Büchi UV/VIS Filter Photometer as detector, 254 nm.

Trihydro-(1α,5α,6β-3-methyl-6-morpholino-3-azabicyclo[3.1.0]hexane-N^3)-boron (**8a**): A mixture of chloroenamine **1a**[2] (4.33 g, 20 mmol), sodium borohydride (7.57 g, 200 mmol) and acetonitrile (120 mL) was stirred at 45°C for 5 d. Removal of excess sodium borohydride by suction, evaporation of the acetonitrile and stirring of the residue with water (20 mL) at room temperature for 5 h gave crude **8a** as a crystalline solid. The boranamine **8a** was isolated by suction, washed with aqueous sodium hydroxide (2N, 2 x 5 mL), dried in vacuo and recrystallized from ether. Yield: 2.25 g (57%); mp 100°C; IR (KBr, cm^{-1}) 2480-2300 (BH); ^1H NMR ($CD_3C_6D_5$) δ 1.23 (t, $^3J_{HH}$ = 6.2 Hz, 1H), 1.55 (H_X, $H_{X'}$, 2H), 2.04 (H_B, $H_{B'}$, 2H), 3.20 (H_A, $H_{A'}$, 2 H, AA'BB'XX'-system; $^2J_{AB}$ = 11.0 Hz), 2.30 (s, 3H), 1.85-2.05 (4H), 3.10-3.55 (4H) (broad, unsplit); ^{13}C NMR ($CDCl_3$) δ 66.6 (t), 60.9 (t), 52.1 (t), 49.7 (d, $^1J_{CH}$ = 170 Hz), 49.4 (q), 25.6 (d, $^1J_{CH}$ = 175 Hz). ^{11}B NMR ($CD_3C_6D_5$) δ -9.6. Anal. Calcd for $C_{10}H_{21}BN_2O$: C, 61.25; H, 10.79; N, 14.29. Found: C, 61.2; H, 10.7; N, 14.3.

4-(1α,5α,6ß-3-Methyl-3-azabicyclo[3.1.0]hex-6-yl)-morpholine (**6a**): A mixture of boranamine **8a** (1.69 g, 10 mmol) and aqueous hydrochloric acid (0.1 N, 100 mL) was stirred for 2 d at 40°C. The solution was cooled in an ice-bath and brought to pH = 13.5 by addition of solid sodium hydroxide. **6a** was extracted from the solution with ether in a Kutscher-Steudel apparatus (2 d) and purified by distillation in a Kugelrohr apparatus. Yield: 1.96 g (93%); bp 92°C/0.04 Torr; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.66-1.82 (H_Y, H_X, $H_{X'}$, 3H), 2,16 (H_B, $H_{B'}$, 2H), 3.16 (H_A, $H_{A'}$, 2H, AA'BB'XX'Y-system; $^2J_{AB}$ =

9.8 Hz), 2.26 (s, 3H), 2,49 (4H) and 3.70 (4H) (AA'XX'-system); ^{13}C NMR ($CDCl_3$) δ 67.0 (t), 53.8 (t), 52.5 (t), 48.7 (d, $^1J_{CH}$ = 166Hz), 40.4 (q), 25.3 (d, $^1J_{CH}$ = 171 Hz). Anal. Calcd for $C_{10}H_{18}N_2O$: C, 65.90; H, 9.95; N, 15.37. Found: C, 65.6; H, 10.1; N, 15.0.

Boranamine 8a by boranation of 6a: A solution of borane - dimethyl sulfide complex (0.76 g, 10 mmol) in ether (5 mL) was added at room temperature to a solution of amine **6a** (1.82 g, 10 mmol) in ether (10 mL). Stirring at room temperature for 12 h, evaporation of the solvent and recrystallization of the residue from ether gave pure **8a**: Yield: 1.80 g (92%); mp 100°C; ^1H and ^{13}C NMR data were identical with those of **8a** obtained from **1a** and $NaBH_4$.

1-Methyl-4-(1α,5α,6ß-3-methyl-3-azabicyclo[3.1.0]hex-6-yl)-piperazine (6b): A mixture of chloroenamine **1b**[2] (2.3 g, 10 mmol), sodium borohydride (3.78 g, 100 mmol) and acetonitrile (60 mL) was stirred at 45°C for 5 d. Removal of excess $NaBH_4$ by suction and evaporation of acetonitrile gave a mixture of **8b/8d** (1.24 g) which directly was deboranated by heating in aqueous hydrochloric acid (1N, 70 mL) at 50°C for 3 d. Working up analogously to the isolation of **6a** gave pure **6b** as a colorless oil. Yield: 0.89 g (45%); bp 72°C/0.005 Torr; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.62-1.80 (H_Y, H_X, $H_{X'}$, 3H), 2,15 (H_B, $H_{B'}$, 2H), 3.15 (H_A, $H_{A'}$, 2H, AA'BB'XX'Y-system; $^2J_{AB}$ = 10.0 Hz), 2.29 (s, 3H), 2.46 (s, 3H), 2.3 - 2.6 (broad, unsplit, 8H); ^{13}C NMR ($CDCl_3$) δ 55.0 (t), 53.6 (t), 51.7 (t), 48.0 (d, $^1J_{CH}$ = 165 Hz), 46.0 (q), 40.2 (q), 25.2 (d, $^1J_{CH}$ = 170 Hz) Anal. Calcd for $C_{11}H_{21}N_3$: C, 67.65; H, 10.84; N, 21.51. Found: C, 67.3; H, 10.8; N, 21.5.

Monoboranamine 8b by boranation of 6b: A solution of borane - dimethyl sulfide complex (0.76 g, 10 mmol) in ether (5 mL) was added at room temperature to a solution of amine **6b** (1.95 g, 10 mmol) in ether (10 mL). Stirring at room temperature for 1 h, evaporation of the solvent and recrystallization of the residue from ether gave pure **8b**. Yield: 1.70 g (81%); mp 114°C; ^1H NMR ($CD_3C_6D_5$) δ 1.31 (t, $^3J_{HH}$ = 6.2 Hz, 1H), 1.59 (H_X, $H_{X'}$, 2H), 2,10 (H_B, $H_{B'}$, 2H), 3.22 (H_A, $H_{A'}$, 2H, AA'BB'XX'-system; $^2J_{AB}$ = 11.4 Hz), 2.08 (s, 3H), 2.33 (s, 3H), 1.6 - 1.8 (2H), 1.9 - 2.2 (4H), 2.2 - 2.5 (2H) (broad, unsplit); ^{13}C NMR ($CDCl_3$) δ 61.2 (t), 55.1 (t), 51.7 (t), 49.5 (q), 49.4 (d, $^1J_{CH}$ = 172 Hz), 46.0 (q), 25.9 (d, $^1J_{CH}$ = 175 Hz); ^{11}B NMR ($CDCl_3$) δ - 10.6. Anal. Calcd for $C_{11}H_{24}BN_3$: C, 63.17; H, 11.57; N, 20.09. Found: C, 63.0; H, 11.6; N, 20.0.

(3-Chloro-1,2,3,6-tetrahydro-1-methyl-4-morpholino-pyridine-N[1])-trihydro-boron (9): Chloroenamine **1a**[2] (2.17 g, 10 mmol) in ether (40 mL) was boranated by the addition of a solution of borane - dimethyl sulfide complex (0.76 g, 10 mmol) in ether (5 mL) at room temperature. Stirring for 30 min at 20°C, removal of insoluble impurities by suction, evaporation of the ether, trituration of the residue with a small amount of ether (2 x 3 mL) gave crude **9** which was recrystallized from ether. Yield: 2.0 g (87%); IR (KBr, cm^{-1}) 2480-2200 (BH), 1635 (C=C); ^1H NMR ($CDCl_3$) δ 2.81 (s, 3H), 2.75 (H_{A1}, 2H), 2.94 (H_{B1}, 2H), 3,79 (H_{X1}, H_{Y1}, 4H) (ABXY-system, $^2J_{AB}$ = 11.6 Hz), 3.26 (H_{A2}, 1H), 3.53 (H_{B2}, 1H), 4.83 (H_{X2}, 1H) (ABX-system, $^2J_{AB}$ = 13.7 Hz), 3.42 (H_{A3}, 1H), 3.64 (H_{B3}, 1H), 4.66 (H_{X3}, 1H) (ABX-system, $^2J_{AB}$ = 16.5 Hz); ^{13}C NMR ($CDCl_3$) δ 141.8 (s), 97.6 (d), 66.3 (t), 63.0 (t), 58.6 (t), 50.5 (q), 48.9 (d, $^1J_{CH}$ = 156 Hz), 47.7 (t); ^{11}B NMR ($CDCl_3$) δ - 10.0. Anal. Calcd for $C_{10}H_{20}BClN_2O$: C, 52.10; H, 8.74; N, 12.15. Found: C, 52.0; H, 8.6; N, 12.2.

Reaction of 9 with sodium borohydride: A mixture of the borane - chloroenamine complex **9** (1.15 g, 5.0 mmol), sodium borohydride (1.89 g, 50 mmol) and acetonitrile (25 mL) was stirred at 45°C for 5 d. Crude **8a** was obtained by removal of excess $NaBH_4$ by suction, evaporation of the solvent, addition of aqueous sodium hydroxide (0.5 N, 15 mL) and extraction with dichloromethane (2 x 20 mL). Recrystallization from ether gave pure **8a**. Yield: 0.45 g (46%); mp 100°C; ^1H and ^{13}C NMR data were identical with those of **8a** obtained from **1a** and $NaBH_4$.

4-[(2,5-Dihydro-1-methyl-pyrrol-3-yl)-methyl]-morpholine (12): Water (60 mL) was added to a mixture of dichloroenamine **2a**[2] (5.0 g, 20 mmol) and sodium borohydride (7.6 g, 200 mmol). The mixture was stirred at room temperature for 20 h. Excess $NaBH_4$ was removed by suction; extraction of the aqueous solution with ether (5 x 50 mL) and evaporation of the ether led to **12** as a colorless oil which was purified by distillation in a Kugelrohr apparatus. Yield: 2.6 g (71%); bp 95°C/0.04 Torr; ^1H NMR ($CDCl_3$) δ 2.39 (4H) and 3.68 (4H) (AA'XX'-system), 2.47 (s, 3H), 3.00 (s, 3H), 3.43 (s, broad, 4H), 5.59 (s, broad, 1H); ^{13}C NMR ($CDCl_3$) δ 138.8 (s), 124.6 (d), 66.7 (t), 62.6 (t), 61.4 (t), 57.5 (t), 53.5 (t), 42.3 (q). Anal. Calcd for $C_{10}H_{18}N_2O$: C, 65.90; H, 9.95; N, 15.37. Found: C, 65.4; H, 9.9; N, 15.2.

Ethyl 6-morpholino-3-azabicyclo[3.1.0]hexane-3-carboxylates 6c and 7c from chloroenamine 1c: Chloroenamine **1c**[2] (5.5 g, 20 mmol) was triturated with solid sodium borohydride (7.6 g, 200 mmol) for 5 minutes. Then 35 mL of water were added. The mixture was stirred for 72 h at room temperature. The resulting oil, a mixture of **6c/7c**, was removed. Further **6c/7c** was obtained by extracting the aqueous layer with ether (3 x 20 mL). The combined crude **6c/7c** (4.25g, 85%) was purified by MPLC (silica gel; ether as solvent) to yield separated diastereomeric compounds **6c** and **7c**.

Ethyl 1α,5α,6β-6-morpholino-3-azabicyclo[3.1.0]hexane-3-carboxylate **(6c)**: Yield: 1.14 g (23%); mp 37°C; IR (KBr , cm^{-1}) 1710 (C=O); ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H), 1.66 (H_X, $H_{X'}$, 2H), 1.84 (t, H_Y, $^3J_{HH}$ = 6.6 Hz, 1H), 3,46-3,57 (H_A, $H_{A'}$, H_B, $H_{B'}$, 4H) (AA'BB'XX'-system), 2.51 (4H) and 3.62 (4H) (AA'XX'-system), 4.16 (q, 2 H); ^{13}C NMR ($CDCl_3$) δ 154.6 (s), 66.9 (t), 60.7 (t), 53.7 (t), 45.8 (t), 45.2 (t), 44.3 (d, $^1J_{CH}$= 175 Hz), 21.8 (d, $^1J_{CH}$= 170 Hz), 21.2 (d, $^1J_{CH}$= 171 Hz), 14.9 (q). Anal. Calcd for $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66. Found: C, 58.8; H, 8.5; N, 10.8.

Ethyl 1α,5α,6α-6-morpholino-3-azabicyclo[3.1.0]hexane-3-carboxylate **(7c)**: Yield: 2.7 g (57%); mp 83 °C; IR (KBr, cm^{-1}) 1710 (C=O); ^1H NMR ($CDCl_3$) δ 1.23 (t, 3H), 1.48 (t, H_Y, $^3J_{HH}$ = 2.2 Hz, 1H), 1.61 (H_X,$H_{X'}$, 2H), 3.40 (H_A,$H_{A'}$, 2H), 3.55 (H_B,$H_{B'}$, 2H) (AA'BB'XX'-system, $^2J_{AB}$= 13.2 Hz), 2.59 (4H) and 3.66 (4H) (AA'XX'-system), 4.10 (q, 2H); ^{13}C NMR ($CDCl_3$) δ 155.1 (s), 66.8 (t), 61.0 (t), 53.5 (t), 49.6 (d, $^1J_{CH}$= 170 Hz), 48.0 (t), 47.6 (t), 24.2 (d, $^1J_{CH}$= 170 Hz), 23.5 (d, $^1J_{CH}$= 170 Hz), 14.7 (q). Anal. Calcd for $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66. Found: C, 59.9; H, 8.5; N, 11.5.

Ethyl 1α,5α,6β-6-morpholino-3-azabicyclo[3.1.0]hexane-3-carboxylate (6c) from chloroenamine 1c and $NaBH_4$ in acetonitrile: Chloroenamine **1c**[2] (2.75 g, 10 mmol) was triturated with solid sodium borohydride (3.8 g, 100 mmol) for 5 minutes. Then 120 mL of acetonitrile were added. The mixture was stirred for 120 h at 70°C. The solvent was evaporated, then 100 mL of water and 90 mL of aqueous 1N HCl were added. Free base was obtained by addition of 15 mL of aqueous 10N NaOH and extracted by dichloromethane (4 x 80 mL). The crude reaction mixture was purified by MPLC (silica gel; ether as solvent) to yield pure **6c**. Yield: 0.83 g (35%); mp 37°C; the ^1H and the ^{13}C NMR spectra were identical with those recorded from **6c** which was obtained from **1c** and $NaBH_4$ in water.

4-(1α,5α,6α-3-Methyl-3-azabicyclo[3.1.0]hex-6-yl)-morpholine (7a) from $LiAlH_4$-Reduction of the Carboxylate 7c: Lithium aluminum hydride (1.52g, 40mmol) was slowly added to an ice-cooled solution of carboxylate **7c** (1.0 g, 4.0 mmol) in ether (20 mL). The mixture was stirred at room temperature for 40 h; then consecutively water (5 mL, to destroy excess $LiAlH_4$) and ether (60 mL) were added. The ethereal layer was separated by centrifugation; the residue triturated with ether (2 x 40 mL). Evaporation of the combined ether extracts gave pure **7a**. Yield: 0.6g (82%); mp 39°C; ^{1}H NMR ($CDCl_3$) δ 1.46 (H_X, $H_{X'}$, 2H), 2.33 (H_A, $H_{A'}$, 2H), 2.97 (H_B, $H_{B'}$, 2H) (AA'BB'XX'-system, $^2J_{AB}$= 8.8 Hz), 1.97 (t, H_Y, $^3J_{HH}$ = 2.0 Hz, 1H), 2.26 (s, 3H), 2.56 (4H) and 3.65 (4H) (AA'XX'-sytem); ^{13}C NMR ($CDCl_3$) δ 66.8 (t), 56.8 (t), 53.6 (t), 47.0 (d, $^1J_{CH}$= 165 Hz), 41.4 (q), 24.1 (d, $^1J_{CH}$= 170 Hz). Anal. Calcd for $C_{10}H_{18}N_2O$: C, 65.90; H, 9.95; N, 15.37. Found: C, 65.9; H, 9.9; N, 15.3.

X-Ray Crystal Structure Analysis of 8a.[18,19] Single crystals of **8a** were obtained by crystallization from ether.

Crystal data: $C_{10}H_{21}BN_2O$, F.W. = 196.1; orthorhombic space group P *nma*; a= 13.572(1), b = 10.030(2), c = 8.715(1) Å; $\alpha = \beta = \gamma = 90°$; V = 1186.4(5) Å^3; 4 molecules per unit cell; D_x = 1.10 g cm^{-3}; crystal size 0.50 x 0.35 x 0.35 mm.

Data collection: Diffractometer Enraf-Nonius-CAD 4, monochromatized Mo-K_α radiation; 771 independent reflexions with 4.00 < 2θ < 50.00° [ω/2θ scan, scan width (0.85 + 0.35 tan θ)°, scan speed 1.15 - 10.06 ° · min^{-1}], no absorption correction.

Structure solution and refinement: Full matrix least-squares method; H atoms refined isotropically, 614 reflections with $I > 2.00\,\sigma(I)$; 139 variables, unit weights, maximum shift/error ratio 0.07, R = 0.044, $R_w = (\Sigma\Delta^2F / \Sigma F_o^2)^{1/2}$ = 0.037.

Acknowledgments: This work was sponsored by the Fonds der Chemischen Industrie. Support of this work by the Deutsche Forschungsgemeinschaft is greatfully acknowledged.

REFERENCES AND NOTES

Dedicated to Prof. Dr. Paul Binger on the occasion of his 60th birthday.

1. Vilsmaier, E.; Stamm, T.; Dauth, W.; Tetzlaff, C.; Barth, S. *Bull. Soc. Chim. Belg.*, submitted for publication.

2. Tetzlaff, C.; Vilsmaier, E.; Schlag, W.-R. *Tetrahedron*, **1990**, *46*, 8117-8130.

3. Brown, H. C.; Murray, L. T. *Inorg. Chem.*, **1984**, *23*, 2746-2753.

4. Alt, G. H.; Cook, A. G. in Enamines, A. G. Cook, Ed.; M. Dekker, New York 1988, 2nd Edition, p. 181-246.

5. Singaram, B.; Goralski, C. T.; Rangaishenvi, M. V.; Brown, H. C. *J. Am. Chem. Soc.*, **1989**, *111*, 384-386; Singaram, B.; Rangaishveni, M. V.; Brown, H. C. *J. Org. Chem.*, **1991**, *56*, 1543-1549.

6. Brown, H. C.; Prasad, J. V. N. V. *Heterocycles*, **1987**, *25*, 641-657.

7. Nemia, M. M. B.; Lee, J.; Joullié, M. M. *Synth. Commun.*, **1983**, *13*, 1117-1123; Irreverre, F.; Morita, K.; Robertson, A. V.; Witkop, B. *J. Am. Chem. Soc.*, **1963**, *85*, 2824-2831; Brown, H. C.; Rangaishenvi, M. V. *J. Heterocycl. Chem.*, **1990**, *27*, 13-24.

8. Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y.; Yamane, S.; Kanazawa, T.; Aoki, T. *J. Am . Chem. Soc.*, **1982**, *104*, 6697-6703; Lyle, R. E.; Carle, K. R.; Ellefson, C. F.; Spicer, C. K. *J. Org. Chem.*, **1970**, *35*, 802-805; Brayer, J. L.; Alazard, J. P.; Thal, C. *Tetrahedron*, **1990**, *46*, 5187-5198.

9. Vilsmaier, E.; Tetzlaff, C.; Denkel, E.; Eisenbrand, G. to be published.

10. Luche, J. L. *J. Am. Chem. Soc.*, **1978**, *100*, 2226-2227; Long, J. R. *Aldrichimica Acta* **1985**, *18*, 87-93.

11. Krief, A.; Surleraux, D. *Synlett* **1991**, 273-275.

12. Durig, J. R.; Li, Y. S.; Odom, J. D. *J. Mol. Struct.*, **1973**, *16*, 443-450.

13. Cassoux, P.; Kuczkowski, R. L.; Bryan, P. S.; Taylor, R. C. *Inorg. Chem.*, **1975**, *14*, 126-129..

14. Iijima, K.; Adachi, N.; Shibata, S. *Bull. Chem. Soc. Jpn.*, **1984**, *57*, 3269-3273.

15. Vilsmaier, E.; Klein, C. M.; Tröger, W. *Chem. Ber.*, **1982**, *115*, 2795-2806.

16. Günther, H. NMR-Spektroskopie, G. Thieme, Stuttgart 1983, 2nd edition, p 235.

17. Nöth, H.; Wrackmeyer, B. in Nuclear Magnetic Resonance Spectroscopy of Boron Compounds, in NMR Basic Principles and Progress, Vol 14, Diel, P.; Fluck, E.; Kosfeld, R. Ed.; Springer Verlag, Berlin 1978, p. 88-90.

18. All calculations were done with the Structure Determination Package (Enraf-Nonius, Delft, The Netherlands).

19. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Center, University Chemical Laboratory, Lensfield, Cambridge, CB2 1EW. The X-ray data are available on request from the Director of the CCDC by quoting the full literature citation of this paper.