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Plyers-shaped diamines II [1]. 3-Amino-2,4-cyclogranatane diastereomers - A study of influence of structure on the properties of diamines

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Abstract

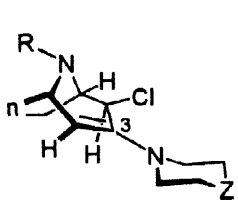
3-Amino-2,4-cyclogranatane 3β- and 3α-diastereomers can be synthesized from the corresponding 3β-carbonitriles by a kinetically and a thermodynamically controlled reductive decyanation, respectively. Comparison of both diastereomers with respect to basicity, ionization potentials and behaviour towards oxygen demonstrates the influence of the lone pair - lone pair interaction on the properties of diamines. An X-ray structural analysis of a protonated syn diamine established an N · · · N -distance of 2.72 Å in this new type of compounds.

Keywords: Polycyclic heterocyclic compounds; Diamines; Oxidation; Ammonium salts

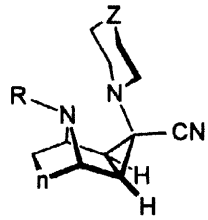
1. Introduction

2,4-Cyclotropanecarbonitriles **3**, 2,4-cyclogranatanecarbonitriles **4** and the corresponding carboxamides **5** with an endo positioned 3-amino moiety represent a new type of diamines with sterically forced interaction of the two N lone pairs (N,N-distance of 2.88 Å in nitrile **4a** [1]).

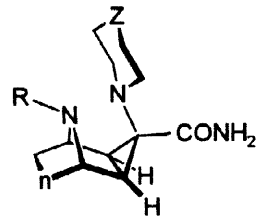
Figure 1



1: n = CH_2
2: n =$(CH_2)_2$



3: n = CH_2
4: n =$(CH_2)_2$



5: n =$(CH_2)_2$

1 - 5: a: R = CH_3, Z = O b: R = CH_3, Z = CH_2 c: R = $CH_2C_6H_5$, Z = O

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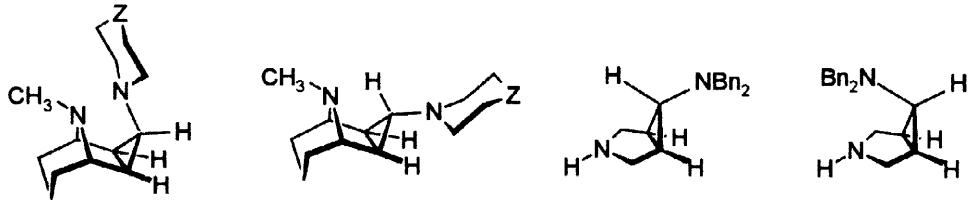
These derivatives were synthesized on the basis of chloroenamines **1** and **2** (Figure 1). The presence of an electron-withdrawing group in **3**, **4** and **5** and the missing availability of the corresponding exo-amino stereoisomer prohibits a clear view about the real effects of the sterically anchored N lone pairs on the properties of the new compounds.

Figure 2



6a,b **7a,b** **8** **9**

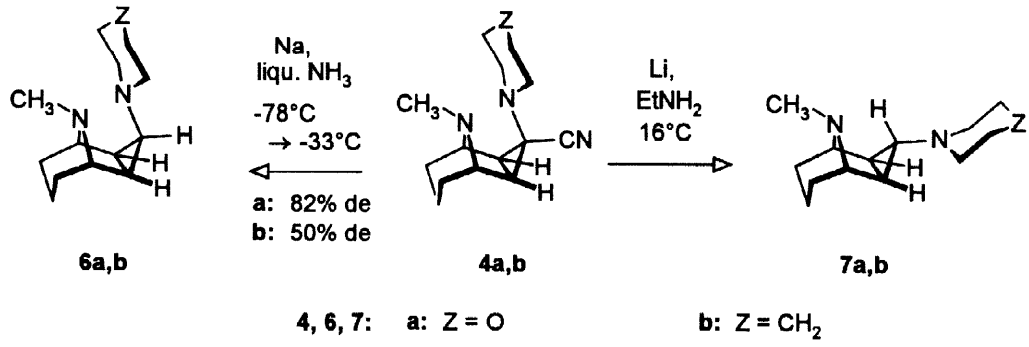
a: Z = O **b:** Z = CH_2

Parent system **6** and its diastereomer **7** were selected as better candidates for studying the influence of lone pair - lone pair interaction on the properties of chelating diamines. A morpholino- or a piperidino moiety were provided as the amino group in 3-position (Figure 2). The results of these investigations are reported in this paper.

2. Synthesis and structure of 3-amino-2,4-cyclogranatane diastereomers 6 and 7

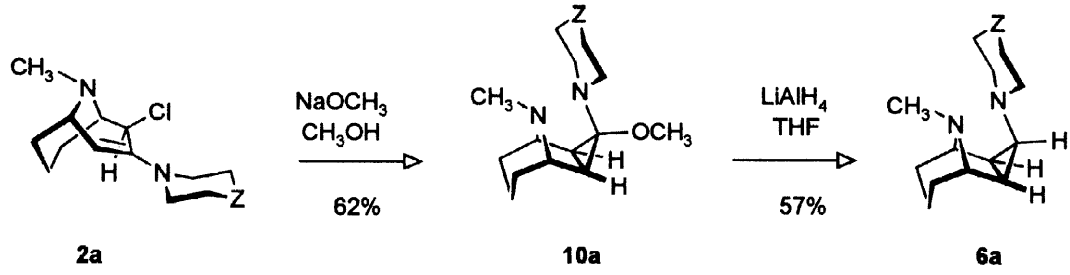
A reductive decyanation of carbonitrile **4** by an alkali metal in liquid ammonia was tried as most promising access to diastereomers **6** and **7**; this method was successfully applied [2] for the synthesis of dibenzylaminoazabicyclohexane diastereomers **8** and **9**. Complementary diastereoselections could be achieved [2] by using different reaction conditions. Analogous treatment of nitriles **4a,b** with a "solution" of sodium in liquid ammonia at -78°C and subsequent warming up caused a decyanation leading to endo-amines **6a,b** as main products (Scheme1). Additionally formed exo-amines **7a,b** were removed quantitatively by extraction with a buffer solution of glycine, sodium chloride and sodium hydroxide to give pure diamines **6a** and **6b** in 67% and 51% yield, respectively. Reaction of nitriles **4a,b** with lithium in boiling ethylamine, on the other hand, provided exo-amines **7a** (89% yield) and **7b** (84% yield). Only products **7a** and **7b** resulting from a substitution with inversion of configuration at C(3) could be determined ^1H NMR spectroscopically in the crude reaction mixture.

Scheme 1



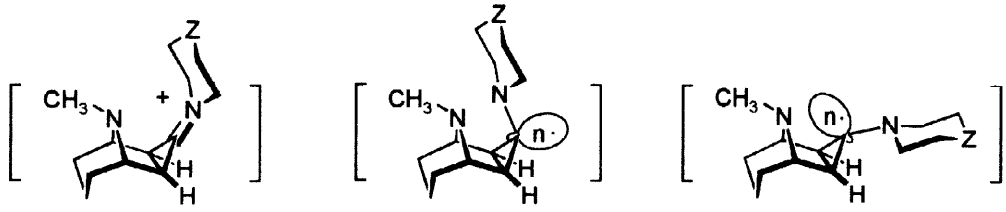
Nucleophilic displacement of the methoxy group in N,O-acetal **10a** by hydride was investigated as alternative access to compounds **6** or **7**. Starting material **10a** could be obtained easily by treatment of chloroenamine **2a** with sodium methoxide in methanol (62% yield). Lithium aluminum hydride was used as hydride reagent for the subsequent nucleophilic substitution which gave endo-morpholino derivative **6a** as single isomer in 57% yield (Scheme 2) (a similar sequence was used in the synthesis of **9** [3]).

Scheme 2



Iminium ion **11** represents the intermediate in the latter displacement reaction. The strong steric shielding of the inside of the annulated cyclopropaniminium species **11** causes the exclusive outside attack of the hydride leading to **6**. Radicals **12** and **14** or carbanions **13** and **15** are involved in the reductive decyanation of nitriles **4**. Obviously, removal of N,N' lone pair repulsion upon transition of **12** → **14** or **13** → **15** causes a strong tendency for isomerization (Figure 3). It is not clear, however, if this inversion takes place in the radical step or in the carbanion step of the overall reaction (see ref. [2]).

Figure 3



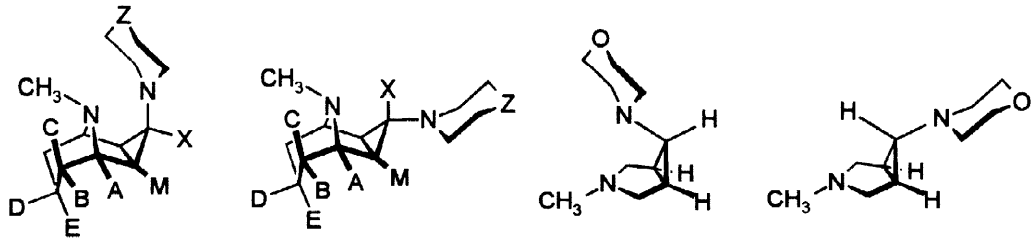
11 **12:** n = 1 **13:** n = 2 **14:** n = 1 **15:** n = 2

11-15: **a:** Z = O **b:** Z = CH_2

The pyramidal geometry of the radicalic center in **14** or of the carbanionic center in **15** allows an easier inside attack of the reagent than the planar arrangement of the cyclopropaniminium moiety in the cationic intermediate **11**.

Configuration of the reaction products **6/7** at the C(3)-atom can be deduced ^{1}H NMR spectroscopically via $^3J_{HH}$ -coupling of the cyclopropane hydrogen atoms XM and XM' ($^3J_{HH}$: **6a/b**: 7.2 Hz; **7a/b**: 1.6 Hz). The absence of any detectable coupling between the hydrogen atoms AM and A'M' indicates that the configuration at C(2) and C(4) was not changed in the reductive decyanation reaction (see ref. [1]). The ^{1}H NMR signals of the piperidine unit of the cyclogranatane skeleton of **7a,b** were simulated with the CALM program [4] as AA'BB'CC'DE-system. The determined and refined coupling constants establish the presence of a chair conformation of the piperidine subunit. An analogous simulation was not possible for diastereomers **6a,b** due to identical chemical shifts of C/C' and E [irradiation at this common signal gave singlets for A/A', B/B' and D (AB, A'B', BD and B'D coupling constants smaller than 1 Hz)]. The absence of a stronger coupling at A/A' ($J_{AC} = J_{A'C'} \approx 2.2$ Hz) indicates the presence of a chair conformation of the piperidine subunit in **6a,b**, too (for assignments of the hydrogen atoms see Figure 4; chemical identical hydrogen atoms which are indicated by a prime are not depicted).

Figure 4



6a,b **7a,b** **16** **17**

6, 7: **a:** Z = O **b:** Z = CH_2

3. Properties of 3-amino-2,4-cyclogranatane diastereomers 6 and 7

3.1 Dynamics of the hetereocyclic ring in 3-position

Dynamics of morpholine are almost not influenced by a 3-azabicyclo[3.1.0]hex-6-yl substituent as shown by compounds **16** ($\Delta G^{\ddagger}$ = 47.7 kJ/mol [5]) and **17** ($\Delta G^{\ddagger}$ = 47.0, 46.0 kJ/mol [5]). The absence of a further substituent in 6-position allows an easy topomerization of methylene H-atoms even if the morpholine is located in the endo-position. The free activation enthalpies $\Delta G^{\ddagger}$ of the dynamics of morpholine or piperidine in **6a,b**, **7a,b** and **10a** were determined by the usual approximation formula [6] for coupling systems; the resulting values are given in Table 1.

Table 1
Free activation enthalpy $\Delta G^{\ddagger}$ of the dynamics of morpholine or piperidine in tricyclic compounds **6a,b**, **7a,b** and **10a** in d_8-toluene (400 MHz)

	Topomerizing H_AH_B	H_A [ppm]	H_B [ppm]	J_{AB} [Hz]	T[a] [K]	T_c[b] [K]	$\Delta G^{\ddagger}$[c] [kJ/mol]
6a	NCH_2	2.26	2.49	10.1	202	222	43.9
6b	NCH_2	2.23	3.23	9.9	190	237	44.2
7a	NCH_2	2.26	2.40	10.6	203	240	48.5
	OCH_2	3.43	3.62	10.2	203	243	48.6
7b	NCH_2	2.24	3.20	10.0	212	258	48.4
10a	NCH_2	2.68	2.90	10.6	203	287	57.6
	OCH_2	3.77	3.86	10.0	203	281	58.3

[a] Temperature for determination of H_A, H_B and J_{AB}.
[b] Coalescence temperature.
[c] Calculation of $\Delta G^{\ddagger}$ according to the approximation formula [6] for coupled H_A and H_B.

The differences of the $\Delta G^{\ddagger}$ values of the dynamics of morpholine or piperidine in **6a/6b** and in **7a/7b** are just outside of the limit of error. The slight facilitation of the dynamics of the heterocyclic ring in endo-position can be interpreted as the consequence of an N,N' lone pair interaction leading to an easier C-N-rotation and ring inversion. In the case of **10a**, the determination of energy of topomerization of hydrogen atoms in morpholine can be used for assignment of 3α-configuration to this compound.

3.2 Basicity

Aminocyclogranatane diastereomers **6a,b** and **7a,b** 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 both endo-diamines **6a,b** and the exo-diamine **7a** were only monoprotonated in the aqueous system; exo-piperidine derivative **7b** took up two protons. pK_a values were determined by application of the Henderson-Hasselbalch equation [7] at the corresponding half-neutralization points (pH = pK_a). The pK_a-values are given in Table 2. As expected, diastereomers **6** and **7** differ clearly in their basicity; the stronger basicity of **6** with respect to **7** indicates the effect of the sterically forced plyers-shaped arrangement of the N lone pairs. The negative structural influence of the additional constraining of a granatane system on basicity can be estimated by comparing the pK_a values of **7a,b** with that of parent compound **18** (pK_a = 10.19, measured in 40% aqueous ethanol [8]) (Figure 6). The lower basicity of **6a** with respect to **4a** (pK_a = 10.73 [1]) possessing the nitrile function is surprising. It should be, however, the consequence of easier evading the plyers-shape arrangement of the two N lone pairs in **6a** due to the missing buttressing effect of the hydrogen atom in 3-position. This effect becomes apparent already by the easier dynamics of morpholine or piperidine in **6a,b** with respect to **7a,b**.

Table 2
pK_a-Values of the diamines **6a,b** and **7a,b** in water (c_o = 1 mmol)

Compound	6a	6b	7a	7b
pK_a	10.49 ± 0.01	10.27 ± 0.03	9.26 ± 0.03	9.36 ± 0.09 5.84 ± 0.09

3.3 Structure of monoprotonated morpholinocyclogranatane 19

Azonia triflate **19** was obtained by treatment of diamine **6a** with one equivalent of trifluoromethane sulfonic acid. Clearly stronger increase [1] of $^1J_{CH}$ coupling of ^{13}C NMR NCH_3-signal (ΔJ = 11.6 Hz) with respect to the morpholine NCH_2-signal (ΔJ = 3.0 Hz) indicates that the added proton is located mainly at N(9)-atom with weak bonding to morpholine N-atom. The change of $^1J_{CH}$ coupling of the cyclopropane unit [C(2)-H/C(4)-H: ΔJ = 10.7 Hz; C(3)-H: ΔJ = 15.7 Hz] should be rather the consequence of additional strain of the tricyclic skeleton upon protonation. Single crystals of ammonium salt **19** were obtained by crystallization from methanol; the salt, however, crystallized as solvate (**19** · CH_3OH). The molecular plot and the numbering of atoms are depicted in Figure 5. Selected bond distances, atomic distances and dihedral angles are listed in Table 3.

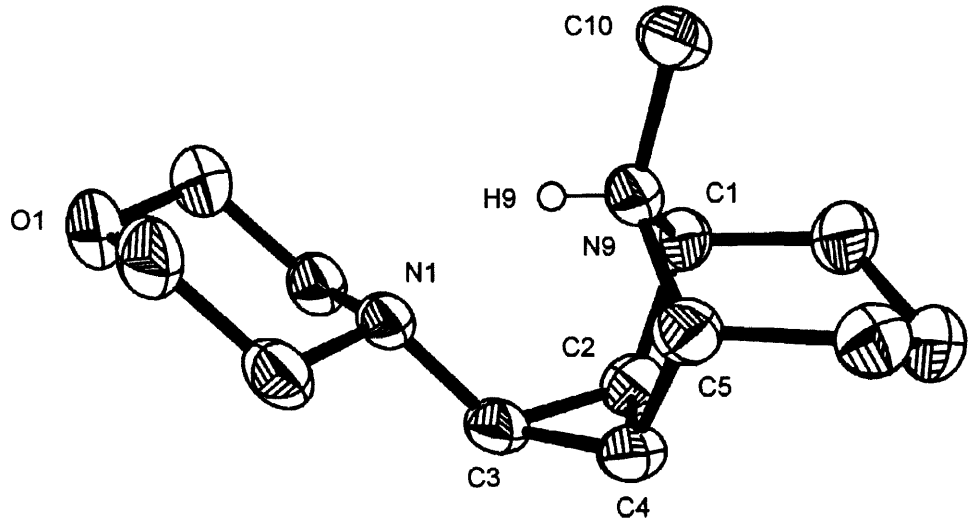


Figure 5 X-Ray plot and numbering of atoms of **19** · CH_3OH (Molecular Graphics from SHELXTL-Plus [9] Software Package; thermal ellipsoids were drawn at the 33% probability level. Hydrogen atoms (except ammonium hydrogen atom), methanol and the trifluoromethanesulfonate anion were omitted for reasons of clarity.

The most interesting detail in the X-ray structural analysis corresponds to the N - H · · N arrangement in the cation of **19** · CH_3OH (Figure 5). The ammonium proton H(9) could be located directly; it is bonded to N(9) with a bonding distance of 0.78(3) Å. A distance of 2.72 Å was found between the two nitrogen atoms N(9) and N(1) [N(9)H(9)N(1) angle: 145.9°]. A value of 0.5° for the angle of the planes C(3)N(1)O(1) and C(10)N(9)C(3) indicates the straight forward direction of N(1) lone pair towards the H(9)-atom. The clear hydrogen bonding in ammonium salt **19** · CH_3OH is underlined additionally by comparing the N(1)N(9)-distance and the ring buckling α with the values of diamine **4a** [shortening of (N1)N(9) distance by 0.16 Å and increase of ring buckling α by 6.7° and 1.6°] [1].

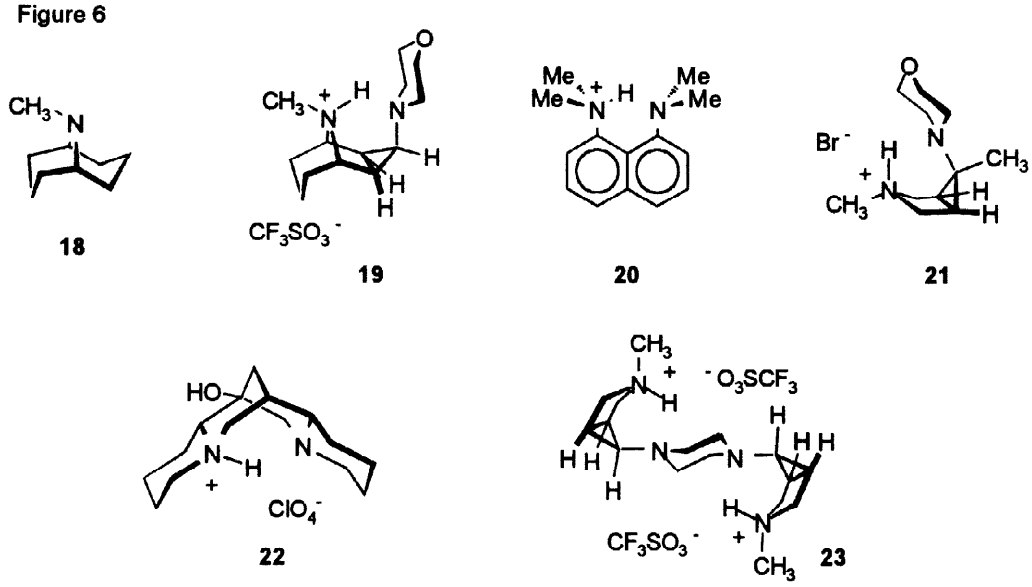
The effect of additional constraining of a 6-amino-3-azoniabicyclo[3.1.0]hexane unit on hydrogen bonding becomes obvious by comparing **19** with the ammonium salts **21** and **23**. Ring buckles $\alpha_2 = 8.1°$ (for **21** [10]) and $\alpha_2 = 22.4°$ (for **23** [11]) were found for these salts leading to N · · N distances of 2.996 [Å] and 2.858 [Å], respectively (Figure 6). There is no detectable ammonium hydrogen interaction with the triflate anion or the solvating methanol in **19**. Thus, salt **19** can be incorporated as a new member into the family of monoprotonated diamines with strong hydrogen bonding beween two trigonal pyramidal nitrogen atoms. Hydrogen bonding is slightly weaker in **19** than in monoprotonated proton sponges of type **20** for which extreme values of 2.52 and 2.62 Å were reported thus far (see ref. [12]). The N · · N distance in the new derivative **19**, however, is comparable to that of monoprotonated diamines of the bispidine type (e.g. monoprotonated 7-hydroxy-β-isosparteine **22**: N · · N distance: 2.68 Å [13]) (Figure 6).

Table 3
Selected bond distances [Å], atomic distances [Å] and interplanar angles [°] of 9-methyl-3-morpholino-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane triflate **19** · CH_3OH.

C1) - C(2)	1.486(5)	C(4) - C(5)	1.573(6)
C(2) - C(3)	1.407(5)	C(3) - C(4)	1.594(6)
C(2) - C(4)	1.542(6)	N(9) - H(9)	0.78(3)
N(9) - C(1)	1.510(5)	N(9) - C(5)	1.523(5)
C(3) - N(1)	1.450(5)	N(1) · · · N(9)	2.72
C(10) - N(9)	1.493(5)	N(1) · · · H(9)	2.04

C(2)C(3)C(4)	C(1)C(2)C(4)C(5)	70.1° (α_1)
C(1)C(2)C(4)C(5)	C(1)N(9)C(5)	46.3° (α_2)
C(3)N(1)O(1)	C(10)N(9)C(3)	0.5°

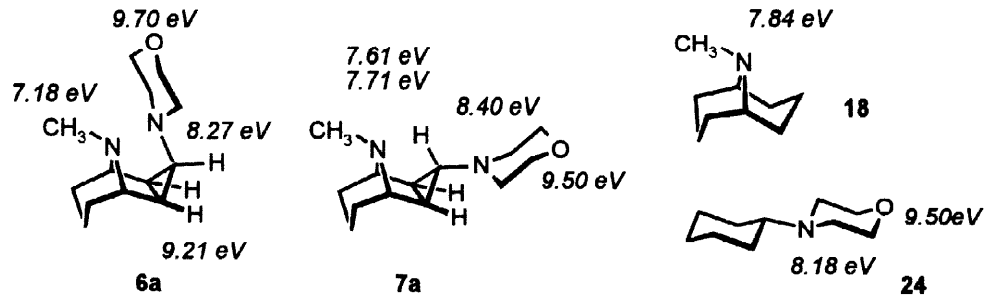
Figure 6



3.4 Ionization potentials of the N lone pairs in morpholinocyclogranatanes **6a/7a**

Ionization potentials of the isomeric diamines **6a** and **7a** were determined by PE spectroscopy. The observed values are given in Figure 7 together with some published ionization potentials of comparable compounds.

Figure 7

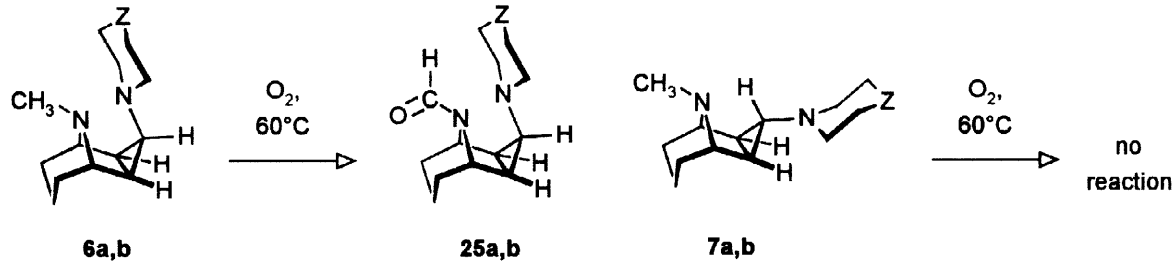


Compound **24** [14] allows the assignment of the bands in the PE spectra of **6a** and **7a** which correspond to morpholine. Ionization of CH_3-N lone pair in **7a** is comparable with that of parent system **18** [15]. It is not clear if the easier removal of the analogous electron from endo-morpholine isomer **6a** is either the consequence of stabilization of the resulting radical cation by the N' lone pair or the result of additional strain in isomer **6a**. The band at 9.21 eV should indicate removal of an electron from the cyclopropane subunit in **6a**; in the case of **7a**, this band overlaps most presumably with the 9.50 eV band of morpholine (Figure 7).

3.5 Autoxidation of aminocyclogranatanes **6a/b**

endo-Aminocyclogranatanes **6a,b** proved to be sensitive against molecular oxygen. Storing endo isomers **6a,b** at 60°C for 24 h in an oxygen atmosphere caused an oxidation of the N-methyl moiety to give formyl derivatives **25a/b** in 78% and 82% yield, respectively. Unchanged starting materials were easily removed by extraction with buffer solution (citric acid / disodium hydrogenphosphate). A very clean autoxidation is underlined by ^{1}H NMR spectroscopic analysis of the reaction mixture indicating only the presence of products **25a,b** besides unchanged starting materials **6a,b**. Interestingly, isomers **7a,b** are not attacked by oxygen under analogous conditions (Scheme 3).

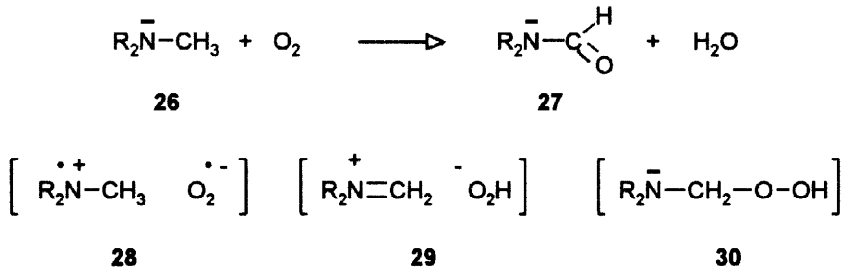
Scheme 3



6, 7, 25: **a:** Z = O **b:** Z = CH_2

Reactions of amino derivatives with oxygen are described in the literature, there are known few examples in which no catalyst or no photo excitation is necessary (for a review see ref. [16]). The easy and highly selective transformation of **6a,b** into **25a,b** is remarkable in this context. It should be also the consequence of the lone pair activation of N(9) by the plyers-shape arrangement of the second N lone pair. In a more general manner, the oxidation process of **26** into **27** can be described by primary formation of intermediate **28**, a subsequent proton transfer to give ion pair **29** and elimination of water from its covalent bonded species **30** (Scheme 4).

Scheme 4



4. Conclusion

Aminocyclogranatanes **6a,b** and their diastereomers **7a,b** can be used as model compounds for studying the effects of N lone pair interaction on the properties of diamines. Basicity, ionization potential and chemical behaviour against oxygen are clearly influenced in a diamine if the N lone pairs are constrained in a plyers-shaped manner as in **6a,b**.

5. 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]. The He (I) PE spectra were recorded with a Perkin PS18 spectrometer and calibrated using Ar and Xe. A resolution of 20 meV was obtained for the $^2P_{3/2}$ line of Ar. Commercially available buffer solutions (Fa. Merck KGaA, Darmstadt) were used.

Tricyclic endo-amines **6a,b** *from nitriles* **4a,b** *- general procedure*: Tricyclic nitrile **4** [1] (1.0 mmol, **4a**: 0.247 g; **4b**: 0.245 g) was added to a "solution" of sodium (0.092 g, 4.0 mmol) in

liquid ammonia at -78°C. Then the cooling bath was removed and the mixture was stirred till the ammonia was evaporated. Extraction of the residue with ether (2 x 15 mL) gave a mixture of crude tricyclic endo-amine **6** and exo-amine **7** (**6/7: a**: 10:1; **b**: 3:1). The less basic exo-amines **7** were separated by addition of 30 mL of an aqueous buffer solution [**6a/7a**: pH = 10.4, glycine (0.1 mol/L; 8.35 mL), sodium chloride (0.1 mol/L; 8.35 mL) and sodium hydroxide (0.1 mol/L; 13.3 mL); for **6b/7b**: pH = 10.1, glycine (0.1 mol/L; 9.1 mL), sodium chloride (0.1 mol/L; 9.1 mL) and sodium hydroxide (0.1 mol/L; 11.8 mL)] and extraction with ether (2 x 20 mL). Addition of an aqueous solution of sodium hydroxide (5M) to the water solution till pH 12 and subsequent extraction with ether (3 x 20 mL) gave endo-amines **6a,b** which were purified by distillation in a Kugelrohr apparatus.

1α,2α,3β,4α,5α-9-Methyl-3-morpholino-9-azatricyclo[3.3.1.0^{2,4}]nonane (**6a**): Yield: 0.148 g (67%); bp 50°C/0.001 mbar; ^{1}H NMR (C_6D_6) δ 0.96 (H_B, $H_{B'}$, 2H), 1.00 (H_M, $H_{M'}$, 2H), 1.38 (H_D, 1H), 1.75 (H_X, 1H), 1.85 (H_C, $H_{C'}$, H_E, 3H), 3.04 (H_A, $H_{A'}$, 2H) (AA'BB'CC'DEMM'X-system, $^3J_{MX} = {}^3J_{M'X} = 7.2$ Hz, $^3J_{AM} = {}^3J_{A'M'} < 0.8$ Hz), 2.42 (s, 3H), 2.48 (m_c, 4H), 3.72 (m_c, 4H) (morpholine); ^{13}C NMR (C_6D_6) δ 67.1 (t, $^1J_{CH} = 141.8$ Hz), 57.3 (d, $^1J_{CH} = 143.0$ Hz), 54.1 (t, $^1J_{CH} = 132.4$ Hz), 49.2 (d, $^1J_{CH} = 156.9$ Hz), 32.8 (q, $^1J_{CH} = 131.5$ Hz), 25.7 (d, $^1J_{CH} = 166.7$ Hz), 21.9 (t), 17.6 (t). Anal. Calcd for $C_{13}H_{22}N_2O$: C, 70.22; H, 9.97; N, 12.60. Found: C, 70.0; H, 9.9; N, 12.6.

1α,2α,3β,4α,5α-9-Methyl-3-piperidino-9-azatricyclo[3.3.1.0^{2,4}]nonane (**6b**): Yield: 0.113 g (51%); bp 50°C/0.001 mbar; ^{1}H NMR (C_6D_6) δ 1.01 (H_B, $H_{B'}$, 2H), 1.08 (H_M, $H_{M'}$, 2H), 1.42 (H_D, 1H), 1.81 (H_X, 1H), 1.88 (H_C, $H_{C'}$, H_E, 3H), 3.12 (H_A, $H_{A'}$, 2H) (AA'BB'CC'DEMM'X-system, $^3J_{MX} = {}^3J_{M'X} = 7.2$ Hz, $^3J_{AM} = {}^3J_{A'M'} < 0.7$ Hz), 2.49 (s, 3H), 1.40 (m_c, 2H), 1.62 (m_c, 4H), 2.54 (m_c, 4H) (piperidine); ^{13}C NMR (C_6D_6) δ 57.7 (d), 55.3 (t), 49.8 (d), 33.5 (q), 26.3 (t), 26.2 (d, $^1J_{CH} = 165.9$ Hz), 25.1 (t), 22.8 (t), 17.8 (t). Anal. Calcd for $C_{14}H_{24}N_2$: C, 76.31; H, 10.98; N, 12.71. Found: C, 76.4; H, 11.0; N, 12.8.

Tricyclic exo-amines **7a,b** - *general procedure*: Tricyclic nitrile **4** [1] (1.0 mmol, **4a**: 0.247 g; **4b**: 0.245 g) was added under stirring at 16°C (boiling temperature of ethylamine) to a "solution" of lithium (0.093 g, 12.0 mmol) in anhydrous liquid ethylamine (80 mL). Then the ethylamine was evaporated at room temperature. Extraction of the residue with ether (2 x 15 mL) gave crude tricyclic exo-amines **7a,b** which were purified by distillation in a Kugelrohr apparatus.

1α,2α,3α,4α,5α-9-Methyl-3-morpholino-9-azatricyclo[3.3.1.0^{2,4}]nonane (**7a**): Yield: 0.198 g (89%); mp 73°C, bp 55°C/0.001 mbar; ^{1}H NMR (C_6D_6) δ 0.97 (H_B, $H_{B'}$, 2H), 1.20 (H_M, $H_{M'}$, 2H), 1.32 (H_D, 1H), 1.74 (H_C, $H_{C'}$, 2H), 2.00 (H_E, 1H), 2.40 (H_X, 1H), 2.90 (H_A, $H_{A'}$, 2H) (AA'BB'CC'DEMM'X-system, $^3J_{AB} = {}^3J_{A'B'} = 2.0$ Hz, $^3J_{AC} = {}^3J_{A'C'} = 3.25$ Hz, $^4J_{AD} = {}^4J_{A'D} = 0.9$ Hz, $^4J_{BB'} = 1.8$ Hz, $^2J_{BC} = {}^2J_{B'C'} = 13.6$ Hz, $^3J_{BD} = {}^3J_{B'D} = 0.5$ Hz, $^3J_{BE} = {}^3J_{B'E} = 6.6$ Hz, $^3J_{CD} = {}^3J_{C'D} = 6.1$ Hz, $^3J_{CE} = {}^3J_{C'E} = 12.4$ Hz, $^2J_{DE} = 13.1$ Hz, $^3J_{AM} = {}^3J_{A'M'} < 0.8$ Hz; $^3J_{MX} = {}^3J_{M'X} = 1.6$ Hz), 2.31 (s, 3H), 2.50 (m_c, 4H), 3.65 (m_c, 4H) (morpholine); ^{13}C NMR (C_6D_6) δ 67.3 (t), 57.1 (d), 54.2 (t), 45.2 (d), 32.1 (q), 26.5 (d, $^1J_{CH} = 167.9$ Hz), 20.9 (t), 17.7 (t). Anal. Calcd for $C_{13}H_{22}N_2O$: C, 70.22; H, 9.97; N, 12.60. Found: C, 70.2; H, 10.1; N, 12.7.

1α,2α,3α,4α,5α-9-Methyl-3-piperidino-9-azatricyclo[3.3.1.0^{2,4}]nonane (**7b**): Yield: 0.184 g (84%); mp 67°C, bp 55°C/0.001 mbar; ^{1}H NMR (C_6D_6) δ 0.97 (H_B, $H_{B'}$, 2H), 1.29 (H_M, $H_{M'}$, 2H), 1.33 (H_D, 1H), 1.74 (H_C, $H_{C'}$, 2H), 2.02 (H_E, 1H), 2.44 (H_X, 1H), 2.95 (H_A, $H_{A'}$, 2H) (AA'BB'CC'DEMM'X-system, $^3J_{AB} = {}^3J_{A'B'} = 2.0$ Hz, $^3J_{AC} = {}^3J_{A'C'} = 3.25$ Hz, $^4J_{AD} = {}^4J_{A'D} = 0.9$ Hz, $^4J_{BB'} = 1.8$ Hz, $^2J_{BC} = {}^2J_{B'C'} = 13.7$ Hz, $^3J_{BD} = {}^3J_{B'D} = 1.2$ Hz, $^3J_{BE} = {}^3J_{B'E} = 6.6$ Hz, $^3J_{CD} = {}^3J_{C'D} = 6.1$ Hz, $^3J_{CE} = {}^3J_{C'E} = 12.4$ Hz, $^2J_{DE} = 13.1$ Hz, $^3J_{AM} = {}^3J_{A'M'} < 0.7$ Hz; $^3J_{MX} = {}^3J_{M'X} = 1.6$ Hz), 1.39 (m_c, 2H), 1.60 (m_c, 4H), 2.61 (broad, 4H) (piperidine), 2.33 (s, 3H); ^{13}C NMR (C_6D_6) δ 57.2 (d), 55.1 (t), 45.7 (d, $^1J_{CH} = 171.1$ Hz), 32.1 (q), 27.0 (d), 26.7 (t), 25.1 (t), 21.0 (t), 17.8 (t). Anal. Calcd for $C_{14}H_{24}N_2$: C, 76.31; H, 10.98; N, 12.71. Found: C, 76.4; H, 11.0; N, 12.7.

1α,2α,3α,4α,5α-3-Methoxy-9-methyl-3-morpholino-9-azatricyclo[3.3.1.0^{2,4}]nonane (**10a**): 4-Chloro-9-methyl-3-morpholino-9-azabicyclo[3.3.1]non-2-ene (**2a**) [1] (0.257 g, 1.00 mmol) was added to a solution of sodium methoxide in methanol [prepared from sodium (0.092 g, 4.00 mmol) and methanol (10 mL)]. The solution was stirred for 10 h at room temperature. Then the solvent was removed. N,O-Acetal **10a** was obtained by extraction with ether (3 x 15 mL) and subsequent distillation in a Kugelrohr apparatus. Yield: 0.155 g (62%); mp 55°C, bp 85°C/0.001 mbar; ^{1}H NMR (C_6D_6) δ 0.86 (H_B, $H_{B'}$, 2H), 1.26 (H_D, 1H), 1.50 (H_M, $H_{M'}$, 2H), 1.69 (H_C, $H_{C'}$, 2H), 1.88 (H_E, 1H), 2.92 (H_A, $H_{A'}$, 2H) (AA'BB'CC'DEMM'-system, $^3J_{AB} = {}^3J_{A'B'} = 2.0$ Hz, $^3J_{AC} = {}^3J_{A'C'} = 3.25$ Hz, $^4J_{AD} = {}^4J_{A'D} = 0.9$ Hz, $^4J_{BB'} = 1.8$ Hz, $^2J_{BC} = {}^2J_{B'C'} = 13.6$ Hz, $^3J_{BD} = {}^3J_{B'D} = 0.6$ Hz, $^3J_{BE} = {}^3J_{B'E} = 6.3$ Hz, $^3J_{CD} = {}^3J_{C'D} = 6.0$ Hz, $^3J_{CE} = {}^3J_{C'E} = 12.4$ Hz, $^2J_{DE} = 13.3$ Hz, $^3J_{AM} = {}^3J_{A'M'} < 0.8$ Hz), 2.27 (s, 3H), 3.24 (s, 3H), 2.81 (broad, 4H), 3.69 (broad, 4H) (morpholine); ^{13}C NMR (C_6D_6) δ 83.4 (s), 68.1 (t), 56.5 (d), 51.1 (q), 49.7 (t), 33.5 (d, $^1J_{CH} = 171.7$ Hz), 32.0 (q), 20.5 (t), 17.0 (t). Anal. Calcd for $C_{14}H_{24}N_2O_2$: C, 66.63; H, 9.59; N, 11.10. Found: C, 66.3; H, 9.5; N, 11.4.

1α,2α,3β,4α,5α-9-Methyl-3-morpholino-9-azatricyclo[3.3.1.0^{2,4}]nonane (**6a**) *from N,O-acetal* **10a**: A solution of N,O-acetal **6a** (0.252 g, 1.00 mmol) in anhydrous tetrahydrofuran (40 mL) was dropped to a suspension of lithium aluminum hydride (0.095 g, 2.5 mmol) in anhydrous tetrahydrofuran (10 mL) under stirring within 30 minutes at room temperature. Stirring was continued for 1 h at room temperature and 12 h at 60°C. Then the solvent was evaporated and the residue was treated with an aqueous solution of potassium hydroxide (3 M, 30 mL). Extraction with ether (3 x 30 mL) and evaporation of the solvent gave crude diamine **6a** which was purified by distillation in a Kugelrohr apparatus. Yield: 0.126 g (57%); bp 50°C/0.001 mbar; ^{1}H and ^{13}C NMR data were identical with those of **6a** which was obtained from nitrile **4a**. Anal. Calcd for $C_{13}H_{22}N_2O$: C, 70.22; H, 9.97; N, 12.60. Found: C, 69.9; H, 10.1; N, 12.8.

Oxidation of 1α,2α,3β,4α,5α-3-amino-9-methyl-9-azatricyclo[3.3.1.0^{2,4}]nonane **6** *- general procedure*: Pure 1α,2α,3β,4α,5α-3-Amino-9-methyl-9-azatricyclo[3.3.1.0^{2,4}]nonane **6** (1.0 mmol, **6a**: 0.222 g; **6b**: 0.220 g) was stored in an oxygen atmosphere (50 mL flask) at 60°C for 24 h. Unreacted starting material **6** was removed by extraction with 20 mL of an aqueous buffer solution of pH = 7 [citric acid (0.1 mol/L; 3.8 mL) and disodium hydrogenphosphate (0.2 mol/L; 16.2 mL]; the residue was distilled in a Kugelrohr apparatus to give the pure formyl derivatives **25a,b**.

1α,2α,3β,4α,5α-9-Formyl-3-morpholino-9-azatricyclo[3.3.1.0^{2,4}]nonane (**25a**): Yield: 0.184 g (78%); mp 45°C, bp 80°C/0.001 mbar; ^{1}H NMR (C_6D_6) δ 0.67 (m_c, 2H), 1.13-1.34 (m, 4H), 1.45 (t, 1H), 1.56 (m_c, 2H), 2.14 (m_c, 2H), 2.30 (broad, 2H), 3.24 (m_c,1H), 3.60 (broad, 2H), 3.81 (broad, 2H), 4.59 (m_c, 1H), 7.70 (s, 1H); ^{13}C NMR (C_6D_6) δ 159.9 (d), 66.5 (t), 54.2 (d), 54.0 (t), 49.1 (d), 47.2 (d, $^1J_{CH}$ = 160.2 Hz), 31.4 (t), 29.4 (t), 22.6 (d, $^1J_{CH}$ = 169.8 Hz), 21.6 (d, $^1J_{CH}$ = 169.8 Hz), 17.9 (t). Anal. Calcd for $C_{13}H_{20}N_2O_2$: C, 66.08; H, 8.53; N, 11.85. Found: C, 66.4; H, 8.5; N, 11.4.

1α,2α,3β,4α,5α-9-Formyl-3-piperidino-9-azatricyclo[3.3.1.0^{2,4}]nonane (**25b**): Yield: 0.193 g (82%); mp 71°C, bp 100°C/0.001 mbar; ^{1}H NMR (C_6D_6) δ 0.72 (m_c, 2H), 1.15-1.86 (m, 12H), 1.54 (t, 1H), 2.35 (very broad, 4H), 3.31 (m_c, 1H), 4.66 (m_c, 1H), 7.78 (s, 1H); ^{13}C NMR (C_6D_6) δ 159.7 (d), 55.0 (t), 54.2 (d), 49.1 (d), 47.7 (d, $^1J_{CH}$ = 159.3 Hz), 31.5 (t), 29.5 (t), 25.6 (t), 24.8 (t), 22.9 (d, $^1J_{CH}$ = 168.8 Hz), 21.9 (d, $^1J_{CH}$ = 168.8 Hz), 18.0 (t). Anal. Calcd for $C_{14}H_{22}N_2O$: C, 71.76; H, 9.46; N, 11.95. Found: C, 71.5; H, 9.6; N, 12.0.

1α,2α,3β,4α,5α-9-Methyl-3-morpholino-9-azoniatricyclo[3.3.1.0^{2,4}]nonane trifluoromethane sulfonate (**19**): A solution of trifluoromethane sulfonic acid in 2-proanol (0.1 M; 10.00 mL) was added to a solution of tricyclic endo-morpholine **6a** (0.222 g, 1.0 mmol) in methanol (50 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 **19**, which was recristallized from methanol. Yield: 0.326 g (88%); mp 117°C (decomp.); ^{13}C NMR (CD_3CN/D_2O 4:1) δ 121.5 (q), 67.0 (t, $^1J_{CH}$ = 144.5 Hz), 60.5 (d, $^1J_{CH}$ = 155.5 Hz), 53.8 (t, $^1J_{CH}$ = 135.4 Hz), 45.4 (d, $^1J_{CH}$ = 172.6 Hz), 30.2 (q, $^1J_{CH}$ = 143.1 Hz), 20.9 (t), 20.8 (d, $^1J_{CH}$ = 177.4 Hz), 14.9 (t). Anal. Calcd for $C_{14}H_{23}F_3N_2O_4S$: C, 45.15; H, 6.23; N, 7.52. Found: C, 45.2; H, 6.3; N, 7.5.

Titration of diamines **6a,b** *and* **7a,b** *with hydrochloric acid*: Freshly distilled diamines **6,7** (0.09 mmol; **6a**,**7a**: 20.0 mg; **6b**,**7b**: 19.8 mg) were dissolved in water (90 mL, bidistilled and saturated with nitrogen) under stirring at room temperature for 24 h. 30 mL of the solution were titrated with aqueous 0.1 M hydrochloric acid each.

X-Ray crystal structure analysis [17] *of 1α,2α,3β,4α,5α-9-methyl-3-morpholino-9-azoniatricyclo[3.3.1.0^{2,4}]nonane trifluoromethane sulfonate* **19** · **CH_3OH**: Single crystals of **19** · CH_3OH were obtained by crystallization from methanol.

Crystal data: $C_{14}H_{23}F_3N_2O_4S$ · CH_3OH, F.W. = 404.45; monoclinic, space group $P2_1/c$; a = 9.202(2), b = 13.779(3), c = 15.418(3) Å; α = γ = 90, β = 94.36(3)°; V = 1949,2(7) Å^3; Z = 4; D_x = 1.378 g · cm^{-3}; crystal size 0.42 x 0.30 x 0.25 mm; colourless prisms. Data collection: Diffractometer STOE - IPDS, temperature: 293(2) K; monochromatized Mo-K_α radiation; 11701 reflections are collected, 2926 independent reflexions (R_{int} = 0.0367); 1.98 < Θ < 26.01°, no absorption correction. Structure solution and refinement: The structure was solved by the direct method using SHELXS-86 [18] and refined by full matrix least squares analysis on F^2 using

SHELXL-93 [19]. The trifluormethyl group in the anion of compound **19** is disordered, all fluorine atoms were refined in split positions with occupancy factors of 0.8 and 0.2. All other non-H atoms were refined anisotropically. The hydrogen atom H(9) could be localized from difference electron density maps and refined isotropically, all other hydrogen atoms were placed in idealized calculated positions and allowed to ride on the corresponding carbon atoms with fixed isotropic contributions. 2175 reflections with $F > 4\ \sigma(F)$ were used, 234 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 1.248, final R indices (obs. data) R1 = 0.0798, wR2= 0.1540.

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6. References

[1] Vilsmaier E, Herweck T, Schummel Mo, Tetzlaff C, Dotzauer M, Bergsträßer U. Tetrahedron, preceding paper.

[2] Vilsmaier E, Milch G, Bergsträßer U. Tetrahedron in print.

[3] Vilsmaier E, Goerz T. Synthesis 1998; in print.

[4] Calm MP Resonans, Version 2.0, Heratonic Programs, Moscow 1991.

[5] Vilsmaier E, Tetzlaff C, Butz V, Maas G. Tetrahedron 1991;47:8133-8144.

[6] Günther H. NMR-Spektroskopie, Stuttgart: G. Thieme, 1983:229-230.

[7] Kunze UR. Grundlagen der quantitativen Analyse, Stuttgart: G. Thieme, 1980:80, 81.

[8] Krabbenhoft HO, Wiseman JR, Quinn CB. J. Am. Chem. Soc. 1974;96:258-259.

[9] SHELXTL-Plus. Release 4.2 Siemens Analytical X-ray Instruments 1991.

[10] Wagemann R, Vilsmaier E, Maas G. Tetrahedron 1995;51:8815-8828.

[11] Butz V, Vilsmaier E, Maas G. J. Chem. Soc. Perkin Trans. 2 1993:1907-1913.

[12] Grech E, Malarski Z, Sawka-Dobrowolska W, Sobczyk L. J. Mol. Struct. 1997;416:227-234.

[13] Pinkerton JMH, Steinrauf LK. J. Org. Chem. 1967;32:1828-1832.

[14] Colonna FP, Distefano G, Pignataro S, Pitacco G, Valentin E. J. Chem. Soc. Faraday Trans. 2 1975:1572-1576.

[15] Nelsen SF, Kessel CR, Brien DJ. J. Am. Chem. Soc. 1980;102:702-711.

[16] Höft E, Schultze H. Z. Chem. 1967;7:137-148.

[17] Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre, 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.

[18] Sheldrick GM. SHELXS-86, Program for the Solution of Crystal Structures; University of Göttingen, Germany, 1986.

[19] Sheldrick GM. SHELXL-93, Program for Crystal Structure Refinement; University of Göttingen, Germany, 1993.