Pergamon

Tetrahedron Vol. 51, No. 32, pp. 8815-8828, 1995
Copyright © 1995 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0040-4020/95 $9.50+0.00

0040-4020(95)00463-7

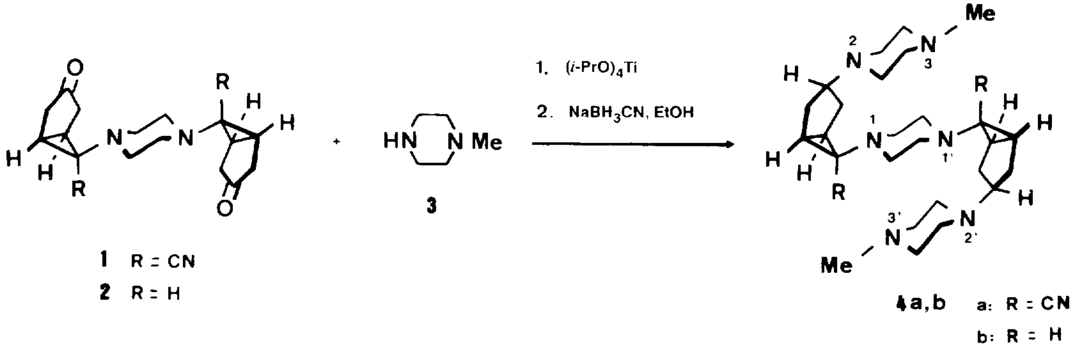
SPATIALLY FIXED OLIGOAMINES IV.[1]
FLEXIBILITY AND PROTONATION OF MEANDER-TYPE OCTAMINES

Rolf Wagemann, Elmar Vilsmaier* and Gerhard Maas[2]

Fachbereich Chemie der Universität Kaiserslautern,
Erwin-Schrödinger-Straße, D-67663 Kaiserslautern, Germany

Abstract: Meander-type octamines **6a** and **6b** possessing three piperazine units, two bicyclo[3.1.0]hexyl- and two azabicyclo[3.1.0]hexyl systems as building blocks, could be obtained by reductive amination of di(oxobicyclohexyl)piperazine **2** with piperazinyl-3-azabicyclohexane derivatives **5a/b**, respectively. The latter were synthesized from N-benzylchloroenamine **11** and sodium borohydride and subsequent removal of the benzylic protection group. Conformation and molecular flexibility of the new oligoamines **6a** and **6b** were studied. Di- and tetraammonium species with definite location of the protons were generated from octamine **6b**. X-Ray structural analysis of diammonium salt **14** · **2 TFA** was used to give an insight into the molecular arrangement of an (azoniabicyclohexyl)piperazine trifluoromethane sulfonate unit.

Reductive amination of bicyclic diketones **1** and **2** with N-methylpiperazine **3** led to hexamines[3] **4a** and **4b**, respectively; octamine[3] **4c** was obtained by reduction of derivative **4a**. Compounds **4** represent a new type of oligoamines in which the anchoring of the N-lone pairs of the central piperazine by the bicyclohexyl building blocks creates a meander type arrangement of the nitrogen atoms. The peripheric piperazine rings are distorted due to N(1)-N(2) and N(1')-N(2')lone pair repulsion (X-ray structural analysis of compound[3] **4a**).



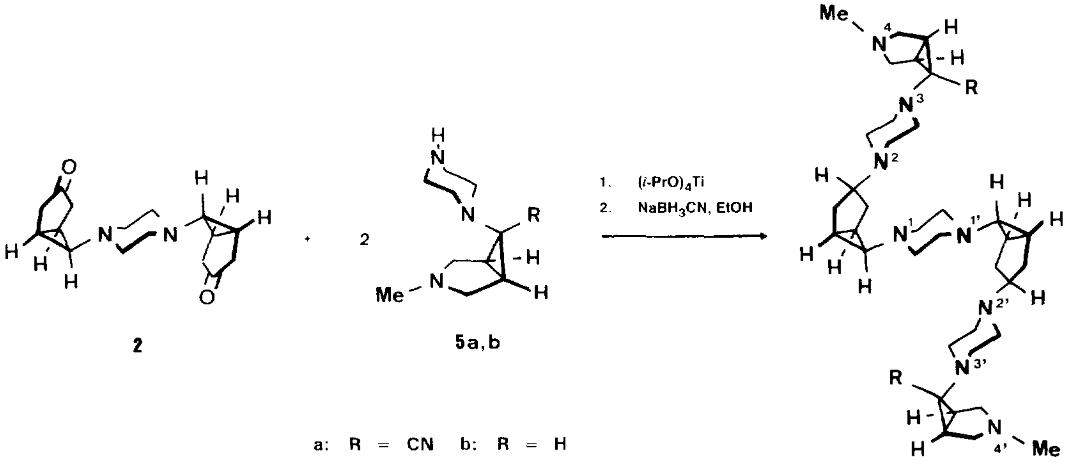
1 R = CN
2 R = H

3

4a,b a: R = CN
b: R = H

4a ⟶ **4c** c: R = CH_2NH_2

An extension of the concept of arrangement of N-lone pairs in a meander type manner is expected by oligoamines **6**. These compounds **6** should be accessible from diketone[3] **2** and triamines **5** by reductive amination. Lone pair anchoring in compounds **5** (see ref.[4-8]) should make them to suitable components for meander oligoamine homologization. Synthesis and properties of these new species **6** of meander oligoamines are reported in this paper.

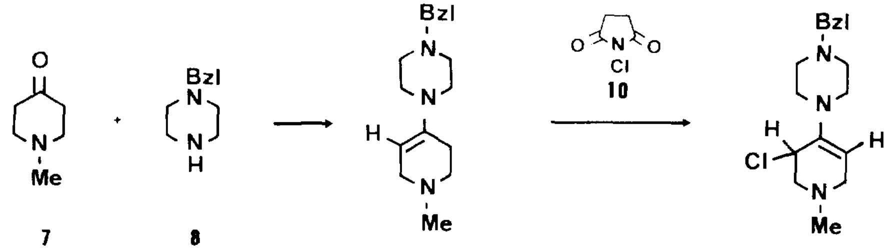


2 **5a,b** **6a,b**

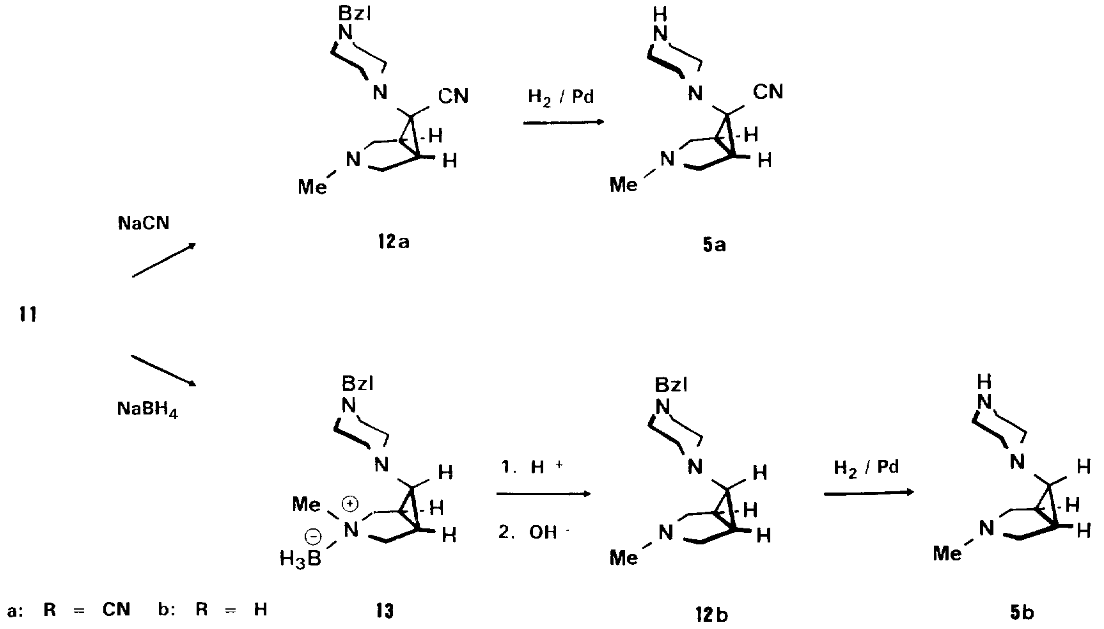
a: R = CN b: R = H

SYNTHESIS OF MEANDER-TYPE OLIGOAMINES 6

Secondary amines **5a** and **5b** as materials for the reductive amination of **2** were accessible via chloroenamine **11**. The latter was easily obtained (88% yield) by monochlorination of enamine **9** with N-chlorosuccinimide **10**.



7 **8** **9** **11**



Reaction of chloroenamine **11** with sodium cyanide gave bicyclic nitrile **12a** (75% yield). The analogous reaction of **11** with sodium borohydride produced bicyclic borane adduct **13** which was isolated (76% yield) and subsequently deboronated by acid to give **12b** (66% yield). Deprotected amines **5a** and **5b** were obtained by removal of the benzylic protection group in **12a** and **12b** by H_2 / Pd, respectively (**5a**: 79% yield; **5b**: 78% yield).

Reductive amination[3,9,10] of diketone **2** with 3-azabicyclohexyl-piperazine **5a** or **5b** and cyanoborohydride led finally to the desired products. Excess starting materials **5a/b** which were added in a twofold stoichiometric excess were removed by trituration with acetonitrile. Subsequent recrystallization of the residue from ethanol gave pure octamines **6** of an all endo-amine configuration in 44% yield (**6a**) and 29% yield (**6b**).

CONFIGURATION, CONFORMATION AND MOLECULAR FLEXIBILITY OF MEANDER-TYPE OLIGOAMINES 6a AND 6b

Configuration of the azabicyclohexyl moieties in **6** is identical with that of the precursors **5a/12a** and **5b/12b/13**: In the nitrile series **5a/12a**, endo-piperazine configuration was established at nitrile **12a** [characteristic $^3J_{CH}$ coupling[3,4,7,8] (4.2 Hz) of the cyano ^{13}C NMR signal]. endo-Piperazine configuration of the compounds **5b/12b/13** was determined via the H_Y signal of the C_1-bridge (best observable at compound **13**, $^3J_{HH}$ = 6.2 Hz; characteristic of syn-standing cyclopropane H-atoms[5,7]). Observation of coalescing piperazine ^1H NMR signals at room temperature for **5a**, **12a** and **13** confirmed the thus deduced configurations (see ref.[4-8]). Analogously, binding of the central piperazine to endo-C(6)/C(6')-postion of the bicyclo[3.1.0]hexyl units in octamines **6a/b** follows from the known configuration of precursor[3] **2**.

Table 1 Selected ^{1}H NMR and ^{13}C NMR data of the bicyclic moieties of hexamines **6a/6b**, the di- and tetraprotonated species **6b · 2 TFA**, **6b · 4 TFA** and diammonium salt **14 · 2 TFA**. δ-Values in ppm (TMS), J in Hz, $^1J_{CH}$-values in [].

	^{1}H NMR Data						^{13}C NMR Data	
	3-Azabicyclo[3.1.0]hexane			Bicyclo[3.1.0]hexane				
	$H_A/H_{A'}$[a]	$H_B/H_{B'}$[b]	NCH_3	$H_M/H_{M'}$[c]	$^3J_{MA}$	H_A	$N\text{-}CH_3$[d]	C(3)[d]
6a[e]	2.29	3.26	2.28	1.41	10.5	3.21[f]	40.4[g] [132]	76.2[g] [134]
6b[e]	2.22	3.18	2.29	1.44	10.5	3.23[f]	40.5[h] [133]	76.3[h] [134]
6b · 2 TFA[i]	3.50	3.40	2.80	1.38	9.8	3.12[j]	41.2[k] [143]	75.1[k] [135]
6b · 4 TFA[i]	3.75	3.42	2.88	1.88	5.6	-[l]	42.4[k] [145]	71.8[k] [153]
14 · 2 TFA[i]	3.56	3.49	2.85	-	-	-	41.4[k] [143]	- -

[a] $H_A/H_{A'}$ are in the endo-position of the 3-azabicyclo[3.1.0]hexane system.- [b] $H_B/H_{B'}$ are in the exo-position of the 3-azabicyclo[3.1.0]hexane system.- [c] $H_M/H_{M'}$ are in the endo-position of the bicyclo[3.1.0]hexane system.- [d] limit of error for $^1J_{CH}$: ± 1 Hz.- [e] $CDCl_3$, 57°C.- [f] $^3J_{NA}$: 8.1.- [g] CD_2Cl_2 20°C.- [h] $CDCl_3$, 20°C.- [i] CD_3CN/D_2O (8:2), 70°C.- [j] $^3J_{NA}$: 8.0.- [k] CD_3CN/D_2O (8:2), 20°C.- [l] signal not detectable.

syn-Piperazine configuration at C(3)/C(3') of the bicyclo[3.1.0]hexyl building blocks of **6a** and **6b** could be established by ^1H and ^{13}C NMR spectroscopy: The ^1H and ^{13}C NMR chemical shift and the $^3J_{HH}$ coupling of the C(3)-H unit of **6a** and **6b** (Table 1) corresponded to the data for comparable syn-compounds (e.g.[3] **4a** or **4b**); they did not agree with the analogous values of anti-bicyclo[3.1.0]hex-3-yl-piperazine or -morpholine systems (see ref.[3,9,10]).

All bicyclic systems in **6** are mainly present in a chair conformation as shown by characteristic NMR-values [bicyclo[3.1.0]hexane: ^1H and ^{13}C NMR chemical shift and the $^3J_{HH}$ coupling of the C(3)-H unit (Table 1, see ref.[3,9,10]); 3-azabicyclo[3.1.0]hexane: ^1H chemical shift of δH_A and δH_B (Table 1) (see ref.[7,8,11])].

Studying of the dynamics of the piperazine rings in octamines **6a** and **6b** informed about the molecular flexibility of the new meander-type oligoamines. Topomerization processes could be observed for all piperazine ^1H NMR signals in chloroform: coalescence of a symmetrical AB-type signal pattern corresponded to the central 6,6'-piperazine. In the case of the two peripheric 3,3'-piperazine rings, coalescence of only one of two doublet - triplet signal pairs could be determined.

Table 2 $\Delta G^{\ddagger}$ - Values of the dynamics of the piperazine rings of the compounds **6a** and **6b**, determined on the basis of ^1H NMR data (400 MHz) and coalescence temperatures (T_c) in $CDCl_3$

	peripheric-piperazine					central-piperazine				
	T [K]	H_A/H_X [ppm]	H_B/H_Y [ppm]	$^2J_{HH}$ [Hz]	T_c [K]	$\Delta G^{\ddagger}$ [a] [kJ/mol]	T [K]	$H_A/H_{A'}$ [ppm]	$H_B/H_{B'}$ [ppm]	T_c [K]	$\Delta G^{\ddagger}$ [b] [kJ/mol]
6a	250	2.72	2.56	11.1	317	64.4	250	2.79	2.50	315	62.7
6b	245	2.58	2.32	11.2	275	54.6	245	2.80	2.50	313	62.2

[a] Calculated with the approximation formula for the coupled case (ref.[12]).- [b] Calculated with the approximation formula for the uncoupled case (ref.[13]). δ-Values could be determined easily in spite of a complicated spin system due to the symmetrical shape of each signal splitting.

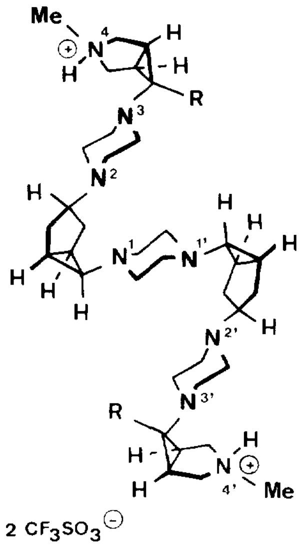
The dynamics of the central piperazine system in octamines **6a** and **6b** were moderately hindered (N,N'-dimethylpiperazine: $\Delta G^{\ddagger}$ 55.6, 55.7 kJ/mol); this is comparable to the situation in hexamine[3] **4b**. The terminal azabicyclohexyl moieties in **6a** showed the expected anchoring effect for the peripheric piperazine units; this is not the case in octamine **6b** due to the missing buttressing effect of the small hydrogen atom in C(6)/C(6')-position of the 3-azabicyclohexane groups (see ref.[5,7]). The bulkiness of the bicyclic substituents combined with the strong tendency of the piperazine units adopting a chair conformation, however, lead to a meander-type geometry of the new octamines **6a** and **6b**.

DI- AND TETRAPROTONATED SPECIES OF MEANDER-TYPE OLIGOAMINES 6b AND 14

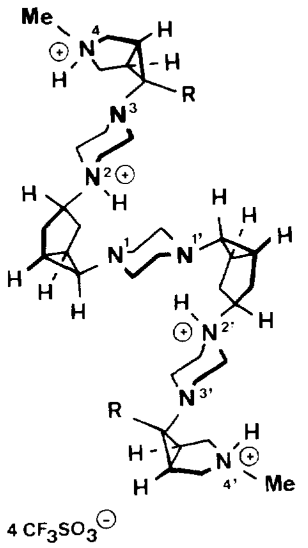
Protonation of parent hexamine **4b** took place at the peripheric piperazine moieties with no clear preference of N(2)/N(2') or N(3)/N(3')-position.[1] Decreasing of amine basicity by an adjacent cyclopropane[14,15] and strong basicity of N(3) of a 3-azabicyclohexane unit[7,8,15] should make octamine **6b** to a suitable species for generation of structurally definite di- and tetraammonium salts. This should be of interest from the point of studying oligoamine - DNA - interactions[16]. Tetramine[7] **14** was chosen additionally as a model substance for determination of spectroscopic data of a protonated azabicyclohexyl-piperazine unit.

Diammonium salts **6b · 2 TFA** and **14 · 2 TFA** and tetraammonium salt **6b · 4 TFA** were obtained from amines **6b** and **14** and two or four eqivalents of trifluoromethanesulfonic acid (TFA-H).

A potential change of $^1J_{CH}$ coupling of NCH_2-units upon protonation of an di- or oligoamine was used for determination of the location of the proton.[1,10,15] The N-CH_3-group (for the 3-azabicyclohexane) and the C(3)-H unit (for the bicyclohexane system) were selected as unequivocally assignable signals in the case of protonation of **6b**. It could be deduced from these data that octamine **6b** is diprotonated almost exclusively at N(3)/N(3') of the terminal azabicyclohexyl moieties (Table 1). Further protonation of **6b · 2 TFA** to **6b · 4TFA** took place at the peripheric piperazine N(2)/N(2')-atoms. Formation of ammonium cations in **6b** was accompanied by a conformational change as a consequence of intramolecular hydrogen bonding: Strong downfield shifting of H_A and only moderate downfield shifting of H_B of the azabicyclohexyl group in **6b · 2 TFA** and **6b · 4 TFA** indicated an inside protonation of this unit and the presence of a boat conformation (see ref.[15]). The strong increase of C(3)-H coupling to 153 Hz and the decrease of $^3J_{AM}$ coupling in **6b · 4 TFA** with respect to **6b** or **6b · 2 TFA** are characteristic of the bicyclohexyl boat structure of the tetraammonium salt.[10] The preference of a boat conformation of the bicyclic units of **6b** upon protonation was clearly favoured[10] by the solvent which was used [CD_3CN/D_2O 8:2; information about the data of a chair conformation of the bicyclic building blocks of the protonated species could not be obtained since all salts of **6b** were insoluble in $CDCl_3$ (see ref.[10,15])]

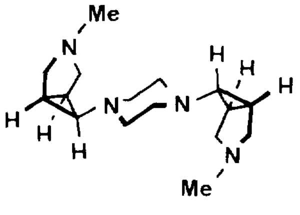


6 · 2TFA

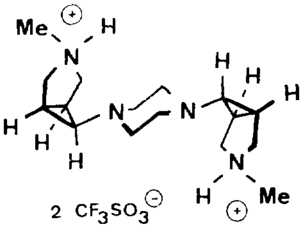


6 · 4TFA

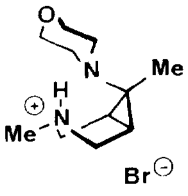
The analogous values for the diammonium salt **14** · **2 TFA** (Table 1) were very close to that which were found for **6b** · **2 TFA** and **6b** · **4 TFA**. This additionally indicated the presence of 3-azoniabicyclohexyl moities in the di- and tetraprotonated species of **6b**. Twofold endo-protonation of **14** and the presence of a boat conformation for the azabicyclohexyl groups in **14** · **2 TFA** were confirmed by an X-ray structural analysis. Single crystals of **14** · **2 TFA** were obtained from acetonitrile / water (8:2). A Schakal plot[17] of the cation of **14** · **2 TFA** is given in Fig. 1. The molecule has a crystallographical center of symmetry; it is, however, not exactly mirror symmetrical. A small distortion with respect to the N(1)-C(6)-axis was observed.



14



14 · 2TFA



15 · HBr

Diammonium bis(trifluoromethanesulfonate) **14 · 2 TFA** showed a shorter N(3)H(3) ··· N(1) distance (and a stronger ring buckling than ammonium bromide[15] **15 · HBr** [N(3)H(3) ··· N(1): 2.64 Å; ring buckle α = 8.1°]. This indicates an increasing intramolecular N-H-interaction in the former case.

Table 3 Selected bond distances, N,N-distances,[a] torsional angles, interplanar angles[a] and hydrogen bonding[a] of 6,6'-(piperazine-1,4-diyl)-bis-(1α,5α,6β-3-methyl-3-azoniabicyclo-[3.1.0]hexane) bis(trifluoromethanesulfonate) (**14 · 2 TFA**)

bond lengths [Å]		N,N-distances [Å]	
C(1) - C(5)	1.505(4)	N(1) - N(1')	2.876(3)
C(1) - C(6)	1.492(4)	N(1) - N(3)	2.858(3)
C(5) - C(6)	1.493(4)	N(1) - N(3')	5.253(3)
		N(3) - N(3')	7.953(3)

torsional angles [°][b]	
$H(1)-C(1)-C(2)-H(2)_A$	85.93(2.56)
$H(4)_A-C(4)-C(5)-H(5)$	-87.34(2.68)
$H(1)-C(1)-C(2)-H(2)_B$	-36.96(2.51)
$H(4)_B-C(4)-C(5)-H(5)$	44.28(2.61)

interplanar angles [°]	
C(1)C(5)C(6) - C(1)C(2)C(4)C(5)	67.1(2)
C(1)C(2)C(4)C(5) - C(2)N(3)C(4)	22.4(3)

H-N or H-O hydrogen bonding

distances [Å]		angles [°]	
H(3) - N(3)	0.86(3)	N(3) - H(3) ··· N(1)	112.1(2.2)
H(3) ··· N(1)	2.42(3)	N(3) - H(3) ··· O(1)[c]	132.3(2.4)
H(3) ··· O(1)[c]	2.33(3)		

---

[a] The numbering of the nitrogen atoms in Fig. 1 and Table 3 in this paper was partially changed with respect to the numbering in the deposited data for better comparison with other systems.- [b] $H(2)_A$ / $H(4)_A$ are in the endo-position and $H(2)_B$ / $H(4)_B$ are in the exo-position of the 3-azoniabicyclo[3.1.0]hexane system.- [c] Nearest oxygen atom of the trifluoromethanesulfonate anion.

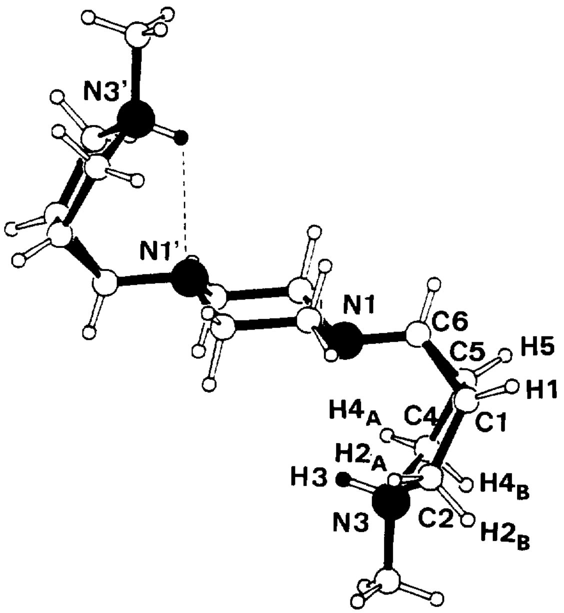


Fig. 1 Schakal-plot[17] of 6,6'-(piperazine-1,4-diyl)-bis-(1α,5α,6β-3-methyl-3-azoniabicyclo-[3.1.0]hexane) dication **14** · **2 TFA**.

Thus, protonation of octamine **6b** indeed led to di- or tetra-ammonium species in which the cations are located in definite positions. This is the consequence of sterical hindrance combined with distinct differences of basicity of the amino groups in this new oligoamine.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were obtained with a Bruker AMX 400 spectrometer (TMS as internal standard). IR spectra were measured on a Perkin-Elmer 397 Infrared Spectrophotometer. A MAT 90 (Finnigan) spectrometer was used for mass spectra. Microanalyses were performed with a Perkin-Elmer 2400 Elemental Analyzer.

1-Benzyl-4-(1,2,3,6-tetrahydro-1-methyl-pyridin-1-yl)-piperazine (**9**): A solution of N-benzylpiperazine (**8**) (28.3 g, 250 mmol), piperidinone **7** (44.07 g, 250 mmol) and 4-toluenesulfonic acid (0.2 g, 1.05 mmol) in toluene (220 mL) was heated in a Dean-Stark-apparatus for 24 h. Removal of the solvent and distillation in vacuo gave pure enamine **9**. Yield: 51.08 g (76%), bp

150°C/0.005 Torr, mp 38°C; ^{1}H NMR (CDCl$_3$) δ 2.24 (H$_{X1}$), 2.54 (H$_{A1}$) (AA'XX'-system, 4H), 2.48 (H$_{X2}$), 2.84 (H$_{A2}$) (AA'XX'-system, 8H), 2.97 (H$_{A3}$, H$_B$), 4.58 (H$_{X3}$) (ABX-system, 3H), 2.34 (s, 3H), 3.51 (s, 2H), 7.23-7.32 (m, 5H); ^{13}C NMR (CDCl$_3$) δ 143.2 (s), 137.8 (s), 128.9 (d), 128.0 (d), 126.8 (d), 97.3 (d), 62.8 (t), 54.2 (t), 52.7 (t), 52.3 (t), 47.3 (t), 45.5 (q), 27.8 (t). Anal. Calcd for $C_{17}H_{25}N_3$: C, 75.23; H, 9.29; N, 15.48. Found: C, 74.5; H, 9.0, N, 15.3.

1-Benzyl-4-(3-chloro-1,2,3,6-tetrahydro-1-methyl-pyridin-1-yl)-piperazine (11): A solution of N-chlorosuccinimide (**10**) (6.68 g, 50 mmol) in dichloromethane (200 mL) was dropped at -50°C during 1 h to a stirred solution of enamine **9** (13.6 g, 50 mmol) in dichloromethane (100 mL). Stirring was continued at -50°C for 1 h. Then cooling was removed to warm up the mixture to room temperature. The crude solution was evaporated in vacuo; chloroenamine **11** was extracted by trituration with pentane (2 x 200 mL). Concentration of the pentane solution to 200 mL and cooling to -20°C gave crystalline chloroenamine **11**. Yield: 13.52 g (88%), mp 39°C; ^{1}H NMR (CDCl$_3$) δ 2.38 (s, 3H), 2.44-2.55 (m, 4H), 2.79-2.85 (m, 4H), 2.92-3.01 (m, 3H), 3.29 (m$_c$, 1H), 3.52 (s, 2H), 4.60 (m$_c$, 1H), 4.74 (m$_c$, 1H), 7.23-7.32 (m, 5H); ^{13}C NMR (CDCl$_3$) δ 142.7 (s), 137.7 (s), 128.7 (d), 127.8 (d), 126.7 (d), 101.9 (d), 62.6 (t), 60.6 (t), 54.1 (t), 53.1 (d), 52.5 (t), 47.3 (t), 44.9 (q). Anal. Calcd for $C_{17}H_{24}ClN_3$: C, 66.76; H, 7.91; N, 13.74. Found: C, 66.7; H, 7.8, N, 13.9.

1α,5α,6β-6-(4-Benzyl-piperazin-1-yl)-3-methyl-3-azabicyclo[3.1.0]hexane-6-carbonitrile (12a): Chloroenamine 11 (6.12 g, 20 mmol) and sodium cyanide (1.46 g, 30 mmol) were heated in a mixture of acetonitrile (100 mL) and water (10 mL) to 60°C for 3 d. The solvent was removed in vacuo, the residue was triturated with aqueous sodium hydroxide solution (5 N, 150 mL) and extracted with dichloromethane (4 x 50 mL). Pure **12a** was obtained from the dichloromethane extract by evaporation of the solvent and crystallization of the residue from ether. Yield: 4.44 g (75%), mp 105°C (decomp.); IR (KBr, cm^{-1}) 2200 (C≡N); ^{1}H NMR (CDCl$_3$) δ 2.18 (2H), 2.55 (2H), 2.76 (2H) and 2.81 (2H) (broad unsplit signals), 2.23 (H$_B$, H$_{B'}$, 2H), 2.28 (H$_X$, H$_{X'}$, 2H), 3.27 (H$_A$, H$_{A'}$, 2H) (AA'BB'XX'-system), 2.26 (s, 3H), 3.50 (s, 2H), 7.23-7.35 (m, 5H); ^{13}C NMR (CDCl$_3$) δ 137.8 (s), 128.7 (d), 127.9 (d), 126.8 (d), 117.5 (t, $^3J_{CH}$ = 4.2 Hz), 62.6 (t), 53.1 (t), 52.5 (t), 49.3 (t), 43.4 (s), 40.0 (q), 33.8 (d, $^1J_{CH}$ = 174 Hz). Anal. Calcd for $C_{18}H_{24}N_4$: C, 72.94; H, 8.16; N, 18.90. Found: C, 72.9; H, 8.1, N, 18.9.

[1α,5α,6β-6-(4-Benzyl-piperazin-1-yl)-3-methyl-3-azabicyclo[3.1.0]hexane-N^3]-trihydroboron (13): A suspension of chloroenamine 11 (6.12 g, 20 mmol) and sodium borohydride (7.56 g, 200 mmol) in acetonitrile (130 mL) was stirred at 70°C for 3 d. Excess borohydride was removed by filtration. The filtrate was evaporated in vacuo, the residue was triturated with water (50 mL), filtered and washed with aqueous sodium hydroxide (1 M, 2 x 20 mL). Recrystallization from ether gave pure **13**. Yield: 4.36 g (76%), mp 110°C; ^{1}H NMR (CDCl$_3$) δ 2.00 (2H), 2.45 (4H) and 2.70 (2H) (broad unsplit signals), 1.84 (H$_Y$, $^3J_{HH}$ = 6.2 Hz), 1.91 (H$_X$, H$_{X'}$, 2H), 2.47 (H$_B$, H$_{B'}$, 2H), 3.29 (H$_A$, H$_{A'}$, 2H) (AA'BB'XX'Y-system), 2.55 (s, 3H), 3.43 (s, 2H), 7.16-7.26 (m, 5H); ^{13}C NMR (CDCl$_3$) δ 138.0 (s), 128.9 (d), 128.1 (d), 126.9 (d), 63.0

(t), 61.3 (t), 53.1 (t), 51.8 (t), 49.5 (q), 49.3 (d, $^1J_{CH}$ = 170 Hz), 25.9 (d, $^1J_{CH}$ = 174 Hz). Anal. Calcd for $C_{17}H_{28}BN_3$: C, 71.58; H, 9.89; N, 14.73. Found: C, 71.8; H, 9.8, N, 14.7.

1α,5α,6β-6-(4-Benzyl-piperazin-1-yl)-3-methyl-3-azabicyclo[3.1.0]hexane (12b): A suspension of borane adduct **13** (5.70 g, 20 mmol) in aqueous hydrochloric acid (1 M, 200 mL) was stirred at 40°C for 2 d. The solution was cooled to 20°C; aqueous sodium hydroxide (5 M) was added till pH = 14. Extraction with ether (3 x 300 mL) gave crude triamine **12b** which was distilled in a Kugelrohr-apparatus (120°C/0.01Torr) to give a colorless oil. Yield: 3.60 g (66%); ^{1}H NMR ($CDCl_3$) δ 1.70 (H_Y, H_X, $H_{X'}$, 3H), 2.12 (H_B, $H_{B'}$, 2H), 3.17 (H_A, $H_{A'}$, 2H) (AA'BB'XX'Y-system), 2.23 (s, 3H), 2.50 (8H, broad unsplit signal), 3.48 (s, 2H), 7.21-7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 138.3 (s), 129.1 (d), 128.1 (d), 126.9 (d), 63.2 (t), 53.8 (t), 53.2 (t), 51.9 (t), 48.2 (d, $^1J_{CH}$ = 164 Hz), 40.4 (q), 25.4 (d, $^1J_{CH}$ = 169 Hz). Anal. Calcd for $C_{17}H_{25}N_3$: C, 75.23; H, 9.29; N, 15.48. Found: C, 75.1; H, 9.2, N, 15.4.

Reductive Debenzylation - General Procedure: A solution of N-benzyl compound **12** (10 mmol, **12a**: 2.96 g; **12b**: 2.71 g) in methanol (80 mL) was added to Pd/C (10%, 1.0 g) and saturated with hydrogen. The mixture was stirred at room temperature (absorption of 220 mL of hydrogen; **12a**: 16 h; **12b**: 6 h). Removal of the catalyst by filtration, evaporation of methanol and distillation of the residue in a Kugelrohr apparatus (**5b**) or recrystallization of the residue from ether (**5a**) gave pure amines **5**.

1α,5α,6β-3-Methyl-6-(piperazin-1-yl)-3-azabicyclo[3.1.0]hexane-6-carbonitrile (**5a**) Yield: 1.63 g (79%), mp 82°C; IR (KBr, cm^{-1}) 2210 (C≡N); ^{1}H NMR ($CDCl_3$) δ 1.40 (broad unsplit signal, 1H), 2.25 (H_B, $H_{B'}$, 2H), 2.33 (H_X, $H_{X'}$, 2H), 3.30 (H_A, $H_{A'}$, 2H) (AA'BB'XX'-system), 2.27 (s, 3H), 2.60 (4H), 2.85 (2H) and 3.00 (2H) (broad unsplit signals); ^{13}C NMR ($CDCl_3$) δ 117.7 (s), 53.3 (t), 51.1 (t), 45.7 (t), 44.3 (s), 40.2 (q), 33.9 (d, $^1J_{CH}$ = 176 Hz). Anal. Calcd for $C_{11}H_{18}N_4$: C, 64.05; H, 8.80; N, 27.16. Found: C, 64.0; H, 8.8, N, 27.2

1α,5α,6β-3-Methyl-6-(1-piperazinyl)-3-azabicyclo[3.1.0]hexane (**5b**) Yield: 1.41 g (78%), bp 65-70°C/0.005 Torr; ^{1}H NMR ($CDCl_3$) δ 1.66 (H_X, $H_{X'}$, 2H), 1.70 (H_Y, 1H), 2.12 (H_B, $H_{B'}$, 2H), 3.12 (H_A, $H_{A'}$, 2H) (AA'BB'XX'Y-system), 2.22 (s, 3H), 2.40 (broad unsplit signal, 4H), 2.83 (4H, XX-part of an AA'XX'-system); ^{13}C NMR ($CDCl_3$) δ 53.7 (t), 53.4 (t), 48.8 (d, $^1J_{CH}$ = 165 Hz), 45.9 (t), 40.3 (q), 25.2 (d, $^1J_{CH}$ = 170 Hz). Anal. Calcd for $C_{10}H_{19}N_3$: C, 66.26; H, 10.56; N, 23.18. Found: C, 66.2; H, 10.5, N, 22.3.

Meander-Type Octamines 6a and 6b - General Procedure: A mixture of diketone[3] **2** (0.55 g, 2.0 mmol), secondary amine **5** (8.0 mmol; **5a**: 1.65 g; **5b**: 1.45 g) and titanium tetraisopropoxide (7.5 mL, 25.5 mmol) was stirred at room temperature for 2 d. Then $NaBH_3CN$ (0.75 g, 12 mmol) and ethanol (40 mL) were added and stirring was continued for 5 d. Water (40 mL) was added, the solid was removed by suction over silicagel and washed with ethanol (20 mL). The filtered solution was concentrated to a volume of 30 mL and excess

$NaBH_3CN$ was destroyed by addition of aqueous hydrochloric acid (1 N, 25 mL) and stirring for 1 h. The mixture was made alkaline with aqueous sodium hydroxide (1 N, 50 mL) and extracted with dichloromethane (4 x 30 mL). Evaporation of the dichloromethane afforded crude oligoamines **6** which were crystallized from ethanol.

6,6'-{4,4'-[6,6'-(Piperazine-1,4-diyl)-bis[1α,3β,5α,6β-bicyclo[3.1.0]hexane-3,3'-diyl]-dipiperazine-1,1'-diyl}-bis-(1α,5α,6β-3-methyl-3-azabicyclo[3.1.0]hexane-6-carbonitrile) (**6a**) Yield: 0.57 g (44%), mp 258°C; IR (KBr, cm^{-1}) 2210 (C≡N); ^1H NMR ($CDCl_3$) δ 1.28 (H_{X1}, $H_{X'1}$, 4H), 1.39 (H_M, $H_{M'}$, 4H), 1.66 (H_Y, 2H), 1.80 (H_N, $H_{N'}$, 4H), 3.21 (H_{A1}, 2H) (AMM'NN'XX'Y-system), 2.26 (s, 6H), 2.25 (H_{A2}, $H_{A'2}$, 4H), 2.29 (H_{X2}, $H_{X'2}$, 4H), 3.27 (H_B, $H_{B'}$, 4H) (AA'BB'XX'-system), 2.25 (4H), 2.55 (8H), 2.60 (4H), 2.76 (4H) and 2.85 (4H) (broad, unsplit signals); ^{13}NMR ($CDCl_3$) δ 118.0 (s), 76.2 (d), 53.5 (t), 52.2 (t), 50.7 (t), 49.7 (t), 49.2 (d), 43.8 (s), 40.4 (q), 34.1 (d, $^1J_{CH}$ = 176 Hz), 25.1 (t), 21.3 (d, $^1J_{CH}$ = 168 Hz). MS (35 V) m/e = 654.2 (M^+, 100%). Anal. Calcd for $C_{38}H_{58}N_{10}$: C, 69.69; H, 8.93; N, 21.39. Found: C, 69.3; H, 8.9; N, 21.2.

6,6'-{4,4'-[6,6'-(Piperazine-1,4-diyl)-bis[1α,3β,5α,6β-bicyclo[3.1.0]hexane-3,3'-diyl]-dipiperazine-1,1'-diyl}-bis-(1α,5α,6β-3-methyl-3-azabicyclo[3.1.0]hexane) (**6b**): Yield: 0.35 g (29%), mp 271°C (decomp.); ^1H NMR ($CDCl_3$) δ 1.28 (H_{X1}, $H_{X'1}$, 4H), 1.41 (H_M, $H_{M'}$, 4H), 1.63 (H_{Y1}, $^3J_{HH}$ = 6.7 Hz, 2H), 1.80 (H_N, $H_{N'}$, 4H), 3.25 (H_{A1}, 2H) (AMM'NN'XX'Y-system), 2.30 (s, 6H), 1.69 (H_{X2}, $H_{X'2}$, 4H), 1.72 (H_{Y2}, $^3J_{HH}$ = 6.7 Hz, 2H), 2.15 (H_{A2}, $H_{A'2}$, 4H), 3.14 (H_B, $H_{B'}$, 4H) (AA'BB'XX'Y-system), 2.35 (4H), 2.50 (16H), 2.60 (4H) (broad, unsplit signals); ^{13}NMR ($CDCl_3$) δ 76.3 (d), 53.9 (t), 52.1 (t), 51.9 (t), 51.5 (t), 49.9 (d, $^1J_{CH}$ = 163 Hz), 48.3 (d, $^1J_{CH}$ = 164 Hz), 40.5 (q), 25.4 (d, $^1J_{CH}$ = 170 Hz), 25.3 (t), 21.3 (d, $^1J_{CH}$ = 167 Hz). MS (35 V) m/e = 604.2 (M^+, 100%). Anal. Calcd for $C_{36}H_{60}N_8$: C, 71.48; H, 10.00; N, 18.52. Found: C, 70.7; H, 9.9; N, 18.4.

Diammonium Salts 6b · 2 TFA, 14 · 2 TFA and Tetraammonium Salt 6b · 4 TFA - General Procedure: A solution of trifluoromethanesulfonic acid in 2-propanol [0.1 M, 2 mL for diammonium salts; 4 mL for tetraammonium salt] was added to amines **6b** or **14** [7] (0.1 mmol; **6b**: 60.5 mg, **14**: 27.6 mg) in acetonitrile (30 mL) at room temperature. The solution was stirred for 1h; then the solvent was evaporated. The residue was triturated with ether (2 x 5 mL) and dried in vacuo. Quantitative yield.

6,6'-{4,4'-[6,6'-(Piperazine-1,4-diyl)-bis[1α,3β,5α,6β-bicyclo[3.1.0]hexane-3,3'-diyl]-dipiperazine-1,1'-diyl}-bis-(1α,5α,6β-3-methyl-3-azoniabicyclo[3.1.0]hexane) bis(trifluoromethanesulfonate) (**6b · 2 TFA**): mp 225°C (decomp.); ^{13}C NMR [CD_3CN/D_2O (8:2)] δ 75.1 (d, $^1J_{CH}$ = 135 Hz), 55.8 (t, $^1J_{CH}$ = 147 Hz), 52.5 (t, $^1J_{CH}$ = 135 Hz), 51.7 (t, $^1J_{CH}$ = 133 Hz), 50.7 (d), 50.6 (t, $^1J_{CH}$ = 136 Hz), 44.1 (d), 41.2 (q, $^1J_{CH}$ = 143 Hz), 26.6 (t), 21.6 (d, $^1J_{CH}$ = 169 Hz), 21.1 (d, $^1J_{CH}$ = 176 Hz). Anal. Calcd for $C_{38}H_{62}F_6N_8O_6S_2$: C, 50.43; H, 6.90; N, 12.38. Found: C, 49.3; H, 6.7; N, 12.1.

6,6'-{4,4'-[6,6'-(Piperazine-1,4-diyl)-bis[1α,3β,5α,6β-bicyclo[3.1.0]hexane-3,3'-diyl]-di(piperazine-1,1'-ium-1,1'-diyl)}-bis-(1α,5α,6β-3-methyl-3-azoniabicyclo[3.1.0]hexane) tetrakis(trifluoromethanesulfonate) (**6b** · **4 TFA**): mp 270°C (decomp.); ^{13}C NMR [CD_3CN/D_2O (8:2)] δ 71.8 (d, $^1J_{CH}$ = 153 Hz), 56.0 (t, $^1J_{CH}$ = 148 Hz), 52.4 (d), 51.0 (t, $^1J_{CH}$ = 138 Hz), 50.8 (t, $^1J_{CH}$ = 144 Hz), 48.9 (t, $^1J_{CH}$ = 133 Hz), 43.8 (d), 42.4 (q, $^1J_{CH}$ = 145 Hz), 26.0 (t), 21.7 (d, $^1J_{CH}$ = 173 Hz), 21.1 (d, $^1J_{CH}$ = 178 Hz). Anal. Calcd for $C_{40}H_{64}F_{12}N_8O_{12}S_4$: C, 39.86; H, 5.35; N, 9.30. Found: C, 39.0; H, 5.3; N, 9.0.

6,6'-(Piperazine-1,4-diyl)-bis-(1α,5α,6β-3-methyl-3-azoniabicyclo[3.1.0]hexane) bis(trifluoromethanesulfonate) (**14** · **2 TFA**)[18]: mp 253°C (decomp.); ^{13}C NMR [CD_3CN/D_2O (8:2)] δ 55.9 (t), 52.7 (t), 43.8 (d, $^1J_{CH}$ = 164 Hz), 41.4 (q), 20.2 (d, $^1J_{CH}$ = 177 Hz). Anal. Calcd for $C_{18}H_{30}F_6N_4O_6S_2$: C, 37.50; H, 5.25; N, 9.72. Found: C, 36.9; H, 5.0; N, 9.3.

X-Ray Crystal Structure Analysis of 14 · 2 TFA.[19,20] Single crystals of **14** · **2 TFA** were obtained by crystallization from acetonitrile - water (8:2).

Crystal data: $C_{18}H_{30}F_6N_4O_6S_2$, F.W. = 576.6; monoclinic, space group $P2_1/c$; a = 6.533(3), b = 12.693(2), c = 14.909(8) Å; $\alpha = \gamma = 90$, β = 91.76(3)°; V = 1235.8(1.5) $Å^3$; 2 molecules per unit cell; D_x = 1.549 g · cm^{-3}; crystal size 0.50 x 0.45 x 0.60 mm.

Data collection: Diffractometer Enraf-Nonius-CAD 4, temperature: 295 K; monochromatized Mo-K_α radiation; 2379 independent reflexions with $4.00 < 2\Theta < 51.00°$ [$\omega/2\Theta$ scan, scan width $(1.20 + 0.35 \tan\Theta)°$, scan speed 1.27 - 4.12 ° · min^{-1}], no absorption correction.

Structure solution and refinement: Full matrix least-squares method; H atoms refined isotropically, 1816 reflections with $I < 2.0\,\sigma(I)$; 223 variables, unit weights, maximum shift/error ratio 0.05, R = 0.040, R_w = 0.037.

Acknowledgments: This work was sponsored by the Fonds der Chemischen Industrie. We want to thank Dr. Heike Slodzyk for mass spectra measurements.

REFERENCES AND NOTES

Dedicated to Prof. Dr. H.-J. Bestmann on the occasion of his 70th birthday.

1. Foregoing paper: Wagemann, R.; Vilsmaier, E.; Wolmershäuser, G. *J. Mol. Struct.*, submitted for publication.

2. New address: Universität Ulm, Abteilung Organische Chemie I, 89069 Ulm (Germany).

3. Wagemann, R.; Seibel, J.; Vilsmaier, E.; Maas, G. *Tetrahedron*, **1994**, *50*, 731-748.

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

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

6. Butz, V.; Vilsmaier, E. *Tetrahedron*, **1993**, *49*, 6031-6044.

7. Seibel, J.; Vilsmaier, E.; Fröhlich, K.; Maas, G.; Wagemann, R. *Tetrahedron*, **1994**, *50*, 715-730.

8. Schlag, W.-R.; Vilsmaier, E.; Maas, G. *Tetrahedron*, **1994**, *50*, 3123-3138.

9. Vilsmaier, E.; Fath, J.; Maas, G. *Synthesis*, **1991**, 1142-1146.

10. Vilsmaier, E.; Fath, J.; Tetzlaff, C.; Maas, G. *J. Chem. Soc. Perkin Trans. 2*, 1993, 1895-1900.

11. Tetzlaff, C.; Butz, V.; Vilsmaier, E.; Wagemann, R.; Maas, G.; Ritter v. Onciul, A.; Clark, T. *J. Chem. Soc. Perkin Trans. 2*, 1993, 1901-1905.

12. Günther, H. NMR-Spektroskopie, G. Thieme, Stuttgart 1983, 2nd edition, p. 229-230.

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

14. Christensen, J. J.; Izatt, R. M.; Wrathall, D. P.; Hansen, L. D. J. Chem. Soc. A 1969, 1212-1223.

15. Butz, V.; Vilsmaier, E.; Maas, G. *J. Chem. Soc. Perkin Trans. 2*, 1993, 1907-1913.

16. Bloomfield, V. A.; Wilson, R. W. Interaction of Polyamines with Polynucleotides in Morris, D. R.; Marton, L. J. Polyamines in Biology and Medicine (Vol 8 of The Biochemistry of Disease, Farber, E.; Pitot, H. C. Ed.), M. Dekker, New York 1981, p. 183-206.

17. Keller, E. SCHAKAL, Universität Freiburg (Germany), 1990.

18. Seibel, J. Dissertation, Universität Kaiserslautern (Germany) 1992.

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

20. 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.

(*Received in Germany* 18 *May* 1995; *accepted* 8 *June* 1995)