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FUNCTIONALIZED CHLOROENAMINES IN AMINOCYCLOPROPANE SYNTHESIS - XIII.[1] AZAANNULATED CYCLOPROPANES - RIGID BUILDING BLOCKS FOR OLIGOAMINES

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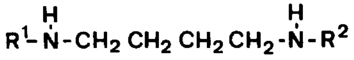
Abstract: Oligoamines **5**, **6** and **7** with rigid 3-azabicyclo[3.1.0]hexyl building blocks were synthesized from di(chloroenamines) **8** and nucleophiles. Sodium borohydride as nucleophile led to endo,endo-tetramines **5a,b**; the same stereochemical result generating **5d** and **5f** was observed for cyanide or methyllithium as reagents. Methylmagnesium bromide reacted with **8** to give mainly exo,exo-tetramine **7f** besides small amounts of isomers **5f** and **6f**. Basicity, conformation and molecular flexibility of the new tetramines **5** - **7** were studied. X-Ray structural analyses pointed out a meander shape of tetramine **5f** and a linear arrangement of tetramine **7f**.

Putrescine (**1**), spermidine (**2**) and spermine (**3**), naturally occurring oligoamines, strongly influence cell proliferation processes.[2,3] Interactions of these oligoamines with DNA, therefore, were explored intensively.[4,5] Structural properties of the oligoamines are important in the formation of the ammonium DNA - phosphate complexes. Oligoamines possessing rigid building blocks should be of interest in this context. Our investigations about rigid diamines with an azabicyclohexane skeleton[1,6-9] prompted us to synthesize analogous oligoamines **4** and to study their properties. Two azabicyclo[3.1.0]hexane units are connected by a piperazine moiety in compounds of type **4** for which three diastereomers **5**, **6** and **7** must be considered.

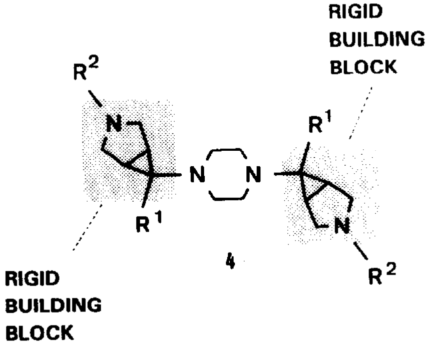


$R^1-\overset{H}{N}-CH_2CH_2CH_2CH_2-\overset{H}{N}-R^2$

1 $R^1, R^2 = H$

2 $R^1 = H, R^2 = (CH_2)_3NH_2$

3 $R^1, R^2 = (CH_2)_3NH_2$



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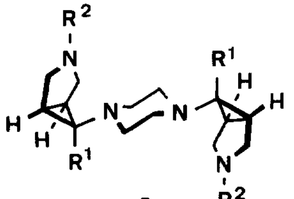
Interest was applied specially to endo,endo-diastereomers **5** since here molecular flexibility should be mostly restricted. Difunctional chloroenamines **8** were provided as starting materials. Reaction of **8** with sodium borohydride or cyanide should lead[6,7] to endo,endo-oligoamines **5** (R^1 = H, CN); methylmetal compounds and di(chloroenamine) **8** were chosen as starting materials for a practicable access[8] to diastereomers **5**, **6** and **7** (R^1 = CH_3).



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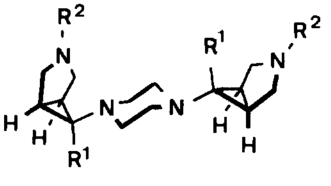

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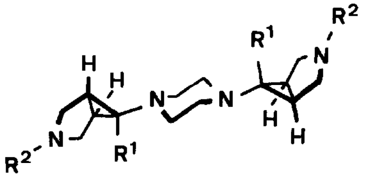

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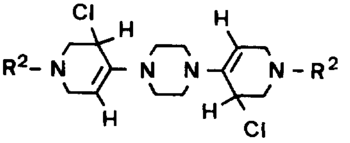

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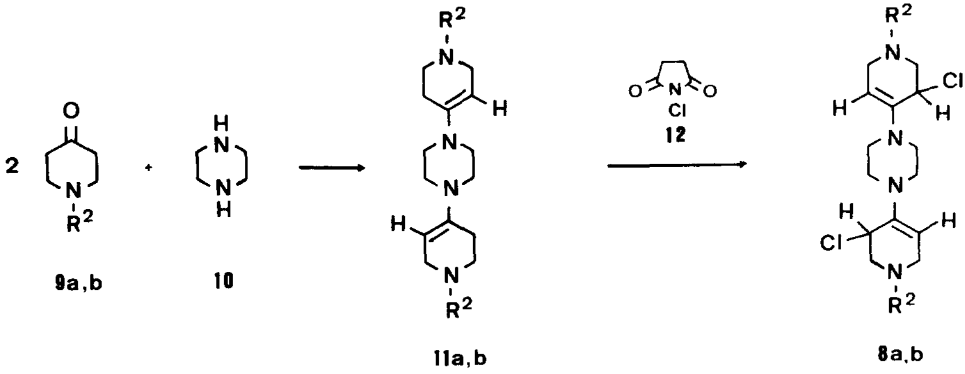
5 - **7**: a: R^1 = H, R^2 = Me; b: R^1 = H, R^2 = Bzl;
c: R^1 = H, R^2 = H; d: R^1 = CN, R^2 = Me;
e: R^1 = CH_2NH_2, R^2 = Me; f: R^1 = Me, R^2 = Me

SYNTHESIS OF 1,4-DI-(3-AZABICYCLO[3.1.0]HEXYL)-PIPERAZINES 5, 6 AND 7

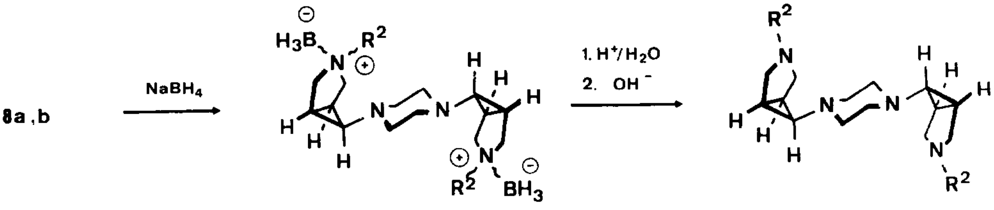
Di(enamines) **11a,b** were easily obtained from piperidinones **9a,b** and piperazine (**10**) by a standard procedure. Chlorination of **11a,b** with N-chlorosuccinimide (**12**) in dichloromethane at



8a, **9a**, **11a**: R^2 = Me **8b**, **9b**, **11b**: R^2 = Bzl

-50°C gave di(chloroenamines) **8** (**8a**: 49%; **8b**: 70% yield). The monochlorination of both enamine units of **11** generating **8** was clearly established by the ^{13}C NMR data of the products indicating only one single C=C-double bond [**8a**: 143.0 (s), 103.1 (d); **8b**: 143.2 (s), 102.8 (d)] and only one single CHCl-moiety [**8a**: 53.3 (d); **8b**: 53.5 (d)].

Reaction of di(chloroenamines) **8a,b** with sodium borohydride in acetonitrile provided bicyclic compounds: Thereby, di(borane-adduct) **13a** was isolated in 43% yield as product of starting material **8a**. Excessive interaction of 1 N aqueous hydrochloric acid (80°C, 24 h) was necessary for deboronation of **13a** to give **5a** (75% yield). The corresponding N-benzyl borane adduct **13b** was hydrolyzed very easily; here, acidic destroying of excess borohydride cleaved already the borane - amine complex leading to oligoamine **5b** (48% yield) as isolable reaction product. N-unsubstituted cyclopropanopyrrolidine **5c** (85% yield) could be obtained by hydrogenolysis of N-benzyl oligoamine **5b** in methanol in the presence of Pd/C.

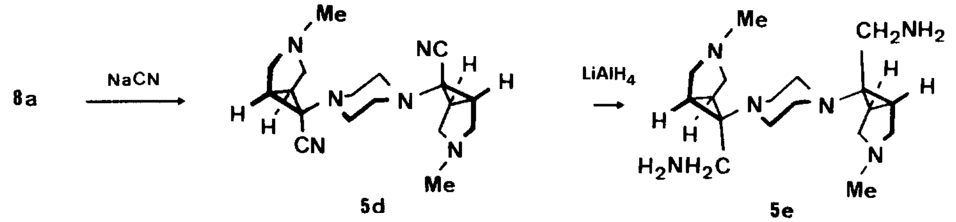


13a,b **5a,b**

5a, 8a: R^2 = Me **5b,8b**: R^2 = Bzl

5c: R^2 = H

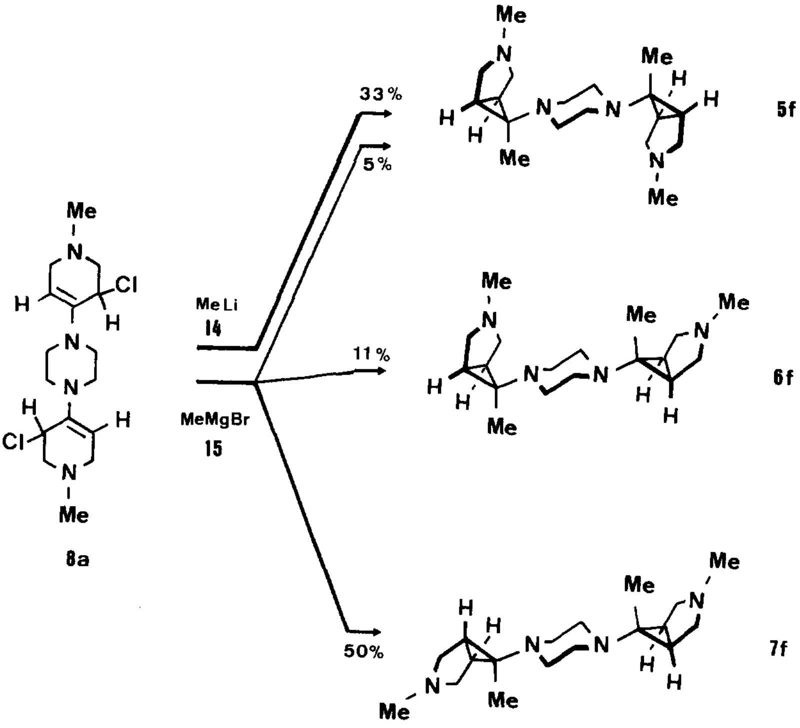
$$\mathbf{5b} \xrightarrow{H_2/\,Pd} \mathbf{5c}$$



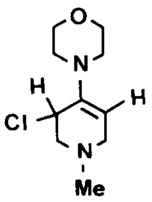
5d **5e**

Reaction of di(chloroenamine) **8a** with sodium cyanide provided bicyclic dinitrile **5d** (84% yield) which could be reduced to hexamine **5e** by lithium aluminum hydride (64% yield).

Di(chloroenamine) **8a** was transformed into pure endo,endo-tetramine **5f** (33% yield) by methyllithium (**14**); diastereomers **6f** or **7f** could not be detected ^1H NMR spectroscopically in the crude reaction mixture. The analogous interaction of methylmagnesium bromide (**15**) with di(chloroenamine) **8a** led to a mixture of three diastereomers **5f**, **6f** and **7f**. The latter was produced with remarkable selectivity (50% yield of pure isomer **7f**); isomers **5f** (5% yield) and **6f** (11% yield) were isolated as pure compounds by chromatography.



Formation of endo,endo-tetramine **5f** as only isolable product from the chloroenamine - methyllithium reaction was in accordance with the exclusive generation of diamine[8] **17** from chloroenamine **16** and methyllithium (**14**). Methylmagnesium bromide (**15**), however, showed different stereoselection in the reaction with chloroenamine **16** on the one hand (gave equal amounts of **17** and **18**)[8] and di(chloroenamine) **8a** on the other hand.



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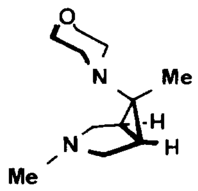

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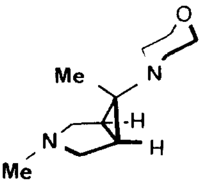

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CONFIGURATION OF 1,4-DI-(3-AZABICYCLO[3.1.0]HEXYL)-PIPERAZINES 5, 6 AND 7

The number of the ^{13}C NMR signals indicated the highly symmetric structure of the bicyclic compounds **5**, **7** and **13a**: Only two signals at all were found for the cyclopropane moieties and only one triplet appeared for the piperazine methylene groups of **5**, **7** and **13a**. Different configurations of the two azabicyclohexyl moieties in compound **6f** caused two sets of signals for the constitutionally identical piperazine substituents.

endo-Piperazine configuration of **5b,c** and **13a** was established by the $^3J_{HH}$ coupling of the triplet of the C(6)-H-signal (**5b**: $^3J_{HH}$ = 6.0 Hz; **5c**: $^3J_{HH}$ = 6.8 Hz; **13a**: $^3J_{HH}$ = 6.1 Hz). These values are characteristic of coupling of syn H-atoms of a cyclopropane ring system (e.g. ref.[7] and references cited therein). The configuration of **5a** [C(6)-H-signal superposed by a multiplet] was deduced on the basis of the configuration of the corresponding precursor **13a**. endo-Piperazine configuration of **5d** / **5e** was indicated by the magnitude of the $^3J_{CH}$ coupling of 4.1 Hz splitting the nitrile ^{13}C NMR signal of **5d** into a triplet (e.g. ref.[6] and references cited therein).

X-Ray structural analyses showed the endo,endo-configuration of **5f** (Fig. 1) and the exo,exo-configuration of **7f** (Fig. 2) and allowed indirectly the assignment of the endo,exo-configuration of the third isomer **6f**. The ^{13}C NMR δ-values of the C-methyl moiety in **5f** and **7f** are in accordance with this structural information: Highfield shifting of this signal (δ = 3.9 ppm) corresponds to compound **7f** with an endo-methyl moiety and lowfield shifting of this signal (δ = 14.7 ppm) is characteristic of isomer **5f** with the methyl group in exo-position.

The plots of the X-ray structural analyses indicate a meander type arrangement (isomer **5f**) or a linear shape (isomer **7f**) of the new type of oligoamines depending on the configuration of the 3-azabicyclo[3.1.0]hexyl building blocks.

CONFORMATION AND BASICITY OF 1,4-DI-(3-AZABICYCLO[3.1.0]HEXYL)-PIPERAZINES 5, 6 AND 7

X-Ray analyses demonstrate clearly the presence of a chair conformation for endo,endo-isomer **5f** and a boat conformation for exo,exo-tetramine **7f** in the solid state. This result for isomer **5f** is in accordance with an X-ray structural analysis[9] of **17**; the boat conformation, found for **7f**, is confirmed by a ^{1}H NMR spectroscopic conformational study with diamine[9] **18**. The interplanar angles C(1)C(2)C(4)C(5) / C(2)N(2)C(4) of **5f** (24.0°) and **7f** (28.6°) show a clear buckling of the pyrrolidine system in both cases.

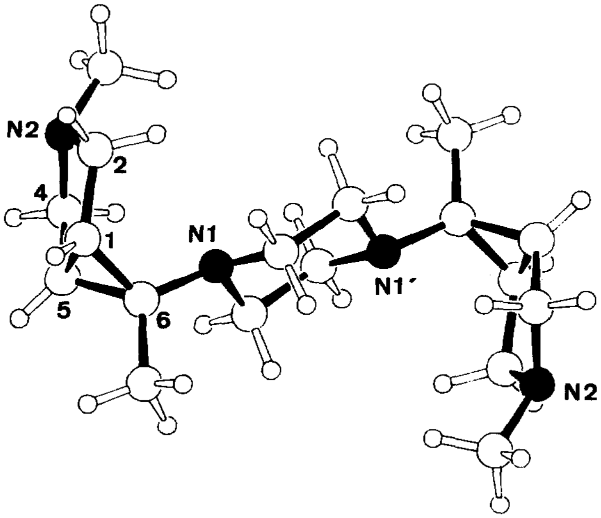


Fig. 1 Schakal-plot[10] of 1,4-Bis-(1α,5α,6β-3,6-dimethyl-3-azabicyclo[3.1.0]hex-6-yl)-piperazine (**5f**)

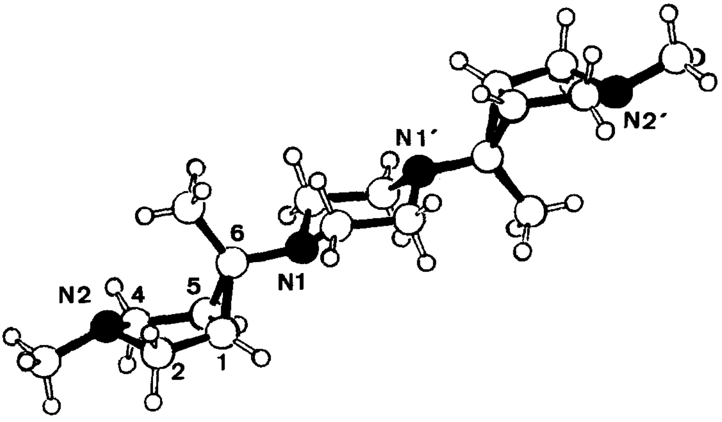


Fig. 2 Schakal-plot[10] of 1,4-Bis-(1α,5α,6α-3,6-dimethyl-3-azabicyclo[3.1.0]hex-6-yl)-piperazine (**7f**)

Table 1 Selected bond distances, N,N-distances,[a] torsional angles and interplanar angles[a] of 1,4-bis-(3,6-dimethyl-3-azabicyclo[3.1.0]hex-6-yl)-piperazine diastereomers **5f** and **7f**

bond lengths [Å]	**5f**	**7f**	N,N-distances [Å]	**5f**	**7f**
C(1) - C(5)	1.505(3)	1.500(3)	N(1) - N(1')	2.823(4)	2.844(2)
C(1) - C(6)	1.497(3)	1.508(3)	N(1) - N(2)	3.319(4)	4.269(2)
C(5) - C(6)	1.507(3)	1.506(3)	N(1) - N(2')	5.540(3)	7.083(2)
			N(2) - N(2')	8.688(4)	11.345(2)

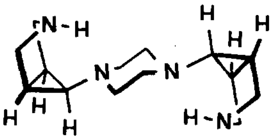
torsional angles [°][b]	**5f**	**7f**
H(1)-C(1)-C(2)-H(2)$_A$	113.84	-83.90
H(4)$_{A'}$-C(4)-C(5)-H(5)	-117.30	-86.53
H(1)-C(1)-C(2)-H(2)$_B$	- 5.83	37.73
H(4)$_{B'}$-C(4)-C(5)-H(5)	2.21	-35.05

interplanar angles [°]	**5f**	**7f**
C(1)C(5)C(6) - C(1)C(2)C(4)C(5)	65.4(2)	63.9(1)
C(1)C(2)C(4)C(5) - C(2)N(2)C(4)	24.0(2)	28.6(2)

[a] The numbering of the nitrogen atoms in Fig. 1, Fig. 2 and Table 1 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-azabicyclo[3.1.0]hexane system.

A potential influence of the conformation of the pyrrolidino ring on the geometry of the cyclopropane system of a 3-azabicyclo[3.1.0]hexyl compound can be excluded by comparing the bond lengths C(1)-C(5), C(1)-C(6) and C(5)-C(6) of **5f** and **7f**.

The conformation of the 3-azabicyclo[3.1.0]hexane units in the oligoamines **5**, **6** and **7** in solution could be deduced from ^{1}H NMR data: A "zero-coupling" between H$_A$/H$_{A'}$(endo-H-atoms) and H$_X$/H$_{X'}$ indicates[9] the presence of a boat conformation (clearly found for **5c**, **7f** and one azabicyclohexyl moiety of **6f**); highfield shifting of H$_A$/H$_{A'}$(endo-H-atoms) and a visible coupling between $H_A/H_{A'}$ (endo-H-atoms) and $H_X/H_{X'}$, on the other hand, are characteristic[9] of a chair conformation (clearly found for **5a**, **5b**, **5d**, **5e**, **5f** and one azabicyclohexyl moiety of **6f**). The dihedral angles H(1)-C(1)-C(2)-H(2)$_A$ / H(4)$_{A'}$-C(4)-C(5)-H(5) in **5f** (chair) and **7f** (boat) from the X-ray structural analyses (Table 1) underline the correctness of the conformational analysis on the basis of the coupling between $H_A/H_{A'}$ and $H_X/H_{X'}$. In the case of **5c** the ^1H NMR data additionally informed about the axial position of the hydrogen atom at the N(3)-nitrogen atom. The ^1H NMR signal of the pyrrolidine CH_2-unit of **5c** gave a further splitting at -28°C (toluene) due to coupling with the N(3)-H-atom. Values of $^3J_{HH}$ = 7.0 Hz for $H_A/H_{A'}$ and $^3J_{HH}$ = 11.2 Hz for $H_B/H_{B'}$ are consistent only with an axial N(3)-H-atom.



5c

Basicity of the tetramines **5**, **6** and **7** was studied in water at 25°C, aqueous hydrochloric acid (1 N for **5a**, **c**, **d**; 0.1 N for **5f**, **6f** and **7f**) was used for the titration in water. pK_a-values were determined by the application of the Henderson - Hasselbalch equation[11] at the corresponding half neutralization points leading to the simple expression: pH = pK_a. The pH of aqueous solutions was measured with a combined glass electrode; aqueous buffer solutions of pH 4.0, 7.0 and 9.0 were used for the calibration. The used concentrations (c_0) and the pK_a-values are given in Table 2.

Table 2. pK_a-Values of oligoamines **5**, **6** and **7** in water

Compound	$c_0 \cdot 10^{-3}$ [a]	pK_a[b]	Compound	$c_0 \cdot 10^{-3}$ [a]	pK_a[b]
5a	1.00	10.65	**5f**	1.00	10.52
5c	1.90	10.70	**6f**	1.00	10.35 [c]
5d	0.96	8.65			8.98 [c]
5e	0.50	10.20 [d]	**7f**	1.00	9.20
		7.42 [d]			

[a] 50 mL of the solution were used for each titration.- [b] Limit of error for pK_a-units: ± 0.02.- [c] Uptake of one proton.- [d] Uptake of two protons.

For all tetramines with two identical azabicyclohexyl moieties (**5** and **7**) only one single step appeared in the titration curves corresponding to the uptake of two protons. The titration plot of **6f**, however, showed a very slight bending in the area of the first neutralization point and a sharp step for the uptake of the second proton. Hexamine **6e** gave two clear steps in the titration curve corresponding to two protons each. The uptake of only two protons by tetramines **5** - **7** and the basicity differences of **5f**, **6f** and **7f** correspond quite well to the behaviour of diamines[1] **17** and **18**. Twofold protonation of **5** - **7** and the uptake of the first two protons in **5e** should take place at the pyrrolidine nitrogen atoms N(3) and N(3').[12] Deactivation of the piperazine moiety in **5** - **7** by the cyclopropane ring (see ref. [1]) prevents futher protonation in the aqueous system. It is known, that introduction of a cyano group into the *α*-position of an aminoalkane decreases basicity by about 5 pK-units (e.g. *α*-aminoacetonitrile[13] pK_a: 5.3; methanamine[13] pK_a: 10.7). A cyano group interacts as electron deficient moiety also with an adjacent cyclopropane system[14]; this generates a situation in **5d** which is similar to a vinylogous *α*-aminonitrile and which makes understandable the decrease of basicity of **5d** with respect to that of **5a** or **5f**.

Tertiary amines generally are less strong bases than the secondary analogues. In contrast to this, N-methyl compound **5a** showed the same basicity as the corresponding N-H-derivatives **5c**. This unexpected behaviour can be attributed to conformational differences of **5a** (chair conformation) and **5c** (boat conformation).

MOLECULAR FLEXIBILITY OF 1,4-DI-(3-AZABICYCLO[3.1.0]HEXYL)-PIPERAZINES 5, 6 AND 7

Free activation enthalpy $\Delta G^{\ddagger}$ of topomerization of the hydrogen atoms of the piperazine unit gave an insight into the molecular flexibility of the oligoamines **5**, **6** and **7** possessing rigid azabicyclohexyl building blocks. The $\Delta G^{\ddagger}$-values for this topomerization process were obtained by temperature dependent ^1H NMR spectroscopy. In the case of tetramines **5**, a change of the piperazine H-signals from an AA'XX'-system into an A_4-system should be observed. The 400 MHz spectra allowed an easy determination of δH_A and δH_X due to a symmetrical shape of each of the signal pattern. The $\Delta G^{\ddagger}$-values were estimated by application of the formula for the coalescence of uncoupled signals.[15] The applicability of this approximation in the case of a piperazine system was demonstrated with N,N'-dimethylpiperazine: A value of 55.7 kJ/mol ($H_A/H_{A'}$: 2.49 ppm; $H_X/H_{X'}$: 2.09 ppm; T_c = 285 K; $C_6D_5CD_3$), thus obtained, agrees sufficiently well with the value of 55.6 kJ/mol (CD_2Cl_2) reported by Petrakis.[16] A change from an ABXY system to an AA'XX' system for the piperazine ^1H NMR signals could be observed for tetramine **6f** with increasing temperature. Due to partial superposition of the signals, the $\Delta G^{\ddagger}$ values also were determined with the approximation formula for the exchange of noncoupling protons.[15]

Table 3. $\Delta G^{\ddagger}$ - Values of the dynamics of the piperazine ring of compounds **5a**, **5c**, **5d**, **5f**, **6f** and **7f** determined on the basis of ^1H NMR data (400 MHz) and coalescence temperatures (T_c) in $C_6D_5CD_3$.

Compound	T [K]	$H_{AA'}$or H_A, H_Y [ppm]	$H_{XX'}$or H_B, H_X [ppm]	T_c [K] [kJ/mol]	$\Delta G^{\ddagger}$ [a]
5a	230	2.45	2.22	265	52.9
5c	245	2.29	1.77	295	57.1
5d	270	2.46	2.06	330	64.9
5e	290	2.83	2.37	340	66.6
5f	270	2.58	2.27	332	66.0
6f	282	2.47[b]	2.27[c]	313	63.2
		2.62[d]	2.49[e]	310	63.7
7f	220	2.61	2.52	242	50.0

[a] Calculated with the approximation formula for the uncoupled case (ref.[15]).- [b] H_Y.- [c] H_X.- [d] H_A.- [e] H_B.-

The rigid 3-azabicyclo[3.1.0]hexyl moieties at the piperazine unit of **5**, **6** and **7** act as equatorial anchoring groups leading to definite geometries in all cases. Rotation of the azabicyclo[3.1.0]hexyl units at the piperazine group additionally can be hindered in the case of their fixation in endo position in compounds **5**. As expected, hindrance of this rotation depends on the substituent R^1 [no additional hindrance for R^1 = H (see ref.[7]) and moderate additional hindrance for R^1 = CN (see ref.[6]) and R^1 = Me (see ref.[8])]. Thus, meander type tetramines **5** with further substituents in 6,6'-position (R^1 = H) should be the most interesting representants of the new oligoamines.

EXPERIMENTAL

^1H 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. The amines were titrated with a Metrohm Titrino SM 702 apparatus using Metrohm electrodes [combined pH-glass electrode with Ag/AgCl/KCl (3 N) as inner reference electrode].

Piperidone Enamine 11 - General Procedure: A solution of piperidinone **9** (0.1 mol, **9a**: 11.3 g; **9b**: 18.9 g), 4-toluenesulfonic acid (0.2 g, 1.05 mmol) and piperazine (**10**) (4.3 g, 0.05 mol) in benzene (150 mL) was heated in a Dean-Stark apparatus for 11 h. Concentration of the solution to 20 mL and standing at room temperature gave crystalline enamines **11** which were isolated by suction and washed with ice-cold ether.

1,4-Bis-(1,2,3,6-tetrahydro-1-methyl-pyridin-4-yl)-piperazine (**11a**): Yield: 12.1 g (88%), mp 118°C; IR (KBr, cm^{-1}) 1640 (C=C); ^1H NMR ($CDCl_3$) δ 2.25 (4H), 2.55 (4H) (AA'BB'-system), 2.34 (s, 6H), 2.85 (s, 8H), 2.98 (m_c, 4H), 4.62 (t, 2H); ^{13}C NMR ($CDCl_3$) δ 143.2 (s), 97.8 (d), 54.1 (t), 52.2 (t), 47.3 (t), 45.5 (q), 27.7 (t). Anal. Calcd for $C_{16}H_{28}N_4$: C, 69.52; H, 10.21; N, 20.27. Found: C, 69.5; H, 10.4; N, 20.5.

1,4-Bis-(1-benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)-piperazine (**11b**): Yield: 20.1 g (93%), mp 128°C; IR (KBr, cm^{-1}) 1640 (C=C); ^1H NMR ($CDCl_3$) δ 2.21 (4H), 2.58 (4H) (AA'BB'-system), 2.85 (s, 8H), 3.06 (m_c, 4H), 3.57 (s, 4H), 4.60 (t, 2H), 7.24-7.36 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 143.6 (s), 138.4 (s), 129.1 (d), 128.1 (d), 126.9 (d), 97.7 (d), 62.7 (t), 52.7 (t), 49.8 (t), 47.3 (t), 27.8 (t). Anal. Calcd for $C_{28}H_{36}N_4$: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.4; H, 8.4; N, 13.1.

Di(chloroenamines) 8 - General Procedure: A solution of N-chlorosuccinimide (**12**) (5.34 g, 40 mmol) in dichloromethane (140 mL) was dropped at -50°C during 1 h to a stirred solution of enamine (20 mmol, **11a**: 5.53 g; **11b**: 8.57 g) in dichloromethane (60 mL). Stirring was continued at -50°C for 1 h. Then cooling was removed to warm up the mixture to room temperature. Succinimide was removed by extraction with saturated aqueous sodium carbonate solution (3 x 80 mL). Removing the solvent in vacuo and trituration of the residue with pentane (150 mL) gave pure chloroenamines **8**. Recrystallization from ether led to colorless crystals.

1,4-Bis-(3-chloro-1,2,3,6-tetrahydro-1-methyl-pyridin-4-yl)-piperazine (**8a**): Yield: 3.38 g (49%), mp 148°C (decomp.); IR (KBr, cm^{-1}) 1640 (C=C); ^1H NMR ($CDCl_3$) δ 2.82 (H_{B1}, 2H), 2.95 (H_{A1}, 2H), 4.80 (H_{X1}, 2H) (ABX-system), 2.85 (H_{B2}, 2H), 3.30 (H_{A2}, 2H), 4.61 (H_{X2}, 2H) (ABX-system), 2.39 (s, 6H), 2.83-2.91 (m, 4H), 3.00-3.09 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 143.0 (s), 103.1 (d), 60.8 (t), 54.3 (t), 53.3 (d), 47.5 (t), 45.2 (q). Anal. Calcd for $C_{16}H_{26}Cl_2N_4$: C, 55.65; H, 7.59; N, 16.23. Found: C, 55.8; H, 7.7; N, 16.3.

1,4-Bis-(1-benzyl-3-chloro-1,2,3,6-tetrahydro-pyridin-4-yl)-piperazine (**8b**): Yield: 6.96 g (70%), mp 155°C (decomp.); IR (KBr, cm^{-1}) 1640 (C=C); ^1H NMR ($CDCl_3$) δ 2.94-3.08 (H_{A2}, H_{B1}, 4H and m, 4H), 3.33 (H_{A1}, 2H), 4.80 (H_{X1}, 2H), 2.81 (H_{B2}, 2H), 4.59 (H_{X2}, 2H) (2 ABX-systems), 2.85-2.92 (m, 4H), 3.56 (H_{B3}, 2H), 3.73 (H_{A3}, 2H) (AB-system), 7.23-7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 143.2 (s), 137.7 (s), 128.9 (d), 128.2 (d), 127.1 (d), 102.8 (d), 61.6 (t), 57.9 (t), 53.5 (d), 52.6 (t), 47.4 (t). Anal. Calcd for $C_{28}H_{34}Cl_2N_4$: C, 67.60; H, 6.89; N, 11.26. Found: C, 67.2; H, 7.0; N, 10.8.

Reaction of Di(chloroenamines) 8 with Sodium Borohydride - General Procedure: A suspension of di(chloroenamine) **8** (10 mmol; **8a**: 3.45 g; **8b**: 4.97 g) and sodium borohydride (3.78 g, 100 mmol) in acetonitrile (120 mL) was stirred at 70°C for 100 h. Excess sodium borohydride was removed by suction; the solvent was evaporated and the residue dissolved in water (50 mL). Aqueous hydrochloric acid (1 N) was added at 0°C to the solution till pH 1. The acidic solution was stirred till the end of hydrogen evolution. Basification by aqueous sodium hydroxide (1 N) till pH 10 and extraction with ether (3 x 80 mL) gave crude products **13a** and **5b**, respectively. Pure products were obtained by crystallization from acetonitrile.

[6,6'-(Piperazine-1,4-diyl)]-bis-[trihydro-(1α,5α,6β-3-methyl-3-azabicyclo[3.1.0]hexane-N^3,$N^{3'}$]-boron (**13a**): Yield: 1.30 g (43%), mp 273°C; IR (KBr, cm^{-1}) 2220-2400 (B-H); ^{1}H NMR ($CDCl_3$) δ 1.92 (H_Y, $^3J_{XY}$ = $^3J_{X'Y}$ = 6.1 Hz, 2H), 2.01 (H_X, $H_{X'}$, 4H), 2.55 (H_A, $H_{A'}$, 4H), 3.39 (H_B, $H_{B'}$, 4H) (AA'BB'XX'Y-system), 2.64 (s, 6H), 2.30-2.70 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 61.2 (t), 51.9 (t), 49.7 (q), 49.6 (d, $^1J_{CH}$ = 160 Hz), 26.1 (d, $^1J_{CH}$ = 175 Hz). Anal. Calcd for $C_{16}H_{34}B_2N_4$: C, 63.20; H, 11.27; N, 18.42. Found: C, 63.0; H, 11.2; N, 18.4.

1,4-Bis-(1α,5α,6β-3-benzyl-3-azabicyclo[3.1.0]hex-6-yl)-piperazine (**5b**): Yield: 2.05 g (48%), mp 135°C; ^{1}H NMR ($CDCl_3$) δ 1.71 (H_X, $H_{X'}$, 4H), 1.78 (H_Y, $^3J_{XY}$ = $^3J_{X'Y}$ = 6.0 Hz, 2H), 2.29 (H_A, $H_{A'}$, 4H), 3.14 (H_B, $H_{B'}$, 4H) (AA'BB'XX'Y-system), 2.50 (s, broad, 8H), 3.66 (s, 4H), 7.22-7.35 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 140.0 (s), 128.7 (d), 128.1 (d), 126.6 (d), 58.8 (t), 52.1 (t), 52.0 (t), 48.2 (d, $^1J_{CH}$ = 167 Hz), 24.7 (d, $^1J_{CH}$ = 171 Hz). Anal. Calcd for $C_{28}H_{36}N_4$: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.1; H, 8.7; N, 13.2.

1,4-Bis-(1α,5α,6β-3-methyl-3-azabicyclo[3.1.0]hex-6-yl)-piperazine (**5a**): Di(borane) adduct **13a** (1.30 g, 4.3 mmol) was added to a mixture of aqueous hydrochloric acid (1 N, 60 mL) and acetonitrile (10 mL) and stirred at 80°C for 24 h. The solvent was evaporated in vacuo, the residue was dissolved in water (30 mL) and brought to pH 12 by addition of aqueous sodium hydroxide (5 N). Extraction with dichloromethane (3 x 20 mL) at 0°C gave crude **5a** which was recrystallized from acetonitrile. Yield: 0.88 g (75%), mp 140°C; ^{1}H NMR ($CDCl_3$) δ 1.70-1.80 (H_X, $H_{X'}$, H_Y, 6H), 2.24 (H_A, $H_{A'}$, 4H), 3.26 (H_B, $H_{B'}$, 4H) (AA'BB'XX'Y-system), 2.32 (s, 6H), 2.45 (s, broad, 8H). ^{13}C NMR ($CDCl_3$) δ 53.8 (t), 52.0 (t), 48.3 (d, $^1J_{CH}$ = 165 Hz), 40.3 (q), 25.3 (d, $^1J_{CH}$ = 170 Hz); MS (70 eV) m/e = 277.0 ([M + 1]$^+$, 10%), 190.6 (93%), 94.2 (100%). Anal. Calcd for $C_{16}H_{28}N_4$: C, 69.52; H, 10.21; N, 20.27. Found: C, 69.7; H, 10.1; N, 20.5.

1,4-Bis-(1α,5α,6β-3-azabicyclo[3.1.0]hex-6-yl)-piperazine (5c): A solution of di(benzyl) compound **5b** (0.86 g, 2.0 mmol) in methanol (150 mL) was added to Pd/C catalyst (10%) (0.40 g) in a hydrogen atmosphere and stirred for 24 h. The reaction was stopped when the theoretical amount of hydrogen (90 mL) was consumed. Removal of the catalyst by filtration and evaporation of the methanol gave crude **5c** which was recrystallized from acetonitrile. Yield: 0.42 g (85%), mp 215°C (decomp.); ^1H NMR ($CDCl_3$) δ 1.45-1.53 (m, 4H), 1.76 (t, $^3J_{HH}$ = 6.8 Hz), 1.90-2.85 (m, unsplit, 10 H), 2.91-3.06 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 53.8 (t), 48.1 (t), 44.8 (d, $^1J_{CH}$ = 162 Hz), 23.1 (d, $^1J_{CH}$ = 169 Hz). Anal. Calcd for $C_{14}H_{24}N_4$: C, 67.70; H, 9.74; N, 22.56. Found: C, 67.4; H, 9.6; N, 22.5.

6,6'-(Piperazine-1,4-diyl)-bis-(1α,5α,6β-3-methyl-3-azabicyclo[3.1.0]hexane-6-carbonitrile) (5d): Di(chloroenamine) **8a** (3.45 g, 10 mmol) and sodium cyanide (1.23 g, 25 mmol) were heated in a mixture of acetonitrile (80 mL) and water (8 mL) to 50-60°C for 16 h. Then the solvent was removed in vacuo and the residue was dissolved in dichloromethane (60 mL). Washing the solution with water (2 x 50 mL) and evaporating the dichloromethane gave crude dinitrile **5d** which was recrystallized from acetonitrile. Yield: 2.73 g (84%), mp 231°C (decomp.); IR (KBr, cm^{-1}) 2110 ($C\equiv N$); ^1H NMR ($CDCl_3$) δ 2.27 (H_A, $H_{A'}$, 4H), 2.33 (H_X, $H_{X'}$, 4H), 3.32 (H_B, $H_{B'}$, 4H) (AA'BB'XX'-system), 2.29 (s, 6H), 2.62-2.76 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 117.3 (t, $^3J_{CH}$ = 4.1 Hz), 53.2 (t), 49.2 (t), 43.7 (s), 40.1 (q), 34.0 (d, $^1J_{CH}$ = 175 Hz). Anal. Calcd for $C_{18}H_{26}N_6$: C, 66.23; H, 8.03; N, 25.74. Found: C, 66.4; H, 8.3; N, 25.8.

1,4-Bis-{1α,5α,6β-6-(aminomethyl)-3-methyl-3-azabicyclo[3.1.0]hex-6-yl}-piperazine (5e): Lithium aluminum hydride (1.14 g, 30 mmol) was added to a suspension of dinitrile **5d** (0.49 g, 1.5 mmol) in ether (100 mL). The mixture was refluxed for 3 d. Excess lithium aluminum hydride was destroyed at -20°C by aqueous potassium hydroxide (20%, 30 mL). Insoluble crude hexamine **5e** was obtained by filtration at room temperature and washing with water (5 mL) and ether (5 mL). Extraction with acetonitrile (90 mL) at 80°C, concentration of the filtrate to 60 mL and cooling at 0°C gave pure crystals of **5e**. Yield: 0.32 g, (64%), mp 198°C; ^1H NMR ($CDCl_3$) δ 0.94 (broad, unsplit, 4H), 1.75 (m_c, 4H), 2.17 (m_c, 4H); 2.30 (s, 6H), 2.55 (H_X, $H_{X'}$, 4H), 2.85 (H_A, $H_{A'}$, 4H) (AA'XX'-system), 2.75 (s, 4H), 3.14 m_c, 4H); ^{13}C NMR ($CDCl_3$) δ 55.2 (s), 54.2 (t), 50.1 (t), 43.5 (t), 40.4 (q), 32.4 (d, $^1J_{CH}$ = 167 Hz). Anal. Calcd for $C_{18}H_{34}N_6$: C, 64.63; H, 10.25; N, 25.12. Found: C, 64.6; H, 10.0; N, 24.8.

1,4-Bis-(1α,5α,6β-3,6-dimethyl-3-azabicyclo[3.1.0]hex-6-yl)-piperazine (5f) from Di(chloroenamine) 8a and Methyllithium (14): An ethereal solution of methyllithium (**14**) (1.6 M; 18 mL, 28.8 mmol) was dropped at -20°C within 1 h to a mixture of di(chloroenamine) **8a** (1.0 g, 2.9 mmol) in ether (100 mL). Stirring was continued at -20°C for 10 h, then the suspension was warmed up till 10°C very slowly (4 h). The crude reaction mixture was hydrolyzed by addition of ice (20 g) and of H_2SO_4 (95%, 3 mL). The clear solution was extracted with ether (3 x 30 mL), basified by saturated aqueous NaOH solution till pH = 14 was reached and extracted with ether (200 mL) in a Kutscher-Steudel apparatus for 4 d. Drying the ethereal solution with $MgSO_4$, removal of the ether by evaporation and distillation of the residue in a Kugelrohr apparatus at 100-110°C / 0.0001 Torr gave pure tetramine **5f** as colorless crystals. Yield: 0.29 g (33%), mp 185°C (decomp.); ^{1}H NMR ($CD_3C_6D_5$) δ 0.83 (s, 6H), 1.36 (H_{X1}, $H_{X'1}$, 4H), 2.17 (H_{A1}, $H_{A'1}$, 4H), 3.17 (H_B, $H_{B'}$, 4H) (AA'BB'XX'-system), 2.35 (s, 6H), 2.27 (H_{X2}, $H_{X'2}$, 4H), 2.58 (H_{A2}, $H_{A'2}$, 4H) (AA'XX'-system). ^{13}C NMR ($CDCl_3$) δ 54.3 (t), 49.4 (s), 48.5 (t), 40.3 (q), 35.1 (d, $^1J_{CH}$ = 166 Hz), 14.7 (q). Anal. Calcd for $C_{18}H_{32}N_4$: C, 71.01; H, 10.59; N, 18.40. Found: C, 70.8; H, 10.5; N, 18.3.

Reaction of Di(chloroenamine) 8a with Methylmagnesium Bromide (15): An ethereal solution of methylmagnesium bromide (**15**) (3 M; 20 mL, 60 mmol) was dropped at room temperature within 1 h to a mixture of di(chloroenamine) **8a** (1.0 g, 2.9 mmol) in ether (100 mL). The suspension was refluxed for 4 d. Then the crude reaction mixture was worked up as described above. The ethereal solution from the Kutscher-Steudel extraction was evaporated to give a mixture of the 3 diastereomeric tetramines **5f**, **6f** and **7f**. The crude amines were dissolved in ether (30 mL); standing for 16 h at 4°C gave crystalline exo,exo-tetramine **7d** which was isolated by suction (0.40 g, 45%). The amines in the remaining solution were separated by chromatography (column: ϕ: 2 cm, length: 20 cm; basic Al_2O_3). Elution with ether gave further exo,exo-isomer **7f** as first and endo,exo-isomer **6f** as second fraction. endo,endo-Tetramine **5f** was obtained by subsequent elution with methanol.

1,4-Bis-(1α,5α,6β-3,6-dimethyl-3-azabicyclo[3.1.0]hex-6-yl)-piperazine **(5f)** Yield: 0.043 g (5%); mp 185°C (decomp.); 1H NMR data identical with those of **5f** which was obtained from the reaction of **8a** with methyllithium (**14**).

1-(1α,5α,6β-3,6-Dimethyl-3-azabicyclo[3.1.0]hex-6-yl)-4-(1α,5α,6α-3,6-dimethyl-3-azabicyclo-[3.1.0]hex-6-yl)-piperazine **(6f)** Yield: 0.096 g, 11%), mp 112°C; ^{1}H NMR ($CD_3C_6D_5$) δ 0.80 (s, 3H), 1.37 (s, 3H), 1.33 (H_{X1}, $H_{X'1}$, 2H), 2.18 (H_{A1}, $H_{A'1}$, 2H), 3.18 (H_{B1}, $H_{B'1}$, 2H) (AA'BB'XX'-system), 1.41 (H_{X2}, $H_{X'2}$, 2H), 2.89 (H_{A2}, $H_{A'2}$, 2H), 2.46 (H_{B2}, $H_{B'2}$, 2H) (AA'BB'XX'-system), 2.16 (s, 3H), 2.34 (s, 3H), 2.30 (broad, 2H), 2.50 (broad, 4H), 2.60 (broad, 2H). ^{13}C NMR ($CDCl_3$) δ 55.5 (t), 53.7 (t), 49.8 (s), 48.4 (t), 48.2 (t), 47.0 (s), 41.5 (q), 40.1 (q), 34.7 (d, $^1J_{CH}$ = 169 Hz), 31.2 (d, $^1J_{CH}$ = 169 Hz), 14.7 (q) , 3.6 (q). Anal. Calcd for $C_{18}H_{32}N_4$: C, 71.01; H, 10.59; N, 18.40. Found: C, 71.2; H, 10.8; N, 18.5.

1,4-Bis-(1α,5α,6α-3,6-dimethyl-3-azabicyclo[3.1.0]hex-6-yl)-piperazine **(7f)** Yield: 0.443 g (50%), mp 195°C; ^{1}H NMR ($CD_3C_6D_5$) δ 1.34 (s, 6H), 1.42 (H_{X1}, $H_{X'1}$, 4H), 2.87 (H_{A1}, $H_{A'1}$, 4H), 2.44 (H_B, $H_{B'}$, 4H) (AA'BB'XX'-system), 2.15 (s, 6H), 2.50 (s, 8H). ^{13}C NMR ($CDCl_3$) δ 55.0 (t), 48.5 (t), 47.2 (s), 41.4 (q), 31.4 (d, $^1J_{CH}$ = 168 Hz), 3.9 (q). Anal. Calcd for $C_{18}H_{32}N_4$: C, 71.01; H, 10.59; N, 18.40. Found: C, 71.1; H, 10.4; N, 18.4.

X-Ray Crystal Structure Analysis of 5f.[17,18] Single crystals of **5f** were obtained by crystallization from ether.

Crystal data: $C_{18}H_{32}N_4$, F.W. = 304.5; triclinic, space group $P\bar{1}$; a = 6.375(3), b = 6.470(6), c = 11.115(4) Å; α = 97.34(5), β = 101.29(3), γ = 94.99(5)°; V = 442.9(9) Å^3; 1 molecule per unit cell; D_x = 1.142 g · cm^{-3}; crystal size 0.60 x 0.50 x 0.15 mm.

Data collection: Diffractometer Enraf-Nonius CAD 4, monochromatized Mo-K_α radiation; 1567 independent reflections with $4.00 < 2\Theta < 50.00°$ [$\omega/2\Theta$ scan, scan width (0.95 + 0.35 tan Θ)°, scan speed 1.8 - 5.0 ° · min^{-1}], no absorption correction.

Structure solution and refinement: Full matrix least-squares method; H atoms refined isotropically, 997 reflections with $I_{obs} > 2\,\sigma(I_{obs})$; 164 variables, unit weights, weighting scheme $w = 4 \cdot F_{obs}^2/[\sigma(I)^2 + (P \cdot F_{obs}^2)^2]$, P = 0.015; maximum shift/error ratio 0.03, R = 0.046, R_w = 0.038.

X-Ray Crystal Structure Analysis of 7f.[17,18] Single crystals of **7f** were obtained by crystallization from ether.

Crystal data: $C_{18}H_{32}N_4$, F.W. = 304.5; monoclinic, space group $P2_1/c$; a = 9.986(3), b = 5.830(2), c = 15.491(22) Å; $\alpha = \gamma$ = 90, β = 95.74(5)°; V = 897.3(19) Å^3; 2 molecules per unit cell; D_x = 1.127 g cm^{-3}; crystal size 0.70 x 0.50 x 0.30 mm.

Data collection: Diffractometer Enraf-Nonius CAD 4, monochromatized Mo-K_α radiation; 1741 independent reflections with $4.00 < 2\Theta < 50.00°$ [$\omega/2\Theta$ scan, scan width (0.85 + 0.35 tan Θ)°, scan speed 2.5 - 4.0 ° · min^{-1}], no absorption correction.

Structure solution and refinement: Full matrix least-squares method; H atoms refined isotropically, 1164 reflections with $I_{obs} > 2\,\sigma(I_{obs})$; 164 variables, unit weights, weighting scheme $w = 4 \cdot F_{obs}^2/[\sigma(I)^2 + (P \cdot F_{obs}^2)^2]$, P = 0.015; maximum shift/error ratio 0.09, R = 0.053, R_w = 0.050.

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18. 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.

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