Functionalized Chloroenamines in Aminocyclopropane Synthesis Part 12.[1] Basicity and Protonation Behaviour of 6-Amino-3-azabicyclo[3.1.0]hexane Derivatives

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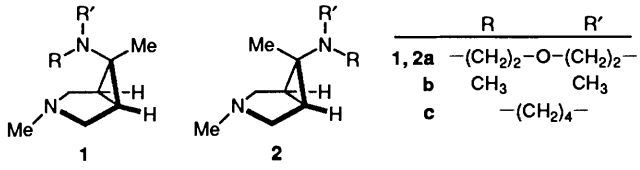
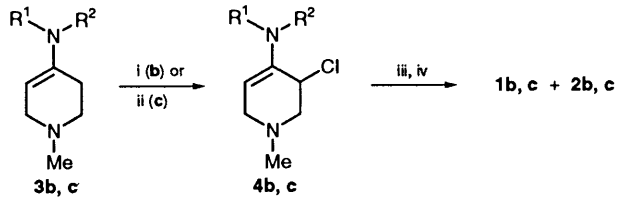
Bicyclic *endo* diamines **1a–c** are more basic than the diastereomeric *exo* diamines **2a–c** by about one pK_a unit. Configuration and conformation of some compounds **5**, the monoammonium salts of the *endo* diamines **1**, have been studied by ^1H NMR spectroscopy. X-Ray structure analysis of salt **5n Br**, possessing the N(3)–H proton in the *endo* position, indicates a hydrogen bonding with the bromide anion rather than with the C(6)–morpholine unit.

Diastereomeric compounds **1a** and **2a** represent a new type of diamine in which definite N–N distances are established by the bicyclic system.[2] Structural studies showed that the 3-azabicyclo[3.1.0]hexane skeleton prefers a chair conformation in compound **1a**[3] and a boat conformation in the diastereomer **2a**.[3] Basicities of these new diamines **1a**/**2a** and of two further pairs of analogous diastereomeric compounds **1b**/**2b** and **1c**/**2c** are reported in this paper. Results from the investigation of the conformation and the configuration of the monoammonium salts of **1** are included.



Scheme 1



Scheme 2 *Reagents:* i, *N*-chlorosuccinimide (for **3b**); ii, dimethyl sulfide–*N*-chlorosuccinimide complex (for **3c**); iii, methylmagnesium bromide; iv, $NaOH/H_2O$

Results and Discussion

Reaction of methylmagnesium bromide with chloroenamines **4b,c** was chosen as a simple and direct route[2] to both diastereomers of diamines **1b**/**2b** and **1c**/**2c**, respectively. Separation by extracting the aqueous solution at different pH values with ether and subsequent chromatography gave pure substances **1b** (8%) and **2b** (43%) from **4b**; analogously **1c** (9%) and **2c** (35%) were obtained from **4c**. Pyrrolidine or dimethylamine instead of morpholine as the amino moiety in chloroenamine **4** favoured strongly the formation of *exo* diamines **2** upon reaction with methylmagnesium bromide. Products from a direct displacement of chlorine in **4b**/**c** by the methyl moiety could not be detected in the crude reaction mixture.

The configuration of the diamines **1b**/**2b** and **1c**/**2c** was established by direct comparison of their ^1H and ^{13}C NMR data with those of **1a** and **2a**.[2] Characteristic differences of the basicities of **1b**/**1c** and **2b**/**2c** (see next section) confirmed the assignment of configuration. Chloroenamine **4b** was obtained by chlorination of enamine **3b** with *N*-chlorosuccinimide at −78 °C; an analogous direct monochlorination could not be realized with the more stronger basic enamine **3c**. Here, enamine **3c** was reacted with succinimidosulfonium chloride[4] to produce an enaminosulfonium salt which, without isolation, gave chloroenamine **4c** upon standing for 24 h at room temperature (see ref 5).

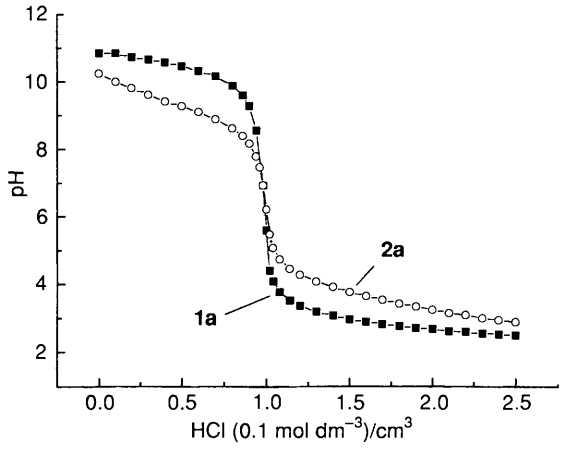


Fig. 1 Titration of the diastereomeric diamines **1a** and **2a** in water with 0.1 mol dm^{-3} aqueous hydrochloric acid

Basicities of the Bicyclic Diamines **1a–c** *and* **2a–c** *and Site of Monoprotonation.*—Diamines **1a–c** and **2a–c** were titrated in water with 0.1 mol dm^{-3} aqueous hydrochloric acid. The pH of the aqueous solution was measured with a combined glass electrode; aqueous buffer solutions of pH 4.0, 7.0 and 9.0 were used for the calibration. Figs. 1, 2 and 3 show the curves for the titrations of **1a**/**2a**, **1b**/**2b** and **1c**/**2c** in water.

Titration curves showed that *endo* diamines **1a–c** could only be monoprotonated in the aqueous system. Diastereomeric compounds **2b** and **2c** behaved as real diamines taking up two protons with two discrete steps in the titration curves. A second step was not clearly detectable with **2a**.

pK_a values were determined by application of the Henderson–Hasselbalch equation[6] at the corresponding half-neutralization points leading to the simple expression: pH = pK_a. The pK_a values are given in Table 1. *endo* Diamines **1** are stronger bases than the *exo* diastereomers **2** by 1.1–1.2 units.

The various amino groups which were used as substituent in

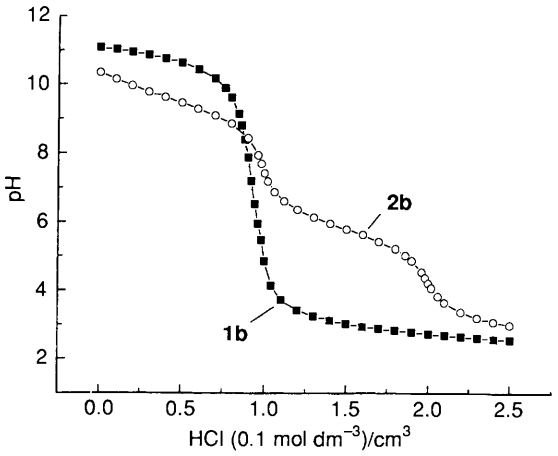


Fig. 2 Titration of the diastereomeric diamines **1b** and **2b** in water with 0.1 mol dm^{-3} aqueous hydrochloric acid

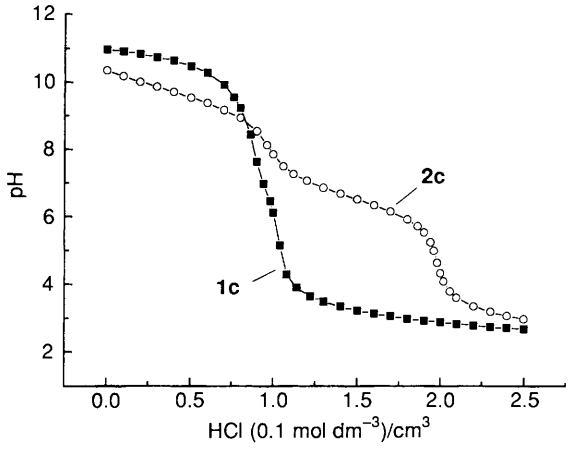


Fig. 3 Titration of the diastereomeric diamines **1c** and **2c** in water with 0.1 mol dm^{-3} aqueous hydrochloric acid

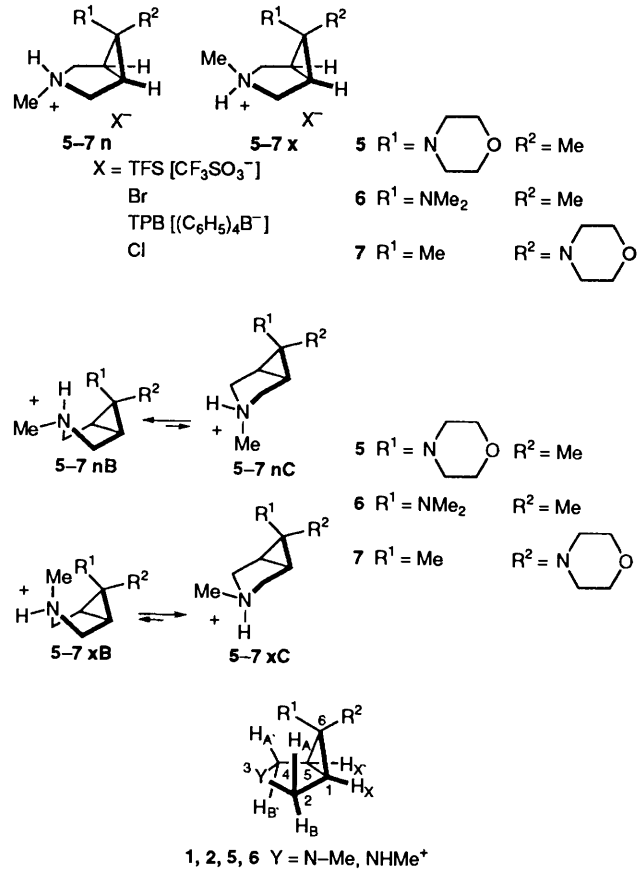
Table 1 pK_a values[a] of the diamines **1a–c** and **2a–c** in water (c_0 = 2 10^{-3} mol dm^{-3})[b]

Compound	Uptake of H$^+$	pK_a	Compound	Uptake of H$^+$	pK_a
1a	1	10.44	**2a**	1	9.26
1b	1	10.64	**2b**	1	9.41
				1	5.80
1c	1	10.47	**2c**	1	9.53
				1	6.51

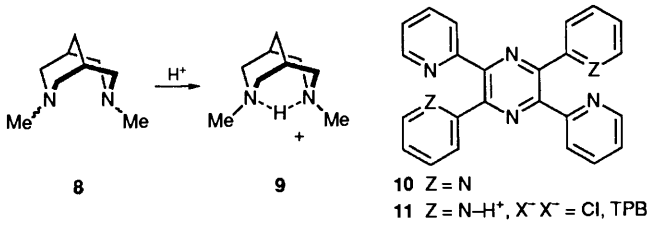
[a] Limit of error for pK_a units: ± 0.05. [b] 50 cm^3 of the solution were used for each titration.

the 6-position of **1** and **2** differ strongly in basicity as shown by the pK_a values of the corresponding *N*-methyl species (*N*-methylmorpholine: 7.41;[7] trimethylamine: 9.76;[8] *N*-methylpyrrolidine: 10.46[9]). The same magnitude within the pK_a values of **1a**, **1b** and **1c** on the one hand, and of **2a**, **2b** and **2c** on the other hand indicates that the amino moiety at C(6) is not involved in the first protonation step. It is known that the basicity of an amine is decreased by an adjacent cyclopropyl group.[10] This 'cyclopropane-induced' decrease in basicity can be seen clearly from the pK_a value for the second protonation step of **2b** and **2c** (Table 1). As expected, this pK_a value is influenced by the nature of the amino group in the 6-position indicating additionally the site of the attack of the second proton.

Two diastereomeric monoammonium salts with an *exo* (=**x**) or *endo* (=**n**) located N(3)–hydrogen atom could be expected from the monoprotonation of **1** or **2**; a boat (**B**) and a chair (**C**) conformation are to be considered for each diastereomer.



Scheme 3



Scheme 4

The formation of an intramolecular hydrogen bond in the case of **5 nB** could be seen as a simple reason for the differences in the basicities and in the number of protons taken up by **1** and **2**. This would be well comparable to the increase of basicity in *N*,*N*′-dimethylbispidine **8** (pK_a: 11.88[11]) with respect to *N*-methylpiperidine (pK_a: 10.08[9]) and the formation only of a monoammonium salt **9** from **8**.[11]

Further information about the structure of monoammonium salts **5** and **6**, therefore, seemed to be of interest.

Configuration and Conformation of the Monoammonium Salts **5** *and* **6**.—Monoammonium salts **5 TFS**, **5 Br**, **5 TPB** and **6 Cl** were prepared. The monoprotonation of diamines **1a** and **1b** at the N(3)-nitrogen atom of the 3-azabicyclo[3.1.0]hexane system additionally could be established from the ^{13}C NMR data: The reactions **1a**⟶**5 TFS**, **5 Br** or **5 TPB** and **1b**⟶**6 Cl** caused an increase of the $^1J_{CH}$ coupling constants of the 2-CH_2/4-CH_2 methylene moiety by *ca.* 10 Hz. The analogous coupling of the morpholino NCH_2 unit, however, remained unchanged (Table 2). About 10–13 Hz[12] increases of the $^1J_{CH}$ coupling of

Table 2 Change of ^{13}C NMR chemical shifts of the cyclopropane system and the N-CH-units of the amines **1a**, **1b** and **2a** upon monoprotonation; influence of the protonation upon the $^{1}J_{CH}$ coupling of the N-CH-moieties, $^{1}J_{CH}$ [Hz][a] in ( )

Compound	Solvent[b]	Pyrrolidine N-CH_3	Pyrrolidine N-CH_2	NR^1R^2 N-CH_2/NCH_3	Cyclopropane [d]	Cyclopropane [s]	Proportion and structure of isomers[c]	
1a	i	40.1 (126)	54.1 (136)	48.4 (133)	34.6	49.3	—	**C**
	ii	41.8 (134)	56.2 (136)	51.0 (133)	36.8	52.1	—	**C**
	iii	40.1 (132)	54.5 (136)	49.1 (133)	35.6	50.1	—	**C**
5 TFS	i	39.1 (143)	55.5 (145)	48.7 (136)	33.6	50.9	50	**xC**
		43.2 (143)	56.6 (145)	49.6 (136)	29.8	47.0	50	**nB**
	iii	42.5 (142)	57.4 (148)	50.5 (133)	29.8	47.3	>90	**nB**
5 Br	i	38.8 (*d*)	54.7 (145)	48.7 (133)	33.4	*e*	>90	**xC**
	ii[f]	41.3 (144)	58.1 (146)	51.1 (134)	36.0	54.0	80	**nB**
		44.6 (144)	59.4 (145)	52.0 (136)	31.9	47.2	20	**xC**
5 TPB	iii	42.0 (144)	57.1 (146)	50.3 (134)	30.0	*e*	100	**nB**
1b	i	40.7 (131)	54.3 (136)	40.2 (132)	35.2	50.0	—	**C**
6 Cl	i	38.5 (145)	54.2 (146)	40.3 (134)	33.7	50.2	80	**xC**
		43.5 (144)	55.3 (146)	41.0 (134)	30.0	47.2	20	**nB**

[a] Limit of error for $^{1}J_{CH}$: ± 1 Hz. [b] i: $CDCl_3$; ii: D_2O; iii: CD_3CN; room temperature. [c] Identification of structure according to the ^{1}H NMR data (see Table 3). [d] *J* not detectable owing to coalescence. [e] Signal not detectable. [f] 15 °C.

Table 3 ^{1}H NMR chemical shifts of the pyrrolidine—methylene hydrogen atoms of the diamines **1a** and **1b** and their monosalts **5** and **6**

Compound	Solvent[a]	*T*/°C	$H(2)_A$[b] $H(4)_{A'}$ (ppm)	$J_{A,NH}$ $J_{A',NH}$/Hz	$H(2)_B$[c] $H(4)_{B'}$ (ppm)	$J_{B,NH}$ $J_{B',NH}$/Hz	$H_A\ \Delta\delta$[d]	$H_B\ \Delta\delta$[d]	Proportion and structure of isomers[e]	
1a	i	25	2.10		3.13				—	**C**
	iii	25	2.07		3.00				—	**C**
5 TFS	i	−28	2.68	8.0[f]	4.00	6.1[f]	0.58	0.87	45	**xC**
			3.91	5.4[g,h]	3.36	7.2[f,g]	1.81	0.23	55	**nB**
	iii	0	3.67	*j*	3.33	*j*	1.60	0.33	>95[k]	**nB**
1a	ii	25	2.56		3.19				—	**C**
5 Br	ii	25	3.77		3.45		1.21	0.26	80	**nB**
			2.82		3.87		0.26	0.68	20	**xC**
	i	−33	2.64	*j*	4.05	*j*	0.54	0.92	>95	**xC**
1b	i	25	2.23		3.02				—	**C**
6 Cl	i	−20	2.68	7.2	3.97	6.6	0.45	0.95	75	**xC**
			3.80	*l*	3.20	*l*	1.57	0.18	25	**nB**

[a] i: $CDCl_3$; ii: D_2O; iii: CD_3CN. [b] $H(2)_A$ and $H(4)_{A'}$ are in the *endo* position of the azabicyclohexane skeleton. [c] $H(2)_B$ and $H(4)_{B'}$ are in the *exo* position of the azabicyclohexane skeleton. [d] Differences in chemical shifts of the corresponding signals of the free base and the monosalt in the given solvent. [e] Boat conformation is assigned by the 'zero-coupling' between $H(2)_A/H(4)_{A'}$ and the cyclopropane proton $H(1)_X/H(5)_{X'}$. [f] Coupling was determined by irradiation at the cyclopropane $C(1)H_X/C(5)H_{X'}$ signal. [g] Coupling is not observable at 20 °C. [h] Coupling was determined by irradiation at the morpholine NCH_2 signal. [j] Coupling not determined. [k] Signals of the second isomer in the expected areas only as very small buckling detectable. [l] Coupling was not observable even at −40 °C.

the 2-CH_2- and 6-CH_2-units were reported upon protonation of piperidines.

^{13}C NMR data of the salts **5 TFS** and **6 Cl** in chloroform or **5 Br** in water showed the presence of two species (Table 2). The observation of two diastereomeric salts, however, is more likely than the appearance of two invertomers of one diastereomer since both species could be recognized in the ^{13}C NMR at room temperature.

Protonation of amines **1a** and **1b** was accompanied in the ^{13}C NMR spectra by almost no change of the signals for one species and by a distinct change, especially of the C(1)/C(5) and of the C(6) signal, for the second species. Only small high field shifting in the ^{13}C NMR spectra was reported for protonation of *N*-methylpiperidine [$\Delta\delta$: N-Me: −2.6;[12,13] C(2)/C(6): −1.5;[12,13] C(3)/C(5): −2.5;[12] −2.3;[13] C(4): −2.5,[12] −2.0[13]]. Similar values were found for the protonation of 4-*tert*-butyl-*N*-methylpiperidine if the configuration of the base (N–Me_{eq} and 4-C-Bu^t_{eq}) was not changed upon protonation. The diastereomeric salt with an axial *N*-methyl group led to a larger high field shifting especially for C(3)/C(5) ($\Delta\delta$ = −7.5[12] for N–Me_{ax}, $\Delta\delta$ = −1.8[12] for N–Me_{eq}). An identical configuration (equatorial *N*-methyl group) and conformation (chair conformation), therefore, can be predicted from the ^{13}C NMR data for those salt species **5** and **6** which show almost the same signals as the corresponding free amines **1**. Information about the structure of the second cationic species was not available from the ^{13}C NMR spectra.

Further insights into the structural properties of the monoammonium salts **5** and **6** were obtained from the ^{1}H NMR data (Table 3). The ^{1}H NMR spectrum of **5 TFS** in $CDCl_3$ equally showed the presence of two species at room temperature. A chair conformation (**C**) could be established for one species and a boat conformation (**B**) was deduced for the other species owing to the $^{3}J_{HH}$ coupling between $H(2)_A/H(4)_{A'}$, and $H(1)_X/H(5)_{X'}$ ('zero-coupling' $J_{A,X}$ in one case, small $J_{A,X}$ coupling in the other case; $H_{B,B'}$ was assigned due to the larger $J_{B,X}$ coupling in both cases). At −28 °C additionally the $^{3}J_{HH}$ coupling between N(3)H and $H(2)_A/H(4)_{A'}$ and $H(2)_B/H(4)_{B'}$ became detectable by irradiation of the cyclopropane $C(1)H_X/C(5)H_{X'}$ signal or the morpholine NCH_2-signal (in this special case the morpholine OCH_2 signal disturbed by superposition on the $H(2)_A/H(4)_{A'}$ signal; coupling with $H(1)_X/H(5)_{X'}$ does not take place) (Fig. 4). The observed coupling constants $^{3}J_{HH}$ correspond to a N(3)-hydrogen atom in the axial position in both cases; an analogous equatorial N(3)-hydrogen atom would lead to a smaller coupling (see ref.

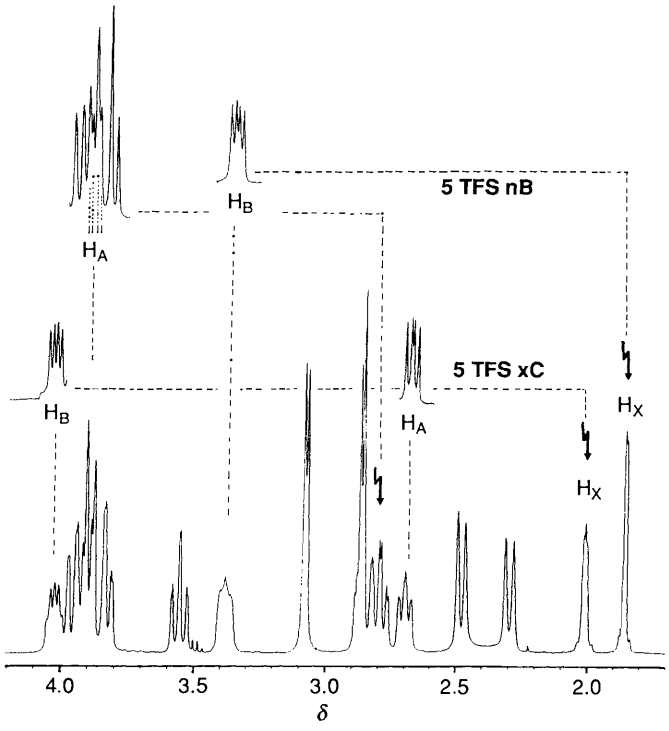


Fig. 4 ^{1}H NMR spectrum of **5 TFS** ($CDCl_3$, −28 °C, 400 MHz); identification of the $^3J_{HH}$ coupling between the pyrrolidine CH_AH_B hydrogen atoms and the adjacent N(3)-hydrogen atom by decoupling experiments

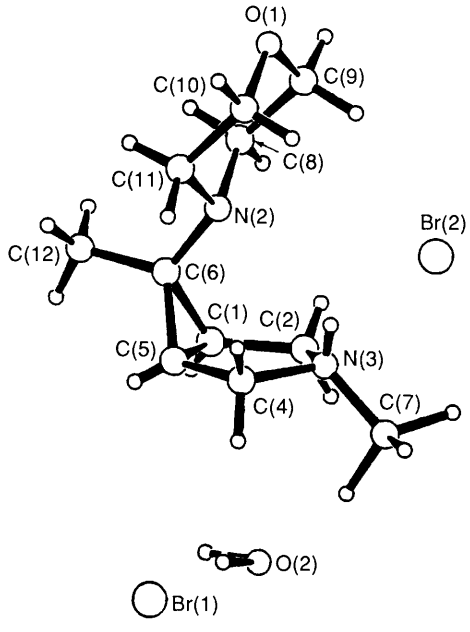


Fig. 5 Schakal-plot[16] of ammonium salt **5nBr**·H_2O

1). Thus, structures **5 TFS xC** and **5 TFS nB** could be deduced in a simple way. At room temperature $^3J_{HH}$ coupling of the N(3)-hydrogen atom with adjacent C–H moieties disappeared for **5 TFS nB** but remained for **5 TFS xC** indicating an intramolecular hydrogen bond in the case **5 TFS nB**.

Similar $^3J_{HH}$ coupling constants allowed the establishment of an **xC** structure for one of the **6 Cl** ammonium salts; the corresponding coupling of the N(3)-hydrogen atom could not be observed in the other diastereomer even at low temperatures as a result of a fast intramolecular hydrogen exchange rate. A **6 Cl nB** structure could be deduced for this diastereomer from the

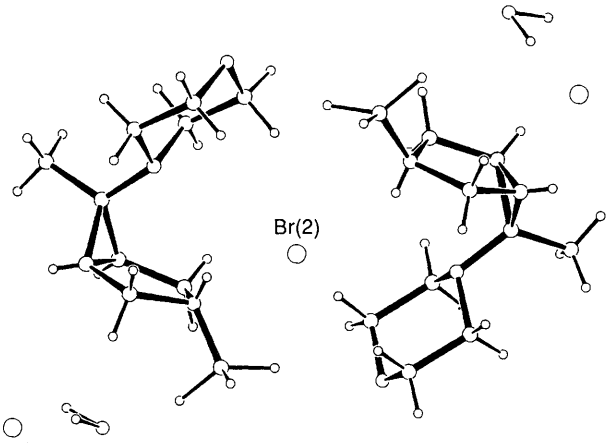


Fig. 6 Detail of the crystal structure of **5n Br**·H_2O. Both halves of the plot are symmetrically related by a C_2 axis (perpendicular to the plane of the paper). The central bromide anion is located on this C_2 axis. The two bromide anions at the corners of the plot are located on a second C_2 axis.

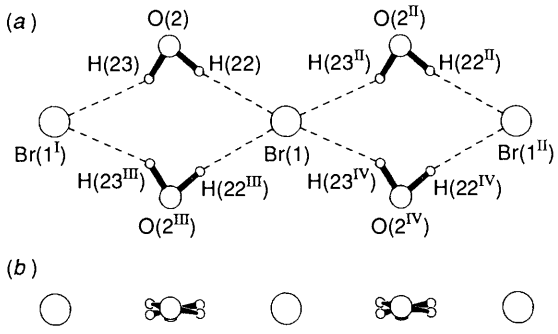


Fig. 7 The bromide anions on the C_2 axis (0.5, y, 0.5) are connected by two symmetrically related water molecules each. All heavy atoms are located in one plane. (*a*) Projection onto the plane of the heavy atoms. (*b*) Projection perpendicular to this plane.

total agreement of the ^{1}H and the ^{13}C NMR 3-azoniabicyclohexane signals with those of **5 TFS nB**.

Monoprotonation of diamines **1a** and **1b** led to an interesting shift of the ^{1}H NMR pyrrolidine CH_AH_B signals (see Table 3). Both H_A (0.5–0.6 ppm) and H_B (0.9–1.0 ppm) were shifted clearly downfield if the chair conformation remained on protonation. Protonation accompanied by a change from chair to boat conformation, however, caused an extreme downfield shifting of the H_A ^{1}H NMR signal (1.6–1.8 ppm) whereas that of H_B was nearly unaffected (0.2–0.3 ppm). It is known that a cyclopropane ring behaves anisotropically causing a high field shifting of protons above or below the bonds of the ring.[14] The *endo* hydrogen atoms $H(2)_A/H(4)_A$, of a 3-azabicyclo[3.1.0]hexane skeleton are located much closer to the cyclopropane C(1)–C(6)/C(5)–C(6) bonds in a chair conformation than in a boat conformation. Thus, high field shifting of H_A with respect to H_B should indicate the presence of a chair conformation of a 3-azabicyclo[3.1.0]hexane system.

Differences $\Delta\delta$ between the chemical shifts of the H_{ax} and H_{eq} hydrogen atom of the NCH_2 group of various piperidines have been discussed rather extensively in the literature.[15] High field shifting of H_{ax} was argued to be the consequence of a neighbouring anti-axial N-lone pair. $\Delta\delta H_{ax}H_{eq}$, therefore, was used for the determination of the axial or equatorial location of the N-lone pair in a piperidine system.[15] The differences of the $\Delta\delta$-values for **1a** (1.03 ppm, $\delta H_A \ll \delta H_B$, chair) and **2a** (0.11 ppm, $^{2,3}\delta H_A > \delta H_B$, boat, both values in $CDCl_3$) should not be the consequence of an axial or equatorial N-lone pair (equatorial *N*-methyl group and axial N-lone pair in both cases). This additionally becomes obvious from the $\Delta\delta$ values of

Table 4 Selected bond lengths (Å), torsional angles and interplanar angles (°) for **5n Br**·H_2O[a]

Bond lengths			
C(1)–C(5)	1.50(1)	N(3)–C(2)	1.51(1)
C(1)–C(6)	1.50(1)	N(3)–C(7)	1.46(1)
C(5)–C(6)	1.51(1)	C(4)–N(3)	1.53(1)
Torsional angles			
H(1)–C(1)–C(2)–$H(2)_A$	100.0(1.2)	$H(4)_A$–C(4)–C(5)–H(5)	−87.6(1.5)
H(1)–C(1)–C(2)–$H(2)_B$	−18.9(1.6)	$H(4)_B$–C(4)–C(5)–H(5)	32.1(1.7)
H–N(3)–C(2)–$H(2)_A$	24.8(1.3)	H–N(3)–C(4)–$H(4)_A$	−19.1(0.9)
H–N(3)–C(2)–$H(2)_B$	145.2(0.8)	H–N(3)–C(4)–$H(4)_B$	−138.9(0.8)
Interplanar angles			
C(1)C(5)C(6)–C(4)C(5)C(1)C(2)	65.8		
C(4)C(5)C(1)C(2)–C(2)N(3)C(4)	8.1		

[a] The numbering of the atoms in Figs. 4–6, Table 4 and Table 5 in this paper was changed partially with respect to the numbering in the deposited data; it was adjusted to the general numbering in a 3-azabicyclo[3.1.0]hexane system for better comparison with other data.

Table 5 Hydrogen bonding in the crystal of **5n Br**·H_2O[a]

Hydrogen bond length/Å		Angle/°	
N(3)–H(3)	0.72	N(1)–H(3)···Br(2)	140.0
H(3)–Br(2)	2.62	H(3)···Br(2)···H(3)	115.3
N(3)–Br(2)	3.207(8)		
Br(1)···O(2)	3.531(11)	O(2)···Br(1)···O(2)[b]	64.6(3)
Br(1)···O(2)[c]	3.503(11)	O(2)[c]···Br(1)···O(2)[d]	65.2(3)
		Br(1)[e]···O(2)···Br(1)	115.1(2)
O(2)–H(22)	1.00	H(22)–O(2)–H(23)	84
O(2)–H(23)	0.98	O(2)–H(22)···Br(1)	165.4
H(22)···Br(1)	2.55	O(2)–H(23)···Br(1)[e]	145.3
H(23)···Br(1)[e]	2.65	H(22)···Br(1)···H(22)[b]	59
		H(23)···Br(1)[e]···H(23)[b]	48

[a] The numbering of the atoms in Figs. 4–6, Table 4 and Table 5 in this paper was changed partially with respect to the numbering in the deposited data; it was adjusted to the general numbering in a 3-azabicyclo[3.1.0]hexane system for better comparison with other data. The positions of the hydrogen atoms were taken from ΔF maps and were not refined. The location of the hydrogen atoms of the water molecules in the crystal are strongly defective.[b] Symmetry operation $1-x, y, 1-z$.[c] Symmetry operation $x, y-1, z$.[d] Symmetry operation $1-x, y-1, 1-z$.[e] Symmetry operation $x, 1+y, z$.

N-methylene hydrogen atoms of the two diastereomeric ammonium salts of **1** with blocked N-lone-pairs but different conformations. A large $\Delta\delta$ for $H(2)_A/H(4)_A$ and $H(2)_B/H(4)_B$ is found for **5 TFS xC** (1.32 ppm) and a smaller $\Delta\delta$ is observed for **5 TFS nB** (0.55 ppm, both values in $CDCl_3$). This really should indicate the anisotropic effect of the cyclopropane ring on $H(2)_A/H(4)_A$ of a 3-azabicyclo[3.1.0]hexane skeleton in the chair conformation.

X-Ray Structural Analysis of Monoammonium Salt **5n Br**·H_2O.—Single crystals of **5 Br** were obtained from an acetonitrile—toluene solution. The crystal which was used for the X-ray structural analysis proved to be a **5n Br** diastereomer containing one molecule of water per formula unit. A boat conformation was found for the 3-azoniabicyclo[3.1.0]hexane cation in **5n Br**. The *N*-hydrogen atom is located at the N(3)-atom; only a small bending of the N(3)-H group towards the N(2)-atom is observed (ring buckle α 8.1°; N(2),N(3) distance: 2.996 Å). Hydrogen bonding from N(3)-H takes place to the bromide anion rather than with the morpholine nitrogen atom N(2).

Hydrogen bonding between N(3)–H(3) and Br(2) acts as the ordering element of the crystal structure. The bromide anion is located on a C_2 axis; two ammonium units are then connected via hydrogen bonding to one bromide anion. The excess positive charge is compensated for by a second bromide anion which is situated on another C_2 axis. Each of these two bromide anions in one unit cell is connected to bromide anions of a neighbouring cell (translation $y \pm 1$) by two water molecules. Thus a continuous band is built up by planar Br–O–Br–O-trapeziums possessing a C_2 axis. The hydrogen atoms of the water molecules are placed slightly above and below this plane. Selected X-ray structural data of the azoniabicyclo[3.1.0]-hexane cation of **5n Br**·H_2O are given in Table 4; data on the hydrogen bonding are given in Table 5 and Fig. 7.

Hydrogen bonding with the anion rather than with a second intramolecular amino moiety was found in the X-ray crystal structure of **11C**.[17] This is quite similar to the situation in the crystal of **5 Br n**·H_2O. The corresponding tetraphenylborate **11 TPB**, however, showed a strong intramolecular hydrogen bonding.[17]

Effects of Solvent and Anion on the Ratio of Diastereomeric Salts **5n**/**5x** *or* **6n**/**6x**.—Hydrogen bonding between the N(3)-H hydrogen atom and the amino group in the 6-position is less predominant in chloroform but stronger in acetonitrile. Acetonitrile is known to be a favourable solvent for intramolecular N···H···N bonding.[18] Bromide instead of trifluoromethanesulfonate or tetraphenylborate as anion caused a weakening of this N(3)–H···N–C(6) bonding (see Table 3). Thus each of the two 3-azoniabicyclo[3.1.0]hexane diastereomers could be observed under certain conditions as almost pure species: an *endo* protonated salt **5n** as a boat conformation was found exclusively for **5 TPB** in acetonitrile and only an *exo* protonated salt **5x** as a chair conformation was seen for **5 Br** in chloroform. Water as solvent negated the anion influence: a ratio of 2:8 of *exo* (**5x**) to *endo* protonated species (**5n**) was found equally for **5 Br** and **5 TFS**.

Tetraphenylborate **TPB** as anion of **5** and acetonitrile as solvent should be the best conditions for strong intramolecular hydrogen bonding. Even in this best case, **5 TPB** in acetonitrile, the $^1J_{CH}$ coupling constants (see Table 2) did not indicate an equal presence of the ammonium hydrogen atom at the morpholine nitrogen atom.

In spite of this fact, intramolecular hydrogen bonding between the morpholino group and the N(3)-H ammonium moiety is effective in **5n** and **6n** in solution as indicated by the basicity of the amines **1** and the disappearance of the $^3J_{N\text{-}H,C\text{-}H}$ coupling for **5n**/**6n**. A further indication of this N–H···N interaction was obtained by determination of the dynamics of morpholine in ammonium salts **5 TFS** and **5 Br**: almost identical $\Delta G^{\ddagger}$ values of the morpholine dynamics were observed for **5 TFS** and **5 Br** in water. These values are much higher than that of the free amine **1a** in the same solvent (Table 6).

Table 6 $\Delta G^{\ddagger}$ values of the dynamics of the morpholine ring of the ammonium salts **5 Br** and **5 TFS** and the free base **1a** determined on the basis of ^{1}H NMR data and coalescence temperatures (T_c) in water, 400 MHz

Compound	T/°C	Group	$H_{A/X}$	$H_{B/Y}$	$^2J_{HH}$/Hz	T_c/°C	$\Delta G^{\ddagger,a}$/k J mol^{-1}
1a[b]	2	OCH_2	3.83	3.66	10.0	34	62.2
		NCH_2	2.71	2.46	11.0	35	61.2
5 Br	30	OCH_2	3.86	3.71	11.3	97	75.8
5 TFS	30	OCH_2	3.86	3.67	12.0	95	74.7
		NCH_2	2.77	2.54	12.0	96	74.5

[a] Calculated with the approximate formula for the coupled case.[19] [b] 0.12 mol dm^{-3} NaOD solution in D_2O was used as solvent.

Experimental

^{1}H NMR and ^{13}C NMR spectra were obtained with a Bruker AMX 400 spectrometer (Me_4Si as internal standard; J values in Hz). IR spectra were measured on a Perkin-Elmer 397 Infrared Spectrophotometer. 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 mol dm^{-3}) as inner reference electrode; additionally a Pt electrode was used for compensation of interfering effects].

3-*Chloro*-4-*dimethylamino*-1,2,3,6-*tetrahydro*-1-*methylpyridine* **4b**.—A suspension of *N*-chlorosuccinimide (13.4 g, 0.1 mol) in dichloromethane (200 cm^3) was added slowly and under stirring at −78 °C to a solution of enamine **3b**[20] (14.0 g, 0.1 mol) in dichloromethane (50 cm^3). Stirring was continued for 2 h at −78 °C and for 2 h at room temp. Then the solvent was removed under reduced pressure. Chloroenamine **4b** was extracted from the residue with pentane (4 × 200 cm^3) and purified by distillation. Yield 7.6 g (44%) of colourless oil, b.p. 63 °C/0.001 Torr (Found: C, 53.7; H, 8.4; N, 15.6. $C_8H_{15}ClN_2$ requires C, 55.06; H, 8.62; N, 16.04%); ν_{max}(film)/cm^{-1} 1630 (C=C); δ_H($CDCl_3$) 2.39 (3 H, s), 2.66 (6 H, s), 2.70–2.80 (2 H, m), 3.00 (1 H, m$_c$), 3.37 (1 H, m$_c$) and 4.57–4.60 (2 H, m); δ_C($CDCl_3$) 39.9 (q), 45.2 (q), 53.6 (d), 54.3 (t), 60.7 (t), 99.8 (d) and 142.8 (s).

3-*Chloro*-1,2,3,6-*tetrahydro*-1-*methyl*-4-*pyrrolidinylpyridine* **4c**.—Dimethyl sulfide (6.2 g, 0.1 mol) was added under stirring to a solution of *N*-chlorosuccinimide (13.4 g, 0.1 mol) in dichloromethane (200 cm^3) at −20 °C (N_2 atmosphere to exclude moisture, see refs. 4, 5). Addition of enamine **3c**[21] (16.6 g, 0.1 mol) and stirring the mixture for 12 h at room temp. gave chloroenamine **4c** which was isolated by removal of the solvent and subsequent extraction of the residue with pentane (5 × 50 cm^3). Recrystallization from pentane led to colourless crystals of **4c**. Yield 10.0 g (50%), m.p. 31 °C (Found: C, 59.0; H, 8.3; N, 14.0. $C_{10}H_{17}ClN_2$ requires C, 59.84; H, 8.54; N, 13.96%); ν_{max}(film)/cm^{-1} 1640 (C=C); δ_H($CDCl_3$) 1.87 (4 H, m$_c$), 2.39 (3 H, s), 2.68 (1 H, m$_c$), 2.77 (1 H, m$_c$), 2.98 (2 H, m$_c$), 3.02 (1 H, m$_c$), 3.20 (2 H, m$_c$), 3.41 (1 H, m$_c$), 4.33 (1 H, m$_c$) and 4.55 (1 H, m$_c$); δ_C($CDCl_3$) 24.4 (t), 45.2 (q), 46.9 (t), 54.2 (t), 54.8 (d), 60.5 (t), 95.2 (d) and 139.9 (s).

6-*Amino*-3,6-*dimethyl*-3-*azabicyclo*[3.1.0]*hexanes* **1b**/**2b** *and* **1c**/**2c**.—Compounds **1b**/**2b** and **1c**/**2c** were prepared according to ref. 2 from a solution of chloroenamine **4** (10 mmol, **4b**: 1.74 g **4c**: 2.00 g) in ether (100 cm^3) and a 2 mol dm^{-3} ethereal solution of methylmagnesium bromide (15 cm^3, 30 mmol) at room temp. Stirring was continued for 72 h. Hydrolysis with water (50 cm^3) and 20% sulfuric acid (10 cm^3), extraction with ether (2 × 50 cm^3) and basification with 20% aq. sodium hydroxide gave free *exo*-amines **2b**,**c** which were extracted with ether (5 × 50 cm^3). Addition of solid sodium hydroxide (10 g, 250 mmol) to the remaining aq solution and extraction with ether (4 × 50 cm^3) provided *endo*-amines **1b**,**c**. The crude diamines **1b**,**c** and **2b**,**c** were purified by chromatography (60 cm × 2.5 cm column, basic Al_2O_3, ether–pentane 1 : 1).

(1α,5α,6β)-3,6-*Dimethyl*-6-*dimethylamino*-3-*azabicyclo*-[3.1.0]*hexane* **1b**. Yield 0.12 g (8%), b.p. 110 °C/14 Torr (Found: C, 69.4; H, 11.6; N, 18.0. $C_9H_{18}N_2$ requires C, 70.13; H, 11.69; N, 18.18%); δ_H($CDCl_3$) 0.92 (3 H, s), 1.51 (2 H, H_X, $H_{X'}$), 2.23 (2 H, H_A, $H_{A'}$), 3.02 (2 H, H_B, $H_{B'}$) (AA'BB'XX'-system), 2.21 (3 H, s) and 2.22 (6 H, s); δ_C($CDCl_3$) 12.9 (q), 35.2 (d, $^1J_{CH}$ 166), 40.2 (q), 40.7 (q), 50.0 (s) and 54.3 (t).

(1α,5α,6β)-3,6-*Dimethyl*-6-*pyrrolidin*-1-*yl*-3-*azabicyclo*-[3.1.0]*hexane* **1c**. Yield 0.16 g (9%), b.p. 85 °C/0.05 Torr (Found: C, 72.8; H, 11.3; N, 14.5. $C_{11}H_{20}N_2$ requires C, 73.30; H, 11.20; N, 15.56%); δ_H($CDCl_3$) 0.95 (3 H, s), 1.52 (2 H, H_X, $H_{X'}$), 2.08 (2 H, H_A, $H_{A'}$), 3.09 (2 H, H_B, $H_{B'}$) (AA'BB'XX'-system), 1.71 (4 H, m$_c$), 2.18 (3 H, s) and 2.56 (4 H, m$_c$); δ_C($CDCl_3$) 13.5 (q), 24.0 (t), 34.8 (d, $^1J_{CH}$ 169), 40.4 (q), 44.9 (s), 46.6 (t) and 54.5 (t).

(1α,5α,6α)-3,6-*Dimethyl*-6-*dimethylamino*-3-*azabicyclo*-[3.1.0]*hexane* **2b**. Yield 0.66 g (43%), b.p. 63 °C/23 Torr (Found: C, 70.0; H, 11.7; N, 18.0. $C_9H_{18}N_2$ requires C, 70.13; H, 11.69; N, 18.18%); δ_H($CDCl_3$) 1.13 (3 H, s), 1.48 (2 H, H_X, $H_{X'}$), 2.64 (2 H, H_B, $H_{B'}$), 2.75 [2 H, H_A, $H_{A'}$ (AA'BB'XX'-system)] and 2.25 (9 H, s); δ_C($CDCl_3$) 2.1 (q), 31.8 (d, $^1J_{CH}$ 169), 40.3 (q), 41.5 (q), 47.5 (s) and 55.0 (t).

(1α,5α,6α)-3,6-*Dimethyl*-6-*pyrrolidin*-1-*yl*-3-*azabicyclo*-[3.1.0]*hexane* **2c**. Yield 0.63 g (35%), b.p. 58 °C/0.1 Torr (Found: C, 73.3; H, 11.1; N, 15.3. $C_{11}H_{20}N_2$ requires C, 73.30; H, 11.20; N, 15.56%); δ_H($CDCl_3$) 1.14 (3 H, s), 1.49 (2 H, H_X, $H_{X'}$), 2.64 (2 H, H_B, $H_{B'}$), 2.74 (2 H, H_A, $H_{A'}$) (AA'BB'XX'-system), 1.70 (4 H, m$_c$), 2.24 (3 H, s) and 2.59 (4 H, m$_c$); δ_C($CDCl_3$) 3.6 (q), 23.8 (t), 30.8 (d, $^1J_{CH}$ 168), 41.6 (q), 42.6 (s), 47.3 (t) and 55.1 (t).

(1α,5α,6β)-3,6-*Dimethyl*-6-*morpholino*-3-*azoniabicyclo*-[3.1.0]*hexane Trifluoromethanesulfonate* **5 TFS**.—A solution of trifluoromethanesulfonic acid in propan-2-ol (0.1 mol dm^{-3}; 5 cm^3) was added to diamine **1a** (98 mg, 0.5 mmol) in acetonitrile (50 cm^3). The solution was stirred for 1 h; then the solvent was evaporated. The residue was triturated with diethyl ether (2 × 5 cm^3) and dried *in vacuo* to give the pure monoammonium salt **5 TFS** in quantitative yield; m.p. 152 °C (Found: C, 41.6; H, 6.0; N, 8.0. $C_{12}H_{21}F_3N_2O_4S$ requires C, 41.62; H, 6.07; N, 8.09%). δ_H($CDCl_3$, 25 °C) 1.11 and 1.12 (3 H, CH_3, s); the remaining signals are better separated allowing an exact assignment to each isomer (number of H atoms correspond to the relative numbers in one isomer); **xC** isomer: 1.98 (2 H, H_{X1}, $H_{X1'}$), 4.03 (2 H, H_{B1}, $H_{B1'}$), 2.69 (2 H, H_{A1}, H_{A1}), (AA'BB'XX'-system, 3-azabicyclo[3.1.0]hexane unit), 2.85 (3 H, N–CH_3, d), 2.27 (2 H, H_{A2}), 2.84 (2 H, H_{B2}), 3.53 (2 H, H_{X2}) and 3.92 (2 H, H_Y) (ABXY-system, morpholine); **nB** isomer: 1.84 (2 H, H_{X1}, $H_{X1'}$), 3.37 (2 H, H_{B1}, $H_{B1'}$), 3.86 (2 H, H_{A1}, H_{A1}), (AA'BB'XX' system, 3-azabicyclo[3.1.0]hexane units), 3.06 (3 H, N–CH_3, s), 2.46 (2 H, H_{A2}), 2.77 (2 H, H_{B2}), 3.80 (2 H, H_{X2}) and 3.86 (2 H, H_Y) (ABXY system, morpholine).

(1α,5α,6β)-3,6-*Dimethyl*-6-*morpholino*-3-*azoniabicyclo*-[3.1.0]*hexane Bromide* **5 Br**.—An aqueous solution of hydrobromic acid (48%; 0.08 cm^3, 0.5 mmol) was added to a solution of *endo* amine **1a** (98 mg, 0.5 mmol) in water (1 cm^3) and stirred for 1 h. Extraction with dichloromethane (3 × 2 cm^3) and evaporation of the solvent gave pure **5 Br**. Yield 100 mg (72%) m.p. 161 °C (Found: C, 47.4; H, 7.7; N, 10.1. $C_{11}H_{21}BrN_2O$ requires C, 47.66; H, 7.64; N, 10.11%); δ_H($CDCl_3$, −33 °C) 1.13 (3 H, CH_3, s), 2.01 (2 H, H_{X1}, $H_{X1'}$), 2.64 (2 H, H_{A1}, $H_{A1'}$), 4.04 (2 H, H_{B1}, $H_{B1'}$) (AA'BB'XX'-spin system, 3-azabicyclo-[3.1.0]hexane unit), 2.34 (2 H, H_{A2}), 2.88 (2 H, H_{B2}), 3.58 (2 H,

H_{X2}), 3.98 (2 H, H_Y) (ABXY spin system, morpholine) and 2.80 (3 H, N–CH_3, s).

(1α,5α,6β)-3,6-*Dimethyl*-6-*morpholino*-3-*azoniabicyclo*-[3.1.0]*hexane Tetraphenylborate* **5 TPB**.—Solutions of NaB(C_6H_5)$_4$ (821 mg, 2.4 mmol) in acetonitrile (5 cm^3) and hydrobromide **5 Br** (220 mg, 0.8 mmol) in acetonitrile (15 cm^3) were combined. The resulting precipitate of NaBr was removed by filtration. Evaporating the acetonitrile from the clear filtrate and triturating the remaining residue with water (4 × 2 cm^3) and ether (2 × 5 cm^3) gave **5 TPB**. Yield 370 mg (90%), m.p. 168 °C (Found: C, 81.1; H, 7.8; N, 5.4. $C_{35}H_{41}BN_2O$ requires C, 81.38; H, 7.99; N, 5.42%); δ_H(CD_3CN, 31 °C) 1.06 (3 H, CH_3, s), 1.72 (2 H, H_{X1}, $H_{X1'}$), 3.26 (2 H, H_{B1}, $H_{B1'}$), 3.48 (2 H, H_{A1}, $H_{A1'}$) (less split signals, 3-azabicyclo[3.1.0]hexane unit), 2.73 (3 H, N–CH_3, s), 2.44 (2 H, H_{A2}), 2.70 (2 H, H_{B2}), 3.64 (2 H, H_{X2}), 3.77 (2 H, H_Y) (ABXY spin system, morpholine), 6.85 (4 H, t), 7.01 (8 H, t) and 7.30 (8 H, unsplit, signal).

1α,5α,6β-3,6-*Dimethyl*-6-*dimethylamino*-3-*azoniabicyclo*-[3.1.0]*hexane Chloride* **6 Cl**.—Aqueous hydrochloric acid (10 cm^3; 0.1 mol dm^{-3}) was added to a solution of *endo* amine **1b** (154 mg, 1.0 mmol) and stirred for 1 h. Evaporation of water, trituration of the residue with ether (2 × 5 cm^3) and drying *in vacuo* gave pure **6 Cl** in quantitative yield; m.p. 52 °C (Found: C, 55.9; H, 10.3; N, 14.5. $C_9H_{19}ClN_2$ requires C, 56.85; H, 10.08; N, 14.74%); δ_H($CDCl_3$, −20 °C) (number of H-atoms correspond to the relative numbers in one isomer); **xC** isomer: 1.04 (3 H, CH_3, s), 1.92 (2 H, H_{X1}, $H_{X1'}$), 3.97 (2 H, H_{B1}, $H_{B1'}$), 2.68 (2 H, H_{A1}, $H_{A1'}$) (AA'BB'XX'-system, 3-azabicyclo-[3.1.0]hexane-unit), 2.30 [6 H, N(CH_3)$_2$, s] and 2.72 (3 H, N-CH_3, d); **nB** isomer: 1.08 (3 H, CH_3, s), 1.81 (2 H, H_{X1}, $H_{X1'}$), 3.20 (2 H, H_{B1}, $H_{B1'}$), 3.80 (2 H, H_{A1}, $H_{A1'}$) (AA'BB'XX'-system, 3-azabicyclo[3.1.0]hexane unit), 2.38 [6 H, N, N(CH_3)$_2$, s] and 2.96 (3 H, N–CH_3, s).

X-Ray Crystal Structure Analysis of **5N Br**.—Single crystals of **5n Br**·H_2O were obtained by crystallization from acetonitrile–toluene (1 : 1).

Crystal data. $C_{11}H_{21}BrN_2O{\cdot}H_2O$, M = 295.5. Monoclinic, a = 17.191(2), b = 5.935(3), c = 14.152(2) Å; α = 90, β = 112.88(1), γ = 90°; V = 1330.3(5) Å^3; space group $C2$, Z = 4, D_x = 1.47 g cm^{-3}. Colourless crystal. Crystal dimensions 0.6 × 0.3 × 0.3 mm, μ(Mo-Kα) = 30.5 cm^{-1}.

Data collection and processing. Enraf-Nonius-CAD 4 diffractometer; $\omega/2\theta$ mode with ω scan width = 0.85 + 0.35 tan θ, ω scan speed 1.8–4.0 deg min^{-1}, graphite-monochromated Mo-Kα radiation; 1142 reflections measured (4.00 < 2θ < 47.00°), 1093 unique, 1004 observed with $I > 3.00\ \sigma(I)$. An empirical (Fourier series) absorption correction was applied.

Structure analysis and refinement. The structure was solved by direct methods. Refinement was performed by a full-matrix-least-squares program. Hydrogen atoms were localized in a ΔF map and included in structure factor calculations. Refinement converged at R = 0.0436 and R_w = 0.0559; unit weights were applied. The largest shift/error ratio at this stage was 0.03. The residual density was < 0.45 [near Br(1)]. The given coordinates represent the correct absolute structure; inversion of the sign of the coordinates gave R = 0.0497, R_w = 0.0615.[22]*

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* Tables of atomic coordinates, bond lengths and angles, and temperature factors have been deposited at the Cambridge Crystallographic Data Centre. For details of the deposition scheme see 'Instructions for Authors'. *J. Chem. Soc. Perkin Trans. 2*, 1993, issue 1.

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