Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 675–681

TETRAHEDRON: *ASYMMETRY*

Synthesis and stereoselective dealkylation of *N*-chiral quarternary *N*-alkyl galanthaminium halides

Manfred Hirnschall,[a] Matthias Treu,[a] Kurt Mereiter,[b] Christian Hametner,[a] Johannes Fröhlich[a] and Ulrich Jordis[a,*]

[a]*Institute of Applied Synthetic Chemistry, Vienna University of Technology, Getreidemarkt 9/163OC, A-1060 Vienna, Austria*
[b]*Institute of Chemical Technologies and Analytics, Vienna University of Technology, Getreidemarkt 9, A-1060 Vienna, Austria*

Received 17 October 2002; accepted 28 November 2002

Abstract—The synthesis of *N*-chiral galanthaminium halides and their stereoselective dealkylation is described. The stereochemistry of two key compounds was determined by X-ray structure analysis.

1. Introduction

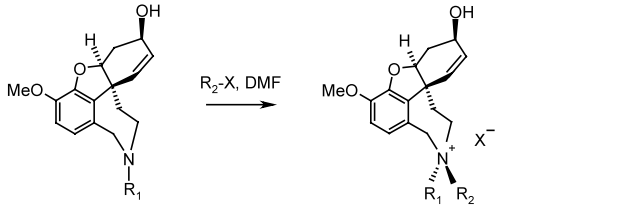
Galanthamine (Reminyl®, Nivalin®), which has been introduced into the European market and approved by the FDA for the treatment of Alzheimer's disease, is a reversible, competitive acetylcholinesterase inhibitor and has also been found to allosterically modulate nicotinic acetylcholine receptors.[1,2] Attempts to develop second generation galanthamine analogs have led to a demand for a protocol which allows selective *N*-demethylation of quarternary galanthaminium salts. The crystal structures of two chiral galanthaminium salts have been published.[3] Surprisingly, literature on the chemistry of chiral quarternary ammonium salts is relatively scarce.

Cooke and Partman reported the demethylation of quarternary ammonium salts by reaction with Super Hydride®,[4] whereas Fellows and co-workers employed L-Selectride® as the reagent for the dealkylation of an achiral benzyl ammonium derivative.[5] Fleischhacker and Richter reported the ring opening of a morphine derivative on reaction with Super Hydride®.[6] Manoharan has described the *N*-demethylation of a quarternary morphinium derivative.[7]

Based on these precedences, our strategy for the preparation of new *N*-substituted galanthamine derivatives consisted of galanthamine alkylation followed by the removal of the *N*-methyl substituent.

2. Results and discussion

The *N*-chiral quarternary ammonium halides **4a–d** and **ent-4b–ent-4c** were prepared in 88–100% yields starting either from (−)-galanthamine **1** or the appropriately substituted (−)-galanthamine derivatives *N*-butylgalanthamine **2**[8] and *N*-saccharinylbutylgalanthamine **3**[9] by treatment with an excess of alkylating agent in dry DMF (see Scheme 1). As NMR techniques for structure elucidation of quarternary galanthaminium derivatives were not successful, the absolute stereochemistry of **4b** and **ent-4b** was determined by X-ray crystal analysis (Figs. 1 and 2). For this purpose **4b** was recrystallized from ethanol/water yielding a crystalline hydrate **4b**·1.5H_2O which was subjected to X-ray analysis at $T=297$ and 213 K in view of a phase transition briefly



1 R_1 = Me
2 R_1 = Bu
3 R_1 = C_4H_8sacc

4a R_1 = R_2 = Me, X = I
4b R_1 = Me, R_2 = Bu, X = I
4c R_1 = Me, R_2 = C_4H_8sacc, X = Br
4d R_1 = Me, R_2 = Bn, X = Br
ent-4b R_1 = Bu, R_2 = Me, X = I
ent-4c R_1 = C_4H_8sacc, R_2 = Me, X = I

Scheme 1. Synthesis of galanthaminium halides.

* Corresponding author. E-mail: ujordis@pop.tuwien.ac.at

0957-4166/03/$ - see front matter
doi:10.1016/S0957-4166(03)00116-2

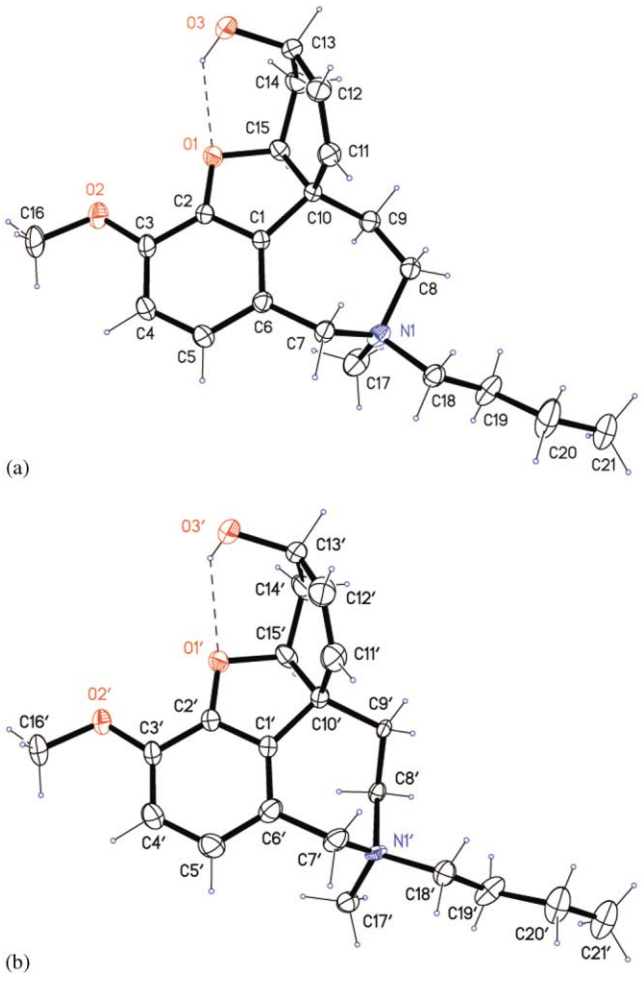


Figure 1. Thermal ellipsoid plots (20% ellipsoids) of the two independent *N*-butylgalanthaminium cations with (a) chair and (b) boat conformation of the azepine ring in the solid state structure of **4b**·1.5H_2O at $T=213$ K. Iodide ions and water molecules omitted.

described in Section 4. At 213 K **4b**·1.5H_2O contains two independent *N*-butylgalanthaminium cations of which one adopts the usual chair conformation for the azepine ring (Fig. 1(a)), whereas the second stands out by having this ring in the unusal boat conformation (Fig. 1(b)). **Ent-4b** gave crystals suitable for X-ray diffraction by crystallization from DMF forming thereby the solvate **ent-4b**·DMF which was X-rayed at $T=223$ K (see Section 4). This compound also contains two independent galanthaminium cations but both of which are similar and have the usual chair-conformation of the azepine ring (Fig. 2).

As the protocol given by Manoharan[7] using sodium thiophenolate led to side reactions without indication of the formation of the desired products, borohydride reagents were employed for the dealkylation experiments. In a model reaction, dealkylation of methylgalanthaminium iodide **4a**[10] using L-Selectride® or Super Hydride® ($LiBHEt_3$) in dry THF at 65°C gave rise to (−)-galanthamine in 90–100% yield. When *N*-chiral galanthaminium starting materials were subjected to the reaction conditions optimized for the model reaction, loss of the least sterically hindered alkyl substituent was observed. The fact that substrates bearing more sterically demanding substituents (**4b**, **4c**) compared to **4a** underwent the dealkylation reaction only with Super Hydride® but not with L-Selectride® can be explained by the greater steric demand of the latter reagent. On the other hand, high stereochemical preferences were observed only with the large saccharinylbutyl substituents of **4c** and **ent-4c** but not with **4b** or **ent-4b**, which gave a mixture of dealkylated products **A**, **B**, and **C**. When the saccharine derivative **ent-4c** was employed for degradation, a concomitant reductive ring-opening reaction at the saccharine moiety occurred, leading to compound **6** (see Scheme 2 and Table 1). These results exemplify the stereochemical preference for the *N*-dealkylation of *N*-chiral quarternary salts, but lack practical synthetic value for the modification of the *N*-substituent of galanthamine.

3. Conclusion

In summary, we have prepared diastereomerically pure quarternary galanthaminium derivatives and have shown that treatment with L-Selectride® or Super Hydride® under optimized conditions leads to cleavage of the least sterically hindered alkyl moiety without a ring opening side reaction. Although the aim of solving the absolute stereochemistry of two representative compounds by X-ray diffraction was initially considered straightforward, complications caused by peculiar solid-state structures and crystallography made the X-ray analysis a challenge. Nevertheless, a case could be found (**4b**·1.5H_2O) where solid state packing requirements force the azepine ring of the galanthamine moi-

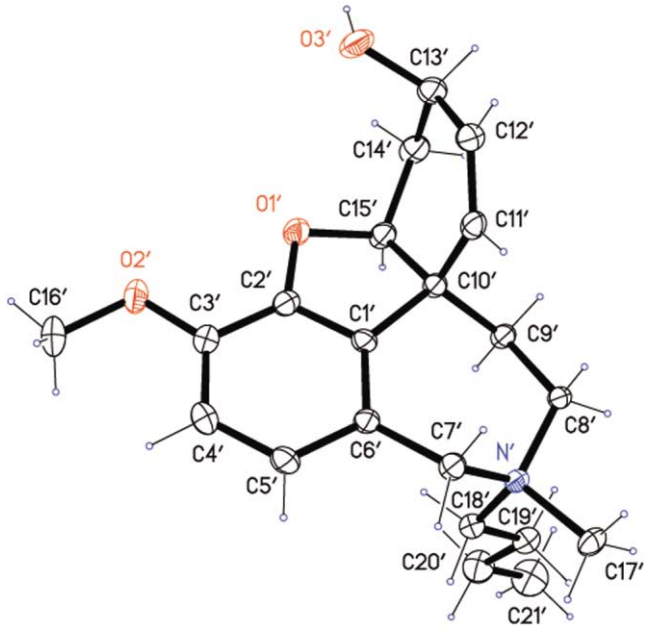
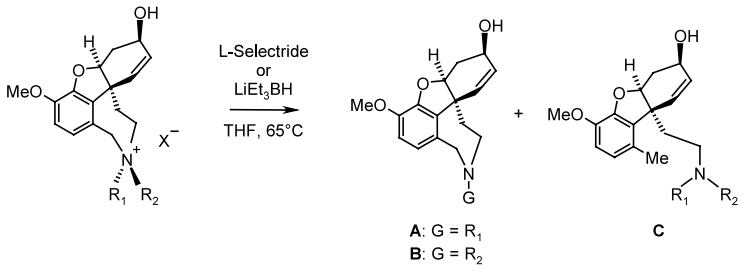
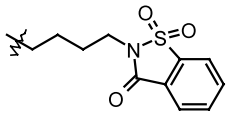
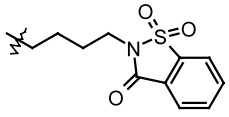
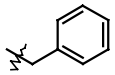
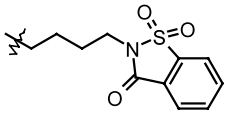
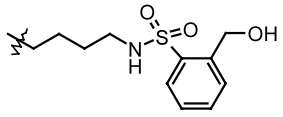


Figure 2. Thermal ellipsoid plot (20% ellipsoids) of one of the two independent but similar *N*-butylgalanthaminium cations in the solid state structure of **ent-4b**·DMF at $T=223$ K.



Scheme 2. Dealkylation of galanthaminium halides.

Table 1. Dealkylation of galanthaminium halides **4a–d** and **ent-4b–ent-4c**

	R_1	R_2	X^-	Method	A %	B %	C%
4a	Me	Me	I^-	I	90 [a]	-	-
4a	Me	Me	I^-	II	quant [c]	-	-
4b	Me	Bu	I^-	I	no reaction		
4b	Me	Bu	I^-	II	15 [b]	47 [b]	38 [b]
4c	Me		Br^-	I	no reaction		
4c	Me		Br^-	II	91 [a]	-	-
4d	Me		Br^-	II	90 [a]	-	-
ent-4b	Bu	Me	I^-	II	6 [b]	85 [b]	9 [b]
ent-4c		Me	I^-	II	74 [a] of **6** 		

Method I: L-Selectide®, THF, 65°C. Method II: Super Hydride®, THF, 65°C.
[a] Isolated yield.
[b] Yield determined by HPLC.
[c] Yield estimated by TLC.

ety out of the favoured chair form and into the less favourable boat conformation.

4. Experimental

4.1. General

Melting points were measured on a Kofler hot stage microscope. Optical rotations were determined on a Perkin Elmer 241 polarimeter using a 1 dm cell with 1 ml cell volume. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 or a Bruker Avance 400 FT NMR spectrometer in $CDCl_3$ or DMSO-d_6 using tetramethylsilane as an internal standard. Thin layer chromatography (TLC) was performed on precoated plates (Merck TLC aluminum sheets silica 60 F_{254}) with detection by UV light or with phosphomolybdic acid in aqueous EtOH and heating. All reactions were magnet-

ically stirred under an argon atmosphere. All liquid reagents were freshly distilled prior to use.

4.2. Preparation of *N*-alkylgalanthaminium halides. General procedure

A solution of the tertiary amine in dry DMF (5 mL/1 g amine) was treated with the alkylating agent (1.1 equiv.). The mixture was poured into EtOAc (50 mL/1 ml DMF), the precipitate was collected by filtration, triturated with EtOAc and dried (50°C/50 mbar).

4.3. (4a*S*,6*R*,8a*S*,11*S*)-4a,5,9,10,11,12-Hexahydro-6-hydroxy-3-methoxy-11,11-dimethyl-6*H*-benzofuro[3a,3,2-ef][2]benzazepinium iodide, 4a

Tertiary amine: (−)-galanthamine (7.00 g, 24.36 mmol); alkylating agent: MeI; reaction conditions: 30 min/25°C; yield: 10.39 g (99%); specific rotation: $[\alpha]_{589}^{20}=-106.7$, $[\alpha]_{578}^{20}=-110.9$, $[\alpha]_{546}^{20}=-128.5$, $[\alpha]_{436}^{20}=-227.3$, $[\alpha]_{365}^{20}=-366.1$ (*c* 0.165, H_2O); mp 287–289°C (lit.:[10] 286–291°C). ^{1}H NMR (DMSO-d_6): δ 6.88 (d, $J=8.1$ Hz, 1H), 6.78 (d, $J=8.1$ Hz, 1H), 6.21 (d, $J=10.0$ Hz, 1H), 5.90 (dd, $J=10.2$, 4.3 Hz, 1H), 5.07 (d, $J=14.2$ Hz, 1H), 4.65 (b, 1H), 4.53–4.38 (m, 2H), 4.09 (b, 1H), 3.85 (s, 3H), 3.70–3.55 (m, 1H), 3.38 (s, 6H), 2.95–2.78 (m, 2H), 2.42–1.80 (m, 3H); ^{13}C NMR (DMSO-d_6): δ 146.5 (s), 145.3 (s), 132.6 (s), 131.0 (s), 125.5 (d), 123.5 (d), 117.5 (t), 112.2 (d), 86.5 (d), 62.2 (t), 59.5 (t), 55.7 (q), 32.2 (t).

4.4. (4a*S*,6*R*,8a*S*,11*S*)-11-Butyl-4a,5,9,10,11,12-hexahydro-6-hydroxy-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-ef][2]benzazepinium iodide, 4b

Tertiary amine: (−)-galanthamine (5.00 g, 17.40 mmol); alkylating agent: BuI; reaction conditions: 24 h/65°C; yield: 8.17 g (99%); specific rotation: $[\alpha]_{589}^{20}=-114.9$, $[\alpha]_{578}^{20}=-119.5$, $[\alpha]_{546}^{20}=-136.2$, $[\alpha]_{436}^{20}=-235.6$, $[\alpha]_{365}^{20}=-375.9$ (*c* 0.174, H_2O); mp 188–190°C. Anal. calcd for $C_{21}H_{30}INO_3\times0.5\ H_2O$: C, 52.51; H, 6.50; N, 2.92. Found: C, 52.13; H, 6.19; N, 3.23%. ^{1}H NMR (DMSO-d_6): δ 6.88 (d, $J=8.1$ Hz, 1H), 6.78 (d, $J=8.1$ Hz, 1H), 6.25 (d, $J=10.0$ Hz, 1H), 5.90 (dd, $J=10.2$, 4.3 Hz, 1H), 5.06 (d, $J=14.2$ Hz, 1H), 4.65 (b, 1H), 4.53–4.38 (m, 2H), 4.09 (b, 1H), 3.85 (s, 3H), 3.70–3.55 (m, 2H), 3.38 (s, 5H), 2.85–2.75 (m, 2H), 2.42–2.05 (m, 3H), 2.00–1.80 (m, 3H), 1.41 (sextet, $J=7.4$ Hz, 2H), 1.02 (t, $J=7.4$ Hz, 3H); ^{13}C NMR (DMSO-d_6): δ 146.4 (s), 145.3 (s), 132.6 (s), 130.0 (s), 125.5 (d), 123.7 (d), 118.5 (t),112.5 (d), 86.4 (d), 59.8 (t), 59.4 (t), 55.6 (q), 45.9 (t), 35.7 (t), 30.7 (t), 23.7 (t), 19.4 (t), 13.5 (q).

4.5. (4a*S*,6*R*,8a*S*,11*S*)-4a,5,9,10,11,12-Hexahydro-6-hydroxy-3-methoxy-11-methyl-11-[4-(1,1,3-trioxo-2*H*-1,2-benzoisothiazolyl)butyl]-6*H*-benzofuro[3a,3,2-e,f]-[2]benzazepinium bromide, 4c

Tertiary amine: (−)-galanthamine (400 mg, 1.39 mmol); alkylating agent: 2-(4-bromobutyl)-1,2-benzoisothiazol-3(2*H*)-one, 1,1-dioxide; reaction conditions: 24 h/65°C; yield: 756 mg (88%); specific rotation: $[\alpha]_{589}^{20}=-93.4$, $[\alpha]_{578}^{20}=-98.9$, $[\alpha]_{546}^{20}=-110.8$, $[\alpha]_{436}^{20}=-185.9$, $[\alpha]_{365}^{20}=-302.2$ (*c* 0.109, H_2O); mp 262–263°C. Anal. calcd for $C_{28}H_{33}BrN_2O_6S\times0.5\ H_2O$: C, 54.72; H, 5.58; N, 4.56. Found: C, 54.73; H, 5.46; N, 4.74%. ^{1}H NMR (DMSO-d_6): δ 8.36–8.28 (m, 1H), 8.16–8.00 (m, 3H), 6.89 (d, $J=8.1$ Hz, 1H), 6.78 (d, $J=8.1$ Hz, 1H), 6.25 (d, $J=10.0$ Hz, 1H), 5.90 (dd, $J=10.2$, 4.3 Hz, 1H), 5.04 (d, $J=14.2$ Hz, 1H), 4.65 (b, 1H), 4.53–4.38 (m, 2H), 4.11 (b, 1H), 3.83 (s, 3H), 3.70 (b, 1H), 3.35 (s, 7H), 2.85–2.75 (m, 2H), 2.38–1.72 (m, 7H); ^{13}C NMR (DMSO-d_6): δ 158.6 (s) 146.5 (s), 145.4 (s), 136.7 (s), 135.8 (d), 135.3 (d) 132.7 (s), 130.0 (d), 126.4 (s), 125.1 (d), 123.7 (d), 121.5 (d), 118.2 (d), 112.2 (d), 86.5 (d), 59.9 (t), 59.4 (d), 55.6 (q), 45.9 (s), 38.0 (t), 35.7 (t), 30.7 (t), 25.1 (t), 19.1 (t).

4.6. (4a*S*,6*R*,8a*S*,11*S*)-4a,5,9,10,11,12-Hexahydro-6-hydroxy-3-methoxy-11-methyl-11-(phenylmethyl)-6*H*-benzofuro[3a,3,2-ef][2]benzazepinium bromide, 4d

Tertiary amine: (−)-galanthamine (1.00 g, 3.48 mmol); alkylating agent: benzyl bromide; reaction conditions: 12 h/25°C; yield: 1.40 g (88%); specific rotation: $[\alpha]_{589}^{20}=-96.15$, $[\alpha]_{578}^{20}=-100.0$, $[\alpha]_{546}^{20}=-113.9$, $[\alpha]_{436}^{20}=-197.1$, $[\alpha]_{365}^{20}=-314.4$ (*c* 0.208, H_2O); mp 169–170°C (lit.:[10] 192°C). ^{1}H NMR (DMSO-d_6): δ 7.76–7.64 (m, 2H), 7.60–7.43 (m, 3H), 6.91–6.75 (m, 2H), 6.26 (d, $J=10.0$, 1H), 5.88 (dd, $J=10.0$, 4.1 Hz, 1H), 5.33–4.99 (m, 3H), 4.76–4.55 (m, 2H), 4.28–3.98 (m, 2H), 3.37 (s, 3H), 3.61–3.35 (m, 2H), 2.78 (s, 3H), 2.37–1.74 (m, 3H); ^{13}C NMR (DMSO-d_6): 162.7 (s), 146.4 (s), 145.3 (s), 133.5 (d), 132.8 (s), 130.4 (d), 128.8 (d), 128.0 (s), 125.2 (d), 123.8 (d), 118.1 (s), 112.1 (d), 86.5 (d), 59.4 (q), 59.1 (t), 55.6 (q), 45.9 (s), 35.8 (t), 31.8 (t), 31.2 (t), 30.7 (t).

4.7. (4a*S*,6*R*,8a*S*,11*R*)-11-Butyl-4a,5,9,10,11,12-hexahydro-6-hydroxy-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-ef][2]benzazepinium iodide, ent-4b

Tertiary amine: (4a*S*,6*R*,8a*S*)-11-butyl-4a,5,9,10,11,12-hexahydro-3-methoxy-6*H*-benzofuro[3a,3,2-ef][2]benzazepine-6-ol (1.00 g, 3.04 mmol); alkylating agent: MeI; reaction conditions: 20 min/25°C; yield: 1.35 g (94%); specific rotation: $[\alpha]_{589}^{20}=-122.7$, $[\alpha]_{578}^{20}=-131.0$, $[\alpha]_{546}^{20}=-147.45$, $[\alpha]_{436}^{20}=-242.2$, $[\alpha]_{365}^{20}=-381.4$ (*c* 0.121, H_2O); mp 224–226°C. Anal. calcd for $C_{21}H_{30}INO_3\times0.25\ H_2O$: C, 53.00; H, 6.46; N, 2.94. Found: C, 52.74; H, 6.16; N, 2.92%. ^{1}H NMR (DMSO-d_6): δ 6.82–6.76 (m, 2H), 6.25 (d, $J=10.0$ Hz, 1H), 5.90 (dd, $J=10.2$, 4.3 Hz, 1H), 5.10 (d, $J=14.2$ Hz, 1H), 4.61 (b, 1H), 4.55–4.33 (m, 2H), 4.12 (b, 1H), 3.88 (s, 3H), 3.70–3.55 (m, 2H), 3.38 (s, 5H), 2.92–2.80 (m, 2H), 2.42–1.95 (m, 3H), 1.90–1.75 (m, 3H), 1.40 (sextet, $J=7.4$ Hz, 2H), 1.05 (t, $J=7.4$ Hz, 3H); ^{13}C NMR (DMSO-d_6): δ 146.3 (s), 145.5 (s), 132.7 (s), 130.0 (s), 125.5 (d), 123.3 (d), 118.5 (t),112.3 (d), 86.4 (d), 59.6 (t), 59.3 (t), 55.6 (q), 45.9 (t), 35.3 (t), 30.5 (t), 23.9 (t), 19.4 (t), 13.5 (q).

4.8. (4a*S*,6*R*,8a*S*,11*R*)-4a,5,9,10,11,12-Hexahydro-6-hydroxy-3-methoxy-11-methyl-11-[4-(1,1,3-trioxo-2*H*-1,2-benzoisothiazolyl)butyl]-6*H*-benzofuro[3a,3,2-e,f][2]-benzazepinium iodide, ent-4c

Tertiary amine: 2-[4-[(4a*S*,6*R*,8*aS*)-5,6,9,10,11,12-hexahydro-6-hydroxy-3-methoxy-4a*H*-benzofuro[3a,3,2-e,f]-[2]benzazepine-11-yl]butyl]-1,2-benzoisothiazol-3(2*H*)-one, 1,1-dioxide (750 mg, 1.47 mmol); alkylating agent: MeI; reaction conditions: 20 min/25°C; yield: 920 mg (96%); specific rotation: $[\alpha]_{589}^{20}=-104$. 9, $[\alpha]_{578}^{20}=-109.8$, $[\alpha]_{546}^{20}=-126.0$, $[\alpha]_{436}^{20}=-213.0$, $[\alpha]_{365}^{20}=-291.9$ (*c* 0.123, H_2O); mp. 177–179°C. Anal. calcd for $C_{28}H_{33}IN_2O_6S$* 0.25 H_2O: C, 51.18; H, 5.14; N, 4.26. Found: C, 50.90; H, 5.05; N, 4.48%. ^{1}H NMR (DMSO-d_6): δ 8.32–8.23 (m, 1H), 8.15–7.95 (m, 3H), 6.92–6.70 (m, 2H), 6.27 (d, $J=9.0$ Hz, 1H), 5.90 (dd, $J=9.7$, 4.1 Hz, 1H), 5.12 (d, $J=14.1$ Hz, 1H), 4.68 (b, 1H), 4.60–4.37 (m, 2H), 4.09 (b, 1H), 3.71 (s, 3H), 3.70 (b, 1H), 3.67 (b, 2H), 3.38 (s, 3H), 3.30 (s, 2H), 3.15 (b, 2H), 2.45–2.01 (m, 3H), 1.92–1.51 (m, 5H); ^{13}C NMR (DMSO-d_6): δ 158.6 (s) 146.4 (s), 145.2 (s), 136.5 (s), 135.8 (d), 135.3 (d) 132.7 (s), 129.9 (d), 126.2 (s), 125.0 (d), 123.3 (d), 121.4 (d), 117.9 (d), 111.9 (d), 86.3 (d), 59.4 (t), 55.5 (q), 53.1 (q), 45.9 (s), 38.0 (t), 35.8 (t), 30.8 (t), 24.8 (t), 18.7 (t).

4.9. Dealkylation of galanthaminium derivatives. General procedure

Method A: to **4a** (500 mg, 1.16 mmol) in dry THF (8 mL) L-Selectride® (1 M in dry THF, 2.9 mL, 2.9 mmol) was added over a period of 30 min at 65°C and stirred for 5 h at this temperature. 2N HCl (20 mL) was added dropwise, and the mixture was concentrated in vacuo to a volume of 20 mL and washed with EtOAc (2×20 mL, discard). The pH of the solution was adjusted to 9 using conc. NH_4OH, and the aqueous layer was extracted with CH_2Cl_2 (5×15 mL). The combined organic layer was washed with water (2×20 mL) and brine (1×20 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by MPLC (10 g SiO_2, $CHCl_3$:MeOH:conc. NH_4OH = 94:5:1). Yield: colorless solid (300 mg, 90%). The identity of the obtained substance with an authentic sample of galanthamine was confirmed by TLC, HPLC and NMR. *Method B*: When Super Hydride® was used under the same conditions, a quantitative yield was obtained.

4.10. X-Ray structure determinations of 4b·1.5H_2O and ent-4b·DMF

General: X-ray data collection was carried out with a Bruker AXS Smart CCD area detector diffractometer, graphite monochromatized Mo Kα radiation from a sealed X-ray tube, λ(Mo-Kα) = 0.71073 Å, and a Bruker AXS Kryoflex cooling unit. Data treatment and reduction was carried out with Bruker AXS programs.[11] The structures were solved with direct methods using program SHELXS97 and were refined on F^2 using program SHELXL97.[12] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were mainly inserted in idealized positions and rode on the atoms to which they were bonded. Crucial hydrogen atoms (OH, H_2O) were refined in *x*,*y*,*z* using distance restraints.

Crystal data for 4b·1.5H_2O at $T=297$ K: $C_{21}H_{33}INO_{4.5}=C_{21}H_{30}NO_3^+\cdot I^-\cdot 1.5H_2O$, $M_r=498.38$, yellow prism of 0.64×0.23×0.18 mm obtained from ethanol/water 10:1 by solvent evaporation, monoclinic, space group *C*2 (no. 5), $a=25.109(6)$ Å, $b=8.809(2)$ Å, $c=10.446(3)$ Å, $\beta=93.22(1)°$, $V=2306.9(10)$ Å^3, $Z=4$, $D_x=1.435$ Mg/m^{-3}, $\mu=1.415$ mm^{-1}, $T=297(2)$ K. 15139 reflections with $\theta<25°$ were measured, corrected for absorption, and merged to 4080 unique reflections, $R_{int}=0.023$. Final refinement: 259 parameters, $R1=\Sigma||F_o|-|F_c||/\Sigma|F_o|=0.034$, $wR2=[\Sigma(w(F_o^2-F_c^2)^2)/\Sigma(w(F_o^2)^2)]^{1/2}=0.084$, and $S=1.07$ for all reflections; $R1=0.033$ for the 3988 observed data [$I>2\sigma(I)$].[13] Selected bond distances and angles (Å, °): O1–C2 1.370(5), O1–C15 1.457(5), O2–C3 1.350(6), O2–C16 1.445(7), O3–C13 1.447(6), N–C7 1.535(5), N–C8 1.484(10), N–C17 1.450(7), N–C18 1.520(5), C1–C2 1.382(5), C1–C6 1.397(6), C1–C10 1.503(5), C2–C3 1.397(6), C3–C4 1.384(7), C4–C5 1.399(7), C5–C6 1.386(7), C6–C7 1.528(7), C8–C9 1.303(9), C9–C10 1.545(6), C10–C11 1.509(6), C10–C15 1.538(6), C11–C12 1.322(7), C12–C13 1.459(9), C13–C14 1.499(9), C14–C15 1.511(6), C18–C19 1.494(6), C19–C20 1.483(8), C20–C21 1.478(9); C6–C7–N–C8 71.6(8), C7–N–C8–C9 −51(2), N–C8–C9–C10 39(2).

The compound has the *N*-butyl group in an equatorial orientation relative to the azepine ring. There is one water molecule in special position on a two-fold axis, which donates hydrogen bonds to two symmetry equivalent further water molecules in general position. This second water molecule donates one hydrogen bond to the iodide ion and one to the galanthamine OH group, which in turn forms a bifurcated hydrogen bond to O(1) (intramolecular) and O(2) (intermolecular). Unusually large anisotropic displacement parameters of atoms N, C(8), and C(9) (same crystallographic atom designation as shown in Figs. 1 and 2) indicated a disorder of the azepine ring with a chair/boat conformation ambiguity. Therefore, a low temperature X-ray diffraction study was carried out showing that there is phase transition which resolved this disorder as subsequently described.

Crystal data for 4b·1.5H_2O at T = 213 K: $C_{21}H_{33}INO_{4.5}=C_{21}H_{30}NO_3^+\cdot I^-\cdot 1.5H_2O$, $M_r=498.38$, same crystal as before, monoclinic, space group $P2_1$ (no. 14), $a=24.951(8)$ Å, $b=8.717(3)$ Å, $c=10.384(4)$ Å, $\beta=93.10(1)°$, $V=2255(1)$ Å^3, $Z=4$, $D_x=1.447$ Mg/m^{-3}, $\mu=1.447$ mm^{-1}, $T=213(2)$ K. 33064 reflections with $\theta<30°$ measured, corrected for absorption, and merged to 12652 unique reflections, $R_{int}=0.030$. Final refinement: 555 parameters, $R1=\Sigma||F_o|-|F_c||/\Sigma|F_o|=0.047$, $wR2=[\Sigma(w(F_o^2-F_c^2)^2)/\Sigma(w(F_o^2)^2)]^{1/2}=0.108$, and $S=1.06$ for all reflections; $R_1=0.041$ for the 6548 observed data [$I>2\sigma(I)$].[13] There are two crystallographically independent molecules with following bond distances and selected angles (Å and °; first/second

molecule): O1–C2 1.356(4)/1.368(4), O1–C15 1.458(4)/1.469(4), O2–C3 1.354(4)/1.360(5), O2–C16 1.436(5)/1.439(5), O3–C13 1.436(5)/1.446(6), N1–C7 1.527(4)/1.504(11), N1–C8 1.567(5)/1.552(10), N1–C17 1.462(5)/1.478(9), N1–C18 1.513(4)/1.537(9), C1–C2 1.385(4)/1.384(4), C1–C6 1.386(4)/1.381(5), C1–C10 1.500(4)/1.500(5), C2–C3 1.389(5)/1.391(4), C3–C4 1.398(6)/1.378(6), C4–C5 1.395(6)/1.399(6), C5–C6 1.391(5)/1.383(6), C6–C7 1.487(5)/1.492(5), C8–C9 1.492(5)/1.512(8), C9–C10 1.539(4)/1.552(6), C10–C11 1.513(4)/1.509(5), C10–C15 1.545(5)/1.529(5), C11–C12 1.322(5)/1.319(6), C12–C13 1.471(6)/1.462(8), C13–C14 1.506(6)/1.501(8), C14–C15 1.505(5)/1.509(5), C18–C19 1.498(5)/1.500(5), C19–C20 1.462(6)/1.509(6), C20–C21 1.505(7)/1.507(7); C6–C7–N1–C8 **76.7(4)/50.9(8)**, C7–N1–C8–C9 **−69.3(3)/39.6(7)**, N1–C8–C9–C10 **69.0(3)/−87.2(7)**.

Compared with the structure at room temperature which adopts space group $C2$ (see above), the low temperature structure of **4b**·1.5H_2O adopts space group $P2_1$ with all previous unit cell base vectors retained. In comparison to room temperature a desymmetrisation of the structure takes place, which leads to two crystallographically independent *N*-butylgalanthamine moieties, two independent iodide ions, and three independent water molecules whereas the basic architecture of the room temperature structure remains unchanged ($P2_1$ is a maximal non-isomorphic subgroup of space group $C2$; C-centering and two-fold axes vanish on transition to $P2_1$). Most interesting result of this transformation is, that the two independent galanthaminium cations in the low temperature structure differ in conformation of the azepine rings. The molecule shown in Fig. 1(a) adopts the usual chair conformation whereas the second one shown in Fig. 1(b) exhibits the unusual boat conformation. Such boat conformation by now has been reported only for two galanthamine type compounds that bear –(C(7)=O)–N(1)R- instead of the groups –C(7)H2–N(1)R- or –C(7)H2–N(1)R_2- in the azepine rings.[14] It should be mentioned here that in the 213 K structure of **4b**·1.5H_2O about 1/3 of the molecules shown in Fig. 1(b) (boat conformation) is by disorder still replaced by molecules with chair conformation. In view of the phase transition from room temperature to 213 K it is expected that this amount of chair-type molecules replacing those shown in Fig. 1(b) decreases at temperatures below 213 K.

Crystal data for ent-4b·DMF: $C_{24}H_{37}IN_2O_4 = C_{21}H_{30}NO_3^+ \cdot I^- \cdot C_3H_7NO$, $M^r = 544.46$, colorless prism of 0.72×0.21×0.10 mm from DMF by room temperature evaporation, triclinic, space group $P1$ (no. 1), $a = 9.397(6)$, $b = 9.774(7)$, $c = 15.075(9)$ Å, $\alpha = 106.70(1)$, $\beta = 95.36(1)$, $\gamma = 90.18(1)°$, $V = 1319.7(15)$ Å^3, $Z = 2$, $D_x = 1.370$ Mg/m^{-3}, $\mu = 1.242$ mm^{-1}, $T = 223(2)$ K. 13556 reflections with $\theta < 25.0°$ measured, corrected for LP and absorption, and merged to 9184 unique reflections, $R_{int} = 0.018$. Final refinement: 220 parameters, $R1 = \Sigma||F_o|-|F_c||/\Sigma|F_o| = 0.033$, $wR2 = [\Sigma(w(F_o^2-F_c^2)^2)/\Sigma(w(F_o^2)^2)]^{1/2} = 0.081$, and $S = 1.08$ for the 8847 unique reflections; $R1 = 0.031$ for the 8847 observed data [$I > 2\sigma(I)$].[13]

The structure contains two crystallographically independent galanthaminium cations (Fig. 2) with essentially agreeing dimensions and chair-type conformation of the azepine rings. Selected bond distances and angles (Å and °; first/second moiety): O1–C2 1.367(5)/1.360(5), O1–C15 1.467(5)/1.472(5), O2–C3 1.364(5)/1.378(6), O3–C13 1.433(5)/1.442(5), O2–C16 1.425(6)/1.425(6), N–C7 1.521(5)/1.517(5), N–C8 1.521(5)/1.515(5), N–C17 1.521(5)/1.534(5), N–C18 1.521(5)/1.522(5), C1–C2 1.388(6)/1.390(6), C1–C6 1.392(6)/1.407(6), C1–C10 1.521(6)/1.510(6), C2–C3 1.403(6)/1.397(6), C3–C4 1.390(6)/1.383(6), C4–C5 1.397(6)/1.411(6), C5–C6 1.404(6)/1.391(6), C6–C7 1.501(6)/1.501(6), C8–C9 1.523(6)/1.529(6), C9–C10 1.547(6)/1.531(6), C10–C11 1.512(6)/1.524(6), C10–C15 1.555(5)/1.558(5), C11–C12 1.336(6)/1.327(6), C12–C13 1.508(6)/1.516(6), C13–C14 1.518(7)/1.514(7), C14–C15 1.520(6)/1.516(6), C18–C19 1.512(7)/1.517(6), C19–C20 1.526(7)/1.520(7), C20–C21 1.482(14)/1.515(8), C6–C7–N–C8 74.9(5)/73.9(4), C7–N–C8–C9 −72.6(5)/73.0(4), N–C8–C9–C10 72.0(5)/72.0(5); hydrogen bonds O3→I 3.533(4)/3.550(4).

The structure of **ent-4b**·DMF is pseudosymmetric by deviating moderately from a monoclinic one with 2_1 axes parallel to the crystallographic a-axis and space group $P2_111$. The deviation of the real unit cell angle $\beta = 95.36°$ from 90° is however significant and appears to be caused by the two independent DMF solvent molecules, which differ notably in their spatial orientations and thermal displacements.

Acknowledgements

The authors thank Sanochemia Pharmazeutika AG for their financial support and donation of chemicals.

References

1. Raskind, M. A.; Peskind, E. R.; Wessel, T.; Yuan, W.; Allen, F. H.; Aronson, S. M.; Baumel, B.; Eisner, L.; Brenner, R.; Cheren, S.; Verma, S.; Daniel, D. G.; DePriest, M.; Ferguson, J. M.; England, D.; Farmer, M. V.; Frey, J.; Flitman, S. S.; Harrell, L. E.; Holub, R.; Jacobson, A.; Olivera, G. F.; Ownby, R. L.; Jenkyn, L. R.; Landbloom, R.; Leibowitz, M. T.; Zolnouni, P. P.; Lyketosos, C.; Mintzer, J. E.; Nakra, R.; Pahl, J. J.; Potkin, S. G.; Richardson, B. C.; Richter, R. W.; Rymer, M. M.; Saur, D. P.; Daffner, K. R.; Scinto, L.; Stoukides, J.; Targum, S. D.; Thein, S. G.; Thien, S. G.; Tomlinson, J. R. *Neurology* **2000**, *54*, 2261–2268.
2. (a) Bores, G. M.; Kosley, R. W. *Drugs Future* **1996**, *21*, 621–635; (b) Lilienfeld, S. *CNS Drug Rev.* **2002**, *8*, 159–176.
3. (a) Carroll, P.; Furst, G. T.; Han, S. Y.; Joullie, M. *Bull. Soc. Chim. Fr.* **1990**, 769–780; (b) Matusch, R.; Kreh, M.; Mueller, U. *Helv. Chim. Acta* **1994**, *77*, 1611–1615.
4. Cooke, M. P.; Parlman, R. M. *J. Org. Chem.* **1975**, *40*, 531–532.

5. Fellows, I.; Carr, R. M.; DeBoeck, N.; Montgomery, S.; Waterhouse, I.; Sutherland, D. R. *J. Labelled Compd. Radiopharm.* **1998**, *41*, 1127–1243.
6. Fleischhacker, W.; Richter, B. *Chem. Ber.* **1979**, *112*, 2539–2551.
7. Manoharan, T. S.; Madyastha, M. K.; Bali Singh, B.; Bhatnagar, S. P.; Weiss, U. *Synthesis* **1983**, *10*, 809–812.
8. Stichting Biomedical Research and Advice Group, NL Patent 8 800 350,1989; *Chem. Abstr.* **1989**, *112*, 112096.
9. Jordis, U.; Fröhlich, J.; Treu, M.; Hirnschall, M.; Czollner, L.; Kaelz, B.; Welzig, S. WO 0 174 820, 2001; *Chem. Abstr.* **2001**, *135*, 304054.
10. Han, S. Y.; Sweeney, J. E.; Bachman, E. S.; Schweiger, E. J.; Forloni, G.; Coyle, J. T.; Davis, B. M.; Joullie, M. M. *Eur. J. Med. Chem.* **1992**, *27*, 673–687.
11. Bruker AXS: Programs SMART, version 5.054; SAINT, version 6.2.9; SADABS version 2.03; XPREP, version 5.1; SHELXTL, version 5.1. Bruker AXS Inc., Madison, WI, USA, 2001.
12. Sheldrick, G. M. SHELX97. Program system for crystal structure determination. University of Göttingen, Germany, 1997.
13. CCDC 187697, 187698 and 187699 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).
14. For structural data of galanthamine type compounds see Cambridge Crystallographic Database entries GALAMI, GALANT, HICRAM, NRGLNM, RIWKOX, SIBHAM, VATMEI, VATMIM, and YILTUI (database version of April, 2002), and references cited therein.