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BIDIRECTIONAL CONVERSION OF GALANTHAMINE AND CRININE TYPE HETEROCYCLES

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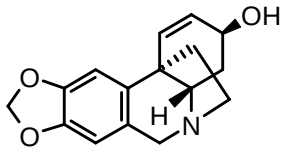
Abstract – The conversion of galanthamine-type molecules into crinine-type compounds and *vice versa* has been accomplished by a ring opening-Michael addition-cascade of a galanthamine-type secondary amine and a crinine-type quarternary ammonium salt.

INTRODUCTION

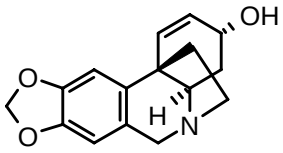
Galanthamine (or galantamine, Reminyl®) is a tertiary alkaloid acetylcholinesterase inhibitor (AChE) which has been approved in several countries for treating symptoms of Alzheimer's type senile dementia.[1,2] Detailed investigations on a side product from the deformylation of bromoformylnarwedine (**7**) revealed the formation of the oxocrinine analog (**9**). This lead to further studies in this field with regard to the biological properties – specially AChE and BChE inhibition – of the target compounds.[3,4]

Various derivatives and analogs of crinine (**1**) have previously been isolated as natural products. Particularly crinine itself was a focal point of interest: (+)-Crinine (**(+)-1**) has been extracted from the bulbs of *Pancratasium maritimum*,[5] *Hippeastrum*-hybrides,[6] *Hymenocallis calathina*,[7] *Nerine corusca* and *Pancratium illyricum*,[8] from *Hippeastrum vittatum*,[9] *Rhodophiala bifida*[10] and from the blossoms of *Lycoris radiata*.[11] (-)-Crinine (**(-)-1**) was found in bulbs of *Ammocharis tinneana*,[12] *Calostemma purpureum*,[13] *Brunsvigia radulosa*,[14] *Crinum powellii*,[15,16] *Nerine bowdenii*,[16] *Buphane fischeri*,[17] *Crinum moorli*,[16,18] *Crinum asiaticum* and *Crinum defixum*.[19] Furthermore the isolation of crinine-type natural products was reported: Oxocrinine (**2**) was extracted from C*rinum americanum*,[20] powellamine (**3**) from bulbs of *Crinum powellii*,[21] maritidine (**4**) from *Narcissus tazetta*[22] and from *Zephyranthes rosea*.[23] Demethylmaritidine (**5**) was found in bulbs of *Hymenocallis rotata*[24] and epivittatine (**6**) in *Boophane flava*.[25] (see Scheme 1)

Scheme 1



(+)-crinine, (+)-1



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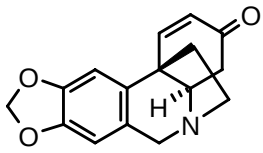
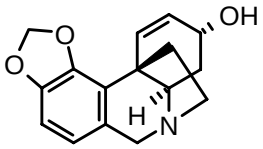


2



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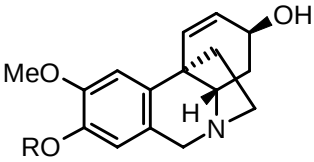
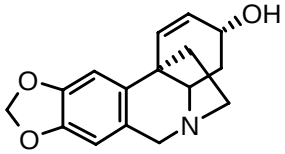


4 R = Me
5 R = H



6

The synthetic approaches[26] to members of the crinine (**1**) and maritidine (**4**) family are divided into two sections: The key step of the first strategy comprises the formation of the bridged ring system by a Pictet-Spengler type cyclization reaction starting from suitable phenylpyrrolidines or phenylindolines,[27-37] whereas the transformation of benzazepine derivatives into crinine analogs by an intramolecular Michael addition represents the second synthetic pathway.[38-44] Only a few quarternary crininium salts are documented.[8,9,15,18,21,45] Although Wildman[46] mentions the instability of such compounds under basic conditions, a controlled transformation into galanthamine-type products has not yet been considerated.

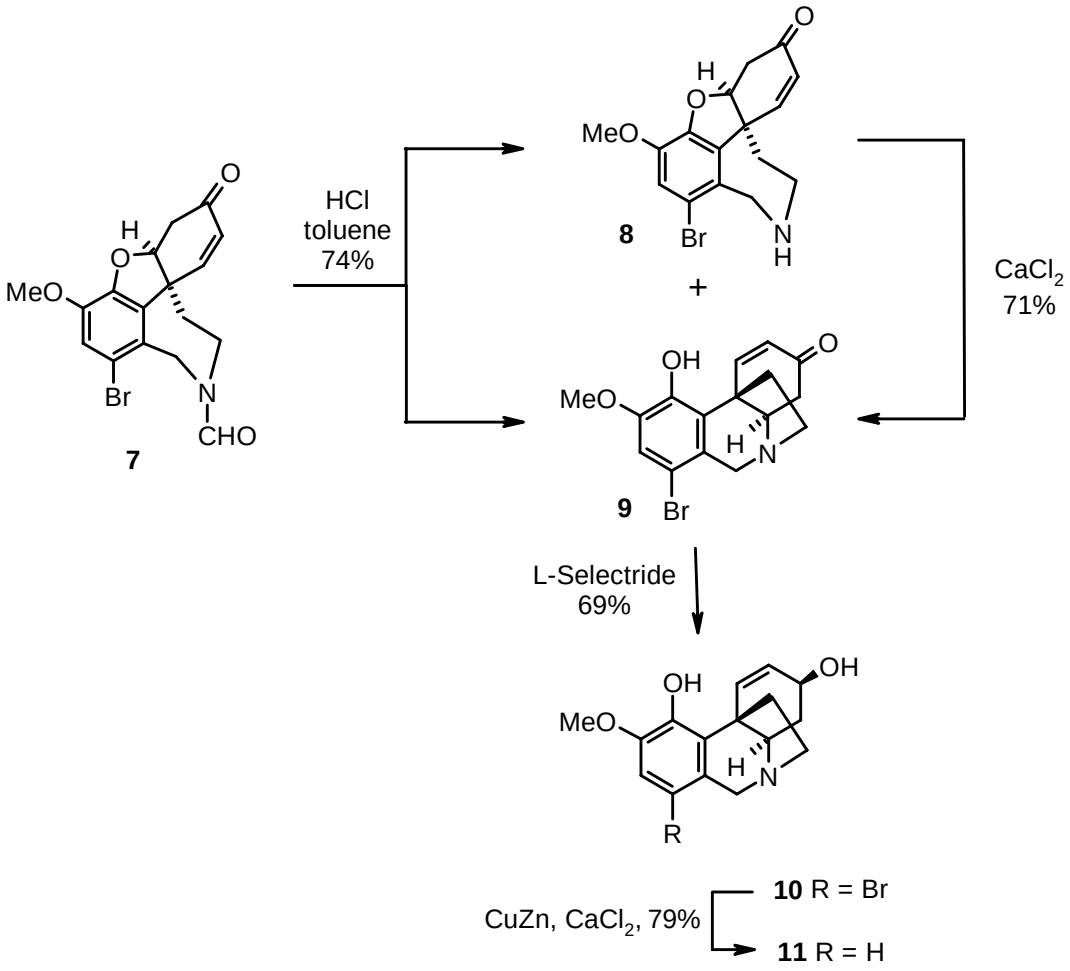
RESULTS AND DISCUSSION

When bromoformylnarwedine (**7**) – an intermediate from the industrial galanthamine synthesis – was treated with concentrated HCl, the main product (**8**) was obtained in 74% yield accompanied by a small amount of compound (**9**). **8** could be converted into **9** by refluxing it in ethanol in presence of $CaCl_2$ with a yield of 71%. The appearance of a phenolic proton, a shift of the olefinic protons and a change of the peak pattern of the protons next to the nitrogen in a ^1H NMR spectrum indicated the formation of the crinine-type compound (**9**) by a ring opening of the furane moiety with concomitant formation of the bridged substructure in a retro-Michael-Michael-addition-cascade. Reduction of the enone (**9**) with L-Selectride® gave the allyl alcohol (**10**) in a yield of 69%, which was debrominated using a freshly prepared copper-zinc-couple[47] in presence of $CaCl_2$ to yield the crinine analog (**11**) of galantamine with a yield of 79% (see Scheme 2).

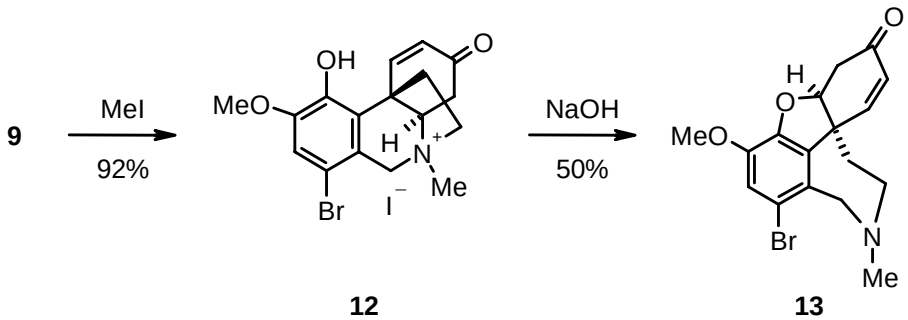
For the conversion of a crinine-type molecule into a galanthamine-type compound, a Hofmann degradation of the quarternary salt (**12**) was envisioned. Thus ketone (**9**), which was almost insoluble in common organic solvents including DMF or DMSO, was dissolved in HMPTA and treated with an

excess of methyl iodide to form the crystalline quarternary salt (**12**). When **12** was treated with NaOH in aqueous ethanol, bromonarwedine (**13**) was formed in a 50% yield and found to be identical with a reference sample.[3] (see Scheme 3).

Scheme 2



Scheme 3



CONCLUSION

To summarize, we have performed the conversion of a galanthamin-type molecule into its crinine analog and *vice versa*. Interestingly, compound (**10**) exhibited the same BChE activity as galanthamine without any AChE inhibition. (see Table 1).

Compound	AChE inhibition [μmol/mL]	BChE inhibition [μmol/mL]
10	> 200	18
11	> 200	29
Galanthamine (Reminyl®)	2.3	18

Table 1

EXPERIMENTAL

General: Melting points were measured on a Kofler melting point. ^{1}H and ^{13}C NMR-spectra were recorded on a Bruker AC-200 (200 MHz) pulse Fourier-transform 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 by heating. All reactions were magnetically stirred under an argon atmosphere. MPLC (medium pressure liquid chromatography) was performed using SiO_2 (Baker), a LC-8A pump (Shimadzu), a SPD-6AV UV-detector (Shimadzu) and Büchi glass colums.

(4a*R,8a*R**)-1-Bromo-4a,5,9,10,11,12-hexahydro-3-methoxy-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-one (8).** (4a*R**,8a*R**)-1-Bromo-4a,5,9,10-tetrahydro-3-methoxy-6-oxo-6*H*-benzofuro[3a,3,2-*ef*][2]benz-azepine-11(12*H*)-carboxaldehyde[48] (40.0 g, 105.7 mmol) was refluxed in toluene (1100 mL) / conc. HCl (500 mL) under vigorous stirring for 24 h. The precipitate of the crude **8** * HCl was collected by filtration and washed with EtOAc (3 x 100 mL). The organic layer was separated and extracted with 2 N HCl (3 x 150 mL). The combined aqueous layers were washed with EtOAc (2 x 150 mL), the crude **8** * HCl (shown to contain small amounts of **9** by TLC)was added and the pH was adjusted to 12 with conc. NaOH, the precipitate of **8** was collected by filtration, washed with Et_2O (2 x 100 mL) and recrystallized from MeOH (1000 mL). Yield: colorless crystals, 27.38 g (74%), mp 192 – 194 °C (MeOH); ^{1}H NMR ($CDCl_3$): δ 7.05 (d, *J* = 10.7 Hz, 1H), 6.90 (s, 1H), 5.90 (d, *J* = 10.7 Hz, 1H), 4.36 – 4.62 (m, 1H), 4.40 (d, *J* = 16.4 Hz, 1H), 3.90 (d, *J* = 16.4 Hz, 1H), 3.75 (s, 3H), 3.10 - 3.35 (m, 2H), 2.95 (d, *J* = 16.0 Hz, 1H), 2.75 (d, *J* = 16.0 Hz, 1H), 1.90 - 2.15 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 146.6 (s), 144.8 (d), 143.7 (s), 132.0 (s), 129.6 (s), 126.6 (d), 116.0 (d), 112.5 (s), 87.9 (d), 55.9 (q), 51.3 (t), 49.5 (t), 45.6 (s), 37.0 (t), 36.3 (t).

(4a*α*,5*β*,10b*β*)-7-Bromo-4,4a-dihydro-10-hydroxy-9-methoxy-3*H*,6*H*-5,10b-ethanophenanthridine-3-one (9). 8 (3.00 g, 8.57 mmol) and $CaCl_2$ (1.50 g, 13.5 mmol) in 70% EtOH (120 mL) were stirred under reflux for 3 h. The mixture was concentrated *in vacuo* to a volume of 50 mL and cooled to 4 °C. The precipitate was filtered, dissolved in $CHCl_3$ (50 mL)/MeOH (50 mL) and treated with charcoal (0.3 g). After filtration and concentration *in vacuo*, the solid was collected and washed with Et_2O (2 x 50 mL).

Yield: colorless crystals, 2.13 g (71%), mp 219 – 224 °C (decomp); ^{1}H NMR (DMSO-d_6): δ 9.10 (br, 1H), 7.87 (d, *J* = 11.1 Hz, 1H), 7.08 (s, 1H), 5.81 (d, *J* = 11.1 Hz, 1H), 3.90 (d, *J* = 16.5 Hz, 1H), 3.75 (s, 3H), 3.55 (d, *J* = 16.5 Hz, 1H), 3.45 – 2.45 (m, 4H), 2.42 – 1.68 (m, 3H); ^{13}C NMR (DMSO-d_6): δ 197.8 (s), 155.6 (d), 147.6 (s), 142.9 (s), 129.3 (s), 126.6 (s), 123.3 (d), 113.7 (s), 109.7 (d), 64.1 (d), 56.2 (q), 55.9 (t), 53.1 (t), 42.8 (s), 39.8 (t), 38.1 (t). Anal. Calcd for $C_{16}H_{16}NO_3Br$*0.33 H_2O: C, 53.95; H, 4.53; N 3.93. Found: C, 53.98; H, 4.53; N, 3.78.

(4a*α*,5*β*,10b*β*)-7-Bromo-4,4a-dihydro-9-methoxy-3*H*,6*H*-5,10b-ethanophenanthridine-3,10-diol (10). To a suspension of **9** (800 mg, 2.28 mmol) in anhydrous THF (10 mL) L-Selectride® (1 M in THF, 15 mL, 15 mmol) was added at rt. The solution was stirred for 1.5 h at this temperature, then 0.5 N HCl (5 mL) was added. The mixture was concentrated to a volume of 5 mL *in vacuo* and partitioned between water (5 mL) and $CHCl_3$ (20 mL)/MeOH (2 mL). The aqueous layer was extracted with $CHCl_3$/10 % MeOH (5 x 30 mL), the combined organic layers were washed with water (1 x 20 mL) and brine (1 x 20 mL), dried (Na_2SO_4) and filtered. After concentration *in vacuo*, the residue was purified by flash chromatography (SiO_2, $CHCl_3$: MeOH : NH_3 = 89 : 10 : 1) and recrystallized from MeOH (5 mL). Yield: colorless crystals, 553 mg (69%), mp 216 - 219 °C (decomp) (MeOH); ^{1}H NMR (DMSO-d_6): δ 7.01 (s, 1H), 6.66 (d, *J* = 9.8 Hz, 1H), 5.46 (d, *J* = 9.8 Hz, 1H), 4.30 – 4.14 (m, 1H), 3.92 (d, *J* = 17.8 Hz, 1H), 3.86 (s, 3H), 3.62 (d, *J* = 17.8 Hz, 1H), 3.39 – 3.19 (m, 1H), 2.93 – 2.67 (m, 2H), 2.50 (s, 1H), 2.39 – 2.21 (m, 1H), 2.19 – 1.99 (m, 1H), 1.88 – 1.66 (m, 1H), 1.50 – 1.22 (m, 1H); ^{13}C NMR (DMSO-d_6): δ 147.6 (s), 143.8 (s), 131.1 (d), 130.9 (s), 130.8 (d), 121.6 (s), 113.3 (d), 109.4 (s), 66.7 (d), 63.4 (d), 56.2 (q), 54.8 (t), 52.5 (t), 48.6 (s), 42.9 (t), 31.5 (t). Anal. Calcd for $C_{16}H_{18}NO_3Br$: C, 54.56; H, 5.15; N 3.98. Found: C, 54.61; H, 5.14; N, 3.87.

(4a*α*,5*β*,10b*β*)-4,4a-Dihydro-9-methoxy-3*H*,6*H*-5,10b-ethanophenanthridine-3,10-diol (11). Zinc powder (300 mg) and CuI (300 mg) in water (4 mL)/EtOH (4 mL) were sonicated for 45 min under argon. **10** (200 mg, 0.57 mmol) and $CaCl_2$ (150 mg, 1.35 mmol) were added, and the mixture was refluxed for 12 h. The suspension was filtered and concentrated, and the residue was purified by flash chromatography (SiO_2, $CHCl_3$: MeOH : NH_3 = 89 : 10 : 1) and recrystallized from MeOH (2 mL). Yield: 122 mg (79%), mp 234 – 239 °C (decomp) (MeOH); ^{1}H NMR (DMSO-d_6): δ 8.37 (br, 1H), 6.77 - 6.62 (m, 2H), 6.41 (d, *J* = 9.8 Hz, 1H), 5.42 (d, *J* = 9.8 Hz, 1H), 4.83 (br, 1H), 4.31 – 4.17 (m, 1H), 4.04 (d, *J* = 17.8 Hz, 1H), 3.73 (s, 3H), 3.47 (d, *J* = 17.8 Hz, 1H), 3.20 – 3.00 (m 1H), 2.73 – 2.40 (m, 2H), 2.32 – 1.91 (m, 2H), 1.72 – 1.20 (m, 3H); ^{13}C NMR (DMSO-d_6): δ 146.0 (s), 143.7 (s), 132.5 (d), 130.2 (d), 129.9 (s), 124.9 (s), 115.8 (d), 109.4 (d), 67.1 (d), 64.1 (d), 55.8 (q), 54.6 (t), 52.3 (t), 42.7 (s), 41.1 (t), 32.2 (t). Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N 5.12. Found: C, 70.12; H, 6.97; N, 5.20.

(4a*α*,5*β*,10b*β*)-7-Bromo-4,4a-dihydro-10-hydroxy-9-methoxy-5-methyl-3-oxo-3*H*,6*H*-5,10b-ethano-phenanthridinium iodide (12). To **9** (500 mg, 1.42 mmol) in anhydrous HMPTA (10 mL) methyl iodide

(232 mg, 1.63 mmol) was added at 15 °C, and the mixture was stirred at this temperature for 12 h. The solution was poured into EtOAc (75 mL)/Et_2O (75 mL), and the precipitate was collected by filtration and washed with Et_2O (3 x 20 mL). Yield: 614 mg (92%) colorless crystals. mp 195 – 197 °C (decomp); Due to broad line width no satisfying ^1H NMR-data could be obtained. ^{13}C NMR (DMSO-d_6): δ 193.8 (s), 151.2 (d), 148.7 (s), 143.3 (s), 127.2 (d), 124.5 (s), 117.7 (s), 115.2 (d), 109.2 (s), 69.6 (q), 65.6 (t), 62.1 (t), 56.5 (q), 49.7 (d), 45.2 (s), 36.1 (t), 34.7 (t). Anal. Calcd for $C_{17}H_{19}NO_3BrI$: C, 41.49; H, 3.89; N 2.85. Found: C, 41.31; H, 4.02; N, 2.89.

(4a*R,8a*R**)-1-Bromo-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]-benzazepin-6-one (13). 12** (300 mg, 0.61 mmol) and NaOH (300 mg, 7.50 mmol) were refluxed in 70% EtOH (10 mL) for 2 h. The solution was concentrated *in vacuo*, and the residue was partitioned between water (15 mL) and EtOAc (15 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL), the combined organic layers were washed with water (2 x 20 mL) and brine (1 x 20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, $CHCl_3$: MeOH : conc. NH_3 = 89 : 10 : 1). Yield: 112 mg (50%), colorless foam. ^1H NMR ($CDCl_3$): δ 7.00 (dd, *J* = 11.1 Hz, *J* = 1.3 Hz, 1H), 6.95 (s, 1H), 6.05 (d, *J* = 11.1 Hz, 1H), 4.74 – 4.65 (m, 1H), 4.23 (d, *J* = 16.9 Hz, 1H), 3.92 (d, *J* = 16.9 Hz, 1H), 3.81 (s, 3H), 3.27 - 2.82 (m, 3H), 2.75 (dd, *J* = 17.1 Hz, *J* = 5.7 Hz, 1H), 2.45 (s, 3H), 2.31 – 1.79 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 194.0 (s), 146.6 (s), 144.5 (d), 144.0 (s), 131.7 (s), 127.9 (s), 127.4 (d), 116.4 (d), 114.1 (s), 88.1 (d), 59.0 (t), 56.2 (q), 53.6 (t), 49.3 (s), 43.0 (q), 37.0 (t), 33.1 (t).

The identity with an authentic sample was confirmed by TLC, HPLC and NMR.

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