Seco-isopowellaminone: a New Heterocycle from Nornarwedine

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It is known that Nornarwedine-type molecules can be converted into crinine-type compounds by a reverse Michael- / Michael addition. Narwedine and bromonarwedine yield, as confirmed by X-ray structure determination, the known seco-powellaminone as well as the novel seco-isopowellaminone.
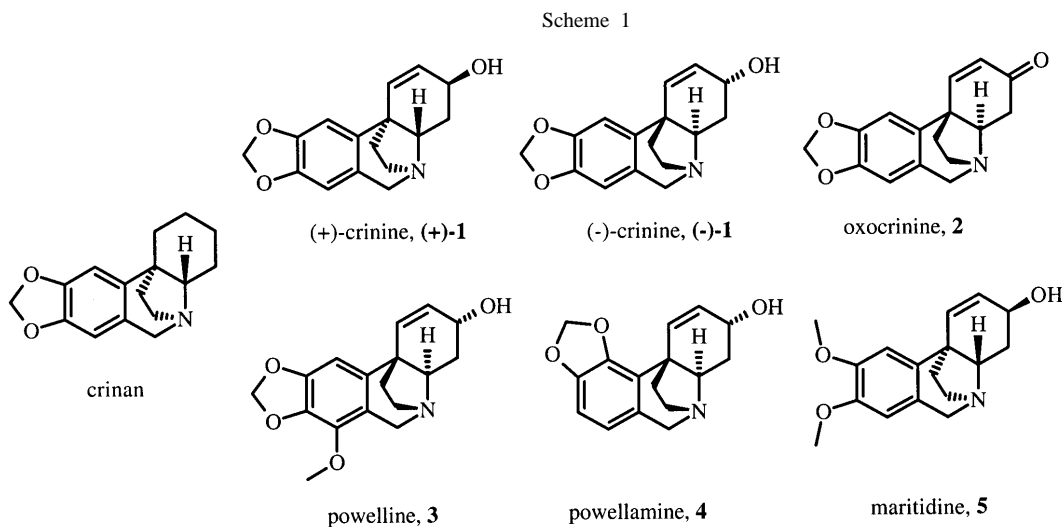
Introduction.

In continuation of our current interest in the chemistry of galanthamine, a natural product now produced in ton-quantities [1] and approved for the treatment of the symptoms of Alzheimer's type senile dementia (galantamine, Reminyl®) [2] we have further investigated [3] the chemistry of nornarwedine and found that it converts readily to crinan-type compounds and to a novel ring system as well. Many crinan derivatives like (+)- [4,5] or (-)-crinine [6,7] ((+)-**1**; (-)-**1**), oxocrinine (**2**) [8], powelline (**3**) [9,10], powellamine (**4**) [11], and maritidine (**5**) [12] are known, either by isolation from natural products or by total synthesis.

Results and Discussion.

Nornarwedine has been described as an intermediate in the biosynthesis of galanthamine[14]but no synthesis was reported so far. We applied an optimized demethylation protocol [15] to narwedine by treating the narwedine-*N*-oxide prepared *in-situ* with $FeSO_4 \cdot 7H_2O$.

Samples of nornarwedines (**9**; **10**) are stable at room temperature as solid or at 50 °C in acidic buffer (trifluoroacetic acid, pH=2.3). However, heating **9** or **10** under basic conditions (phosphate buffer pH = 7.7 or pH = 10.0) leads to a mixture of starting material and 10,11-seco-isopowellamin-3-ones (**12**; **14**), as shown in Scheme 2.

Scheme 1

(+)-crinine, (+)-**1**   (-)-crinine, (-)-**1**   oxocrinine, **2**

crinan   powelline, **3**   powellamine, **4**   maritidine, **5**

These compounds have the common characteristic of a *trans*-fusion between the isoquinoline and the cyclohexene substructure. The only known compound with a *cis*-fusion is **6** [13]. As will be shown below we found a surprisingly simple method to obtain such *cis*-fused systems from nornarwedine.

6
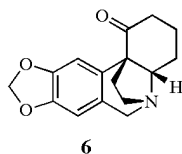
When nornarwedine (**9**) or 8-bromonornarwedine (**10**) were refluxed in ethanol in presence of $CaCl_2$ a remarkable difference between **9** and **10** was observed: While **10** is converted almost instantly to **14** as reported previously [3], **9** under the same conditions yields a mixture of **11** and **12**. This observation prompted us, to extend the reaction time also with **10** and to trace the reaction products by HPLC analysis. Indeed, **13** could be isolated after 1 week (Figures 1 and 2).

Additionally, when **11** (or **13**) was subjected to the same conditions, **9** and **12**, (or **10** and **14**) could not be detected. This fact can be explained by a more favourable conforma-

Scheme 2
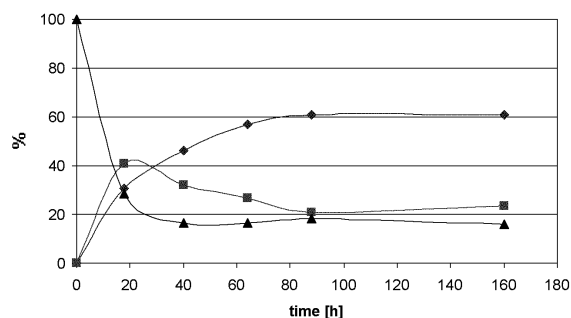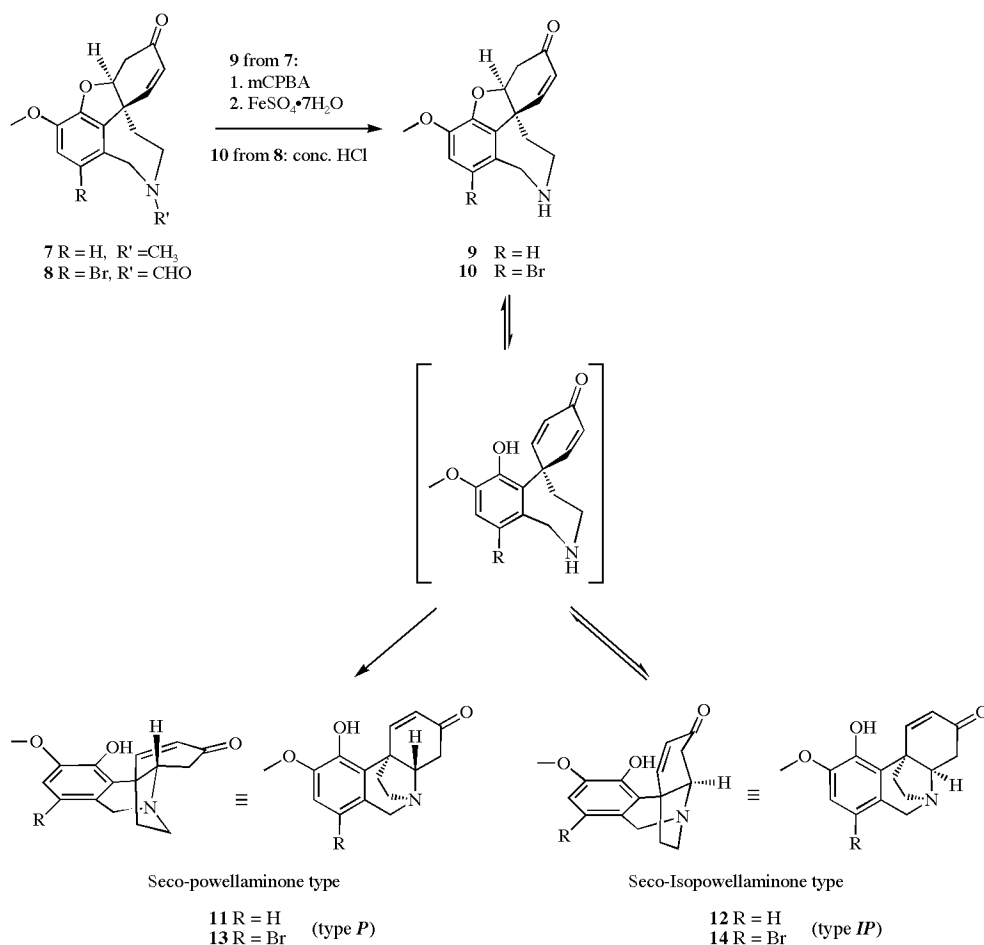
Figure 1. Reaction of **9** to **11** and **12**.
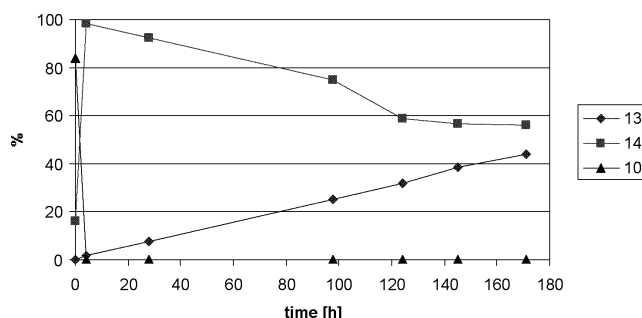
Figure 2. Reaction of **10** to **13** and **14**.

tion for the reverse Michael reaction in **12** or **14** over **11** or **13** and the need for a mildly acidic catalyst (CaCl$_2$).

The structures of the four isomeric seco-powellaminones **11**, **12**, **13**, and **14** were established by single crystal X-ray diffraction. Views of the molecular structures with crystallographic atom designations of the four compounds are shown in Figures 3 and 4. Details on the structure determinations with selected geometric data are given in the experimental

section. All four compounds were found to be racemic and thus crystallising in non-chiral space groups despite being derived from (-)-narwedine as the starting material. The depicted molecules (**11**, **12**, **13**, and **14**) correspond in configuration with the structural formulas of Scheme 1. With respect to the isoquinoline-cyclohexane fusion they are enantiomers of the powelline (**3**) and powellamine (**4**) skeletons shown in Scheme 1. Disregarding absolute configurations,

the basic molecular structure features of **11** and **13** fit well into the pattern of related compounds that were crystallographically studied [16] and which were all of natural origin (or derivatives thereof), enantiopure, and therefore crystallised in chiral space groups (predominantly space group $P2_12_12_1$). The structural differences between the seco-powellaminone type molecules **11** and **13** (type ***P***), and the novel seco-isopowellaminone type molecules **12** and **14** (type ***IP***) are astonishingly small as may be seen from Figures 3 and 4: For ***P*** and ***IP*** the three-ring systems comprised of the hydro-isoquinoline and the annulated 5 ring are practically identical in all conformational aspects. The only differences stems from the isomerism in the link of C14 with C15 (crystallographic atom designations), which is approximately parallel to the phenyl ring for ***P***, and approximately perpendicular to the phenyl ring for ***IP***. This means that the handedness of the chiral C15 is inverted on stepping from ***P*** to ***IP***. The cyclohexenone ring (C10-C15, O3) retains for both configurations its half-chair form with C15 bent off from the plane formed by C10-C11=C12-C13(=O3)-C14 by about 0.6 Å, but for ***P*** it is bent up whereas for ***IP*** it is bent down.

Conclusion.

To summarize, we have shown that powellaminone type molecules and the novel isopowellaminoe type molecules can be readily accessed by conversion of narwedine type molecules *via* a reverse Michael-/Michael addition.

11 = Seco-powellaminone-type
(type ***P***)

12 = Seco-isopowellaminone-type
(type ***IP***)

Figure 3. Comparison of the molecular structures of **11** and **12** in solid state.

13 = Seco-powellaminone-type
(type ***P***)

14 = Seco-isopowellaminone-type
(type ***IP***)
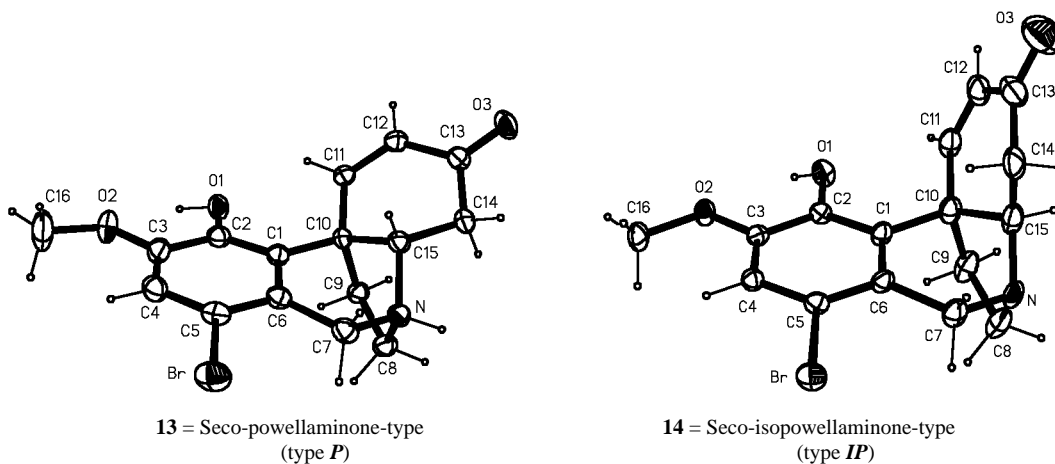
Figure 4. Comparison of the molecular structures of **13** (as **13**•HCl•H$_2$O, for clearity HCl and H$_2$O omitted) and **14** in solid state.

Synergi Polar-RP 4μ (4.6 x 150 mm) column, a 600-MS pump (Waters), a 712 WISP autosampler (Waters) and a 996 photodiode array detector (Waters).

(4aR*,8aR*)-1-Bromo-4a,5,9,10,11,12-hexahydro-3-methoxy-6H-benzofuro[3a,3,2-ef][2]benzazepin-6-one, Bromnornarwedine (**10**) was prepared as previously described [3].

(4aS*,8aS*)-4a,5,9,10,11,12-Hexahydro-3-methoxy-6H-benzofuro[3a,3,2-ef][2]benzazepin-6-one (-)-Nornarwedine (**9**).

To a solution of (-)-narwedine, **7** (5.00 g, 17.5 mmol) in CH$_2$Cl$_2$ (50 mL) m-CPBA (peroxide content 75% by titration, 3.18 g, 18.4 mmol) was added and the clear solution stirred 1.5 h at ambient temperature. At this stage the conversion to the N-oxide is quantitative as determined by HPLC. Then a solution of FeSO$_4$•7H$_2$O (2.44 g, 8.76 mmol) in MeOH (20 mL) was added. The mixture was stirred for 20 min., treated with Na$_2$HPO$_4$•12H$_2$O (4.00 g, 11.2 mmol) in water (20 mL) and stirred for 5 min. The precipitate was collected by filtration, washed with CH$_2$Cl$_2$ (2 x 40 mL). The biphasic mixture was adjusted to pH > 8.5 with conc. ammonia, separated and the aqueous phase was extracted with CH$_2$Cl$_2$ (2 x 50 mL). The combined organic layers were washed with 0.25 N NaOH (1 x 50 mL), and brine (1 x 50 mL), dried (Na$_2$SO$_4$) and filtered. After concentration $in\ vacuo$ the residue was dissolved in MeOH (30 mL) and treated with a solution of oxalic acid dihydrate (3.31 g, 26.3 mmol) in MeOH (30 mL). The precipitate of **9**•C$_2$H$_2$O$_4$ was collected by filtration and washed with MeOH (2 x 10 mL). Yield: colorless crystals, 3.25 g (51%), mp. 200 – 203 °C (decomp.). Treatment of **9**•C$_2$H$_2$O$_4$ with ammonia and extractive workup yielded the free base: colorless crystals, 2.38 g (50%), mp. 168 – 170 °C; ^{1}H NMR (CDCl$_3$): 6.91 (dd, J = 10.4 Hz, 1.9 Hz, 1H), 6.73–6.56 (m, 2H), 6.00 (d, J = 10.4 Hz, 1H), 4.75-4.66 (m, 1H), 3.99 (s, 2H), 3.80 (s, 3H), 3.42 (dt, J = 14.7 Hz, 3.5 Hz, 1H), 3.21-3.08 (m, 1H), 2.72 (dd, J = 17.8 Hz, 3.7 Hz, 1H), 2.19-1.80 (m, 4H); ^{13}C NMR (CDCl$_3$): 194.3 (s), 144.6 (d), 143.8 (s), 133.3 (s), 130.6 (s), 127.7 (s), 127.0 (d), 120.6 (d), 111.7 (d), 87.8 (d), 56.0 (q), 53.9 (t), 49.5 (s), 47.3 (t), 39.7 (t), 37.2 (t).

Anal. Calcd for C$_{16}$H$_{17}$NO$_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.62; H, 6.42; N, 4.99.

rel-(4aS,5R,10bR)-4,4a-Dihydro-10-hydroxy-9-methoxy-3H,6H-5,10b-ethanophenanthridin-3-one, = rel-(4aS,5R,10bR)-10,11-Seco-powellamin-3-one (**11**) and rel-(4aR,5R,10bR)-4,4a-Dihydro-10-hydroxy-9-methoxy-3H,6H-5,10b-ethanophenanthridin-3-one, = rel-(4aR,5R,10bR)-10,11-Seco-isopowellamin-3-one (**12**).

Compound **9** (1.30 g, 4.79 mmol) and CaCl$_2$ (0.80 g, 7.19 mmol) in 70 % ethanol (50 mL) were stirred under reflux for 160 h and the reaction progress followed by HPLC (Figures 1 and 2). The mixture was concentrated $in\ vacuo$, and the residue was partitioned between 2 N HCl (50 mL) and EtOAc (50 mL). The aqueous layer was basified with conc. ammonia and extracted with CH$_2$Cl$_2$ (3 x 50 mL). The combined organic layers were washed with brine (1 x 50 mL), dried (Na$_2$SO$_4$) and filtered. After concentration $in\ vacuo$, the residue was purified by flash chromatography (SiO$_2$, CHCl$_3$:MeOH:NH$_3$ = 95:4:1). Yield: **11**: colorless crystals 0.75 g (58%), mp 200-203 °C, ^{1}H NMR (CDCl$_3$): 8.72 (d, J = 10.6 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 6.40 (d, J = 8.0 Hz, 1H), 5.87 (d, J = 10.6 Hz, 1H), 4.31 (d, J = 16.7 Hz, 1H), 3.76 (s, 3H), 3.64 (d, J = 16.7 Hz, 1H), 3.55-3.39 (m, 1H), 2.92-2.73 (m, 1H), 2.71-2.25 (m, 3H), 2.22-2.01 (m,

1H); ^{13}C NMR (CDCl$_3$): 197.9 (s), 152.6 (d), 145.2 (s), 142.4 (s), 127.8 (d), 127.7 (s), 126.5 (s), 117.3 (d), 109.2 (d), 69.2 (d), 61.0 (t), 56.0 (q), 53.6 (t), 45.8 (s), 42.9 (t), 40.2 (t).

Anal. Calcd for C$_{16}$H$_{17}$NO$_3$•0.25H$_2$O: C, 69.67; H, 6.39; N, 5.08. Found: C, 69.63; H, 6.56; N, 4.89.

Compound **12** was obtained as colorless crystals 0.12 g (9.3 % yield), mp 196-199 °C; ^{1}H NMR (CDCl$_3$): 7.93 (d, J = 9.8 Hz, 1H), 6.69 (d, J = 8.1 Hz, 1H), 6.49 (d, J = 8.1 Hz, 1H), 5.93 (d, J = 9.80 Hz, 1H), 4.21 (d, J = 17.3 Hz, 1H), 3.81 (s, 3H), 3.66 (d, J = 17.3 Hz, 1H), 3.42 (dt, J = 11.4 Hz, 3.1 Hz, 1H), 3.15 (dd, J = 14.0 Hz, 4.1 Hz, 1H), 2.98-2.71 (m, 1H), 2.69-2.21 (m, 3H), 2.06-1.83 (m, 1H); ^{13}C NMR (CDCl$_3$): 198.7 (s), 155.0 (d), 146.0 (s), 143.0 (s), 127.6 (d), 126.3 (s), 124.7 (s), 116.6 (d), 109.4 (d), 64.9 (d), 56.0 (q), 54.4 (t), 53.3 (t), 43.6 (s), 40.1 (t), 38.5 (t).

Anal. Calcd for C$_{16}$H$_{17}$NO$_3$•0.33H$_2$O: C, 69.31; H, 6.42; N, 5.05. Found: C, 69.02; H, 6.26; N, 4.97.

rel-(4aS,5R,10bR)-1-Bromo-4,4a-dihydro-10-hydroxy-9-methoxy-3H,6H-5,10b-ethanophenanthridin-3-one, = rel-(4aS,5R,10bR)-1-Bromo-10,11-seco-powellamin-3-one (**13**) and rel-(4aR,5R,10bR)-1-Bromo-4,4a-dihydro-10-hydroxy-9-methoxy-3H,6H-5,10b-ethanophenanthridin-3-one, = rel-(4aR,5R,10bR)-1-Bromo-10,11-seco-isopowellamin-3-one (**14**).

Compound **10** (2.66 g, 7.60 mmol) and CaCl$_2$ (1.26 g, 11.4 mmol) in 70 % ethanol (100 mL) were stirred under reflux for 170 h. The mixture was concentrated $in\ vacuo$, and the residue was partitioned between 2 N HCl (100 mL) and EtOAc (100 mL). The aqueous layer was basified with conc. ammonia and extracted with CH$_2$Cl$_2$ (3 x 100 mL). The combined organic layers were washed with brine (1 x 50 mL), dried (Na$_2$SO$_4$) and filtered. After concentration $in\ vacuo$, the residue was purified by flash chromatography (SiO$_2$, CHCl$_3$:MeOH:NH$_3$ = 95:4:1). Yield: **13**: colorless crystals, 0.74 g, (28%), mp 241 – 244 °C, ^{1}H NMR (DMSO-d$_6$+10% TFA-d$_1$): 8.65 (d, J = 10.5 Hz, 1H), 8.00 (s, 1H), 6.01 (d, J = 10.5 Hz, 1H), 4.64 (d, J = 15.5 Hz, 1H), 4.39-4.31 (m, 1H), 4.26 (d, J = 15.5 Hz, 1H), 4.21 – 4.08 (m, 1H), 3.83 (s, 3H), 3.56 – 3.34 (m, 1H), 2.98 – 2.79 (m, 2H), 2.65 – 2.42 (m, 2H); ^{13}C NMR (DMSO-d$_6$+10% TFA-d$_1$): 192.7 (s), 148.5 (s), 147.4 (d), 143.7 (s), 129.1 (d), 126.7 (s), 118.4 (s), 115.0 (d), 111.0 (s), 67.0 (d), 58.9 (t), 56.5 (q), 52.9 (t), 46.5 (s), 39.3 (t), 36.5 (t).

Anal. Calcd for C$_{16}$H$_{16}$NO$_3$Br•0.33 H$_2$O: C, 53.95; H, 4.72; N, 3.93. Found: C, 54.01; H, 4.61; N, 3.85. For X-ray work **13** was transformed to the hydrochloride and crystallized from water as **13**•HCl•H$_2$O.

Compound **14** was obtained as colorless crystals, 0.60 g (23% yield), mp 219 – 224 °C, Identical ^{1}H and ^{13}C NMR as previously reported [3].

Anal. Calcd for C$_{16}$H$_{16}$NO$_3$Br•0.33 H$_2$O: C, 53.95; H, 4.72; N, 3.93. Found: C, 53.98; H, 4.53; N, 3.78.

X-Ray Structure Determinations of **11**, **12**, **13**, and **14**.

General.

X-ray data were collected with a Bruker AXS Smart CCD area detector diffractometer, graphite monochromatized Mo K radiation, λ(Mo-K) = 0.71073 Å, and a Bruker AXS Kryoflex cooling unit. Data reductions including corrections for absorption were carried out with Bruker AXS programs [17]. The structures were solved with direct methods using program SHELXS97 and were

refined on F^2 using program SHELXL97 [18] using anisotropic temperature factors for non-hydrogen atoms. Most hydrogen atoms mainly inserted in idealized positions and resided with the atoms to which they were bonded. Crucial hydrogen atoms (OH, H_2O, NH) were refined in x,y,z. Views of the four molecular structures with crystallographic atom designations are shown in Figures 3 and 4.

Crystal Data of **11**.

$C_{16}H_{17}NO_3$, $M_r = 498.38$, colorless plate of 0.76 x 0.24 x 0.06 mm obtained from methanol/water by solvent evaporation, monoclinic, space group $P2_1/c$ (no. 14), $a = 11.539(2)$ Å, $b = 17.100(3)$ Å, $c = 14.971(3)$ Å, $\beta = 104.46(1)°$, $V = 2860.5(9)$ Å^3, $Z = 8$, $D_x = 1.260$ Mg/m^{-3}, $\mu = 0.087$ mm^{-1}, $T = 297(2)$ K. 25029 reflections with $\theta < 25°$ were measured and merged to 5023 unique reflections, $R_{int} = 0.034$. Final refinement: 388 parameters, $R1 = |F_o|-|F_c|/|F_o| = 0.082$, $wR2 = [(w(F_o^2-F_c^2)^2)/(w(F_o^2)^2)]^{1/2} = 0.126$, and $S = 1.01$ for all reflections; $R1 = 0.044$ for the 3188 observed data $[I>2\sigma(I)]$ [19]. The crystal structure contains two crystallographically independent molecules of very similar geometry. There is some solvent in the lattice, namely about $^1/_2$ H_2O or $^1/_4$ CH_3OH per formula unit, which has been omitted, however, in chemical formula and derived quantities. Selected bond distances and angles are (in Å and ° for first/second molecule, e.s.d.'s ~0.003 Å and ~0.2°): O1-C2 1.361/1.355, O2-C3 1.381/1.381, O2-C16 1.406/1.412, O3-C13 1.224/1.218, N-C7 1.470/1.469, N-C8 1.488/1.495, N-C15 1.464/1.468, C1-C2 1.397/1.402, C1-C6 1.401/1.408, C1-C10 1.538/1.533, C2-C3 1.391/1.396, C3-C4 1.369/1.368, C4-C5 1.382/1.386, C5-C6 1.380/1.382, C6-C7 1.515/1.509, C8-C9 1.548/1.544, C9-C10 1.540/1.547, C10-C11 1.495/1.513, C10-C15 1.542/1.539, C11-C12 1.328/1.327, C12-C13 1.451/1.459, C13-C14 1.495/1.489, C14-C15 1.522/1.523, C7-N-C15-C14 161.1/159.5, C1-C10-C11-C12 145.6/145.1, C11-C10-C15-C14 –48.3/-46.5.

Crystal Data of **12**.

$C_{16}H_{17}NO_3$, $M_r = 498.38$, colorless block of 0.35 x 0.33 x 0.20 mm obtained from DMF by solvent evaporation, orthorhombic, space group $Pna2_1$ (no. 33), $a = 13.012(4)$ Å, $b = 11.480(4)$ Å, $c = 8.994(3)$ Å, $V = 1343.5(8)$ Å^3, $Z = 4$, $D_x = 1.341$ Mg/m^{-3}, $\mu = 0.093$ mm^{-1}, $T = 297(2)$ K. 17408 reflections with $\theta < 30°$ were measured and merged to 3834 unique reflections, $R_{int} = 0.029$. Final refinement: 185 parameters, $R1 = 0.051$, $wR2 = 0.098$, and $S = 1.02$ for all reflections; $R1 = 0.037$ for the 3146 observed data $[I>2\sigma(I)]$ [13]. Selected bond distances and angles (Å, °; e.s.d.'s ~0.002 Å and ~0.2°): O1-C2 1.351, O2-C3 1.371, O2-C16 1.427, O3-C13 1.217, C1-C2 1.397, C1-C6 1.410, C1-C10 1.536, C2-C3 1.411, C3-C4 1.379, C4-C5 1.391, C5-C6 1.375, C6-C7 1.516, C7-N 1.471, N-C15 1.470, N-C8 1.506, C8-C9 1.554, C9-C10 1.541, C10-C11 1.506, C10-C15 1.537, C11-C12 1.338, C12-C13 1.468 , C13-C14 1.518, C14-C15 1.513, C7-N-C15-C14 51.4, C1-C10-C11-C12 96.1, C11-C10-C15-C14 57.4; hydrogen bond O1 N 2.671.

Crystal Data of **13** in the Form of its Hydrochloride Monohydrate **13·HCl·H$_2$O**.

$C_{16}H_{19}BrClNO_4 = C_{16}H_{16}BrNO_3·HCl·H_2O$, $M_r = 404.68$, colorless plate of 0.30 x 0.20 x 0.05 mm obtained from **13**, HCl, and water by slow evaporation, monoclinic, space group $P2_1/c$ (no. 14), $a = 7.262(1)$ Å, $b = 21.289(3)$ Å, $c = 10.845(2)$ Å, $\beta = 95.224(3)°$, $V = 1669.7(5)$ Å^3, $Z = 4$, $D_x = 1.610$ Mg/m^{-3}, $\mu = 2.64$ mm^{-1}, $T = 153(2)$ K. 18063 reflections with $\theta < 30°$ were

measured and merged to 4784 unique reflections, $R_{int} = 0.046$. Final refinement: 217 parameters, $R1 = 0.075$, $wR2 = 0.103$, and $S = 1.03$ for all reflections; $R1 = 0.042$ for the 3383 observed data $[I>2\sigma(I)]$ [13]. Selected bond distances and angles are (Å, °; e.s.d.'s ~0.004 Å and ~0.3°): Br-C5 1.907, O1-C2 1.362, O2-C3 1.363, O2-C16 1.434, O3-C13 1.225, N-C7 1.491, N-C8 1.521, N-C15 1.500, C1-C2 1.397, C1-C6 1.422, C1-C10 1.546, C2-C3 1.412, C3-C4 1.381, C4-C5 1.381, C5-C6 1.393, C6-C7 1.508, C8-C9 1.539, C9-C10 1.550, C10-C11 1.516, C10-C15 1.537, C11-C12 1.335, C12-C13 1.475, C13-C14 1.505, C14-C15 1.524; C7-N-C15-C14 156.3, C1-C10-C11-C12 146.0, C11-C10-C15-C14 -48.5; hydrogen-bonds: O1 O4w 2.650, N Cl 3.033, O4w Cl 3.245, O4w O3 2.892.

Crystal Data of **14**.

$C_{16}H_{16}BrNO_3$, $M_r = 498.38$, colorless plate of 0.80 x 0.30 x 0.06 mm obtained from ethylene glycol by slow evaporation, monoclinic, space group $P2_1/n$ (no. 14), $a = 8.998(1)$ Å, $b = 14.235(2)$ Å, $c = 11.751(2)$ Å, $\beta = 93.241(3)°$, $V = 1502.7(4)$ Å^3, $Z = 4$, $D_x = 1.548$ Mg/m^{-3}, $\mu = 2.75$ mm^{-1}, $T = 173(2)$ K. 8476 reflections with $\theta < 30°$ were measured and merged to 3836 unique reflections, $R_{int} = 0.035$. Final refinement: 235 parameters, $R1 = 0.065$, $wR2 = 0.110$, and $S = 1.12$ for all reflections; $R1 = 0.046$ for the 2998 observed data $[I>2\sigma(I)]$ [13]. The structure is disordered and has the atoms N, C8, C9, C11-C15, and O3 in complementary positions at both sides of the phenyl ring plane in a ratio of 76/24%. Selected bond distances and angles for the major part are (Å, °; e.s.d.'s ~0.005 Å and ~0.6°): Br-C5 1.908, O1-C2 1.350, O2-C3 1.364, O2-C16 1.424, C1-C2 1.391, C1-C6 1.413, C1-C10 1.562, C2-C3 1.403, C3-C4 1.387, C4-C5 1.388, C5-C6 1.373, C6-C7 1.509, N-C7 1.478, N-C15 1.464, N-C8 1.498, C8-C9 1.565, C9-C10 1.570, C10-C11 1.483, C10-C15 1.513, C11-C12 1.338, C12-C13 1.457, C13-O3 1.241, C13-C14 1.508, C14-C15 1.508; C7-N-C15-C14 51.4, C1-C10-C11-C12 101.1, C11-C10-C15-C14 57.5; hydrogen bond O1 N 2.619.

REFERENCES AND NOTES

[1a] L. Czollner, W. Frantsits, B. Kueenburg, U. Hedenig, J. Froehlich and U. Jordis, *Tetrahedron Letters,* **39**, 2087 (1998); [b] B. Kueenburg, L. Czollner, J. Froehlich and U. Jordis, *Org. Proc. Res. Dev.,* 1999, **3**, 425.

[2] D. G. Wilkinson, *Expert Review of Neurotherapeutics*, **1**, 153 (2001).

[3] M. Treu, S. Welzig and U. Jordis, *Heterocycles*, **55**, 2397 (2001).

[4] H.-G. Boit, *Chem. Ber.,* **89**, 1129 (1956).

[5] C. Muegge, B. B. Schablinski, K. Obst and W. Doepke, *Pharmazie,* **49**, 444 (1994).

[6] H.-G. Boit, *Chem. Ber.,* **87**, 1704 (1954).

[7] M. A. Schwartz and R. A. Holton, *J. Am. Chem. Soc.,* **92**, 1090 (1970).

[8] A. A. Ali, H. M. E. Sayed, O. M. Abdallah and W. Steglich, *Phytochemistry,* **25**, 2399 (1986).

[9] J. J. Nair, A. K. Machocho, W. E. Campbell, R. Brun, F. Viladomat, C. Codina and J. Bastida, *Phytochemistry,* **8**, 945 (2000).

[10] H.-G. Boit and H. Ehmke, *Chem. Ber.,* **88**, 1590 (1955).

[11]   H.-G. Boit and W. Doepke, *Naturwissenschaften*, **46**, 475 (1959).

[12]   G. Ma, H. Li, C. Lu, X. Yang and S. Hong, *Heterocycles,* **24**, 2089 (1986).

[13]   H. W. Whitlock and G. L. Smith, *J. Am. Chem. Soc.,* **89**, 3600 (1967).

[14]   J. Eichhorn, T. Takada, Y. Kita and M. H. Zenk, *Phytochemistry,* **49**, 1037 (1998).

[15]   U. Jordis, M. Treu, M. Hirnschall, J. Froehlich, L. Czollner, B. Kaelz, T. Kaelz and P. Kuehnhackl, Process for the manufacture of Norgalanthamine, Norgalanthamine-derivatives and their isomers, Austrian Patent Application*, 25.3.2002.

[16a]   R. Roques, J. Lapasset, R. Fourme, D. Andre and M. Renaud, *Acta Crystallogr., Sect.B*, **32**, 1394 (1976); [b] W. H. Watson,V. Zabel, M. Silva and P. Pacheco, *Cryst. Struct. Commun.*, **11**, 157 (1982); [c] W. H. Watson, J. Galloy and M. Silva, *Acta Crystallogr., Sect.C (Cr.Str.Comm.)*, **40**, 156 (1984); [d] J. M. Amigo, J. Bastida-Cuairan, M. M. Reventos, A. Cantarero and T. Debaerdemaeker, *Acta Crystallogr.,* *Sect.C(Cr.Str.Comm.)*, **44**, 1497 (1988); [e] J. Karle, J. A. Estlin and I. L. Karle, *J. Am. Chem. Soc.*, **89**, 6510 (1967); [f] R. Roques, J. P. Declercq, and G. Germain, *Acta Crystallogr.,Sect.B*, **33**, 3696 (1977); [g] J. Clardy, F. M. Hauser, D. Dahm, R. A. Jacobson and W. C. Wildman, *J. Am. Chem. Soc.*, **92**, 6337 (1970); [h] W. H. Watson, Z. Taira, M. Silva and P. Pacheco, *Cryst. Struct. Commun.*, **6**, 797 (1977); [i] S. Ide, B. Sener and S. Ozturk, *J. Chem. Cryst.*, **28**, 577 (1998); [j] V. Zabel, W. H. Watson, P. Pacheco and M. Silva, *Cryst. Struct. Commun.*, **8**, 37 (1979).

[17]   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

[18]   Sheldrick GM (1997): SHELX97. Program system for crystal structure determination. University of Göttingen, Germany

[19]   CCDC 190685 through 190688 contains 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).