HETEROCYCLES, Vol. 55, No. 9, pp. 1727 - 1736, Received, 25th June, 2001

# 12*H*-[2]-BENZOTHIEPINO[6,5*a*,5-*bc*]BENZOFURAN: SYNTHESIS OF A SULFUR-ANALOG OF GALANTHAMINE

**Matthias Treu,[a] Ulrich Jordis,*[a] and Kurt Mereiter[b]**

[a] Department of Organic Chemistry, Vienna University of Technology
Getreidemarkt 9/154, A-1060 Vienna, Austria
ujordis@pop.tuwien.ac.at
[b] Institute of Mineralogy, Crystallography and Structural Chemistry, Vienna University of Technology, Getreidemarkt 9, A-1060 Vienna, Austria

**Abstract –** An analog of the anti-Alzheimer drug galanthamine, carrying a $SO_2$-moiety instead of an amino-functionality, has been synthesized as a racemic mixture using tandem cyclization techniques to form a new four membered heterocyclic ring system.

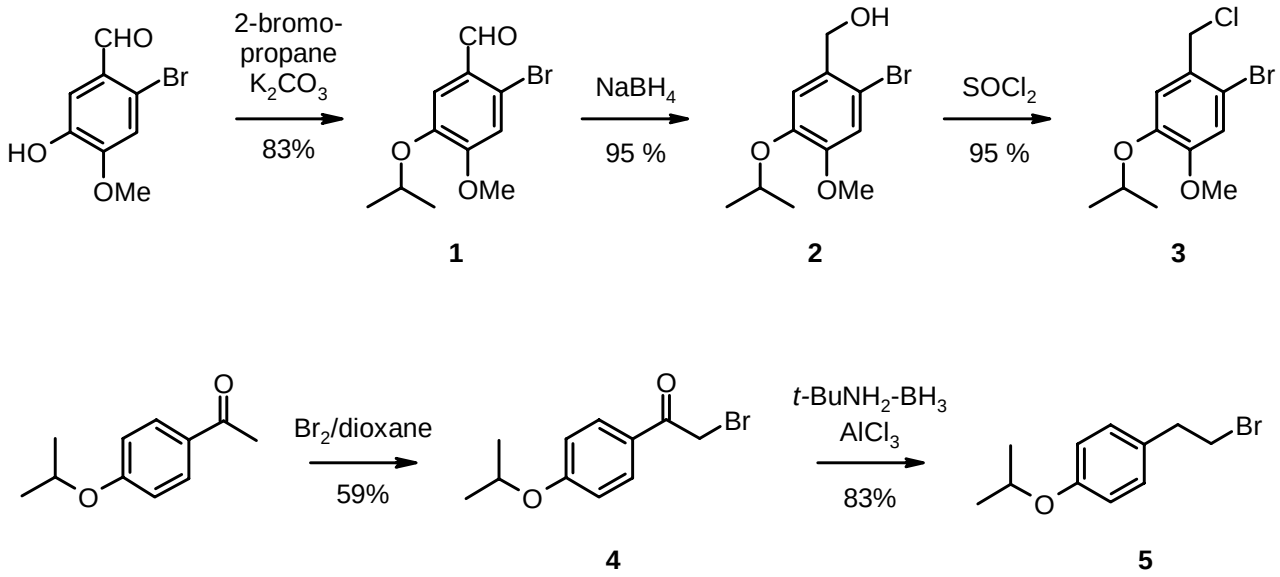
## INTRODUCTION

Galanthamine (or galantamine, Reminyl®) is a tertiary alkaloid acetylcholinesterase inhibitor (AChEI) which has been approved in several countries for treating symptoms of Alzheimer's type senile dementia.[1,2] In the course of our investigations into the oxidative tandem cyclization[3,4,5] leading to galanthamine[6,7,8] and galanthamine analogs we were interested in examining the formal replacement of the amine against a sulfur functionality.

## RESULTS AND DISCUSSION

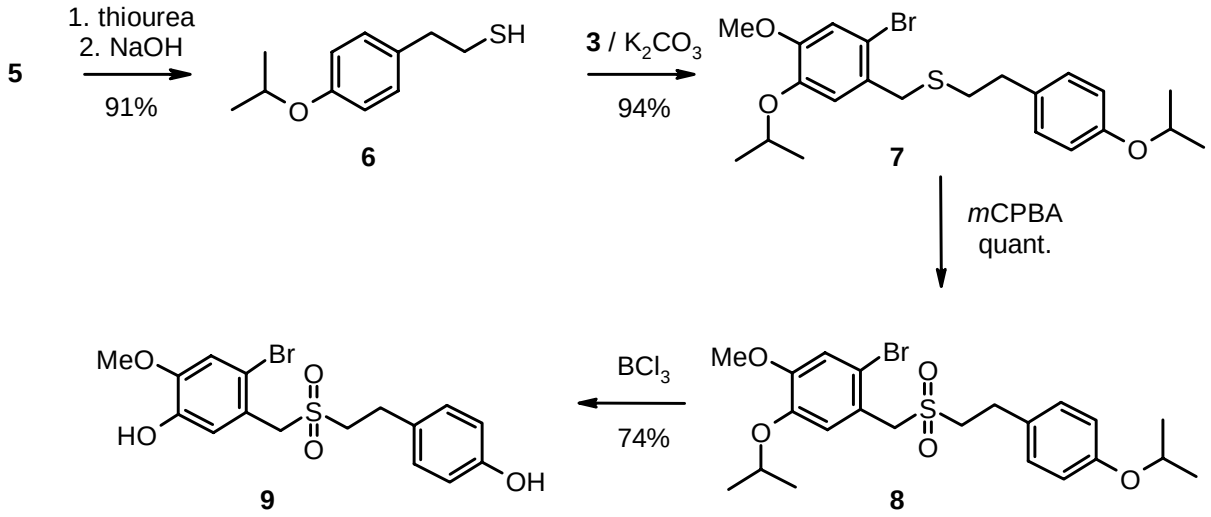
Our strategy (see Schemes 1 and 2) was to synthesize the protected sulfide (**7**) as key intermediate in convergent manner and to try oxidative cyclization on sulfone (**9**), available from **7** by oxidation and selective cleavage of the isopropyl ether in the presence of an arylmethyl ether, since the stability of sulfones towards $K_3[Fe(CN)_6]$ has been established.[9] For the synthesis of **7** a double alkylation of a sulfur nucleophile was envisaged. Thus the known 4-isopropoxyacetophenone[10] was brominated to **4** and the ketone was reduced by using the *tert*-butylamine-borane complex and aluminum chloride[11] to produce **5**. The phenethyl bromide (**5**) was converted to the mercaptane using thiourea followed by hydrolysis. The second alkylating agent (**3**) was prepared starting with 2-bromo-5-hydroxy-4-methoxybenzaldehyde, now available in ton quantities from the industrial synthesis[12] of galanthamine. Aldehyde (**1**)[13] was protected

using 2-bromopropane in the presence of potassium carbonate, reduced using $NaBH_4$ and converted to the benzyl chloride (**3**) using thionyl chloride in 75% overall yield (see Scheme 1), and finally was used for the S-alkylation of **6** to **7**.




**Scheme 1**

Oxidation to sulfone (**8**) proceeded smoothly using *m*-chloroperbenzoic acid. While attempts to deprotect **7** using $BCl_3$ in dichloromethane only gave rise to decomposition products, sulfone (**8**) was selectively deprotected using the same reagent (see Scheme 2).




**Scheme 2**

The oxidative cyclization of **9** was conducted using conditions found optimal in the narwedine synthesis.[12] A yield of 16% was considered satisfactory at that stage since this tandem cyclization can be

looked at as a series of reactions (radical formation, recombination, Michael addition). Attempts to run this reaction either at 0 °C or at reflux temperature did not effect this yield. The structure of the cyclization product (**10**) was verified by $^{1}$H- and $^{13}$C-NMR spectral and elemental analysis and confirmed by X-Ray analysis.

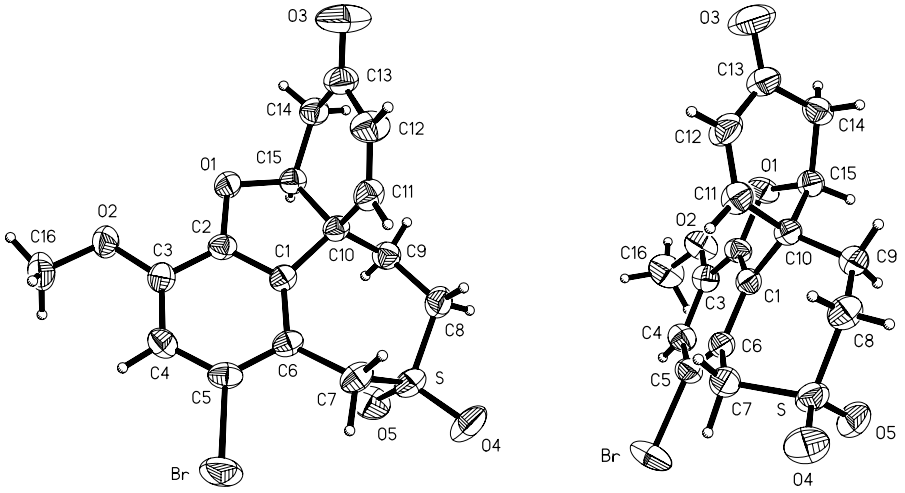
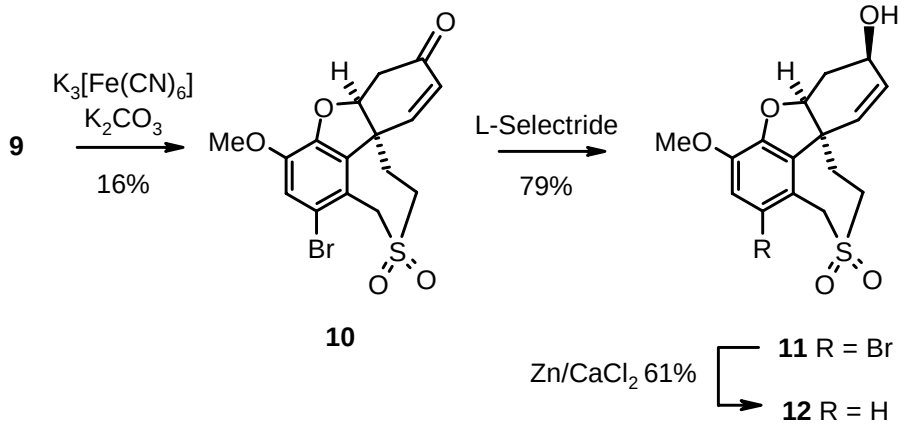



**Figure 1.** Molecular structure of **10** in solid state (50% ellipsoids) seen in two views.

The stereoselective reduction of **10** using L-Selectride® produced bromide (**11**). Attempts to debrominate **11** using tributyltin hydride in the presence of a radical starter (AIBN or dibenzoyl peroxide) failed, but the use of zinc/calcium chloride provided the desired galanthamine analog (**12**) (see Scheme 3).




**Scheme 3**

The observation, that **12** was devoid of any noticeable acetylcholin- (AChE) or butyrylcholinesterase (BuChE) inhibition confirmed the expectation, that the amine functionality is essential for the AChE or BuChE inhibitory activity of galanthamine.

## CONCLUSION

To summarize, we have demonstrated that tandem cyclization can be successfully developed further to access new members of the galanthamine family. Further research in this field is being actively pursued in our laboratory.

## 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.

**2-Bromo-4-methoxy-5-(1-methylethoxy)benzaldehyde (1).** 2-Bromo-5-hydroxy-4-methoxybenzaldehyde (100.0 g, 433 mmol), 2-bromopropane (160.0 g, 1.30 mol), and $K_2CO_3$ (300 g, 2.16 mol, anhydrous, freshly ground) were stirred in acetonitrile (1200 mL) at 60 °C for 48 h. The mixture was filtered and evaporated *in vacuo*. The residue was dissolved in $Et_2O$ (500 mL) and washed with water (250 mL). The aqueous layer was extracted with $Et_2O$ (2 x 100 mL), the combined organic layer was washed with water (2 x 500 mL) and brine (1 x 500 mL), dried over $Na_2SO_4$, and evaporated under reduced pressure. The residue was recrystallized using MeOH (500 mL). Yield: light brown needles, 98.1 g (83%). mp 75 – 76 °C (lit.,[13] 72 – 74 °C). TLC: petroleum ether : EtOAc = 3 : 1, $R_f$ = 0.75. $^{1}H$ NMR ($CDCl_3$): δ 10.13 (s, 1H), 7.40 (s, 1H), 7.03 (s, 1H), 4.61 (septett, *J* = 6.4 Hz, 1H), 3.92 (s, 3H), 1.38 (d, *J* = 6.4, Hz 6H). $^{13}C$ NMR ($CDCl_3$): δ 190.8 (d), 155.6 (s), 147.1 (s), 126.4 (s), 120.0 (s), 115.8 (d), 113.7 (d), 71.5 (d), 56.4 (q), 21.8 (q).

**2-Bromo-4-methoxy-5-(1-methylethoxy)benzenemethanol (2). 1** (6.0 g, 22.0 mmol) was added within 15 min at 15 °C to a suspension of sodium borohydride (1.67 g, 44.1 mmol) in dry EtOH (45 mL) and was stirred at 22 °C for 1 h. After quenching with 2 N $Na_2CO_3$ the reaction was concentrated *in vacuo* and the residue was partitioned between 2 N $NaHCO_3$ (60 mL) and $Et_2O$ (100 mL). The aqueous layer was extracted with $Et_2O$ (3 x 40 mL), the combined organic layers were washed with water (2 x 100 mL) and brine (1 x 100 mL), dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. Yield: colorless crystals, 5.75 g (95%). mp 67 - 69 °C. TLC: petroleum ether : EtOAc = 4 : 1, $R_f$ = 0.25. Anal. Calcd for $C_{11}H_{15}O_3Br$: C, 48.02; H, 5.50. Found: C, 48.11; H, 5.29. $^{1}H$ NMR ($CDCl_3$): δ 7.00 (s, 2H), 4.64 (s, 2H), 4.50 (septett, *J* = 6.4 Hz, 1H), 3.85 (s, 3H), 2.05 (s, 1H), 1.34 (d, *J* = 6.4 Hz, 6H). $^{13}C$ NMR ($CDCl_3$): δ 150.1 (s) 146.5 (s), 131.8 (s), 116.1 (s), 115.9 (d), 112.6 (s), 71.7 (t), 64.3 (d), 56.0 (q), 21.8 (q).

**1-Bromo-2-chloromethyl-5-methoxy-4-(1-methylethoxy)benzene (3). 2** (5.63 g, 20.5 mmol) in dry $CH_2Cl_2$ (60 mL) was treated with thionyl chloride (20 mL, 275 mmol) and stirred for 90 min at rt. After evaporation of the solvent *in vacuo*, the residue was dissolved in $Et_2O$ (100 mL) and washed with water (1 x 100 mL), satd. $NaHCO_3$ (1 x 100 mL) and brine (1 x 100 mL). The organic layer was dried over $Na_2SO_4$/charcoal and filtered, the solvent was evaporated *in vacuo*, and the residue was recrystallized from cyclohexane (80 mL). Yield: colorless solid, 5.72 g (95%). mp 68 - 70 °C. TLC: petroleum ether : EtOAc = 3 : 1, $R_f$ = 0.9. Anal. Calcd for $C_{11}H_{14}O_2BrCl$: C, 45.00; H, 4.81. Found: C, 45.02; H, 4.67. $^1$H NMR ($CDCl_3$): δ 7.05 (s, 1H), 6.97 (s, 1H), 4.66 (s, 2H), 4.51 (septett, *J* = 6.4 Hz, 1H), 3.85 (s, 3H), 1.37 (d, *J* = 6.4 Hz, 6H). $^{13}$C NMR ($CDCl_3$): δ 151.2 (s). 146.8 (s), 128.5 (s), 117.7 (s), 116.1 (d), 114.8 (s), 71.9 (t), 56.2 (d), 46.4 (q), 21.9 (q).

**2-Bromo-1-[4-(1-methylethoxy)phenyl]ethanone (4).** To a solution of 1-[4-(1-methylethoxy)phenyl] ethanone (10.0 g, 56.0 mmol) in dry dioxane (100 mL) bromine (11.7 g, 73.5 mmol) in dry dioxane (70 mL)/dry $Et_2O$ (100 mL) was added within 1 h and stirred at rt for 2 h. $Na_2SO_3$ (5 g) in water (100 mL) was added, and the organic layer was separated and extracted with $Et_2O$ (3 x 100 mL). The combined organic layers were washed with water (2 x 100 mL), satd. $NaHCO_3$ (2 x 150 mL), and brine (1 x 200 mL), dried over $Na_2SO_4$, and filtered. After evaporation of the solvent *in vacuo*, the oily residue was crystallized from petroleum ether (25 mL)/cyclohexane (25 mL) at - 20 °C. Yield: colorless, unstable crystals, 8.80 g (59%). mp 36 - 37 °C. TLC: petroleum ether : EtOAc = 4 : 1, $R_f$ = 0.7. $^1$H NMR ($CDCl_3$): δ 7.93 (d, *J* = 9.5 Hz, 2H), 6.92 (d, *J* = 9.5 Hz, 2H), 4.63 (septett, *J* = 6.4 Hz, 1H), 4.40 (s, 2H), 1.35 (d, *J* = 6.4 Hz, 6H). $^{13}$C NMR ($CDCl_3$): δ 189.8 (s), 162.7 (s), 131.4 (d), 126.4 (s), 115.3 (d), 70.3 (d), 30.7 (t), 21.9 (q).

**1-(2-Bromoethyl)-4-(1-methylethoxy)benzene (5).** To a suspension of anhydrous $AlCl_3$ (5.70 g, 43.0 mmol) in dry $CH_2Cl_2$ (100 mL) borane-*tert.*-butylamine-complex (7.45 g, 85.0 mmol) was added at 0 °C and stirred for 15 min. Then **4** (7.30 g, 28.4 mmol) in $CH_2Cl_2$ (50 mL) was added at the same temperature within 30 min and stirred for 3 h. After hydrolysis with 0.1 N HCl (100 mL) the aqueous layer was extracted with $CH_2Cl_2$ (2 x 30 mL). The combined organic layers were washed with 0.1 N HCl (2 x 50 mL), satd. $NaHCO_3$ (2 x 50 mL) and brine (1 x 100 mL), dried over $Na_2SO_4$, and filtered. The solvent was evaporated *in vacuo*, and the oily residue was purified by Kugelrohr distillation (80 °C/0.05 mbar). Yield: colorless oil, 5.81 g (83%). TLC: petroleum ether, $R_f$ = 0.35. Anal. Calcd for $C_{11}H_{15}OBr$: C, 54.34; H, 6.22. Found: C, 54.34; H, 6.09. $^1$H NMR ($CDCl_3$): δ 7.18 (d, *J* = 9.5 Hz, 2H), 6.87 (d, *J* = 9.5 Hz, 2H), 4.53 (septett, *J* = 6.4 Hz, 1H), 3.53 (t, *J* = 6.9 Hz, 2H), 3.08 (t, *J* = 6.9 Hz, 2H), 1.33 (d, *J* = 6.4 Hz, 6H). $^{13}$C NMR ($CDCl_3$): δ 156.7 (s), 130.7 (s), 129.5 (d), 115.8 (d), 69.8 (d), 38.5 (t), 33.2 (t), 21.9 (q).

**4-(1-Methylethoxy)benzeneethanthiol (6). 5** (20.0 g, 82.5 mmol) and thiourea (6.28 g, 165.0 mmol) were refluxed in EtOH (200 mL) for 12 h. After concentration *in vacuo*, the solid obtained was washed

with petroleum ether (2 x 30 mL) and stirred in 2 N NaOH (200 mL) for 5 h under reflux. The pH was adjusted to 2 with conc. HCl, and the aqueous phase was extracted with $Et_2O$ (3 x 200 mL). The combined organic layers were washed with water (5 x 100 mL) and brine (1 x 100 mL), dried over $Na_2SO_4$, and filtered. The solvent was evaporated *in vacuo*. Yield: 14.7 g (91%) colorless oil. TLC: petroleum ether $R_f$ = 0.15. Anal. Calcd for $C_{11}H_{16}OS$: C, 67.30; H, 8.22. Found: C, 67.35; H, 8.17. $^1$H NMR ($CDCl_3$): δ 7.12 (d, *J* = 9.5 Hz, 2H), 6.82 (d, *J* = 9.5 Hz, 2H), 4.53 (septett, *J* = 6.4 Hz, 1H), 2.85 (m, 4 H), 1.33 (d, *J* = 6.4 Hz, 6H). $^{13}$C NMR ($CDCl_3$): δ 156.5 (s), 131.7 (s), 129.5 (d), 115.8 (d), 69.8 (d), 39.4 (t), 26.2 (t), 22.0 (q).

**1-Bromo-5-methoxy-4-(1-methylethoxy)-2-[[[2-[4-(1-ethylethoxy)phenyl]ethyl]thio]methyl]benzene (7). 6** (13.0 g, 66.2 mmol), **3** (19.4 g, 66.2 mmol) and $K_2CO_3$ (46.2 g, 331.0 mmol, anhydrous, freshly ground) were stirred in dry DMF (300 mL) at 60 °C for 12 h. After filtration and removal of the solvent *in vacuo*, the residue was partitioned between water (250 mL) and $Et_2O$ (250 mL). The aqueous layer was extracted with $Et_2O$ (2 x 100 mL). The combined organic layers were washed with water (3 x 250 mL) and brine (1 x 250 mL), dried over$Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography ($SiO_2$, toluene : petroleum ether = 1 : 2). Yield: colorless oil, 28.2 g (94%). TLC: petroleum ether : EtOAc = 4 : 1, $R_f$ = 0.75. $^1$H NMR ($CDCl_3$): δ 7.08 (d, *J* = 9.5 Hz, 2H), 7.03 (s, 1H), 6.95 (s, 1H), 6.81 (d, *J* = 9.5 Hz, 2H), 4.53 (septett, *J* = 6.4 Hz, 1H), 4.50 (septett, *J* = 6.4 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 2H), 2.83 (m, 2H), 2.70 (m, 2H), 1.36 (d, *J* = 6.4 Hz, 6H), 1.31 (d, *J* = 6.4 Hz, 6H). $^{13}$C NMR ($CDCl_3$): δ 156.4 (s), 150.0 (s), 146.6 (s), 132.4 (s), 129.7 (s), 129.4 (d), 117.8 (s), 116.1 (d), 115.8 (d), 114.7 (s), 71.7 (d), 69.9 (d), 56.2 (q), 36.1 (t), 35.3 (t), 33.3 (t), 22.1 (q), 22.0 (q)

**1-Bromo-5-methoxy-4-(1-methylethoxy)-2-[[2-[4-(1-methylethoxy)phenyl]ethylsulfonyl]methyl]-benzene (8).** 3-Chloroperoxybenzoic acid (*m*-CPBA, 80%, 10.4 g, 60.2 mmol) in $CHCl_3$ (100 mL) was added to **7** (26.0 g, 57.3 mmol) in $CHCl_3$ (300 mL) at 0 °C within 30 min and stirred at this temperature for 2 h. The mixture was filtered and washed with 2 N $NaHSO_3$ (2 x 300 mL), 2 N $NaHCO_3$ (2 x 300 mL) and brine (1 x 300 mL), dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. The residue was washed with $iPr_2O$ (100 mL). Yield: colorless cyrstals, 27.2 g (98%). mp 108 - 109 °C. TLC: petroleum ether : EtOAc = 4 : 1, $R_f$ = 0.3. Anal. Calcd for $C_{22}H_{29}O_5BrS$: C, 54.43; H, 6.02. Found: C, 54.45; H, 5.85. $^1$H NMR ($CDCl_3$): δ 7.2 (s, 2H), 7.12 (d, *J* = 9.5 Hz, 2H), 6.85 (d, *J* = 9.5 Hz, 2H), 4.54 (s, 2H), 4.53 (septett, *J* = 6.4 Hz, 1H), 4.50 (septett, *J* = 6.4 Hz, 1H), 3.84 (s, 3H), 3.34 (m, 2H), 2.95 (m, 2H), 1.27 (d, *J* = 6.4 Hz, 6H), 1.22 (d, *J* = 6.4 Hz, 6H). $^{13}$C NMR ($CDCl_3$): δ 156.1 (s), 150.8 (s), 145.8 (s), 129.7 (s), 129.5 (d), 119.8 (s), 119.2 (d), 116.0 (d), 115.7 (d), 115.6 (s), 70.7 (d), 69.0 (d), 57.5 (t), 55.9 (q), 53.3 (t), 26.4 (t), 21.7 (q), 21.6 (q).

**4-Bromo-5-[[2-(4-hydroxyphenyl)ethylsulfonyl]methyl]-2-methoxyphenol (9).** $BCl_3$ (206 mL, 206 mmol, 1 M in $CH_2Cl_2$) was added to **8** (25.0 g, 51.5 mmol) in dry $CH_2Cl_2$ (500 mL) at - 78 °C within 30

min and stirred for 1 h at this temperature and for 1 h at rt. The mixture was hydrolyzed with water (250 mL) and concentrated to a volume of 200 mL. The precipitate was collected by filtration, washed with water (6 x 60 mL) and triturated with $iPr_2O$ (2 x 100 mL). Yield: colorless crystals, 15.3 g (74%). mp 214 - 216 °C. TLC: EtOAc, $R_f$ = 0.8. Anal. Calcd for $C_{16}H_{17}O_5Br*0.25\ H_2O$: C, 47.89; H, 4.27. Found: C, 47.23; H, 4.35. $^1$H NMR ($CDCl_3$): δ 9.30 (br s, 1H), 9.60 (br s, 1H), 7.18 (s, 1H), 7.12 (d, *J* = 9.5 Hz, 2H), 7.00 (s, 1H), 6.70 (d, *J* = 9.5 Hz, 2H), 4.46 (s, 2H), 3.84 (s, 3H), 3.34 (m, 2H), 2.95 (m, 2H). $^{13}$C NMR ($CDCl_3$): δ 156.0 (s), 148.9 (s), 145.9 (s), 129.5 (s), 128.1 (d), 119.9 (s), 119.2 (d), 115.9 (d), 115.4 (d), 115.3 (s), 57.3 (t), 55.9 (q), 53.5 (t), 26.5 (t).

**(4aR*,8aR*)-1-Bromo-4*a*,5,9,10-tetrahydro-3-methoxy-11,11-dioxo-12*H*-[2]-benzothiepino[6,5*a*,5-*bc*]benzofuran-6-one (10).** To a suspension of **9** (1.00 g, 2.49 mmol) in $CHCl_3$ (100 mL) $K_3[Fe(CN)_6]$ (4.40 g, 13.4 mmol) and $K_2CO_3$ (2.50 g, 17.7 mmol) in water (25 mL) were added at once and stirred vigorously using a mechanical stirrer for 45 min at rt. The mixture was filtered using diatomeous earth and the filtrate was washed with water (3 x 100 mL) and brine (100 mL), dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography ($SiO_2$, $CHCl_3$ : EtOAc = 5 : 2). Yield: colorless crystals, 162 mg, (16%). mp 292 - 294 °C. TLC: EtOAc, $R_f$ = 0.7. Anal. Calcd for $C_{16}H_{15}O_5BrS$: C, 48.13; H, 3.79. Found: C, 47.96; H, 3.83. $^1$H NMR (DMSO-$d_6$): δ 7.18 (b, 1H), 7.08 (s, 1H), 5.95 (d, *J* = 10.3 Hz, 1H), 5.12 (d, *J* = 16.1 Hz, 1H), 4.81 (s, 1H), 4.55 (d, *J* = 15.6 Hz, 1H), 3.78 (s, 3H), 3.31 (s, 2H), 2.97 (dd, *J* = 18.1 Hz, *J* = 3.9 Hz, 1H), 2.87 (dd, *J* = 17.6 Hz, *J* = 2.0 Hz, 1H), 2.47 - 2.33 (m, 2H). $^{13}$C NMR (DMSO-$d_6$): δ 195.4 (s), 148.1 (s), 145.5 (s), 144.5 (d), 131.8 (s), 128.0 (d), 118.5 (s), 117.8 (d), 116.7 (s), 87.2 (d), 80.0 (t), 57.1 (q), 51.1 (s), 49.6 (t), 37.6 (t).

**X-Ray Structure Determination of 10**

Crystal data: $C_{16}H_{15}O_5BrS$, $M_r$ = 399.25, monoclinic, space group $P2_1/c$ (No. 14), *a* = 10.655(5) Å, *b* = 9.844(5) Å, *c* = 14.917(8) Å, $\beta$ = 96.02(1)°, *V* = 1556.0(14) Å$^3$, *Z* = 4, $D_x$ = 1.704 Mg/m$^{-3}$, $\lambda$(Mo-Kα) = 0.71073 Å, $\mu$ = 2.80 mm$^{-1}$, *T* = 297(2) K.

A colorless crystal of 0.10 x 0.18 x 0.30 mm grown from DMF/n-butanol (10:1) was used for X-Ray data collection with a SIEMENS SMART CCD area detector three-circle diffractometer and graphite monochromatized Mo Kα radiation. The intensities of 19086 reflections with θ < 27.5° were measured via ω-scan frames (complete sphere, Δω = 0.3°, 20 sec. per frame), corrected for *LP* and absorption and merged to 3568 unique reflections, $R_{int}$ = 0.036, $R_{sigma}$ = 0.027.

The structure was solved with direct methods and was refined on $F^2$ using program SHELXL97.[8] All non-hydrogen atoms were refined anisotropically, hydrogen atoms isotropically. The final full matrix least-squares refinement varied 269 parameters and converged at $R1 = \Sigma||F_o|-|F_c||/\Sigma|F_o| = 0.052$, $wR2 = [\Sigma(w(F_o^2-F_c^2)^2)/\Sigma(w(F_o^2)^2)]^{½} = 0.088$, and $S = 1.01$ for all 3568 unique reflections; $R1 = 0.033$ for the 2691 observed data [$I>2\sigma(I)$]. Complete crystallographic data (excluding structure factors) have been

deposited with the Cambridge Crystallographic Data Centre as supplementary publication no CCDC 164868. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ (fax: +44 1223 336033, email: deposit@ccdc.cam.ac.uk).

The molecular structure of **10** in solid state is shown in Fig. 1 with selected bond lengths and angles in the caption. The molecule agrees in its general architecture and conformation with the corresponding bromonarwedine ($SO_2$ replaced by a methylamino group). To be more specific, the exchange of the $NCH_3$ function in (bromo)narwedine by the sulfonyl group in **10** leads to a widening of the 7-membered ring (C-N = 1.46 Å *vs*. C-S = 1.77 Å) with a concomitant change in the positions of the ring atoms which also affects the inclination of the spiro-ring C(10) through C(15) relative to the phenyl ring.

Selected bond distances (A) and angles (°): Br-C5 1.898(2), S-C7 1.774(3), S-C8 1.769(3), S-O4 1.438(2), S-O5 1.436(2), O1-C2 1.368(3), O1-C15 1.451(3), O2-C3 1.367(3), O2-C16 1.427(3), O3-C13 1.213(3), C1-C10 1.531(3), C6-C7 1.510(3), C8-C9 1.509(3), C9-C10 1.536(3), C10-C11 1.508(3), C10-C15 1.548(3), C11-C12 1.319(4), C12-C13 1.459(4), C13-C14 1.494(4), C14-C15 1.505(3), C7-S-C8 106.3(1), C7-S-O4 106.8(1), C7-S-O5 108.6(1), C8-S-O4 106.9(1), C8-S-O5 109.1(1), O4-S-O5 118.5(1).

**(4*a*α,6β,8*a*R*)-1-Bromo-4*a*,5,9,10-tetrahydro-3-methoxy-11,11-dioxo-12*H*-[2]-benzothiepino[6,5*a*,5-*bc*]benzofuran-6-ol (11).** To a suspension of **10** (360 mg, 0.90 mmol) in dry THF (4 mL) L-Selectride® (1.35 mL, 1.35 mmol, 1 M in THF) was added dropwise a - 5 °C and stirred for 4 h at rt. The mixture was hydrolyzed with water (2 mL) and concentrated *in vacuo*. The residue was partitioned between EtOAc (15 mL) and 2 N HCl (15 mL). The aqueous layer was extracted with EtOAc (2 x 5 mL), the combined organic layer was washed with 2 N HCl (2 x 15 mL), water (1 x 15 mL), satd. $NaHCO_3$ (1 x 15 mL) and brine (1 x 15 mL), dried over $Na_2SO_4$, filtered and concentrated. The residue was recrystallized from EtOH (1 mL). Yield: colorless solid, 285 mg (79%), mp 216 - 218 °C. TLC: benzene : acetonitrile = 3 : 1, $R_f$ = 0.35. Anal. Calcd for $C_{16}H_{17}O_5BrS*2\ H_2O$: C, 43.95; H, 4.84. Found: C, 43.85; H, 5.08. $^1$H NMR (methanol-$d_4$): δ 7.18 (s, 1H), 6.22 (d, *J* = 10.2 Hz, 1H), 6.08 (dd, *J* = 10.2 Hz, *J* = 4.7 Hz, 1H), 4.95 (d, *J* = 15.8 Hz, 1H), 4.76 (d, *J* = 15.8 Hz, 1H), 4.67 (d, *J* = 1.8 Hz, 1H), 4.24 (s, 1H), 3.88 (s, 3H), 3.69 (t, *J* = 12.3 Hz, 1H), 3.39 - 3.23 (m, 1H), 2.45 (d, *J* = 15.5 Hz, 1H), 2.33 (t, *J* = 15.2 Hz, 1H), 2.28 - 2.21 (m, 2H). $^{13}$C NMR (methanol-$d_4$): δ 146.1(s), 144.6(s), 131.8(s), 128.2 (d), 124.5 (d), 116.3 (s), 115.4 (d), 114.4 (s), 85.2 (d), 59.5 (d), 55.2 (t), 54.5 (q), 49.6 (t), 47.0 (s), 30.9 (t), 29.1 (t).

**(4*a*α,6β,8*a*R*)-4*a*,5,9,10-Tetrahydro-3-methoxy-11,11-dioxo-12*H*-[2]-benzothiepino[6,5*a*,5-*bc*]benzofuran-6-ol (12). 11** (100 mg, 0.25 mmol), $CaCl_2$ (200 mg, 1,8 mmol) and zinc dust (375 mg, 5.7 mmol) were stirred in water (6.5 mL)/EtOH (6.5 mL) under reflux for 5 h. The mixture was filtered and concentrated *in vacuo*. The residue was partitioned between water (20 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL), the combined organic layers were washed with

water (2 x 20 mL) and brine (1 x 30 mL), dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography ($SiO_2$, benzene : acetonitrile = 4 : 1) and triturated with $iPr_2O$ (2 x 10 mL). Yield: colorless crystals, 49 mg (61%), mp 208 - 209 °C ($iPr_2O$). TLC: benzene : acetonitrile = 3 : 1; $R_f$ = 0.5. Anal. Calcd for $C_{18}H_{18}O_5S$: C, 59.61; H, 5.63. Found: C, 59.38; H, 5.72. $^1$H NMR (methanol-$d_4$): δ 6.87 (d, *J* = 8.3 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 6.25 (d, *J* = 10.2 Hz, 1H), 6.03 (dd, *J* = 10.2 Hz, *J* = 4.4 Hz, 1H), 5.02 (d, *J* = 15.8 Hz, 1H), 4.66 - 4.60 (m, 1H), 4.19 (dd, *J* = 15.8 Hz, *J* = 3.2 Hz, 2H), 3.86 (s, 3H), 3.83 - 3.67 (m, 1H), 3.30 - 3.21 (m, 1H), 2.48 - 2.28 (m, 2H), 2.27 - 2.17 (m, 1H), 2.16 - 2.07 (m, 1H). $^{13}$C NMR (methanol-$d_4$): δ 147.9 (s), 145.8 (s), 132.3 (s), 129.5 (d), 126.4 (d), 124.4 (d), 118.7 (s), 112.6 (d), 86.7 (d), 61.1 (d), 58.5 (t), 55.7 (q), 51.4 (t), 48.0 (s), 31.1 (t), 29.8 (t).

**ACKNOWLEDGEMENTS**

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

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