New Benzothiophene Compounds Related to Propafenone ☆

Bernard Unterhalt* and Lucas Rems

Institut für Pharmazeutische Chemie der Westfälischen Wilhelms-Universität Münster, Hittorfstr. 58-62, D-48149 Münster, Germany

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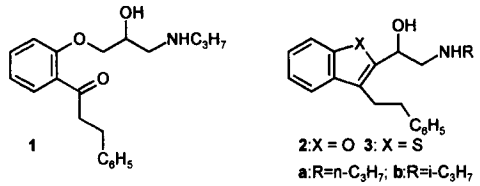
Summary

Benzothiophene compounds **3a** and **3b**, structurally similar to propafenone (**1**), are described.

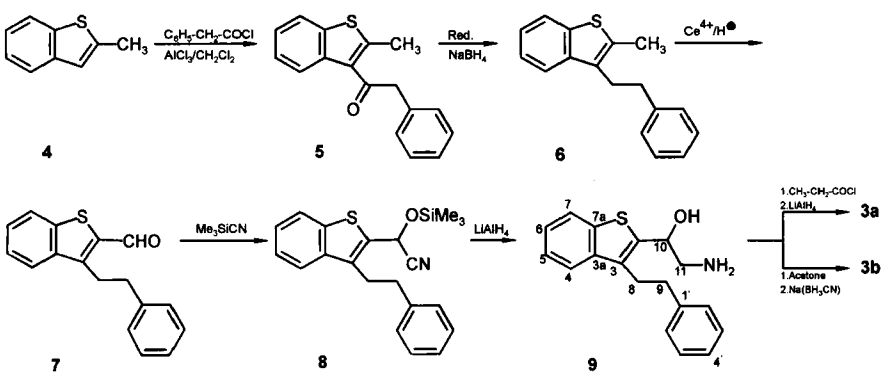
Introduction

The pharmacological activity of antiarrhythmic propafenone (Rytmonorm) (**1**) is due to its blocking of cardiac sodium channels[1]. **1** is a flexible molecule. Its rigidization by ring closure to the benzofuran **2a** as well as by the synthesis of the respective benzothiophene **3a** might influence the pattern of pharmacological activity. While Fleischhacker et al.[2] synthesized **2a** and **2b**, we succeeded in building up the benzothiophene derivatives **3a** and **3b**.



Results and Discussion

Chemical access to the title compounds starts with 2-methylbenzothiophene (**4**)[3], which is acylated to the ketone **5**. Reduction of **5** with $NaBH_4$ gives **6**, which is oxidized to the aldehyde **7** by ceric sulfate. After the addition of trimethylsilyl cyanide the protected cyanohydrin **8** is reduced to the substituted aminoethanol **9** by $LiAlH_4$. Acylation of **9** by propionylchloride and reduction of the corresponding carboxamide lead to **3a**, condensation of **9** with acetone and reduction of the imine to **3b** [Scheme 1].



Scheme

3a and **3b** were studied in guinea-pig isolated papillary muscles and right atria [4]; their inotropic, chronotropic, and β-adrenoceptor-blocking activity were compared with propafenone (**1**). **3a** and **3b** were equally potent as **1** in reducing the isometric force of contraction of papillary muscles [EC_{50} (μmol/l): **3a** (4.9); **3b** (5.2); **1** (7.5)]. **3b** decreased the rate of spontaneous activity of right atria in a similar way as **1**, whereas **3a** showed a more negative chronotropy [EC_{50} (μmol/l): **3a** (8.8); **3b** (16.5); **1** (13.0)]. Contrary to **1**, **3a** and **3b** lacked any β-adrenoceptor blocking activity [5].

Experimental

General: Melting points: Reichert hot-stage microscope (uncorr.).– Elemental analysis: CHN-Analyzer 240 Perkin Elmer.– IR data: Shimadzu 470; Bio-Rad FTS-135.– ^{1}H- and ^{13}C-NMR-spectra: Varian Gemini 200 spectrometer.– MS: Finnigan MAT 44S (70 eV).

2-Methyl-3-phenacetyl-benzothiophene (5)

Phenacetyl chloride (21.0 g, 0.14 mol) is added to a suspension of $AlCl_3$ (21.2 g, 0.16 mol) in dry CH_2Cl_2 (500 ml) with stirring. After cooling to 5 °C **4** (19.7 g, 0.13 mol) dissolved in CH_2Cl_2 (40 ml) is added dropwise. The reaction mixture is stirred for 2h at 20 °C, cautiously hydrolyzed by ice cold water, and extracted several times with Et_2O. The extracts are washed well with 10 % aqueous $NaHCO_3$, dried (Na_2SO_4), evaporated, and purified by Kugelrohr distillation and recrystallization ($MeOH/H_2O$).
Yield 24.2 g (69 %). Mp. 68 °C.– IR (KBr): 1643 cm^{-1} (C=O), 1490, 1441, 1418, 1340.– ^{1}H-NMR ($CDCl_3$): δ = 2.72 (s, 3H, CH_3), 4.28 (s, 2H, CH_2), 7.23–7.45 (m, 7H aromatic), 7.74–7.79 (m, 1H, 7-H), 8.07–8.12 (m, 1H, 4-H).– ^{13}C-NMR ($CDCl_3$): δ = 16.76 (CH_3), 50.24 (CH_2), 121.89 (C-7), 123.50 (C-4), 124.52 (C-5), 125.50 (C-6), 127.09 (C-4′), 128.71 (C-2′, C-6′), 129.64 (C-3′, C-5′), 134.23 (C-3), 137.57 (C-1′), 138.37 (C-7a), 147.85 (C-2), 196.83 (C-8).– MS: *m/z* (%)= 266 (9) [M^+], 175 (100), 147 (34), 103 (13), 91 (9), 69 (13).– $C_{17}H_{14}OS$, Anal. C, H.

2-Methyl-3-phenethyl-benzothiophene (6)

$NaBH_4$ pellets (33.0 g, 0.87 mol) are given to cold trifluoroacetic acid (500 ml) with stirring for 2 h under a nitrogen atmosphere. **5** (24.2 g, 91 mmol) is added dropwise within 10 min, combined with two further pellets of $NaBH_4$, and stirred overnight. The reaction mixture is cautiously hydrolyzed with aqueous NaOH, and extracted four times with Et_2O (50 ml). After drying (Na_2SO_4) and evaporating the crude product is purified by Kugelrohr distillation. Yield 16.0 g (70 %). Bp. 115 °C/ 0.04 mbar.– IR (NaCl: film): 3020 cm^{-1}, 2910, 1450.– ^{1}H-NMR ($CDCl_3$): δ = 2.28 (s, 3H, CH_3), 2.95 (m, 2H, 9-H), 3.12 (m, 2H, 8-H), 7.16–7.46 (m, 7H aromatic), 7.71–7.75 (m, 1H, 7-H), 7.81–7.85 (m, 1H, 4-H).– ^{13}C-NMR ($CDCl_3$): δ = 13.48 (CH_3), 28.64 (C-8), 35.81 (C-9), 121.01 (C-4), 122.23 (C-7), 123.45 (C-6), 123.90 (C-5), 126.06 (C-4′), 128.40 (C-3′, C-5′), 128.63 (C-2′, C-6′), 130.67 (C-3),

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135.06 (C-2), 138.47 (C-7a), 140.15 (C-1'), 141.71 (C-3a).– MS: *m/z* (%)= 252 (18) [M^+], 161 (100), 128 (29),115 (14), 91 (23), 77 (9), 65 (14), 51 (9).– $C_{17}H_{16}S$, Anal. C, H.

3-Phenethyl-benzothiophene-2-carbaldehyde (7)

$Ce(SO_4)_2 \times 4\,H_2O$ (55.1 g, 0.14 mol) is suspended in 50 % HOAc (300 ml). After adding **6** (8.6 g, 0.034 mol) the suspension is refluxed for 2 h with stirring; its colour changes from dark yellow to yellow. The cold mixture is filtered, and the filtrate extracted three times with Et_2O (100 ml). After washing with a saturated aqueous solution of $NaHCO_3$ and drying (Na_2SO_4) the residue left on evaporation is purified by silica gel column chromatography using light petroleum (bp 60–90 °C)-EtOAc (5:1) as eluent. Yield 6.0 g (66 %). Mp. 85 °C.– IR (KBr): 1655 cm^{-1}, 1526, 1494, 1209.– ^{1}H-NMR ($CDCl_3$): 3.04 (t, J = 7.4 Hz, 2H, 9-H), 3.53 (t, J = 7.4 Hz, 2H, 8-H), 6.95–7.14 (m, 2H aromatic, Ph), 7.14–7.38 (m, 3H aromatic, Ph), 7.46 (ddd, J_1 = 7.2 Hz, J_2 = 7.1 Hz, J_3 = 1.9 Hz, 1H, 6-H), 7.53 (ddd, J_1 = 7.2 Hz, J_2 = 7.1 Hz, J_3 = 1.6 Hz, 1H, 5-H), 7.89 (dd, J_1 = 7.2 Hz, J_2 = 1.6 Hz, 1H, 7-H), 7.94 (dd, J_1 = 7.2 Hz, J_2 = 1.9 Hz, 1H, 4-H), 9.80 (s, 1H, CHO).– ^{13}C-NMR ($CDCl_3$): δ = 28.96 (C-9), 37.20 (C-8), 123.60 (C-4), 124.94 (C-6), 126.77 (C-5), 128.24 (C-4'), 128.63 (C-3', C-5'), 128.73 (C-2', C-6'), 138.55 (C-2), 139.34 (C-7a), 140.24 (C-3a), 142.54 (C-1'), 145.78 (C-3), 183.48 (CHO).– MS: *m/z* (%) = 266 (24)[M^+], 237 (8), 175 (49), 147 (32), 115 (9), 103 (15), 91 (100), 77 (13), 65 (26), 51 (13).– $C_{17}H_{14}OS$, Anal. C, H.

3-Phenethyl-α-trimethylsilyloxy-2-benzothienyl-acetonitrile (8)

Trimethylsilyl cyanide (3.1 g, 26 mmol) is given to a solution of **7** (6.8 g, 26 mmol) in CH_2Cl_2 (30 ml) at 0 °C. After adding three drops of $SbCl_5$ the colour is changed from yellow to red-brown. The mixture is stirred at room temperature for 2 h, evaporated without heating, and purified by suspension in *n*-hexane and removal of the supernatant. Yield 8.1 g (85 %). Mp. 81 °C (dec.).– MS: *m/z* (%) = 365 (13) [M^+], 293 (5), 274 (14), 260 (11), 175 (39), 147 (75), 91 (100), 73 (78), 65 (25).

2-(2'-Amino-1'-hydroxy)ethyl-3-phenethyl-benzothiophene (9)

$LiAlH_4$ (0.8 g, 21 mmol) is suspended in dry Et_2O (200 ml), chilled to –40 °C, and combined dropwise with crude **8** (7.4 g, 21 mmol) in dry Et_2O (50 ml) under a nitrogen atmosphere. The reaction mixture is stirred for 2 h, warmed up to room temperature, and stirred for 2 h. After hydrolyzing with water (100 ml) the precipitate is dissolved in potassium sodium tartrate tetrahydrate (6.0 g)/20 % NaOH (100 ml), extracted three times with Et_2O (200 ml), and dried (Na_2SO_4). A saturated solution of HCl in Et_2O is added to pH 5–6, **9**-HCl is precipitated, and purified by silica gel column chromatography using light petroleum (bp. 60–90 °C)-EtOAc (1:1) as eluent. The impurities are separated, the product is dissolved from the column by MeOH. After evaporation a colourless powder (6.3 g, 90%) of mp. 217 °C (dec.) is obtained: crude **9**-HCl.– ^{1}H-NMR (MeOD): δ = 2.13 (dd, J_1 = 12.8 Hz, J_2 = 3.1 Hz, 1H, 11-H), 2.84 (dd, J_1 = 12.8 Hz, J_2 = 10.5 Hz, 1H, 11-H), 2.92-3.26 (m, 4H, 8-H, 9-H), 5.08 (dd, J_1 = 10.5 Hz, J_2 = 3.1 Hz, 1H, 10-H), 7.04–7.08 (m, 2H aromatic, Ph), 7.14–7.29 (m, 3H aromatic, Ph), 7.31–7.46 (m, 2H, 5-H, 6-H), 7.81–7.86 (m, 2H, 4-H, 7-H).

2-(1'-Hydroxy-2'-propylamino)ethyl-3-phenethyl-benzothiophene (3a)

Crude **9**-HCl (2.0 g, 5 mmol) is suspended in CH_2Cl_2 (50 ml), and combined with Et_3N (1.1 g, 10 mmol) after cooling to –50 °C. Propionyl chloride (0.5 g, 6 mmol) is added dropwise, and the reaction mixture is stirred for 2 h at room temperature. After hydrolysis you extract three times with CH_2Cl_2 (50 ml), dry the organic phases (Na_2SO_4), and remove CH_2Cl_2 to get a colourless powder of the propionamide, purified by suspension in *n*-hexane.

Yield 1.7 g (96%). Mp. 148 °C.– $C_{21}H_{23}NO_2S$, Anal. C, H, N.

The propionamide (1.4 g, 4 mmol) is dissolved in dry Et_2O (20 ml), and added dropwise to a suspension of $LiAlH_4$ (0.2 g, 5 mmol) in dry Et_2O (100 ml) at –40 °C. After stirring overnight at room temperature the mixture is cooled to –40 °C, and hydrolyzed with water (10 ml). The slurry is dissolved by adding potassium sodium tartrate tetrahydrate (1.2 g, 4 mmol) and 90% NaOH (30 ml), the ethereal solution is separated, and the water phase carefully washed with Et_2O (60 ml). The combined ethereal layers are dried (Na_2SO_4), and a saturated solution of HCl in Et_2O is added dropwise (pH 5–6). Crystalline **3a-HCl** is filtered off, and recrystallized (MeOH/Et_2O). Yield 1.2 g (79%). Mp. 209 °C.– ^{1}H-NMR (MeOD): δ = 1.03 (t, J = 7.5 Hz, 3H, CH_3), 1.67 (tq, J_1 = 7.9 Hz, J_2 = 7.6 Hz, 2H, CH_2), 2.16 (dd, J_1 = 12.5 Hz, J_2 = 3.1 Hz, 1H, 11-H), 2.79–3.38 (m, 6H, 8-H, 9-H, CH_2), 3.02 (dd, J_1 = 12.5 Hz, J_2 = 10.8 Hz, 1H, 11-H), 5.17 (dd, J_1 = 10.8 Hz, J_2 = 3.1 Hz, 1H, 10-H), 7.03–7.07 (m, 2H aromatic, Ph), 7.18–7.27 (m, 3H aromatic, Ph), 7.28–7.46 (m, 2H, 5-H, 6-H), 7.82–7.88 (m, 2H, 4-H, 7-H).– $C_{21}H_{26}ClNOS$, Anal. C, H, N.

2-(1'-Hydroxy-2'-isopropylamino)ethyl-3-phenethyl-benzothiophene (3b)

Crude **9**-HCl (1.8 g, 5.4 mmol) is dissolved in MeOH (20 ml), acetone (1.0 ml) is added, and the mixture stirred with $NaBH_3CN$ (0.5 g, 8 mmol) for 30 min. After repeating this procedure with acetone (0.5 ml) and $NaBH_3CN$ (0.3 g, 4.8 mmol) it is extracted by Et_2O (50 ml), dried (Na_2SO_4), and treated with a saturated solution of HCl in Et_2O (pH 5–6). Crystalline **3b-HCl** is filtered off. Yield 1.3 g (64 %). Mp. 205 °C (MeOH/Et_2O).– ^{1}H-NMR (MeOD): δ = 1.27 (d, J = 6.5 Hz, 3H, CH_3), 1.33 (d, J = 6.5 Hz, 3H, CH_3), 2.24 (dd, J_1 = 12.5 Hz, J_2 = 3.1 Hz, 1H, 11-H), 2.94–3.35 (m, 6H, 8-H, 9-H, 11-H, CH), 5.21 (dd, J_1 = 10.9 Hz, J_2 = 3.1 Hz, 1H, 10-H), 7.04–7.46 (m, 7H, 5-H, 6-H, 5H aromatic, Ph), 7.82–7.88 (m, 2H, 4-H, 7-H).– $C_{21}H_{26}ClNOS$, Anal. C, H, N.

References

☆ Dedicated to Prof. Dr. W. Wiegrebe, Regensburg, on the occasion of his 65th birthday.

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