

**THIENOSPIRANS V<sup>1</sup>:**  
**THIENOSPIRANS VIA DIRECTED LITHIATIONS<sup>+</sup>**

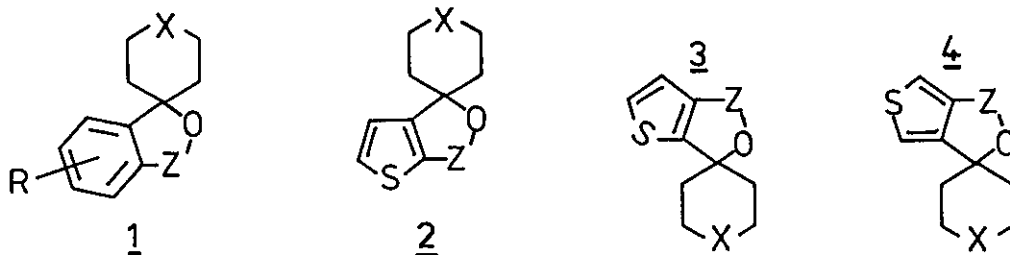
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**Abstract** - Using halogen-metal exchange and ortho-directed metalation methodologies spiro[thieno[b]-furans] 2 and 3 were synthesized starting from 3-bromothiophene, in one case proceeding via cyclization of the 2,3-difunctionalized thiophenes 6 and in the other case proceeding via cyclization of the isomeric compounds 8.

Recently spiro-compounds with the general structure 1 were synthesized and shown to have interesting pharmacological properties<sup>2</sup>.

By combining our interests in spiro-compounds with those in thiophene chemistry we planned to synthesize novel potential pharmaceuticals with general formulae 2, 3 and 4.



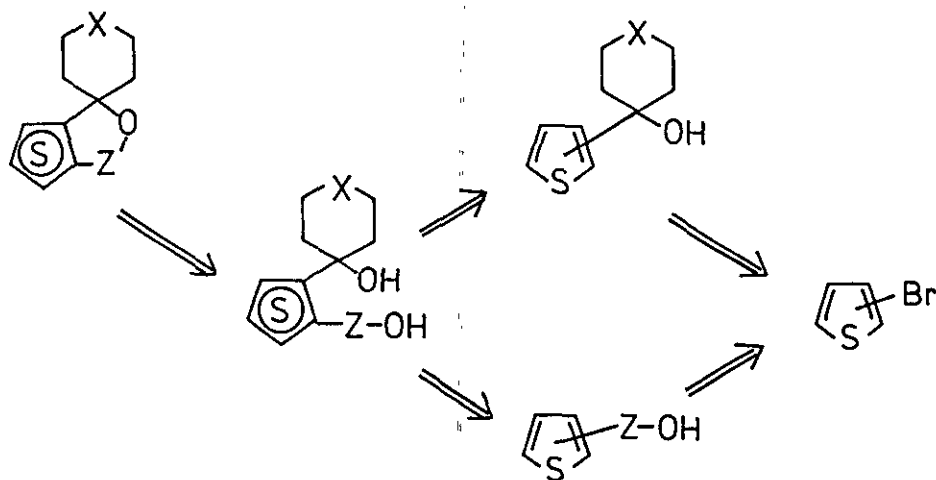
X = CH<sub>2</sub>, CHNMe<sub>2</sub>, NMe

Z = CO, CHPh

+ dedicated to Prof. Dr. V. Gutmann on the occasion of his 65<sup>th</sup> birthday.

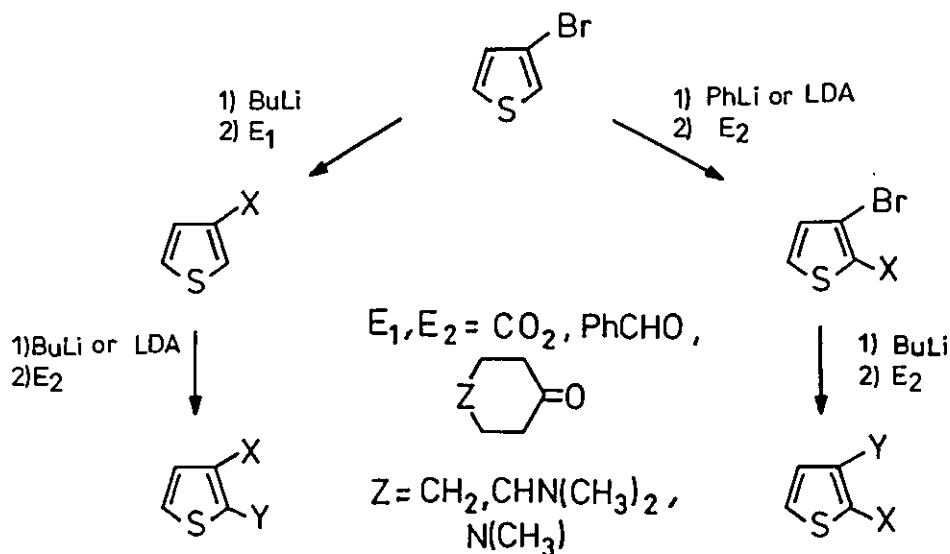
We now report the syntheses of the spiro[piperidine-thieno[b]-furans] 2 and 3; the synthetic problems encountered and solved on the way to target system 4 will be discussed in the following paper<sup>3</sup>.

For both of these systems 2 and 3 the disconnection approach to synthetic analysis suggested strategies based on the concept of consecutive lithiation reactions (Scheme 1):



Scheme 1

Lithiation reactions and metal-halogen exchange in general<sup>4</sup>, and (directed or heteroatom-facilitated) lithiations in particular<sup>5</sup> are powerful tools in organic synthetic methodology. In thiophene chemistry, as well as the electronic, steric, and coordinating effects of ring substituents, the influence of the ring sulphur atom have to be considered<sup>6</sup>. Since few functional groups with efficient directing power to induce  $\beta$ -lithiation are able to overcome the effect of the ring sulphur atom in thiophenes (which promotes  $\alpha$ -lithiation), most 2-substituted thiophenes are lithiated at position 5. In contrast, most 3-substituted thiophenes, which are accessible only with difficulty, can be lithiated smoothly and almost exclusively at position 2. By employing a combination of sequential lithiation and metal-halogen exchange reactions followed by quenching with suitable electrophiles 2,3-difunctionalized precursors of both target systems 2 and 3 should be accessible from 3-bromothiophene<sup>7</sup>.



Scheme 2

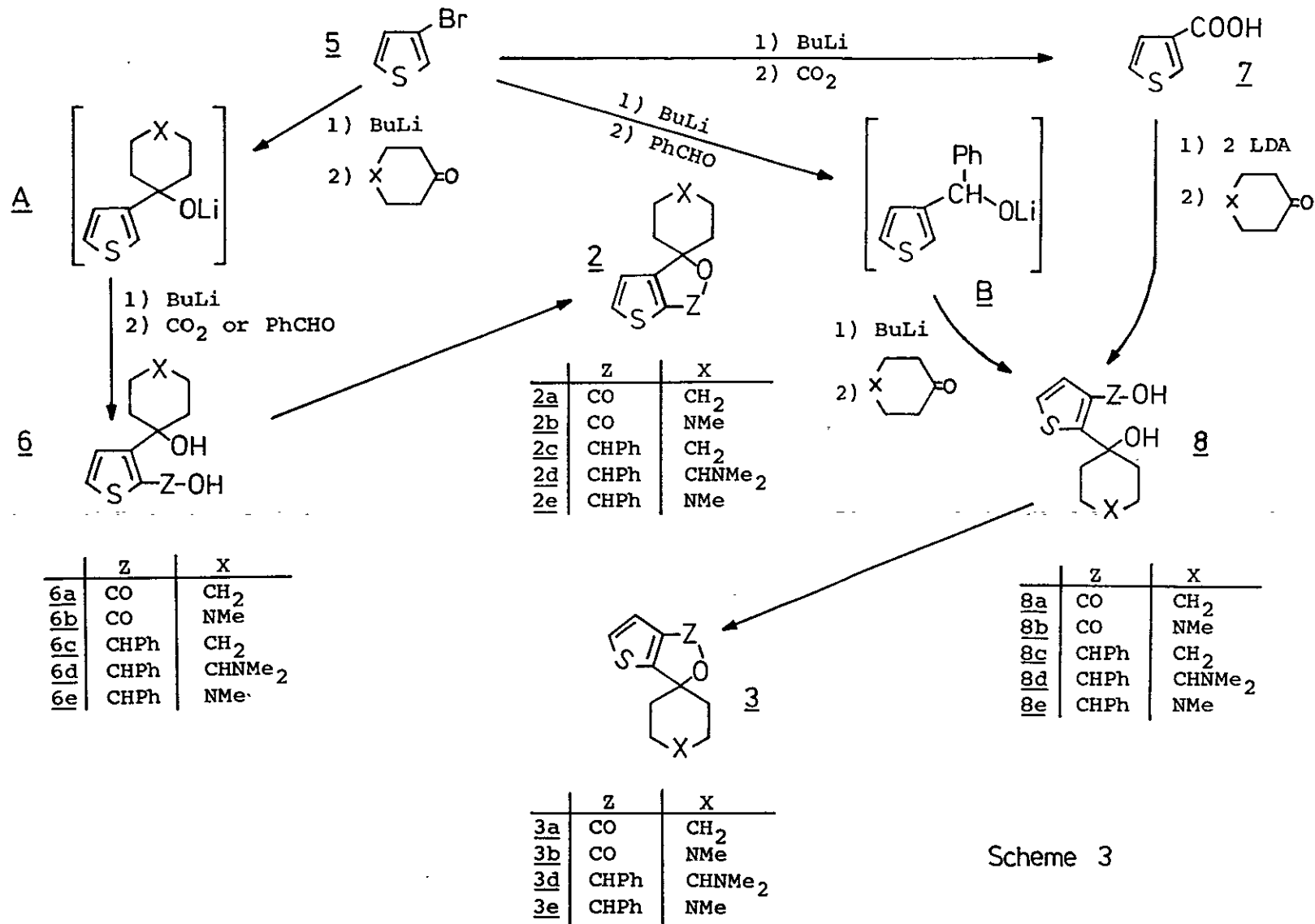
The total synthetic pathways leading to the desired products are shown in Scheme 3 (overleaf), including the cyclization steps which are carried out by standard procedures.

3-Thienyllithium, obtained by initial metal-halogen exchange of 3-bromothiophene (**5**) with *n*-BuLi at  $-80^\circ\text{C}$  (to avoid transmetalation), was reacted with the appropriate cyclic ketone [cyclohexanone ( $X=\text{CH}_2$ ), *N*-methylpiperidin-4-one ( $X=\text{NMe}$ ) or 4-dimethylaminocyclohexanone ( $X=\text{CHNMe}_2$ )] to yield intermediate **A**.

The synthesis of the target compounds **6a-e** was carried out subsequently by directed lithiation of these intermediates in position 2 and quenching of the resulting dilithio-intermediate with carbon dioxide or benzaldehyde, without isolation of **A**. Alternatively treatment of the 3-thienyllithium with carbon dioxide or benzaldehyde as the first step provided a route for the preparation of precursors to the isomeric system **3**.

The intermediate **B** produced by reaction with benzaldehyde reacted with each of the cyclic ketones yielding the diols **8c**, **8d** and **8e** in a direct lithiation step.

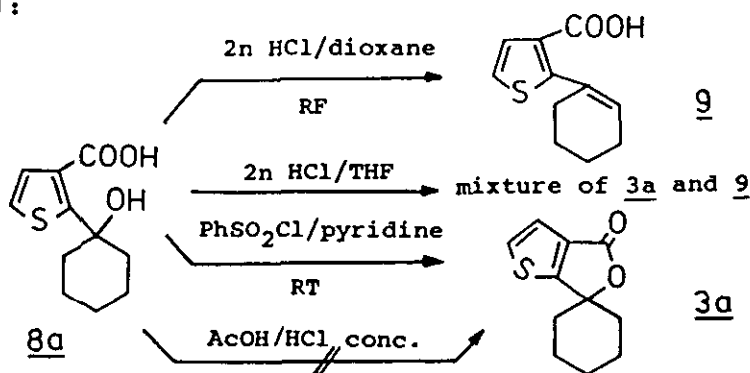
Although, in general, one-pot reactions were preferred, it proved advantageous when carbon dioxide was used as the first electrophile to isolate thiophene-3-carboxylic acid **7**. Further reaction of **7** with two moles of LDA gave lithium 2-lithiothiophene-3-carboxylate which, on subsequent reaction with the cyclic ketones, yielded the hydroxy acids **8a** and **8b**. Thus, the



Scheme 3

2,3-difunctionalized thiophenes, 6 and 8, required for the synthesis of the target ring systems 2 and 3 were made accessible mostly by one-pot reactions in excellent overall yields (50 to 70 %).

As a consequence of their structure most of the tertiary alcohols 6 and 8 were sensitive to acid reaction conditions. Therefore mild reaction conditions for the cyclization reactions had to be employed to prevent eliminations (which occurred with HCl in THF or dioxane) or decompositions (which occurred with a mixture of acetic acid and HCl) as shown in the case of 8a (Scheme 4):



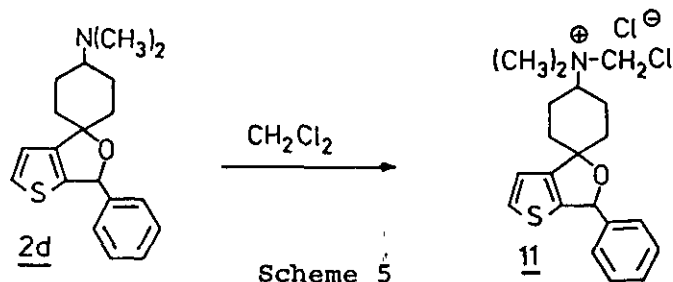
Scheme 4

While, in some cases (2d, 2e, 3d, 3e), mild acidic conditions (AcOH) could be applied, in other cases neutral (acetic anhydride/sodium acetate in benzene for 2b, 3b) or basic (benzenesulfonylchloride/pyridine (3a) or tosylchloride/pyridine (2c)) conditions were preferable. The formation of 2a was achieved in ether saturated with HCl gas, accompanied by some elimination, or with dicyclohexylcarbodiimide/ether with no formation of by-products. Each cyclization step had to be optimized thoroughly to obtain good yields.

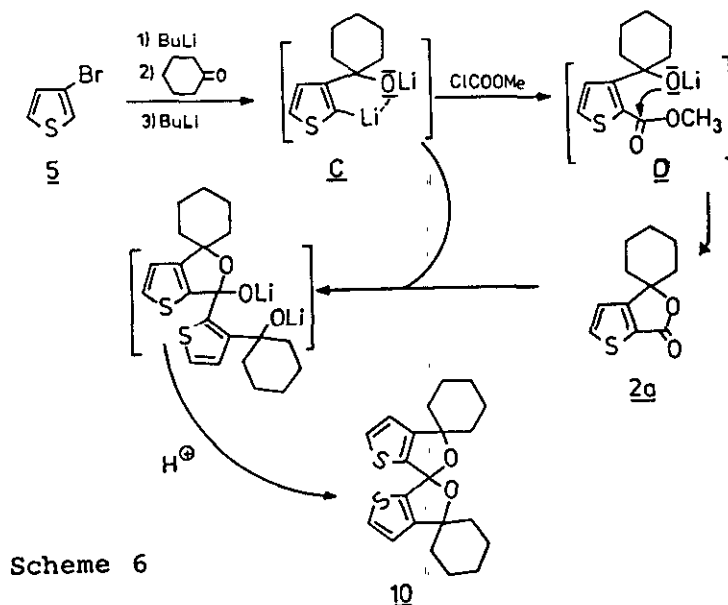
In one case the final spiro-compound (2c) also was obtained in 63 % yield starting from 3-bromothiophene, without isolation of any intermediate. In this case the cyclization was achieved simply by distilling the crude diol 6c.

It should be mentioned that it seems advisable to use diethyl-ether for extraction during work-up of the amino-substituted thieno[c]furans 2d-e and 3d-e, as after stirring a solution

of 2d in  $\text{CH}_2\text{Cl}_2$  over  $\text{MgSO}_4$  overnight for drying the quaternary salt 11 was isolated as the sole product (Scheme 5): The addition of  $\text{CH}_2\text{Cl}_2$  to certain tertiary amines as a preparative useful reaction for synthesis of quaternary nitrogen compounds is reported in the literature<sup>8</sup>.



An attempt to prepare the lactone 2a in a direct way by transesterification of intermediate D, generated by the usual one-pot sequence adding methyl chloroformate after the second lithiation as electrophile, led to the formation of a product which draws from the stereochemical point of view some attention on it: dilithiated 1-(3-thienyl)-cyclohexanol C upon reaction with methyl chloroformate instead of carbon dioxide led to a mixture of the desired lactone 2a and spiroketal 10 as the major product. Formation of 10 is explained by the competing reaction of lactone 2a with the dilithio-intermediate C, as depicted in Scheme 6.



## EXPERIMENTAL

Solvents: diethyl ether ( $\text{Et}_2\text{O}$ ), dried over  $\text{CaCl}_2$ , and tetrahydrofuran, dried over KOH, were distilled from Na/benzophenone.

Butyllithium (BuLi) was prepared according to Gilman<sup>9</sup> in dry ether, the molarity was determined by titration<sup>10</sup>.

Thin-layer-chromatography: (a): "DC-Alufolie Kieselgel 60 F<sub>254</sub>", Merck Art. 5554; (b): "DC-Alufolie Aluminiumoxid neutral 60 F<sub>254</sub> (Typ E)", Merck Art. 5550; eluents: PE (petroleum ether), EE (ethyl acetate), Bz (benzene), EtOH (ethanol),  $\text{Et}_2\text{O}$  (diethyl ether)

"flash"-chromatography:  $\text{SiO}_2$  ("Kieselgel 60, 0.040-0.063 mm", Merck Art. 9385); for resolution of a sample of 1 g 50 g of  $\text{SiO}_2$  were used.

<sup>1</sup>H-nmr (pmr)- and <sup>13</sup>C-nmr (cmr)-spectra were recorded on a JEOL FX 90Q - FT NMR spectrometer, all chemical shifts are given in  $\delta$ , internal standard TMS ( $\delta = 0$ ); solvents: deuteriochloroform ( $\text{CDCl}_3$ ) and hexadeuterodimethylsulfoxide ( $\text{DMSO-d}_6$ ).

IR-spectra were recorded on a Perkin-Elmer Grating Infrared Spectrometer Typ 377, absorptions are given in  $\text{cm}^{-1}$ .

Melting points were determined on a Kofler-Reichert microhot stage apparatus and are uncorrected.

All glassware and syringes used for reactions with BuLi were dried thoroughly, funnels and flasks were flushed with dry nitrogen before being charged with starting compounds.

Microelementary analyses were determined in the Microanalytical Laboratory of the Institute of Physical Chemistry of the University Vienna by Dr. J. Zak.

Chemicals: 3-Bromothiophene<sup>11</sup>, 3,4-dibromothiophene<sup>12</sup>, 3-thiophenecarboxylic acid<sup>13</sup> and 4-dimethylaminocyclohexanone<sup>14</sup> were prepared according to reported methods. N-Methyl-4-piperidone was purchased from Aldrich, necessarily distilled before use in vacuo and then stored under nitrogen at  $-10^\circ\text{C}$ . Under these conditions it could be used without further purification for at least six months. Diisopropylamine (for the preparation of LDA) was distilled three times from KOH-pellets and then kept over a 3Å molecular sieve.

3-(1-Hydroxy-1-cyclohexyl)-2-thiophenecarboxylic Acid(6a): 5.2 g (32 mmol) of 3-bromothiophene in 25 ml of dry THF were added at  $-80^{\circ}\text{C}$  under  $\text{N}_2$  to 45 ml (32 mmol) of 0.7 M-BuLi/ether solution and stirred for 10 min. Then 3.3 g (34 mmol) of cyclohexanone in 25 ml of dry THF were dropped to this mixture. After keeping at  $-80^{\circ}\text{C}$  for 1 h the temperature was raised to  $-30^{\circ}\text{C}$  and one more batch of 45 ml of BuLi solution were added. The mixture was stirred for 1.5 h at  $-20^{\circ}\text{C}$ . After cooling down to  $-100^{\circ}\text{C}$  the solution was poured under  $\text{N}_2$  on crushed solid  $\text{CO}_2$  and was allowed to stand overnight. A variation of this step was to bubble  $\text{CO}_2$  (dried over  $\text{H}_2\text{SO}_4$ ) at  $-80^{\circ}\text{C}$  through the mixture for about 1 h. For work-up the solution was poured on water, washed with ether, acidified with 2N HCl and extracted with ether. After drying ( $\text{MgSO}_4$ ) and evaporation 5.9 g (82 %) of a yellowish oil remained, which crystallized on addition of cyclohexane. Upon recrystallisation from EtOH- $\text{H}_2\text{O}$  4.9 g (68 %) of colourless crystals were obtained; mp  $138-139^{\circ}\text{C}$ ; Rf(a)=0.71 (EtOH); pmr( $\text{CDCl}_3$ ): 7.48 (d,1H), 7.08 (d,1H), 2.20-0.95 (m,10H); cmr(DMSO- $d_6$ ): 164.75 (s), 157.09 (s), 131.39 (d), 128.54 (s), 128.46 (d), 71.68 (s), 37.09 (t), 25.03 (t), 21.51 (t); ir (KBr): 3200, 2920, 2580, 2480, 1660, 1260, 670.

3-(4-Hydroxy-1-methyl-4-piperidinyl)-2-thiophenecarboxylic Acid, Hydrochloride (6b HCl): Following the procedure described above 7.8 g (48 mmol) of 3-bromothiophene in 35 ml of dry THF were added to 64 ml (48 mmol) of 0.75 M-BuLi/ether solution, then 5.5 g (48 mmol) of N-methyl-4-piperidone in 35 ml of dry THF were added dropwise to this mixture. After 1 h at  $-40^{\circ}\text{C}$  one more batch of 64 ml of BuLi-solution was added. Then  $\text{CO}_2$  was added as described above. The work-up procedure was modified as follows: the reaction mixture was poured into water, washed with ether, acidified with 2N-HCl, washed again with ether and evaporated in vacuo. The remaining crystal slurry was taken up with some ice-water, filtered with suction and washed with ice-water to remove co-precipitated inorganic salts: 8.4 g (60 %) of crude crystals, recrystallized from EtOH: 5.5 g (40%); mp  $201-202^{\circ}\text{C}$ ; pmr(DMSO- $d_6$ ): 10.64 (bs,1H), 7.65 (d,1H), 7.13 (d,1H), 6.78 (bs, $\text{H}_2\text{O}$ , -OH, -COOH), 3.69-3.24 (m,4H), 2.84 (s,3H), 2.68-1.96 (m,4H); cmr(DMSO- $d_6$ ): 165.30 (s), 154.36 (s), 132.36 (d), 128.24 (d), 128.08 (s), 67.08 (s), 49.63 (t), 42.64 (q), 33.86 (t);



ir(KBr): 3400, 2940, 2720, 2600, 1665, 1420.

3-(1-Hydroxy-1-cyclohexyl)- $\alpha$ -phenyl-2-thiophenemethanol (6c): 3 g (18.4 mmol) of 3-Bromothiophene in 15 ml of dry THF were added under N<sub>2</sub> at -80°C to 14.7 ml (18.4 mmol) of 1.25 M-BuLi/ether solution. After 10 min at -80°C 1.8 g (18.4 mmol) of cyclohexanone in 10 ml of dry THF were added dropwise. The solution was stirred for 1 h at -70°C, then one more batch of 14.7 ml of BuLi-solution was added. After additional 1.5 h at -20°C 2g (18.8 mmol) of benzaldehyde in 10 ml of dry THF were added dropwise. The mixture was stirred for 1 h, then most of the THF was distilled off. After hydrolysis and extraction with ether 4.7 g (89%) of crude product remained\*) .On addition of cyclohexane the product crystallized and was washed with cold petroleum ether: 2.8 g (53 %) of colourless crystals; mp 80-82°C; Rf(a)=0.5 (Bz/EtOH=9:1);pmr(CDCl<sub>3</sub>): 7.63-7.22 (m,5H), 7.10 (d,1H), 6.93 (d,1H), 6.41 (s, 1H), 4.72 (bs,1H), 3.06 (bs,1H), 2.15-0.85 (m,10H); cmr(CDCl<sub>3</sub>): 145.74 (s), 143.31 (s), 142.33 (s), 127.76 (d), 127.33 (d), 127 (s), 126.46 (d), 123.04 (d), 73.79 (s), 69.79 (d), 39.01 (t), 38.69 (t), 25.09 (t), 21.62 (t), 21.40 (t); ir(KBr): 3200, 2930, 1260, 1145, 1010, 960, 700.

3-(4-Dimethylamino-1-hydroxy-1-cyclohexyl)- $\alpha$ -phenyl-2-thiophenemethanol (6d): Following the lithiation procedure as given for 6c 11.6 ml (18.4 mmol) of 1.6 M-BuLi/ether solution, 3 g (18.4 mmol) of 3-bromothiophene in 15 ml of dry THF, 2.6 g (18.4 mmol) of 4-dimethylamino-cyclohexanone in 15 ml of dry THF, 11.6 ml of BuLi-solution for the second lithiation and 1.95 g (18.4 mmol) of benzaldehyde in 15 ml of dry THF as starting compounds were used. Work-up was modified as follows: the reaction mixture was poured into water, acidified with 2N-HCl, washed several times with ether and basified with 3N-NaOH. The precipitated product was filtered with suction, washed several times with water and dried in vacuo: 2.2 g (36%); mp 172-173°C Rf(b)=0.32 (Bz/EtOH=

\*) When this oily product was distilled in vacuo (0.1 mm Hg, 185°C bath temperature) over a short-path column cyclization to 2c occurred [yield: 3.3 g (63 %)]; physical properties of 2c: see cyclization procedure for product 2c as reported below.

9:1); pmr(CDCl<sub>3</sub>): 7.38-7.03 (m, 5H), 6.97 (d, 1H), 6.71 (d, 1H), 6.5 (s, 1H), 5.69 (bs, 1H), 4.80 (s, 1H), 2.16 (s, 6H), 2.03-1.25 (m, 9H); cmr(DMSO-d<sub>6</sub>): 145.86 (s), 145.57 (s), 144.77 (s), 127.65 (d), 126.57 (d), 123.04 (d), 71.46 (s), 68.27 (d), 62.31 (d), 41.23 (q), 38.20 (t), 23.24 (t) Found: C, 68.58; H, 7.54; N, 4.23. Calcd. for C<sub>19</sub>H<sub>25</sub>NO<sub>2</sub>S (331.47): C, 68.85; H, 7.60; N, 4.23.

4-[2-(1-Hydroxy-1-phenylmethyl)-3-thienyl]-1-methyl-piperidin-4-ol (6e): Following the lithiation and work-up procedure as given above for product 6d from 53 ml (36.8 mmol) of 0.7 M-BuLi/ether solution, 6 g (36.8 mmol) of 3-bromothiophene in 25 ml of dry THF, 4.2 g (36.8 mmol) of N-methyl-4-piperidone in 25 ml of dry THF, 53 ml of BuLi solution for the second lithiation and 3.9 g (36.8 mmol) of benzaldehyde in 25 ml of dry THF 6.9 g (62 %) 6e were obtained. Recrystallisation from acetone gave an analytical sample (5.6 g, i.e. 50 %); mp 171-173°C; Rf(b)=0.47 (Bz/EtOH=9:1); pmr(CDCl<sub>3</sub>): 7.71 -7.28 (m, 5H), 7.16 (d, 1H), 6.99 (d, 1H), 6.67 (s, 1H), 5.92 (bs, 1H), 4.98 (bs, 1H), 3.19-2.41 (m, 4H), 2.31 (s, 3H), 2.15-1.63 (m, 4H); cmr(CDCl<sub>3</sub>): 145.36 (s), 144.88 (s), 127.54 (d), 126.57 (d), 126.40 (d), 123.04 (d), 69.30 (s), 68.16 (d), 50.82 (t), 45.95 (q), 38.41 (t), 37.93 (t); ir(KBr): 3400, 3260, 2800, 1450, 1150, 1020, 780, 710; Found: C, 67.43; H, 7.09; N, 4.57. Calcd. for C<sub>17</sub>H<sub>21</sub>NO<sub>2</sub>S (303.43): C, 67.29; H, 6.98; N, 4.62.

2-(1-Hydroxy-1-cyclohexyl)-thiophene-3-carboxylic Acid (8a): 10g (78 mmol) of 3-Thiophenecarboxylic acid in 100 ml of dry THF were added dropwise under N<sub>2</sub> at -80°C to a LDA-solution (prepared from 17.4 g (172 mmol) of diisopropylamine in 40 ml of dry THF, 180 ml (170 mmol) of 0.94 M-BuLi/ether-solution, 15 min at -10°C). The mixture was kept for 1 h at -50°C. After cooling down to -80°C 9 g (91 mmol) of cyclohexanone in 90 ml of THF were added, the mixture was allowed to warm up to -20°C and poured onto 2N-HCl/ice/water after another 30 min. The acidic aqueous layer was extracted with ether, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated giving 14.4 g (81 %) of colourless crystals after recrystallisation from methanol/water 2:1; mp

140-141°C; Rf(a)=0.31 Bz/AcOH=9:1; pmr(CDCl<sub>3</sub>): 7.95 (s, 2H), 7.64 (d, 1H), 7.15 (d, 1H), 2.40-2.00 (m, 2H), 2.00-1.00 (m, 8H); ir(KBr): 3080, 2920, 2860, 1650, 1515, 1440, 1290, 1280, 970; Found: C, 58.53; H, 6.08. Calcd. for C<sub>11</sub>H<sub>14</sub>O<sub>3</sub>S (226.30): C, 58.39; H, 6.24.

2-(4-Hydroxy-1-methyl-4-piperidinyl)-thiophene-3-carboxylic Acid, Hydrochloride (8b): Following the procedure as given above, 44 mmol of LDA in 50 ml of ether/THF, 2.60 g (20.3 mmol) of 3-thiophene carboxylic acid in 30 ml of dry THF and 2.5 g (22 mmol) of N-methyl-4-piperidone in 25 ml of dry THF were used as starting materials. Work-up was modified as follows: the mixture was poured onto ice/water, the basic solution was washed with ether and then acidified. When concentrating and cooling the aqueous layer 4.7 g (83%) 8b.HCl precipitated in colourless crystals; mp 212-215°C; ir(KBr): 3400, 2940, 1665, 1460, 1430, 1280, 1265, 970, 835, 740, 720.

2-(1-Hydroxy-1-cyclohexyl)- $\alpha$ -phenyl-3-thiophenemethanol (8c): Under N<sub>2</sub> 5 g (30.7 mmol) of 3-bromothiophene in 30 ml of dry THF were added at -80°C to 32 ml (31 mmol) 0.97 M-BuLi/ether solution. After 10 min at -80°C 3.2 g (30.2 mmol) of benzaldehyde in 30 ml of dry THF were added dropwise. The solution was stirred for 1 h at -70°C, then again 30 ml (29 mmol) of BuLi-solution were added. After additional 2 h at -20°C 3 g (30 mmol) of cyclohexanone in 30 ml of dry THF were added dropwise at -50°C. The mixture was stirred for 1 h, then most of the THF was evaporated. After hydrolysis, extraction with ether and trituration of the crude product with cyclohexane 4.1 g (46%) of colourless crystals remained; mp 87-90°C; Rf(a)=0.42 PE/EE=3:1; pmr(CDCl<sub>3</sub>): 7.27 (m, 5H), 6.92 (d, 1H), 6.51 (d, 1H), 6.13 (s, 1H), 5.45 (bs, 2H), 2.60-1.85 (m, 10H); ir(KBr): 3200, 2940, 1020, 950, 740, 700, 610.

4-(3-Dimethylamino-1-hydroxy-1-cyclohexyl)- $\alpha$ -phenyl-3-thiophenemethanol (8d): Following the lithiation procedure as given for 8c 11.8 ml (12.1 mmol) of 1.03 M-BuLi/ether solution, 2.0 g (12.2 mmol) of 3-bromothiophene in 15 ml of dry THF, 1.3 g (12.1 mmol) of benzaldehyde in 15 ml of dry THF, 11.8 ml (12.1 mmol) of BuLi-solution for the second lithiation and 1.7 g (12.1

mmol) of 4-dimethylamino-cyclohexanone in 15 ml of dry THF were used as starting materials. Working-up conditions changed as follows: the reaction mixture was poured onto water, acidified with 2N-HCl, washed several times with ether and basified with 3N-NaOH. The precipitated product was filtered with suction, washed several times with water and dried; an analytical sample was obtained by recrystallisation from acetone: 1.5 g (37%) of colourless crystals; mp 174-176°C; Rf(b)=0.40 (Bz/EtOH=9:1); PMR(CDCl<sub>3</sub>/DMSO-d<sub>6</sub> = 2:1): 7.34-6.90 (m, 5H), 6.75 (d, 1H), 6.44 (d, 1H), 6.19 (d, 1H), 5.30-4.21 (bs, 2H), 2.22 (s, 6H), 2.18-1.5 (m, 9H); cmr(DMSO-d<sub>6</sub>): 149.10 (s), 145.36 (s), 139.30 (s), 129.06 (d), 127.54 (d), 126.13 (d), 120.82 (d), 71.03 (s), 67.67 (d), 62.09 (d), 41.07 (q), 38.01 (d), 23.41 (d); Found: C, 67.68; H, 7.49; N, 3.99. Calcd. for C<sub>19</sub>H<sub>25</sub>NO<sub>2</sub>S 0.32 H<sub>2</sub>O (337.23): C, 67.67; H, 7.66; N, 4.15.

4-[3-(1-Hydroxy-1-phenylmethyl)-2-thienyl]-1-methyl-piperidine-4-ol (8e): Following the lithiation and work-up procedure as given above for product 8d 55 ml (50 mmol) of 0.91 M-BuLi/ether solution, 8 g (49.1 mmol) of 3-bromothiophene in 80 ml of dry THF, 5.5 g (52 mmol) of benzaldehyde in 50 ml of dry THF, 50 ml (45 mmol) of BuLi-solution for the second lithiation and 5.1 g (45 mmol) of N-methyl-4-piperidone in 50 ml of dry THF were used as starting materials; after recrystallisation from acetone 9.5 g (64%) of colourless needles were obtained (in some cases instead of filtration isolation of a semi-crystalline product was accomplished by extraction with ether); mp 149-50°C; Rf(b)=0.48 (Bz/EtOH=9:1); pmr(CDCl<sub>3</sub>): 7.35 (s, 5H), 6.96 (d, 1H), 6.54 (s, 1H), 6.2 (s, 1H), 5.5 (bs, 2H), 2.7-1.9 (m, 11H); ir(KBr): 3440, 2950, 2840, 1450, 1300, 1035, 780, 708; Found: C, 67.22; H, 6.92; N, 4.59. Calcd. for C<sub>17</sub>H<sub>21</sub>NO<sub>2</sub>S (303.43): C, 67.29; H, 6.98; N, 4.62.

6,6'-Spirobis[spiro[cyclohexane-1,4'(6'H)-thieno[2,3-c]-furan]] (10): 10: 5 g (31 mmol) of 3-Bromothiophene in 25 ml of dry THF were added under N<sub>2</sub> to 28 ml (31 mmol) of 1.1 M-BuLi/ether-solution at -80°C and stirred for 5 min. Then 3 g (41 mmol) of cyclohexanone in 25 ml of dry THF were added at the same temperature. After 1 h 28 ml of BuLi-solution were added at -60°C, then the mixture was stirred at -25°C for another 1.5 h.

Upon cooling to  $-50^{\circ}\text{C}$  2.9 g (31 mmol) of methyl chloroformate in 25 ml of dry THF were added. After 1 h the mixture was hydrolyzed with  $2\text{N-HCl}$ , extracted with ether, washed with 10%-aqu.  $\text{NaHCO}_3$ -solution, dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated. The semi-crystalline residue (6 g) was according to nmr a mixture of 10 and 2a with a ratio of 2:1. Trituration with ether left 2.2 g (39%) of colourless crystals. An analytical sample was obtained by recrystallisation from ethanol; mp  $193-194^{\circ}\text{C}$ ;  $R_f(\text{a})=0.71$  (Bz/EtOH=9:1); pmr( $\text{CDCl}_3$ ): 7.36 (d,1H); 6.83 (d,1H), 2.19-1.22 (m,10H); cmr( $\text{CDCl}_3$ ): 153.66 (s), 140.55 (s), 131.71 (d), 119.14 (d), 110.20 (s), 85.22 (s), 38.58 (t), 38.20 (t), 25.14 (t), 22.97 (t); ir(KBr): 3070, 2930, 2860, 1440, 1320, 1115, 1010, 910, 740; Found: C, 67.73; H, 6.37. Calcd. for  $\text{C}_{21}\text{H}_{24}\text{O}_2\text{S}_2$  (372.55): C, 67.70; H, 6.49.

Spiro[cyclohexane-1,4'(6'H)-thieno[2,3-c]furan]-6'-one (2a):

10 g (44.2 mmol) of 6a were dissolved in 100 ml of dry ether and dry HCl gas was bubbled through this solution for 1 h at  $0^{\circ}\text{C}$ . The mixture was stirred for 40 h at room temperature, then poured onto water/ice, the layers were separated and the water layer was extracted with ether. After washing (10%-aqu.  $\text{NaHCO}_3$ -solution), drying ( $\text{MgSO}_4$ ), evaporation and Kugelrohr-distillation 6.5 g (71%) of colourless oil remained; bp(0.2 mm Hg):  $135-140^{\circ}\text{C}$ ;  $R_f(\text{a})=0.39$  (Bz/EtOH=9:1); pmr( $\text{CDCl}_3$ ): 7.76 (d,1H), 7.02 (d,1H), 2.24-1.22 (m,10H); cmr( $\text{CDCl}_3$ ): 167.74 (s), 164.22 (s), 139.46 (d), 128.41 (s), 119.74 (d), 86.47 (s), 35.71 (t), 24.27 (t), 22.32 (t); IR(neat): 3080, 2930, 2820, 1750, 1440, 1280, 1150, 1075, 770, 725; Found: C, 63.26; H, 5.91. Calcd. for  $\text{C}_{11}\text{H}_{12}\text{O}_2\text{S}$  (208.28): C, 63.43; H, 5.81.

1-Methyl-spiro[piperidine-4,4'(6'H)-thieno[2,3-c]furan]-6'-one

(2b): 5.2 g (17.6 mmol) of 6b.HCl, 1 g (12.2 mmol) of sodium acetate and 6 ml of acetic acid anhydride were dissolved in 100 ml of dry  $\text{CHCl}_3$  and dry benzene (2:1) and refluxed for 4 h. Then the mixture was poured into 100 ml of saturated  $\text{Na}_2\text{CO}_3$ -solution and stirred for 0.5 h. After separation and subsequent extraction with  $\text{CHCl}_3$  the collected organic layers were dried ( $\text{MgSO}_4$ ) and left 3.1 g (79%) of nmr-pure crystals after evaporation. For microelementary analysis they were recrystallized from cyclohexane: 2.5 g (64%) of colourless

crystals; mp 103-105°C; Rf(b)=0.5 (Bz/EtOH=9:1); pmr(CDCl<sub>3</sub>): 7.81 (d,1H), 7.00 (d,1H), 2.96-2.44 (m,4H), 2.38 (s,3H), 2.25-1.54 (m,4H); cmr(CDCl<sub>3</sub>): 166.51 (s), 163.30 (s), 139.88 (d), 128.33 (s), 119.35 (d), 83.42 (s), 51.33 (t), 45.56 (q), 35.29 (t); ir(KBr): 2940, 2800, 1750, 1440, 1380,1280, 1110, 980, 920, 780; - Found: C, 59.18; H, 6.00; N, 6.21. Calcd. for C<sub>11</sub>H<sub>13</sub>NO<sub>2</sub>S (223.30): C, 59.17; H, 5.87; N, 6.27.

2b.HCl: 1.2 g (5.4 mmol) of 2b were dissolved in 2N-HCl/EtOH, the solvent was evaporated and the residue triturated with dry ethanol: 1.1 g (79%) of colourless crystals; mp 279-281°C; pmr(DMSO-d<sub>6</sub>): 10.66 (bs,1H), 8.22 (d,1H), 7.39 (d,1H), 3.76-3.21 (m,4H), 2.97 (s,3H), 2.83-2.57 (m,4H); ir(KBr): 3450, 2570, 1750, 1285, 1045, 780; Found: C, 50.71; H, 5.43; N, 5.33. Calcd. for C<sub>11</sub>H<sub>14</sub>NClO<sub>2</sub>S (259.76): C, 50.86; H, 5.43; N, 5.39.

1-Methyl-spiro[piperidine-4,6'(4'H)-thieno[2,3-c]furan]-4'-one (3b): Following the procedure for synthesis of 2b reported above 4.7 g (16.9 mmol) of 8b.HCl, 0.85 g ammonium acetate and 8.3 ml of acetic acid anhydride in 25 ml of dry benzene were used as starting compounds yielding 3.5 g (92%) of colourless crystals after recrystallization from isopropanol/water; mp 101-102°C ; Rf(b)=0.60 (Bz/EtOH=9:1); pmr(CDCl<sub>3</sub>): 7.35 (d,1H), 7.14 (d,1H), 2.75-2.55 (m,4H), 2.38 (s,3H), 2.15-1.95 (m,4H); cmr(CDCl<sub>3</sub>): 165.30 (s), 164.16 (s), 133.50 (s), 131.50 (d), 120.23 (d), 83.76 (s), 51.85 (t), 45.78 (q), 36.46 (t); ir(KBr): 2960, 2930, 2780, 1755, 1235, 1035, 930, 730; Found: C, 58.98; H, 5.98; N, 6.19. Calcd. for C<sub>11</sub>H<sub>13</sub>NO<sub>2</sub>S (223.30): C, 59.17; H, 5.87; N, 6.27.

3b.HCl: the hydrochloride was prepared in analogy to 2b.HCl; mp 255°C; pmr(DMSO-d<sub>6</sub>/D<sub>2</sub>O=1:1): 7.15 (d,1H), 7.03 (d,1H), 3.1-2.6 (m,4H), 2.3 (s,3H), 2.1-1.5 (m,4H); ir(KBr): 3420, 3100, 2980, 2640, 2530, 1760, 1260, 1070, 910, 900, 735; Found: C, 51.23; H, 5.51; N, 5.35. Calcd. for C<sub>11</sub>H<sub>14</sub>NClO<sub>2</sub>S (259.76): C, 50.86; H, 5.43; N, 5.39.

6'-Phenyl-spiro[cyclohexane-1,4'(6'H)-thieno[2,3-c]furan] (2c): 0.8 g (2.8 mmol) of 6c were dissolved in 5 ml of dry pyridine and 0.53 g (2.8 mmol) of tosyl chloride were added in small portions within 15 min to the refluxing solution. After 2 h at

room temperature the mixture was poured onto ice/water, extracted with ether, washed with 10%-aqu.  $\text{NaHCO}_3$ -solution, dried ( $\text{MgSO}_4$ ) and evaporated: 0.5 g (67%) of yellowish oil; bp(0.15 mm Hg): 165-166°C; Rf(a)=0.66 (Bz); pmr( $\text{CDCl}_3$ ): 7.53-7.22 (m, 5H), 7.17 (d, 1H), 6.80 (d, 1H), 6.23 (s, 1H), 2.03-1.23 (m, 10H); cmr( $\text{CDCl}_3$ ): 150.79 (s), 142.13 (s), 141.17 (s), 130.10 (s), 128.46 (d), 128.01 (d), 126.40 (d), 119.10 (d), 85.82 (s), 81.33 (d), 38.69 (t), 37.41 (t), 25.03 (t), 22.65 (t), 22.45 (t); ir(KBr): 2930, 2850, 1490, 1450, 1045, 1010, 960, 900, 730, 695; Found: C, 75.37; H, 6.75. Calcd. for  $\text{C}_{17}\text{H}_{18}\text{OS}$  (270.40): C, 75.51; H, 6.71.

Spiro[cyclohexane-1,6'(4'H)-thieno[2,3-c]furan]-4'-one (3a) : 16.5 g (73 mmol) of 8a and 15 g (85 mmol) of benzenesulfonyl chloride were stirred at room temperature overnight in 30 ml of dry pyridine. The pyridine was distilled off in vacuo, the residue was poured onto 2N-HCl and extracted with ether. After washing (saturated aqu.  $\text{NaHCO}_3$ -solution), drying ( $\text{Na}_2\text{SO}_4$ ), evaporation and recrystallisation from cyclohexane 12.5 g (82%) of colourless crystals remained; mp 54-55°C; bp(0.02 mm Hg): 120°C (Kugelrohr); Rf(a)=0.78 (PE/EE=1:1); pmr( $\text{CDCl}_3$ ): 7.33 (d, 1H), 7.13 (d, 1H), 2.10-1.45 (m, 10H); pmr( $\text{CDCl}_3$ ): 165.36 (s), 164.06 (s), 132.74 (s), 130.95 (d), 119.52 (d), 86.26 (s), 36.19 (t), 23.73 (t), 22.78 (t); ir(KBr): 3080, 2940, 2860, 1760, 1450, 1245, 1075, 1025, 910, 720; Found: C, 63.24; H, 5.93. Calcd. for  $\text{C}_{11}\text{H}_{12}\text{O}_2\text{S}$  (208.28): C, 63.43; H, 5.81.

Syntheses of spiro-systems 2d, 2e, 3d, 3e: 3.5 g (11.5 mmol) of 6d (6e, 8d, 8e) were refluxed in acetic acid for 2 h. The cooled reaction mixture was poured onto water, basified with 40%-NaOH-solution and extracted with diethyl ether. The organic layer was dried ( $\text{MgSO}_4$ ) and evaporated.

4-Dimethylamino-6'-phenyl-spiro[cyclohexane-1,4'(6'H)-thieno[2,3-c]furan] (2d): yield: 2.9 g (89%) of beige crystals; mp 88-90°C; Rf(b)=0.5 (Bz/EtOH=9:1); pmr( $\text{CDCl}_3$ ): 7.51-7.16 (m, 6H), 6.68 (d, 1H), 6.24 (s, 1H), 2.33 (s, 6H), 2.24-1.44 (m, 9H); cmr( $\text{CDCl}_3$ ): 150.89 (s), 142.17 (s), 141.09 (s), 130.25 (d), 128.35 (d), 127.76 (d), 126.24 (d), 118.33 (d), 84.41 (s), 81.54

(d), 62.74 (d), 41.23 (q), 37.60 (t), 36.52 (t), 24.38 (t), 24.06 (t).

1-Methyl-6'-phenyl-spiro[piperidine-4,4'(6'H)-thieno[2,3-c]-furan] (2e): yield: 3.1 g (94%) of yellowish crystals; mp 101-103°C; Rf(b)=0.61 (Bz/EtOH=9:1); pmr(CDCl<sub>3</sub>): 7.51-7.28 (m,5H), 7.24 (d,1H), 6.80 (d,1H), 6.26 (s,1H), 2.86-2.42 (m,4H), 2.32 (s,3H), 2.21-1.69 (m,4H); cmr(CDCl<sub>3</sub>): 149.89 (s), 141.57 (s), 141.09 (s), 130.20 (d), 128.19 (d), 127.70 (d), 126.13 (d), 118.55 (d), 82.46 (s), 81.38 (d), 52.07 (t), 51.74 (t), 45.84 (q), 37.76 (t), 36.73 (t); ir(KBr): 2940, 2780, 1450, 1280, 1140, 1150, 1105, 970, 760, 720, 700; Found: C, 71.74; H, 6.86; N, 4.85. Calcd. for C<sub>17</sub>H<sub>19</sub>NOS (285.41): C, 71.54; H, 6.71; N, 4.91.

4-Dimethylamino-4'-phenyl-spiro[cyclohexane-1,6'(4'H)-thieno[2,3-c]furan] (3d): yield: 2.1 g (65%) of colourless oil; bp(0.1 mm Hg) = 170°C (Kugelrohr); Rf(b)=0.6 (Bz/EtOH=9:1); pmr(CDCl<sub>3</sub>): 7.51- 7.13 (m,5H), 7.13 (d,1H), 6.56 (d,1H), 6.08 (s,1H), 2.27 (s,6H), 2.43-1.54 (m,9H); cmr(CDCl<sub>3</sub>): 146.51 (s), 144.49 (s), 142.06 (s), 128.89 (d), 128.19 (d), 127.49 (d), 126.29 (d), 119.68 (d), 84.68 (s), 81.60 (d), 62.25 (d), 41.29 (q), 38.31 (t), 37.33 (t) 24.60 (t), 24.27 (t); Found: C, 73.10; H, 7.47; N, 4.27. Calcd. for C<sub>19</sub>H<sub>23</sub>NOS (313.46): C, 72.80; H, 7.40; N, 4.47.

1-Methyl-4'-phenyl-spiro[piperidine-4,6'(4'H)-thieno[2,3-c]furan] (3e): yield: 2.5 g (75%) of yellowish oil; bp(0.01 mm)=120°C (Kugelrohr); Rf(b)=0.7 (Bz/EtOH=9:1); pmr(CDCl<sub>3</sub>): 7.20 (m,5H), 7.07 (d,1H), 6.52 (d,1H), 6.05 (s,1H), 2.70-2.40 (m,4H), 2.30 (s,3H), 2.15-1.85 (m,4H); cmr(CDCl<sub>3</sub>): 144.94 (s), 141.36 (s), 129.11 (s+d), 127.98 (d), 127.38 (d), 126.13 (d), 119.25 (d), 83.71 (s), 81.38 (d), 52.60 (t), 45.73 (q), 38.58 (t), 37.60 (t)

For preparation of hydrochlorides the bases were dissolved in dry ethanol and a 2N-HCl/ethanol solution was added. Precipitation was accomplished by dropwise addition of dry ether. All hydrochlorides were very hygroscopic.



2d.HCl: mp 229-232°C; pmr(CDCl<sub>3</sub>): 11.20 (bs,1H), 7.51-7.04 (m, 6H, 6.72 (d,1H), 6.20 (s,1H), 3.20 (m,1H), 2.72 (d,6H), 2.37-1.5 (m,8H); cmr(DMSO-d<sub>6</sub>): 149.59 (s), 141.57 (s), 140.60 (s), 131.23 (d), 128.14 (d), 127.65 (d), 125.92 (d), 118.55 (d), 82.62 (s), 80.73 (d), 62.42 (d), 38.52 (q), 35.60 (t), 34.57 (t), 22.16 (t), 21.73 (t); Found: C, 64.32; H, 6.77; N, 4.03. Calcd. for C<sub>19</sub>H<sub>24</sub>NOSCl·0.28 H<sub>2</sub>O (354.97): C, 64.29; H, 6.97; N, 3.95.

2e.HCl: mp 269-271°C; pmr(DMSO-d<sub>6</sub>): 12.36 (bs,1H), 7.45-7.23 (m,5H), 7.31 (d,1H), 6.87 (d,1H), 6.18 (s,1H), 3.63-2.89 (m,4H), 2.73 (s,3H), 2.18-1.61 (m,4H); ir(KBr): 3400, 2920, 2500, 1450, 1290, 975, 960, 900, 700; Found: C, 62.40; H, 6.32; N, 4.23. Calcd. for C<sub>17</sub>H<sub>20</sub>NOSCl·0.3 H<sub>2</sub>O (327.28): C, 62.39; H, 6.34; N, 4.28.

3e.HCl: mp 221-223°C; pmr(CDCl<sub>3</sub>): 7.40 (s,5H), 7.31 (d,1H), 6.59 (d,1H), 6.11 (s,1H), 3.60-3.20 (m,4H), 2.80 (d,3H), 2.30-2.10 (m,4H); ir(KBr): 3400, 2920, 2630, 2510, 1440, 1280, 1140, 715, 700; Found: C, 62.58; H, 6.16; N, 4.33. Calcd. for C<sub>17</sub>H<sub>20</sub>NOSCl·0.25 H<sub>2</sub>O (326.38): C, 62.56; H, 6.33; N, 4.29.

6'-Phenyl-spiro[cyclohexane-1,4'(6'H)-thieno[2,3-c]furan]-4-yl-chloromethyl-dimethylammoniumchloride (11): According to the procedure for 2d reported above 1.6 g (4.8 mmol) of 6d in 50 ml of acetic acid were used as starting material. Work-up was modified in so far as methylene chloride was used for extraction. The solution was stirred with MgSO<sub>4</sub> for 3 days. After filtration and evaporation 1.35 g (49%) of a brown solid oil remained. By dropwise addition of dry ether to a solution in 10 ml of dry chloroform 11 could be precipitated as a beige, very hygroscopic powder: 1 g (37%); mp 272-275°C; pmr(CDCl<sub>3</sub>): 7.42-7.13 (m,6H), 6.75 (d,1H), 6.20 (s,1H), 4.18 (m,1H), 3.44 (s,8H), 2.50-1.70 (m,8H); cmr(DMSO-d<sub>6</sub>): 149.32 (s), 141.68 (s), 140.92 (s), 131.66 (d), 128.41 (d), 127.97 (d), 126.29 (d), 118.71 (d), 82.36 (s), 80.99 (d), 71.68 (d), 50.33 (q), 36.14 (t), 35.16 (t), 22.16 (t), 21.78 (t); Found: C, 57.26; H, 6.50; N, 3.28. Calcd. for C<sub>20</sub>H<sub>25</sub>NOSCl<sub>2</sub>·1.2 H<sub>2</sub>O (420.00): C, 57.19; H, 6.58; N, 3.33.

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