# THIENOSPIRANS VI[1]: SPIRO-SUBSTITUTED THIENO[3,4-c]-FURANS BY REGIOSELECTIVE LITHIATIONS+

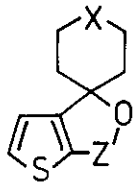
Fritz Sauter*, Peter Stanetty, and Hannes Fröhlich
Technical University Vienna
Institute of Organic Chemistry
Getreidemarkt 9, A-1060 Vienna, Austria

Abstract - The title substances 3 were obtained by cyclization of 3,4-disubstituted thiophenes 5 and 6, prepared in one-pot reactions starting from 3,4-dibromothiophene by means of two consecutive lithiations and additions of carbonyl compounds. By a combination of variation of the solvent and of the lithiating agent in the second metalation step and by influence of the substituent introduced in the first step it became possible to obtain good yields of either 3,4-disubstituted thiophenes (5 and 6) by metal-halogen exchange , 2,3-disubstituted 4-bromothiophenes (7) by directed lithiation, or 2,4-disubstituted 3-bromothiophenes (9) by a -I-effect controlled ortho-metalation.

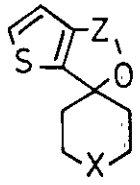
In continuation of our work on thienospirans with general formulae 1 and 2[2] the present paper deals with a synthesis of the isomeric spirocyclic system 3.

+) Dedicated to Prof. Dr. A. Neckel on the occasion of his 60th birthday.

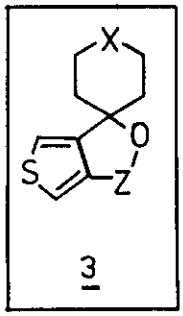
Taking into account that lithiations of thiophenes occur preferentially at the α-position (2 and/or 5) the concept used previously for synthesis of compounds 1 and 2 had to be modified for the synthesis of compounds 3. A good starting material seemed to be 3,4-dibromothiophene, which offered the possibility of functional group interconversion of both bromine atoms by metal-halogen exchange techniques, only described in few examples in the literature[3].



1

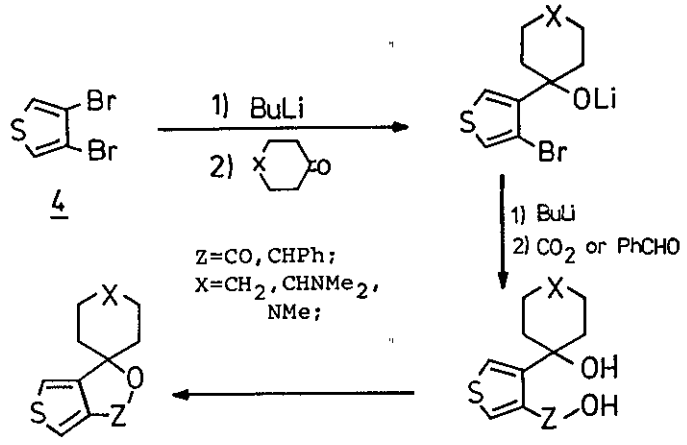


2



3

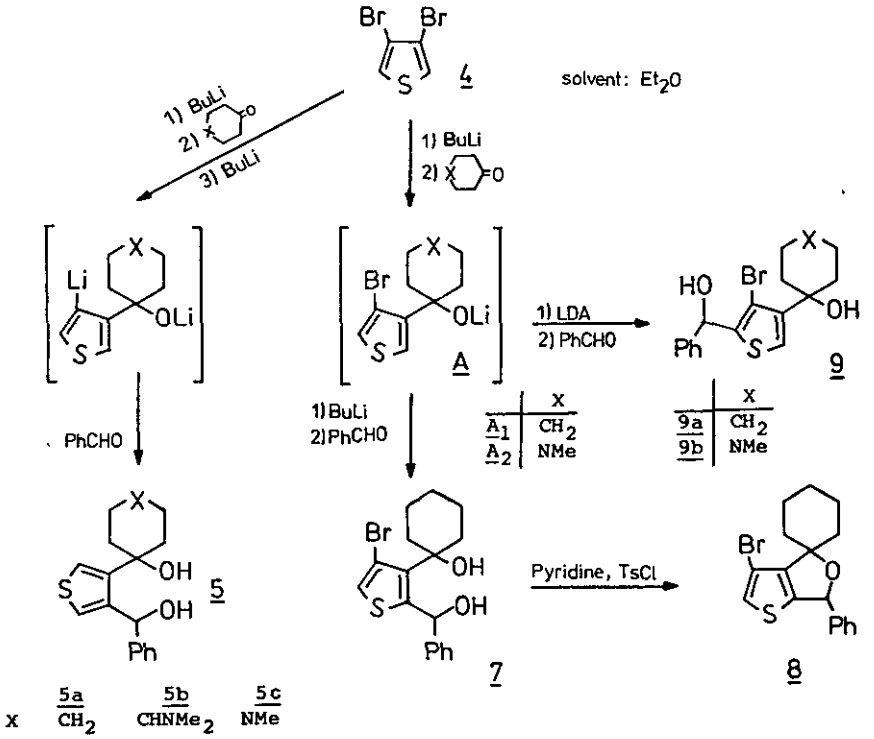
By employing this strategy we tried to realize the synthetic route shown in Scheme 1.




Scheme 1

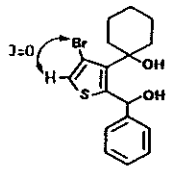
Using ether as the solvent for the whole one-pot sequence very good results could be achieved with basic ketones (X = $CHNMe_2$, NMe), which afforded disubstituted thiophenes 5b and 5c (Scheme 2) in 50-60 % overall yields. With cyclohexane, however, a bromine-containing trisubstituted thiophene 7 was obtained

surprisingly as the major product, while the desired 3,4-disubstituted derivative 5a was isolated as a by-product (Scheme 2).

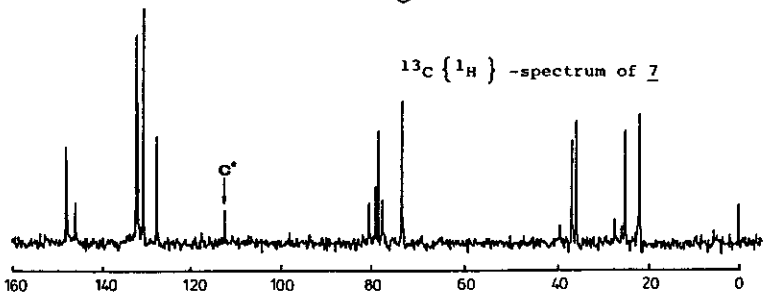



Scheme 2

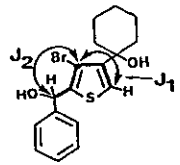
Structural proof of the main product was obtained by its cyclization to the thieno[b]furan 8 and by spectroscopic comparison with isomer 9a. The diols 9a and 9b were obtained by lithiation of intermediate $A_1$ and $A_2$ with LDA, adjacent to bromine (i.e. regioselective metalation of the most acidic ring position) and subsequent quenching with benzaldehyde.
Significant differentiation between isomers 7 and 9a is possible by careful analysis of the $^{13}C$-$^{1}H$-coupled nmr-spectra.
While in 7 there is no coupling of the carbon atom (which can easily be identified by the heavy-atom effect) carrying the bromine atom with neighbouring protons ($J_1$ and $J_2$ are too small), expected couplings with both $H_1$ ($J_1$ = 12 Hz) and $H_2$ ($J_2$ = 3 Hz) can be observed in the corresponding nmr-spectrum of 9a (Scheme 3).

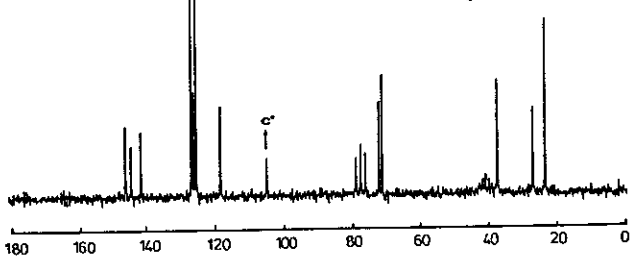



$^{13}C\{^{1}H\}$ -spectrum of 7

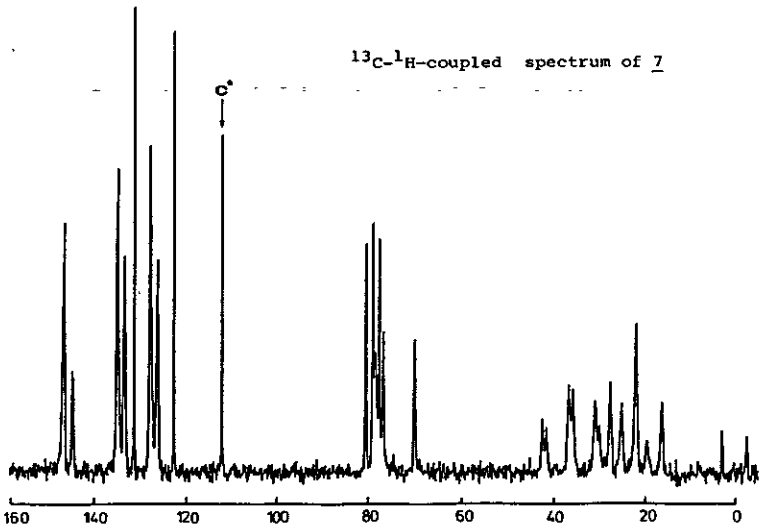


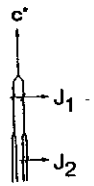

$^{13}C\{^{1}H\}$ -spectrum of 9a



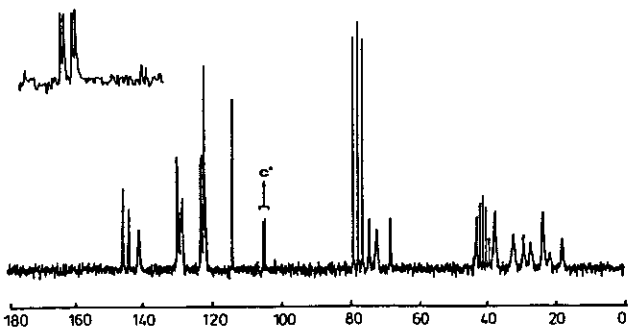




$^{13}C$-$^{1}H$-coupled spectrum of 7

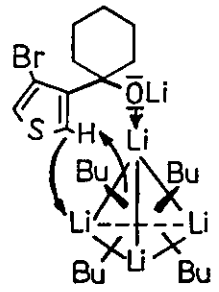


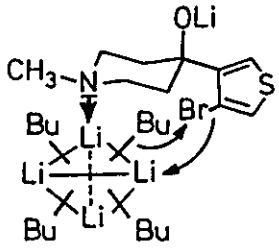

$^{13}C$-$^{1}H$-coupled spectrum of 9a



The differential lithiation behavior of intermediates $\underline{A}_1$ and $\underline{A}_2$ can be explained by comparing the transition states, $\underline{C}$ and $\underline{D}$[4].




$\underline{C}$



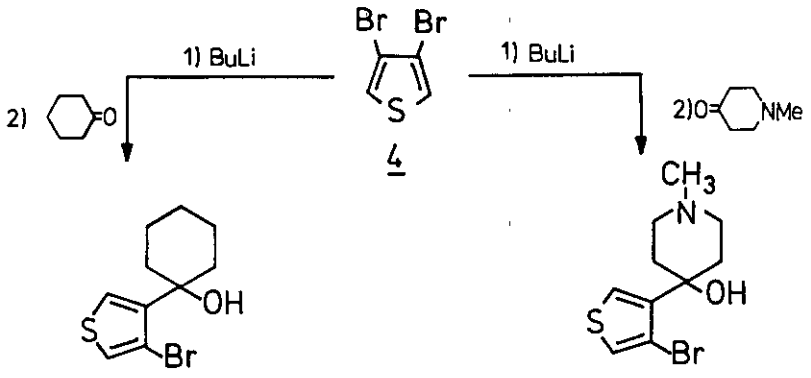

$\underline{D}$

In $\underline{C}$ the most efficient electron-donating centre is oxygen: therefore reaction with n-BuLi in ether leads via complexation with the internal alkoxide ion to exclusive lithiation (= i.e. ortho-directed lithiation). Decreased reactivity of the C-Br bond in $\underline{C}$ arises through a deactivating +I-effect of the ortho-substituent introduced in the first lithiation step. This fact together with the reduced reactivity of n-BuLi in ether as a solvent is responsible for not occurring the usually preferred fast metal-halogen exchange. By contrast, in transition state $\underline{D}$ initial coordination by the more nucleophilic nitrogen-atom may be the reason for an increased reactivity of the n-BuLi, so that steric and electronic effects favour metal-halogen exchange.

The final problem which remained to be solved was to find reaction conditions favouring metal-halogen exchange in intermediate $\underline{A}_1$ (Scheme 2), so that the 3,4-disubstituted precursor $\underline{5a}$ could also be synthesized selectively. The fact that n-BuLi exists as a dimeric complex in THF - by contrast to tetrameric aggregates in ether - is the reason for the known increased reactivity of this reagent in THF. But it was not possible to use THF as a solvent for the whole one-pot sequence, as examination in the first lithiation step resulted only in poor yields under these changed conditions (Scheme 4).

Use of ether as the solvent gave preferential metal-halogen exchange, while replacement of ether by THF (or by a mixture of

both solvents) led to concomitant ortho-metalation at the free 2- and/or 5-positions, thus yielding complex mixtures upon subsequent reaction with cyclic ketones.

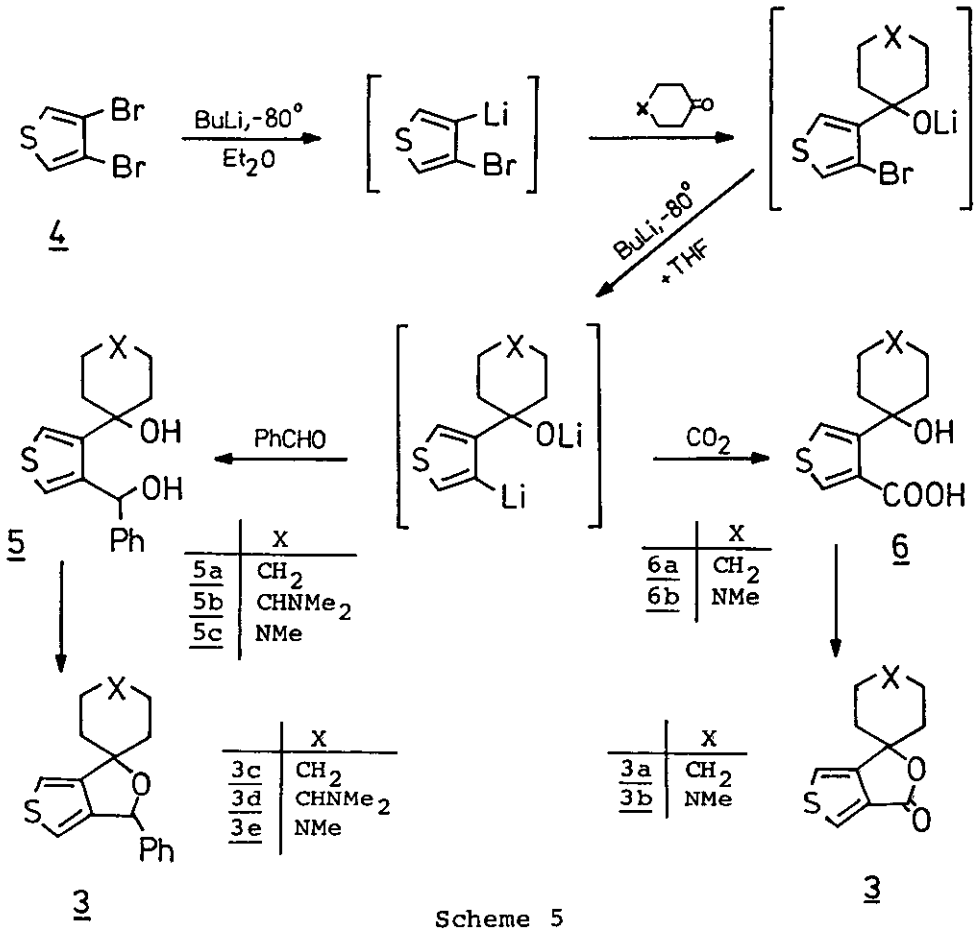



| | 10a | 10b |
|---|---|---|
| in THF | 28% | 35% |
| in $Et_2O$ | 90% | 84% |

Scheme 4

In the light of these observations we developed a procedure using ether for the initial metal-halogen exchange, which enabled us to avoid undesired lithiations; the second step was carried out by addition of THF (or replacement of the ether by THF). The reactivity of the n-BuLi was increased in the presence of THF to such an extent that we were able to achieve the desired second metal-halogen exchange, which now occurred selectively before directed ortho-lithiation could reach importance. After quenching with benzaldehyde or $CO_2$ we obtained diol 5a and hydroxy acid 6a, respectively.

Cyclizations to the target ring system 3 were achieved under the optimized conditions used to synthesize the isomeric thieno-spirans 1 and 2[2] . The reaction sequences leading to the title compounds are summarized in Scheme 5.


Br
Br
S
4
BuLi,-80°
Et2O
Li
Br
OLi
Br
BuLi,-80°
+THF
X
OH
OH
Ph
5
PhCHO
OLi
Li
CO2
OH
COOH
6
5a CH2
5b CHNMe2
5c NMe
6a CH2
6b NMe
O
Ph
3
3c CH2
3d CHNMe2
3e NMe
3a CH2
3b NMe
O
O
3

Scheme 5

## EXPERIMENTAL

Solvents: Diethyl ether ($Et_2O$), dried over $CaCl_2$, and tetrahydrofuran, dried over KOH, were distilled from Na/benzophenone.
Butyllithium (BuLi) was prepared according to Gilman[5] in dry ether, the molarity was determined by titration[6].
Thin-layer-chromatography: (a): "DC-Alufolie Kieselgel 60 $F_{254}$", Merck Art. 5554; (b): "DC-Alufolie Aluminiumoxid neutral 60 $F_{254}$ (Typ E)", Merck Art. 5550; eluents: PE (petroleum ether), EE (ethyl acetate), Bz (benzene), EtOH (ethanol), $Et_2O$ (diethyl ether)
"flash"-chromatography: $SiO_2$ ("Kieselgel 60, 0.040-0.063 mm", Merck Art. 9385); for resolution of a sample of 1 g, 50 g of $SiO_2$ were used.
$^1$H-nmr (pmr)- and $^{13}$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: deuterochloroform ($CDCl_3$) and hexadeuterodimethylsulfoxide (DMSO-$d_6$).
Ir-spectra were recorded on a Perkin-Elmer Grating Infrared Spectrometer Typ 377, absorptions are given in $cm^{-1}$.
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[7], 3,4-dibromothiophene[8] and 4-dimethylaminocyclohexanone[9] 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°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.

4-(1-Hydroxycyclohexyl)-$\alpha$-phenyl-3-thiophenemethanol (5a):

4 g (16.5 mmol) of 3,4-Dibromothiophene in 15 ml of dry ether were added under $N_2$ at -80°C to 22.6 ml (16.5 mmol) of 0.73 M

BuLi/ether solution and stirred for 10 min; subsequently then 1.6 g (16.5 mmol) of cyclohexanone in 15 ml of dry ether were added and the solution was stirred for 30 min at -80°C, then diluted with 100 ml of dry THF. One more batch of 22.6 ml (16.5 mmol) of BuLi-solution was added, followed by 1.75 g (16.5 mmol) of benzaldehyde in 20 ml of dry THF, then the mixture was allowed to warm up slowly to room temperature. Most of the solvent was removed in vacuo, the remaining solution was poured onto water and extracted with ether. After drying ($MgSO_4$), evaporation and recrystallisation (cyclohexane) 2 g (42%) of colourless crystals were left; mp 82-96°C; Rf(a)=0.47 (PE/EE=1:1), pmr($CDCl_3$): 7.52-7.20 (m,5H), 7.07 (d,1H), 6.59 (dd,1H,J=0.48 Hz), 6.07 (d,1H,J=0.48 Hz), 4.82 (bs,1H), 3.53 (bs,1H), 2.24- 1.25 (m,10H); cmr($CDCl_3$): 147.86 (s), 143.79 (s), 142.98 (s), 127.98 (d), 127.16 (d), 126.98 (d), 126.14 (d), 121.69 (d), 72.55 (s), 70.92 (d), 38.31 (t), 25.36 (t), 21.78 (t); ir(KBr): 3400, 2940, 1020, 960, 810, 700; Found: C, 70.67; H, 6.97. Calcd. for $C_{17}H_{20}O_2S$ (288.41): C, 70.80; H, 6.99.

4-(4-Dimethylamino-1-hydroxy-cyclohexyl)-α-phenyl-3-thiophenemethanol (5b): According to the procedure for preparation of 5a from the above following quantities of starting materials were used: 2.93 g (12.1 mmol) of dibromothiophene in 15 ml of dry ether, 2 x 11.8 ml (12.1 mmol) of 1.03 M BuLi/ether solution, 1.28 g (12.1 mmol) of benzaldehyde in 10 ml of dry ether, 1.7 g (12.1 mmol) of 4-dimethyl-aminocyclohexanone in 15 ml of dry THF. Work-up was modified as follows: the concentrated reaction mixture was poured onto water; on addition of some ml of ether and vigorous shaking crystallisation was induced. After recrystallisation from i-propanol 1.89 g (47%) of colourless crystals were obtained; mp 178-180°C; Rf(b)=0.52 (Bz/EtOH=9:1); pmr($CDCl_3$/DMSO-$d_6$=1:1): 7.31- 6.97 (m,5H), 6.88 (d,1H), 6.34 (d,1H), 5.94 (s,1H), 5.92 (br s,1H),5.16 (br s,1H), 2.22 (s,6H), 2.34-1.38 (m,9H); cmr(DMSO-$d_6$): (s), 144.99 (s), 127.38 (d), 126.46 (d), 126.24 (d), 124.56 (d), 119.96 (d), 70.22 (s), 69.03 (d), 62.25 (d), 41.02 (q), 37.17 (t), 23.14 (t); Found: C, 67.74; H, 7.50; N, 4.14. Calcd. for $C_{19}H_{25}NO_2S \cdot 0.3\ H_2O$ (336.87): C, 67.74; H, 7.66; N, 4.16.

4-[4-(1-Hydroxy-1-phenylmethyl)-3-thienyl-]-1-methyl-4-piperidinol (5c): The procedure for 5a, reacting 4 g (16.5 mmol) of 3,4-dibromothiophene in 15 ml of dry ether with 22.6 ml (16.5 mmol) of 0.73 M BuLi/ether solution, then with 1.87 g (16.5 mmol) of N-methyl-4-piperidone in 15 ml of dry ether followed by 22.6 ml (16.5 mmol) of BuLi solution and 1.75 g (16.5 mmol) of benzaldehyde in 15 ml of dry ether, was changed as follows: ether was used as solvent for the whole sequence, so the dilution with THF has to be neglected. For work-up the reaction mixture was poured onto 2N-HCl, washed with ether and basified. The precipitated product was dried in vacuo and washed with diethyl ether at -10°C: 2.73 g (56%) of colourless crystals; mp 208-210°C; Rf(b)=0.42 (Bz/EtOH=9:1); pmr(DMSO-$d_6$): 7.55-7.29 (m,5H), 7.26 (d,1H), 6.89 (d,1H), 6.29 (s,1H), 6.00- 4.80 (br s,2H), 2.61-2.29 (m,4H), 2.19 (s,3H), 2.06-1.65 (m,4H); cmr(DMSO-$d_6$): 148.23 (s), 145.14 (s), 144.71 (s), 127.27 (d), 126.40 (d), 126.19 (d), 124.72 (d), 120.23 (d), 68.97 (d), 68.32 (s), 50.71 (t), 45.51 (q), 37.49 (t), 37.22 (t); ir(KBr): 3400, 2840, 1450, 1270, 1020, 860, 830, 780, 700, 695.

4-(1-Hydroxy-1-cyclohexyl)-3-thiophene Carboxylic Acid (6a): According to the procedure for 5a following amounts of starting products were used: 5 g (20 mmol) of 3,4-dibromothiophene in 15 ml of dry ether, 29.5 ml (20 mmol) of 0.73 M BuLi/ether solution, 2 g (20 mmol) of cyclohexanone in 15 ml of dry ether and 29.5 ml (20 mmol) of BuLi solution for the second lithiation. Then $CO_2$, dried over $H_2SO_4$, was bubbled through the solution for 1 h, the temperature was kept below -70°C. The mixture was allowed to warm up to room temperature, poured onto water, basified and washed with ether. Then the aqueous layer was acidified with 2N-HCl and extracted with ether. After drying ($MgSO_4$), evaporation and recrystallisation from benzene 1.9 g (41%) of colourless crystals remained: mp 148-150°C; Rf(a)=0.38 (EE); pmr(DMSO-$d_6$): 11.20-6.30 (br s,2H), 8.23 (d,1H), 7.10 (d,1H), 2.34-0.98 (m,10H); cmr(DMSO-$d_6$): 166.33 (s), 150.35 (s), 137.51 (d), 131.82 (s), 122.23 (d), 70.22 (s), 37.01 (t), 25.30 (t), 21.56 (t); ir(KBr): 3475, 2920, 1660, 1440, 1270.

4-(4-Hydroxy-1-methyl-4-piperidinyl)-3-thiophenecarboxylic Acid, Hydrochloride (6b.HCl): The reaction was performed according to

the procedure for 6a above: 4 g (16 mmol) of 3,4-dibromothiophene in 15 ml of dry ether, 22.6 ml (16 mmol) of 0.73 M BuLi/ether solution, 1.87 g (16 mmol) of N-methyl-4-piperidone in 15 ml of dry ether, further 22.6 ml of BuLi-solution and $CO_2$ were the starting compounds. Work-up was changed as follows: the solvent was removed to a large extent, the mixture was poured onto water, basified, washed with ether, acidified and washed again several times with ether. The aqueous layer was evaporated in vacuo. The remaining crystal paste was cooled, triturated with ice-water, filtered off and dried in vacuo: 1.8 g (50%) of colourless crystals impurified with little amounts of inorganic salts; pmr(DMSO-$d_6$): 10.58 (br s,1H), 8.33 (d,1H), 7.44 (d,1H), 4.30 (br s,2H), 3.46-2.95 (m,4H), 2.69 (s,3H), 2.34-1.86 (m,4H); cmr(DMSO-$d_6$): 166.98 (s), 147.16 (s), 138.43 (d), 131.55 (s), 123.48 (d), 66.10 (s), 49.58 (t), 42.69 (q), 37.60 (t).

4-Bromo-3-(1-hydroxycyclohexyl)-α-phenyl-2-thiophenemethanol (7): Procedure analogous to preparation of 5c: starting materials were 5 g (20,6 mmol) of 3,4-dibromothiophene in 20 ml of dry ether, 2 x 26.2 ml (20.6 mmol) of 0.79 M BuLi/ether solution for both lithiations, 2.0 g (20.6 mmol) of cyclohexanone in 20 ml of dry ether and 2.23 g (20.6 mmol) of benzaldehyde in 25 ml of dry ether. The whole reaction sequence is performed in ether as solvent. For working up the mixture was poured onto water and extracted with ether. After drying ($MgSO_4$) and evaporation the crystalline crude product showed, due to pmr, a ratio of 80:20 for 7 and 5a. Recrystallisation from cyclohexane yielded pure 7 (4.3 g, 57%) as colourless crystals; mp 123-140°C; Rf(a)=0.50 (PE/EE=1:1); pmr($CDCl_3$): 7.53-7.21 (m,5H); 7.17 (s,1H), 6.26 (d,1H,J = 5 Hz); 4.45 (OH,d,1H,J = 5 Hz), 2.88-2.24 (m,2H), 2.39 (br s,1H), 1.83 - 1.06 (m,8H); cmr(DMSO-$d_6$): 143.19 (s), 143.04 (s), 141.20 (s), 128.19 (d), 127.87 (d), 126.68 (d), 123.80 (d), 109.12 (s), 76.34 (s), 71.41 (d), 35.81 (t), 34.80 (t), 24.49 (t), 21.35 (t), 21.24 (t); ir(KBr): 3300, 2920, 2850, 1450, 1400, 1140, 980, 700, 610; Found: C, 56.07; H, 5.25. Calcd. for $C_{17}H_{19}BrO_2S$ (367.31): C, 55.59; H, 5.21.

3-Bromo-4-(1-hydroxycyclohexyl)-α-phenyl-2-thiophenemethanol (9a): 4 g (16.5 mmol) of 3,4-Dibromothiophene in 15 ml of dry

ether were added dropwise at -80°C under $N_2$ to 22.6 ml of (16.5 mmol) of 0.73 M BuLi/ether solution, followed after 10 min by 1.6 g (16.5 mmol) of cyclohexanone in 15 ml of dry ether. After 30 min an LDA solution (prepared from 1.7 g (17 mmol) of diisopropylamine in 5 ml of dry ether and 22.6 ml (16 mmol) of 0.73 M BuLi/ether solution under $N_2$ at -10°C, stirred for 15 min at room temperature) was added at -70°C. The mixture was stirred for 3 h, then 1.75 g (16.5 mmol) of benzaldehyde in 15 ml of dry ether were added. After 30 min the solution was poured onto water, extracted with ether, dried ($MgSO_4$) and evaporated. The remaining oil was resolved by flash-chromatography ($SiO_2$, eluent: PE/EE=2:1): 2.35 g (54%) of 10a (intermediate after first lithiation) and 2.1 g (35%) of 9a, colourless crystals; mp 145-146°C; Rf(a)=0.2 (PE/EE= 1:1); pmr($CDCl_3$): 7.63-7.26 (m,5H), 7.20 (s,1H), 6.15 (d,1H, J = 2.6 Hz), 2.85 (OH,d,1H,J=2.6 Hz), 2.26 (s,1H), 2.14-1.00 (m,10H); cmr($CDCl_3$): 146.88 (s), 145.26 (s), 142.28 (s), 127.38 (d), 126.68 (d), 125.92 (d), 118.77 (d), 105.11 (s), 71.35 (s), 70.38 (d), 35.43 (t), 35.40 (t), 24.60 (t), 20.97 (t); ir(KBr): 3450, 2920, 1140, 1130, 1060, 1040, 1010, 700, 690; Found: C, 55.52; H, 5.17. Calcd. for $C_{17}H_{19}BrO_2S$ (367.31): C, 55.59; H, 5.21.
Physical properties of 10a see procedure for 10a below.

4-[4-Bromo-5-(1-hydroxy-1-phenylmethyl)-3-thienyl]-1-methyl-4-piperidinol (9b): According to the procedure for 9a the following amounts of starting materials were used: 4 g (16.5 mmol) of 3,4-dibromothiophene in 15 ml of dry ether, 22.6 ml (16.5 mmol) of 0.73 M BuLi/ether solution, 1.87 g (16.5 mmol) of N-methyl-4-piperidone in 15 ml of dry ether, 16 mmol LDA/ether solution and 1.75 g (16.5 mmol) of benzaldehyde in 15 ml of dry ether. In this case the second lithiation was performed for 3 h at -45°C. The mixture was allowed to warm up to room temperature, poured onto water, acidified, washed with ether, basified and extracted with $CH_2Cl_2$. After drying ($MgSO_4$) and evaporation a yellowish, tough oil remained, which was dissolved in 20 ml of benzene. On addition of 500 ml of cyclohexane 3.4 g (56%) of colourless crystals precipitated; mp 101-104°C; Rf(b)=0.3 (Bz/EtOH=9:1); pmr($CDCl_3$): 7.50-7.20 (m,5H), 6.99 (s,1H), 6.08 (s,1H), 3.40 (br s,1H), 2.85-1.49 (m,9H) 2.26 (s,3H); cmr($CDCl_3$): 147.10 (s), 144.61 (s), 142.39 (s), 128.19

(d), 127.49 (d), 126.19 (d), 119.82 (d), 105.81 (s), 70.60 (d), 68.70 (s), 50.44 (t), 50.40 (t), 45.67 (q), 35.43 (t); ir(KBr): 3400, 2920, 2840, 2800, 1450, 1295, 1275, 1150, 1060, 780, 700; Found: C, 52.06; H, 5.36; N, 3.77. Calcd. for $C_{17}H_{20}BrNO_2S \cdot 0.55$ $H_2O$ (392.24): (382.33): C, 52.06; H, 5.42; N, 3.57.

1-(4-Bromo-3-thienyl)-cyclohexan-1-ol (10a): Under $N_2$ 2.8 g (11 mmol) of 3,4-dibromothiophene in 15 ml of dry ether were added to 14.5 ml (11 mmol) of 0.79 M BuLi/ether solution at -80°C, followed by 1.1 g (11 mmol) of cyclohexanone in 10 ml of dry ether. After 1 h stirring the mixture was poured onto water, extracted with ether, dried ($MgSO_4$) and evaporated: 2.7 g (90%) of colourless crystals; mp 49-51°C; Rf(a)=0.78 (PE/EE=1:1); pmr($CDCl_3$): 7.38 (d,1H), 7.31 (d,1H), 2.28 (s,1H), 2.13-1.01 (m,10H); cmr($CDCl_3$): 146.77 (s), 125.22 (d), 121.26 (d), 108.25 (s), 72.44 (s), 36.36 (t), 25.25 (t), 21.67 (t); ir(KBr): 3400, 3100, 2920, 2840, 1440, 1135, 1250, 1045, 970, 795, 790.

4-(4-Bromo-3-thienyl)-1-methyl-4-piperidinol (10b):According to the procedure for 10a reported above 2.6 g (10.8 mmol) of 3,4-dibromothiophene, 13.7 ml (10.7 mmol) of 0.79 M BuLi/ether solution and 1.2 g (10.6 mmol) of N-methyl-4-piperidone, both dissolved in 15 ml of dry ether were reacted. Work-up was changed as follows: the mixture was poured onto 2N HCl, washed with ether, basified with 3N NaOH and extracted with ether. After drying ($MgSO_4$) and evaporation 2.5 g (84%) of colourless crystals remained; mp 128-130°C; Rf(b)=0.52 (Bz/EtOH=9:1); pmr($CDCl_3$): 7.28 (d,1H), 7.21 (d,1H), 2.84-2.37 (m,5H), 2.31 (s,3H), 2.24-1.79 (m,4H); cmr ($CDCl_3$): 147.37 (s), 125.92 (d), 122.61 (d), 107.93 (s), 68.76 (s), 50.88 (t), 46.11 (q), 35.33 (t); ir(KBr): 3400, 3100, 2930, 2840, 1460, 1275, 1150, 970, 860, 790.

Spiro[cyclohexane-1,1'-[1H,3H]thieno[3,4-c]furan]-3'-one (3a): 0.55 g (2.43 mmol) of 6a and 0.50 g (2.43 mmol) of dicyclohexyl- carbodiimid were stirred in 20 ml of dry ether for 20 min at room temperature. Then the precipitated dicyclohexylurea was filtered off, by evaporation 0.48 g (95%) of crystalline crude product were obtained. For removing traces of dicyclohexylurea still present the product was purified by

flash-chromatography on $SiO_2$ (eluent: PE/EE=1:1): 0.38 g (75%) of colourless crystals; mp 109-110°C; Rf(a)=0.56 (PE/EE=1:1); pmr($CDCl_3$): 7.84 (d,1H), 7.08 (d,1H), 2.11-1.02 (m,10H); cmr($CDCl_3$): 162.43 (s), 154.58 (s), 132.96 (s), 125.54 (d), 115.08 (d), 85.55 (s), 36.36 (t), 24.16 (t), 22.21 (t); ir(KBr): 3100, 2900, 1735, 1260, 1200, 1080, 920, 790; Found: C, 63.29; H, 5.80. Calcd. for $C_{11}H_{12}O_2S$ (208.28): C, 63.43; H, 5.81.

1-Methyl-spiro[piperidine-4,1'-[1H,3H]-thieno[3,4-c]furan]-3'-one (3b): 1.4 g of 6b.HCl, 1 g of sodium acetate and 2 ml of acetic anhydride were refluxed in 15 ml of benzene for 4 h. Then the mixture was cooled, poured onto saturated $Na_2CO_3$-solution and stirred for 1 h. After separation of the benzene layer, extraction with $CHCl_3$, drying ($MgSO_4$), evaporation and recrystallisation from cyclohexane 0.5 g of yellowish crystals remained; mp 122-125°C; Rf(b)=0.53 (Bz/EtOH=9:1); pmr($CDCl_3$): 7.82 (d, 1H), 7.06 (d,1H), 2.79-2.49 (m,4H), 2.36 (s,3H), 2.14-1.79 (m,4H); cmr($CDCl_3$): 162.05 (s), 154.03 (s), 132.74 (s), 126.13 (d), 115.13 (d), 82.46 (s), 51.36 (t), 45.73 (q), 36.30 (t); ir(KBr): 3100, 2700, 1745, 1560, 1220, 1070, 925, 785; Found: C, 59.22; H, 5.91; N, 6.35. Calcd. for $C_{11}H_{13}NO_2S$ (223.30): C, 59.17; H, 5.87; N, 6.27.

3'-Phenyl-spiro[cyclohexane-1,1'-[1H,3H]-thieno[3,4-c]-furan] (3c): 1 g (3.5 mmol) of 5a and 0.66 g (3.5 mmol) of tosylchloride were refluxed in 15 ml of pyridine for 3 h, then the mixture was poured onto ice/conc. HCl, extracted with ether, dried ($MgSO_4$) and evaporated. The crude product was purified by flash-chromatography ($SiO_2$,eluent:PE/EE=6:1). 3c was a colourless oil; yield: 0.5 g (53%); bp(0.3 mm Hg): 100-115°C (Kugelrohr); Rf(a)=0.37 (PE/EE=3:1); pmr($CDCl_3$): 7.50-7.20 (m, 5H), 6.86 (d,1H), 6.76 (dd,1H,J=1.2 Hz), 5.98 (dd,1H,J=1.2 Hz), 2.12-1.13 (m,10H); cmr($CDCl_3$): 152.73 (s), 148.73 (s), 142.06 (s), 128.24 (d), 127.59 (d), 126.51 (d), 113.89 (d), 112.75 (d), 83.33 (s), 78.61 (d), 38.31 (t), 37.38 (t), 25.14 (t), 23.03 (t); ir(KBr): 2940, 1450, 1020, 775, 735, 695; Found: C, 75.12; H, 6.78. Calcd. for $C_{17}H_{18}OS \cdot 0.08\ H_2O$ (271.84): C, 75.11; H, 6.73.

4-Dimethylamino-3'-phenyl-spiro[cyclohexane-1,1'-[1H,3H]-thieno[3,4-c]furan] (3d): 2.7 g (8.1 mmol) of 5b were refluxed in acetic acid for 2 h, poured onto water, basified with 40%-NaOH-solution, extracted with ether, dried ($MgSO_4$) and evaporated: 1.9 g (70%) of yellowish oil; bp(0.01 mm Hg): 140°C (Kugelrohr); Rf(b)=0.7 (Bz/EtOH=9:1); pmr($CDCl_3$): 7.52-7.13 (m,5H), 6.78 (d,1H), 6.68 (dd,1H,J=0.9 Hz), 5.97 (d,1H,J=0.9 Hz), 2.29 (s,6H), 2.58-1.48 (m,9H); cmr($CDCl_3$): 153.22 (s), 148.24 (s), 142.11 (s), 128.19 (d), 127.43 (d), 126.24 (d), 114.21 (d), 112.05 (d), 81.65 (s), 78.61 (d), 62.69 (d), 41.28 (q), 37.55 (t), 36.63 (t), 24.49 (t), 24.22 (t).

For preparation of 3d.HCl the oil was dissolved in dry ethanol, saturated HCl/EtOH-solution was added, then the product was precipitated by dropwise addition of dry ether; mp:150-154°C; pmr($CDCl_3$/DMSO-$d_6$=1:1): 11.0 (br s,1H), 7.25-6.93 (m,5H), 6.72 (d, 1H), 6.56 (dd,1H,J=0.85 Hz), 5.78 (d,1H,J=0.85 Hz), 3.38-2.94 (m,1H), 2.69 (d,6H), 2.34-1.41 (m,8H); cmr($CDCl_3$/DMSO-$d_6$=1:1): 149.70 (s), 145.74 (s), 140.00 (s), 126.46 (d), 125.75 (d), 124.45 (d), 113.13 (d), 111.61 (d), 78.29 (s), 76.72 (d), 61.44 (d), 37.33 (q), 34.30 (t), 33.43 (t), 20.75 (t), 20.43 (t); Found: C, 61.95; H, 6.89; N, 3.73. Calcd. for $C_{19}H_{24}ClNOS \cdot 1.02\ H_2O$ (368.30): C, 61.69; H, 7.13; N, 3.80.

1-Methyl-3'-phenyl-spiro[piperidine-4,1'-[1H,3H]-thieno[3,4-c]-furan] (3e): The reaction was carried out analogous to the procedure for 3d reported above; starting product: 2.5 g (8.2 mmol) of 5c; yield (after Kugelrohr-destillation): 1.93 g (82%) of yellowish oil; bp(0.01 mm Hg): 140°C (kugelrohr); Rf(b)=0.7 (Bz/ EtOH=9:1); pmr($CDCl_3$): 7.59-7.23 (m,5H), 6.86 (d,1H), 6.69 (dd, 1H,J=1.3 Hz), 5.99 (d,1H,J=1.2 Hz), 2.74-2.44 (m,4H), 2.33 (s, 3H), 2.15-1.79 (m,4H); cmr($CDCl_3$): 151.59 (s), 147.75 (s), 141.30 (s), 127.81 (d), 127.16 (d), 125.92 (d), 113.89 (d), 112.48 (d), 79.65 (d), 78.13 (s), 51.69 (t), 45.62 (q), 37.38 (t), 36.52 (t); ir(neat): 2940, 2790, 1280, 1140, 1030, 775, 730, 700; Found: C, 71.08; H, 6.82; N, 4.53. Calcd. for $C_{17}H_{19}NOS \cdot 0.1\ H_2O$ (287.21): C, 71.09; H, 6.74; N, 4.88.

3e.HCl: mp:205-208°C (dec); ir(KBr): 3400, 2960, 1620, 1440, 1260, 985, 800, 730, 690; Found: C, 62.10; H, 6.23; N, 4.19. Calcd. for $C_{17}H_{20}ClNOS \cdot 0.38\ H_2O$ (328.72): C, 62.12; H, 6.37; N, 4.26.

3'-Bromo-6'-phenyl-spiro[cyclohexane-1,4'(6'H)-thieno[2,3-c]-furan] (8): According to the procedure for 3c reported above 1 g (3.1 mmol) of 7 and 0.58 g (3.1 mmol) of tosylchloride were reacted in 20 ml of dry pyridine. The of crude product was purified by flash chromatography ($SiO_2$, eluent: PE/EE=6:1) yielding 0.6 g (63%) of yellow crystals, 0.26 g of starting material could be recovered; mp 94-97°C; Rf(a)=0.73 (PE/EE=6:1); pmr($CDCl_3$): 7.53-7.22 (m, 5H), 7.12 (d,1H,J=0.9 HZ), 6.16 (d,1H,J=0.9 Hz), 2.20-1.30 (m, 10H); cmr($CDCl_3$): 147.96 (s), 142.22 (s), 141.41 (s), 128.42 (d), 127.98 (d), 127.00 (d), 126.24 (d), 102.78 (s), 86.10 (s), 81.10 (d), 36.36 (t), 35.22 (t), 25.03 (t), 22.32 (t), 21.83 (t); ir(KBr): 3100, 2930, 2850, 1490, 1450, 1290, 900, 760, 700.

REFERENCES


1) P. Stanetty, H. Fröhlich, and F. Sauter, poster presented at the XIIth International Conference on Organometallic Chemistry, September 8th-13th, 1985, Congress Center Hofburg, Vienna, abstract book, page 118.
2) F. Sauter, P. Stanetty, and H. Fröhlich, Thienospirans V, the preceeding paper in this journal.
3) S. Gronowitz, P. Moses, A.-B. Hornfeldt, and R. Hakansson, Ark. Kemi, **17** , 165 (1961).
   P. Shu and L. Chiang, J. Chem. Soc. Chem. Comm., **1981** , 920.
4) D. W. Slocum and P. L. Gierer, J. Org. Chem., **41** , 3668 (1976).
5) H. Gilman, J. Am. Chem. Soc., **71** , 1499 (1949).
6) H. Gilman, J. Am. Chem. Soc., **66** , 1515 (1944).
7) S. Gronowitz and T. Raznikiewicz, Org. Synth. Coll. Vol.V, 149, (1973).
8) V. Meyers and H. Kreis, Chem. Ber., **16** , 2172 (1883).
9) N. N. Nelson and G. A. Mortimer, J.Org. Chem., **22** , 1151 (1957).


Received, 17th March, 1987