

## Some Substitution Reactions of 2-Phenylthiophene

NINA GJØS\* and SALO GRONOWITZ

*Division of Organic Chemistry, University of Lund, Chemical Center, P.O.B. 740,  
S-22007 Lund 7, Sweden*

Isomer distributions in some electrophilic substitution reactions of 2-phenylthiophene, all yielding the 5-substituted compound as the main product, have been investigated. In addition, a few per cent of the 3-isomer were also detected. Bromination with bromine in acetic acid yielded 4 % 3-bromo-2-phenylthiophene, Vilsmeier formylation yielded only 0.05 % 3-formyl-2-phenylthiophene, while Friedel-Crafts acetylation under two different conditions, acetic anhydride/phosphoric acid and acetyl chloride/tin tetrachloride in benzene solution, yielded 1 % and 0.1 % 3-isomer, respectively. Authentic samples of 3- and 4-substituted 2-phenylthiophenes were prepared by other routes. No 4-substituted 2-phenylthiophenes could be detected in the reaction products by GLC.

Metalation with butyllithium in ether led only to 5-substitution. The product was identified as the carboxylic acid.

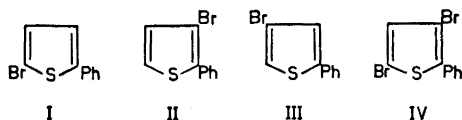
During recent years there has been increased interest in the quantitative study of electrophilic substitution of thiophene. The  $\alpha/\beta$ -ratios have been carefully determined for a number of reactions and the applicability of linear free energy treatments to electrophilic substitution at the  $\alpha$ - and  $\beta$ -positions has been studied.<sup>1-4</sup> The development of GLC analysis has also led to accurate studies of isomer distributions on substitution of 2- and 3-substituted thiophenes. Thus Östman<sup>5</sup> has studied the nitration of 2- and 3-thiophene aldehyde, thiophene nitrile, and nitrothiophenes. The effect of a few substituents at the 5-position upon the rate of chlorination and bromination at the 2-position has also been studied, and the Hammett relation could be applied to the data obtained.<sup>2</sup>

We have studied some reactions of 2-phenylthiophene in order to investigate the effect of the phenyl group on substitution in the thiophene ring in connection with a program on the directing effects of aromatic rings as substituents. We hope that such a study will contribute to the understanding of the rather complex behaviour of biphenyl upon substitution. A number of substitution reactions of 2-phenylthiophene have been described in the literature, but no attempts have been made to determine the minor isomers.<sup>6-8</sup>

\* Taken in part from the Ph.D. thesis of N. Gjøes, University of Lund, 1971.

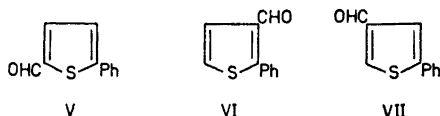
In an earlier paper,<sup>9</sup> we described the nitration of 2-phenylthiophene, which gave a mononitrated mixture consisting of 60 % 5-nitro-2-phenylthiophene and 40 % 3-nitro-2-phenylthiophene, the phenyl ring acting as an *ortho-para* directing group. With more selective electrophilic reagents the amount of the 3-isomer is expected to decrease. An obvious comparison is with the bromination of biphenyl<sup>10</sup> which only yields a few per cent of *ortho*-substitution.

The isomer distribution in the nitration<sup>9</sup> was determined by NMR spectral analysis, and we have now investigated the nitration product more accurately by GLC which, however, gave very similar results (59 % 5-nitro-2-phenylthiophene and 41 % 3-nitro-2-phenylthiophene). No other isomer could be detected. This reaction was carried out with cupric nitrate in acetic anhydride, and we obtained the same isomer distribution using nitric acid in acetic anhydride at  $-20$  to  $-30^{\circ}\text{C}$ .



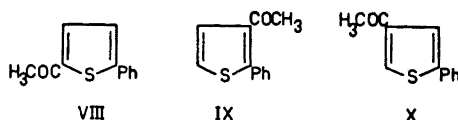
Bromination with bromine in refluxing acetic acid yielded a monobrominated fraction consisting of two isomers in the ratio 96:4, as determined by combined GLC-mass spectrometry analysis. Recrystallization of the crude reaction product from ethanol yielded the main component pure, and it was identified as 5-bromo-2-phenylthiophene (I) partly by its melting point in accordance with literature values and partly by the NMR spectrum, which showed two doublets with a coupling of 3.9 Hz, characteristic for 2,5-disubstituted thiophenes. The minor component had the same GLC retention time as an authentic sample of 3-bromo-2-phenylthiophene (II), which was prepared in the following way. 3-Bromo-2-thienyllithium, obtained by halogen-metal exchange between 2,3-dibromothiophene and ethyllithium, was reacted with cyclohexanone to give 3-bromo-2-(1-cyclohexenyl)thiophene, which was aromatized with 2,5-dichloro-5,6-dicyanobenzoquinone (DDQ). In order to check that no 4-isomer had been formed which could have been overlooked if its retention time on the column used was the same as for one of the other isomers, 4-bromo-2-phenylthiophene (III) was prepared from 2,4-dibromothiophene in the same way as II. As III had a longer retention time than the other two, GLC analysis indicated that this compound was not formed in the bromination reaction, at any event to an extent less than 0.5 %.

In addition to the two monobromo compounds, about 5 % of a dibromophenylthiophene was formed, with the same retention time as the product from the bromination of II, which undoubtedly must be 3,5-dibromo-2-phenylthiophene (IV).



Formylation of 2-phenylthiophene with *N,N*-dimethylformamide and phosphorus oxychloride yielded as the main product 5-formyl-2-phenylthiophene (V), obtained pure after recrystallization of the crude reaction product from aqueous ethanol. The structure was confirmed by the NMR spectrum, as the two thiophene doublets showed a coupling of 4.0 Hz. In order to establish whether any other isomers had been formed, 3-formyl-2-phenylthiophene (VI) and 4-formyl-2-phenylthiophene (VII) were prepared by halogen-metal exchange between the corresponding bromo-2-phenylthiophenes and ethyllithium, followed by reaction with *N,N*-dimethylformamide. Careful GLC analysis showed the formylation product to contain about 0.05 % of a compound with the same retention time as VI, while VII was not detected. The NMR spectrum of VI showed coupling between the aldehyde hydrogen and both the 4- and 5-hydrogens in the thiophene ring. The aromatic quartet at lowest field was assigned to the 4-hydrogen by comparison with the effect of an aldehyde group in the 3-position on the chemical shift of the other hydrogens in the thiophene ring,<sup>11</sup> and the size of the coupling to the aldehyde proton was 0.4 Hz. The coupling to the 5-hydrogen was somewhat larger (0.8 Hz), as is usually found in 3-thiophene aldehydes.<sup>12</sup>

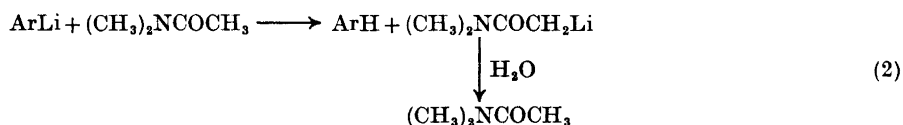
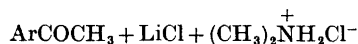
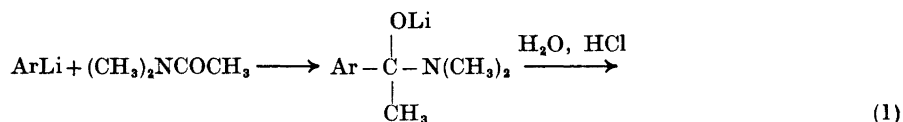
Acetylation with acetic anhydride and phosphoric acid yielded as the main product 5-acetyl-2-phenylthiophene (VIII), confirmed by its NMR data and melting point in accordance with literature values. GLC-mass spectrometry investigations of the reaction product showed in addition to about 30 %



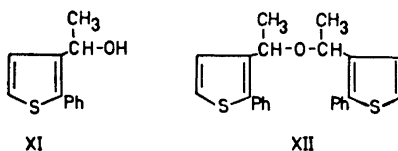
of unreacted 2-phenylthiophene about 1 % of a second acetyl compound with the same retention time as 3-acetyl-2-phenylthiophene (IX), while the 4-isomer (X) was not detected. The reaction was also carried out under other conditions, reaction with acetyl chloride and tin tetrachloride in benzene solution also yielded the 5-isomer as the main product, but now the amount of the 3-isomer was only 0.1 %. As the amount of unreacted 2-phenylthiophene was about 10 %, these acetylation conditions seem to be better than those first described. The higher selectivity in the tin tetrachloride catalyzed reaction might be due both to electronic effects and steric factors. It seems reasonable that the acetyl chloride-tin tetrachloride complex has greater spatial requirements than the attacking reagent in acetic anhydride- $H_3PO_4$ .

The 4-isomer (X) was prepared by halogen-metal interconversion between III and ethyllithium followed by reaction with *N,N*-dimethylacetamide, analogous to the reaction with *N,N*-dimethylformamide that yielded VII. However, further investigations showed this reaction of an aryllithium compound with dimethylacetamide not to be as general as with dimethylformamide. Starting from II, less than 10 % of 3-acetyl-2-phenylthiophene (IX) was formed in the reaction with dimethylacetamide, while the main product was 2-phenylthiophene. About the same yield of 4-acetyl-3-phenylthiophene<sup>13</sup> was formed in the corresponding reaction with 4-bromo-3-phenylthiophene.

In this case 3-phenylthiophene was the main product. In contrast, both bromo compounds gave good yields of aldehydes when reacted with dimethylformamide. Evidently some sort of an *ortho* effect is responsible for these poor yields of acetylation product, since the phenyl and bromo groups are *ortho* to each other in both compounds that did not react in the expected manner, while III, as well as 5-bromo-3-phenylthiophene,<sup>13</sup> gave satisfactory results. Since 2-phenylthiophene was the main product, when we expected IX, metal-halogen exchange must have occurred, and in addition to the "normal" reaction (1) it may be proposed that the aryllithium compound metalates *N,N*-dimethylacetamide (reaction 2).



In an attempt to show that  $(\text{CH}_3)_2\text{NCOCH}_2\text{Li}$  could be an intermediate in the reaction, the reaction mixture was hydrolyzed with deuterioacetic acid in a separate experiment, and the NMR spectrum of the isolated dimethylacetamide showed a proportion of 2.75 : 1 between the two different types of methyl groups. In  $(\text{CH}_3)_2\text{NCOCH}_2\text{D}$  the proportion should be 3 : 1, and consequently our sample contains some non-deuterated dimethylacetamide (possibly unreacted starting material). Thus, this experiment supports the proposed reaction path (2).



3-Acetyl-2-phenylthiophene (IX) was more conveniently prepared from 3-bromo-2-phenylthiophene in a two-step reaction. The bromo compound was first reacted with ethyllithium at  $-70^\circ\text{C}$  and then with acetaldehyde, in analogy with the preparation of 3-(1-hydroxyethyl)thiophene.<sup>14</sup> Basic hydrolysis of the reaction mixture yielded 3-(1-hydroxyethyl)-2-phenylthiophene (XI) as the main product, together with some unreacted starting material and 2-phenylthiophene, and XI was obtained pure by column chromatography on silica gel. On the other hand, acidic hydrolysis yielded in addition to XI, minor amounts (about 5 %) of the ether XII which was separated by column chromatography. The NMR spectrum of XII showed two methyl

doublets, thus indicating the presence of both the racemic and the meso forms, and the methine protons gave a quartet with peaks that were partly split again. The mass spectrum showed a parent peak at  $m/e$  390. Oxidation of XI with chromium(VI) oxide in pyridine gave IX in good yield, analytically pure after recrystallization from aqueous ethanol.

Since no 4-substituted products were detected, these electrophilic substitution reactions of 2-phenylthiophene show the phenyl group to increase the reactivity of the 3-position relative to the 4-position in the thiophene ring, consistent with this group being considered as an *ortho-para* directing substituent due to its electron-donating conjugation effect. Furthermore, the reactivity of the 3-position relative to the 5-position has also increased, compared to thiophene itself, where nitration yields 15 % of the isomer.<sup>15</sup> The difference between the  $\alpha/\beta$  ratio of thiophene<sup>1</sup> (490) and the 5- to 3-ratio of 2-phenylthiophene in the bromination with bromine in acetic acid (24) is even larger. However, the reaction conditions are not identical. The results in the formylation and acetylation are more difficult to evaluate, but it appears that more 3-isomer is formed in the  $\text{SnCl}_4$  catalyzed acetylation of 2-phenylthiophene than of thiophene. The results obtained are collected in Table 1, and it is quite obvious that the isomer distributions obtained are quite sensitive to the electrophilic reagent and the conditions employed. Both electronic and steric factors are certainly responsible for the varying 5- to 3-ratio obtained in electrophilic substitution of 2-phenylthiophene.

Table 1. Isomer distribution in substitution reactions of 2-phenylthiophene.

Reagent	Isomer distribution (%)	
	5-position	3-position
$\text{Cu}(\text{NO}_3)_2 - \text{Ac}_2\text{O}$ or $\text{HNO}_3 - \text{Ac}_2\text{O}$	59	41
$\text{Br}_2 - \text{HOAc}$	96	4
$(\text{CH}_3)_2\text{NCHO} - \text{POCl}_3$	99.95	0.05
$\text{Ac}_2\text{O} - \text{H}_3\text{PO}_4$	99	1
$\text{CH}_3\text{COCl} - \text{SnCl}_4 - \text{C}_6\text{H}_6$	99.9	0.1
$n\text{-C}_4\text{H}_9\text{Li}$	100	—

Metalation with butyllithium was also investigated. 2-Phenylthiophene was treated with butyllithium in anhydrous ether at room temperature and the product isolated as the carboxylic acid after reaction with solid carbon dioxide in ether. NMR spectrometry showed 2-phenyl-5-thiophenecarboxylic acid to be the main product, as the spectrum in addition to the phenyl hydrogen resonances showed two doublets with a coupling of 3.9 Hz. GLC analysis after esterification of the crude acid with diazomethane showed only one peak, *i.e.* no  $\beta$ -isomer was found. This is not unexpected since the sulphur atom activates the  $\alpha$ -position to such a great extent in this reaction.<sup>11</sup>

#### EXPERIMENTAL

*Nitration of 2-phenylthiophene with nitric acid in acetic anhydride.* 2 ml of a solution of 2 ml fuming nitric acid in 20 ml of acetic anhydride was added with stirring to 550 mg (3.3 mmol) of 2-penta-deuteriophenylthiophene in 2 ml of acetic anhydride at  $-20$  to

-30°C. The mixture was stirred until the temperature in the cooling bath had reached 0°C. It was then poured onto ice, which caused the precipitation of 570 mg of a brown solid. The residue in the reaction vessel was extracted with chloroform, which yielded an additional 66 mg of product after evaporation of the chloroform. The crude products were then chromatographed on alumina to yield, with a 1:1 mixture of hexane and benzene as eluent, a first fraction consisting of 350 mg (50%) of a mixture of 5-nitro-2-phenyl (*d<sub>5</sub>*) thiophene and 3-nitro-2-phenyl (*d<sub>5</sub>*) thiophene in the ratio 60:40 as determined by NMR analysis. Continued elution yielded 45 mg of a red solid with molecular weight 418, as determined by mass spectrometry, and the NMR spectrum showed only one peak at  $\tau = 2.06$  ppm, indicating that this compound is in all probability a dinitrated dimer of 2-phenylthiophene. GLC investigations were carried out on the product from the nitration with cupric nitrate,<sup>9</sup> and these demonstrated the presence of 59% of the 5-isomer (retention time 6.4 min) and 41% of the 3-isomer (retention time 4.0 min) on a 3% OV 17 column at 180°C.

**Bromination of 2-phenylthiophene.** 2.5 g (16 mmol) of bromine in 25 ml of acetic acid was added dropwise with stirring to 2.5 g (16 mmol) of 2-phenylthiophene in 30 ml of acetic acid. The mixture was then refluxed for 5 h, cooled and poured into 200 ml of water. After standing over night the grey precipitate was filtered off, and the yield of this crude product was 3.4 g (89%). No additional product was obtained after extraction of the mother liquor with ether. GLC (5% NPGS, 180°C) and mass spectrometry showed that the reaction product consisted of the following compounds, the figures in parentheses indicate area percentage and retention times: 2-phenylthiophene (5%, 2.7 min), 3-bromo-2-phenylthiophene (4%, 6.1 min), 5-bromo-2-phenylthiophene (87%, 7.8 min) and 3,5-dibromo-2-phenylthiophene (4%, 12.7 min). The ratio between the two monobromo compounds was found to be 96:4 after calibrating the various peaks with known amounts. Fractional crystallization from aqueous ethanol yielded pure 5-bromo-2-phenylthiophene as white crystals, m.p. 84.5–84.7°C; literature value<sup>7</sup> m.p. 85–86°C. NMR ( $(\text{CH}_3)_2\text{SO}$ ):  $\tau_{3,4} = 2.60$  and 2.70 ppm,  $J_{34} = 3.9$  Hz,  $\tau_{\text{C}_6\text{H}_5} = 2.2 - 2.7$  ppm.

**3-Bromo-2-(1-cyclohexenyl)thiophene** was prepared from 100 g (0.41 mol) of 2,3-dibromothiophene,<sup>18</sup> 500 ml of 1.02 N ethyllithium, 40 g (0.41 mol) of cyclohexanone and 150 ml of anhydrous ether in the same way as described earlier for 4-bromo-3-(1-cyclohexenyl)thiophene.<sup>13</sup> Fractional distillation yielded 60 g (60%) of 3-bromo-2-(1-cyclohexenyl)thiophene, b.p. 149–150°C/11 mmHg. NMR ( $\text{CDCl}_3$ ):  $\tau_{4,5} = 2.94$  and 3.10 ppm,  $J_{4,5} = 5.4$  Hz,  $\tau_{\text{CH}} = 3.78$  ppm,  $\tau_{\text{CH}_2} = 7.4 - 8.5$  ppm. (Found: M.wt. 243; C 49.6; H 4.74; Br 32.6; S 13.4. Calc. for  $\text{C}_{10}\text{H}_{11}\text{BrS}$  (243.2): C 49.39; H 4.56; Br 32.86; S 13.19.)

**3-Bromo-2-phenylthiophene.** 50 g (0.21 mol) of 3-bromo-2-(1-cyclohexenyl)thiophene in 50 ml of benzene was added dropwise with stirring to a mixture of 104 g (0.46 mol) of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) and 450 ml of benzene. The reaction mixture grew warm and refluxed spontaneously for 0.5 h and then with heating for 1.5 h. After cooling to room temperature, the precipitate was filtered off and the benzene solution washed several times with 2 N sodium hydroxide until no more precipitate was formed in the aqueous layer. The organic phase was then washed with N hydrochloric acid and water and dried over magnesium sulphate. The benzene was distilled off and the residue chromatographed on alumina (Fluka, type 507 c, neutral) using hexane as eluent. Evaporation of the hexane yielded 33 g (66%) of 3-bromo-2-phenylthiophene, a liquid with b.p. 154–156°C/16 mmHg. NMR ( $(\text{CH}_3)_2\text{SO}$ ):  $\tau_{4,5} = 2.33$  and 2.81 ppm,  $J_{4,5} = 5.4$  Hz,  $\tau_{\text{C}_6\text{H}_5} = 2.2 - 2.6$  ppm. (Found: M.wt. 239; C 50.5; H 3.08; Br 32.9; S 13.7. Calc. for  $\text{C}_{10}\text{H}_7\text{BrS}$  (239.1): C 50.23; H 2.95; Br 33.41; S 13.41.)

**3,5-Dibromo-2-phenylthiophene.** 2.4 g (15 mmol) of bromine in 25 ml of acetic acid was added dropwise with stirring to 3.6 g (15 mmol) of 3-bromo-2-phenylthiophene in 50 ml of acetic acid. The mixture was refluxed for 5 h, cooled, and poured into 200 ml of water, whereupon an oil precipitated which solidified after neutralization with sodium carbonate. Filtration gave 4.2 g (88%) of a crude product which GLC showed to contain about 5% of the starting bromo compound. Recrystallization from aqueous ethanol yielded 3,5-dibromo-2-phenylthiophene as white crystals, m.p. 55–56°C. NMR ( $(\text{CH}_3)_2\text{SO}$ ):  $\tau_4 = 2.65$  ppm,  $\tau_{\text{C}_6\text{H}_5} = 2.3 - 2.6$  ppm. (Found: M.wt. 318; C 38.1; H 2.05; Br 50.3; S 10.0. Calc. for  $\text{C}_{10}\text{H}_6\text{Br}_2\text{S}$  (318.0): C 37.77; H 1.90; Br 50.25; S 10.08.)

**4-Bromo-2-(1-cyclohexenyl)thiophene.** 33.6 g (0.14 mol) of 2,4-dibromothiophene,<sup>17</sup> 200 ml of 0.85 N ethyllithium, 13.6 g (0.14 mol) of cyclohexanone and 100 ml of ether

was reacted in the same way as previously described for the preparation of 4-bromo-3-(1-cyclohexenyl)thiophene.<sup>13</sup> Fractional distillation yielded 26.8 g (79 %) of 4-bromo-2-(1-cyclohexenyl)thiophene, b.p. 166°C/13 mmHg. NMR (CDCl<sub>3</sub>):  $\tau_{3,5}$  = 3.02 and 3.17 ppm,  $J_{35}$  = 1.4 Hz,  $\tau_{\text{CH}}$  = 3.82 ppm,  $\tau_{\text{CH}_2}$  = 7.5–8.6 ppm. (Found: M.wt. 243; C 49.2; H 4.50; Br 32.7; S 12.9. Calc. for C<sub>10</sub>H<sub>11</sub>BrS (243.2): C 49.39; H 4.56; Br 32.86; S 13.19.)

*4-Bromo-2-phenylthiophene.* 17.0 g (70 mmol) of 4-bromo-2-(1-cyclohexenyl)thiophene, 31.8 g (140 mmol) of DDQ and 175 ml of benzene were reacted in the same way as described above for 3-bromo-2-phenylthiophene. After column chromatography 9.9 g (59 %) of 4-bromo-2-phenylthiophene was obtained, m.p. 68–70°C after recrystallization from aqueous ethanol. NMR ((CH<sub>3</sub>)<sub>2</sub>SO):  $\tau_{3,5}$  = 2.35 and 2.47 ppm,  $J_{35}$  = 1.5 Hz,  $\tau_{\text{C}_6\text{H}_5}$  = 2.2–2.7 ppm. (Found: M.wt. 239; C 50.2; H 2.98; Br 33.7; S 13.2. Calc. for C<sub>10</sub>H<sub>7</sub>BrS (239.1): C 50.23; H 2.95; Br 33.41; S 13.41.) GLC (5 % NPGS, 180°C) retention time: 9.4 min.

*Formylation of 2-phenylthiophene.* 1.2 g (8 mmol) of phosphorus oxychloride was added dropwise with stirring and ice-cooling to a mixture of 2.00 g (12.5 mmol) of 2-phenylthiophene and 1.16 g (16 mmol) of *N,N*-dimethylformamide. After stirring for 0.5 h the mixture was heated for 0.5 h at 100–105°C, cooled, and poured onto ice, whereupon sodium acetate was added to adjust the pH to 5. The mixture was allowed to stand overnight, was then extracted with ether and the ether phase washed with sodium bicarbonate and water and dried over magnesium sulphate. The ether was evaporated, leaving 2.06 g of a solid which was shown by GLC (5 % NPGS, 190°C) to consist of about 20 % of 2-phenylthiophene (retention time 1.7 min) and about 80 % 5-formyl-2-phenylthiophene (10.8 min). In addition, the reaction product also contained about 0.05 % of a compound with the same retention time (5.8 min) as 3-formyl-2-phenylthiophene described below. 4-Formyl-2-phenylthiophene (retention time 9.6 min) was not detected in the product. Fractional crystallization of the crude product from aqueous ethanol yielded pure 5-formyl-2-phenylthiophene as white crystals with m.p. 93–93.5°C; literature value<sup>8</sup> m.p. 92°C. NMR ((CH<sub>3</sub>)<sub>2</sub>SO):  $\tau_4$  = 1.93 ppm,  $\tau_3$  = 2.27 ppm,  $J_{34}$  = 4.0 Hz,  $\tau_{\text{C}_6\text{H}_5}$  = 2.0–2.5 ppm,  $\tau_{\text{CHO}}$  = –0.09 ppm.

*4-Formyl-2-phenylthiophene* was prepared analogously to 5-formyl-3-phenylthiophene<sup>13</sup> from 2.00 g (8.4 mmol) of 4-bromo-2-phenylthiophene, 11 ml of 0.94 N ethyllithium and 1.00 g (14 mmol) of *N,N*-dimethylformamide. Column chromatography of the crude product on silica gel using hexane as eluent yielded 0.31 g of a mixture of 2-phenylthiophene and 4-bromo-2-phenylthiophene. Further elution with benzene yielded 0.98 g (62 %) of 4-formyl-2-phenylthiophene, m.p. 69–70°C after crystallization from aqueous ethanol. NMR (CDCl<sub>3</sub>):  $\tau_5$  = 2.01 ppm,  $\tau_3$  = 2.32 ppm,  $J_{35}$  = 1.3 Hz,  $\tau_{\text{C}_6\text{H}_5}$  = 2.3–2.8 ppm,  $\tau_{\text{CHO}}$  = 0.15 ppm. (Found: M.wt. 188; C 69.7; H 4.27; S 16.9. Calc. for C<sub>11</sub>H<sub>8</sub>OS (188.3): C 70.18; H 4.28; S 17.03.)

*3-Formyl-2-phenylthiophene* was prepared analogously to 5-formyl-3-phenylthiophene<sup>13</sup> from 5.00 g (21 mmol) of 3-bromo-2-phenylthiophene, 25 ml of 1.07 N ethyllithium and 2.5 g (34 mmol) of *N,N*-dimethylformamide. Column chromatography of the crude product on silica gel using hexane as eluent yielded 0.13 g of 2-phenylthiophene, and continued elution with benzene yielded 2.52 g (64 %) of 3-formyl-2-phenylthiophene, m.p. 58–59°C after crystallization from aqueous ethanol. NMR (CDCl<sub>3</sub>):  $\tau_4$  = 2.42 ppm,  $\tau_5$  = 2.75 ppm,  $J_{45}$  = 5.4 Hz,  $\tau_{\text{C}_6\text{H}_5}$  = 2.53 ppm,  $\tau_{\text{CHO}}$  = 0.12 ppm,  $J_{5-\text{CHO}}$  = 0.8 Hz,  $J_{4-\text{CHO}}$  = 0.4 Hz. (Found: M.wt. 188; C 70.1; H 4.25; S 16.8. Calc. for C<sub>11</sub>H<sub>8</sub>OS (188.3): C 70.18; H 4.28; S 17.03.)

*Acetylation of 2-phenylthiophene.* (a) *With acetic anhydride-phosphoric acid.* A mixture of 10.0 g (62 mmol) of 2-phenylthiophene and 3.2 g (31 mmol) of acetic anhydride was heated to 70–75°C. 0.3 g of 85 % phosphoric acid was added and the reaction mixture refluxed for 2 h, then cooled and extracted with ether. The ether phase was washed with sodium bicarbonate and water and dried over magnesium sulphate. Evaporation of the ether left 7.3 g of a yellow solid which was shown by GLC (5 % NPGS, 190°C) and mass spectrometry to consist of about 30 % of 2-phenylthiophene (retention time 1.3 min) and 70 % of a 99 : 1 mixture of 5-acetyl-2-phenylthiophene (12.7 min) and an acetyl phenylthiophene with the same retention time (4.8 min) as 3-acetyl-2-phenylthiophene. 4-Acetyl-2-phenylthiophene (retention time 11.5 min) was not detected in the reaction product. Crystallization of the crude product from ethanol yielded pure 5-acetyl-2-phenylthiophene, m.p. 113–115°C; literature value<sup>6</sup> m.p. 114°C. NMR ((CH<sub>3</sub>)<sub>2</sub>SO):  $\tau_4$  = 2.17 ppm,  $\tau_3$  = 2.50 ppm,  $J_{34}$  = 4.1 Hz,  $\tau_{\text{C}_6\text{H}_5}$  = 2.2–2.7 ppm,  $\tau_{\text{CH}_3}$  = 7.46 ppm.

(b) *With acetyl chloride-tin tetrachloride.* 8.15 g (31 mmol) of tin tetrachloride was added dropwise with stirring to a mixture of 5.00 g (31 mmol) of 2-phenylthiophene, 50 ml of benzene and 2.42 g (31 mmol) of acetyl chloride cooled to 0°C. After stirring for 1 h at room temperature, 20 ml of 1.2 N hydrochloric acid was added and the two phases separated. The water layer was then extracted with benzene, and the combined benzene solutions were washed with water and dried over magnesium sulphate. The benzene was distilled off, leaving 5.79 g of a solid which was shown by GLC to contain, besides about 10 % of 2-phenylthiophene, the same two acetyl compounds as formed under (a) in the proportions of 99.9 to 0.1. The 4-isomer was not detected in this acetylation either.

*4-Acetyl-2-phenylthiophene* was prepared analogously to 5-acetyl-3-phenylthiophene<sup>13</sup> from 2.00 g (8.4 mmol) of 4-bromo-2-phenylthiophene, 15 ml of 1.09 N ethyllithium and 2.1 g (24 mmol) of *N,N*-dimethylacetamide. Chromatography of the crude solid on silica gel yielded 0.1 g of a 1 : 4 mixture of 2-phenylthiophene and 4-bromo-2-phenylthiophene using hexane as eluent, and continued elution with benzene yielded 1.19 g (71 %) of 4-acetyl-2-phenylthiophene, white crystals with m.p. 88–89°C after crystallization from aqueous ethanol. NMR (CDCl<sub>3</sub>):  $\tau_5 = 2.08$  ppm,  $\tau_3 = 2.92$  ppm,  $J_{35} = 1.4$  Hz,  $\tau_{\text{C}_6\text{H}_5} = 2.3$ –2.8 ppm,  $\tau_{\text{CH}_3} = 7.49$  ppm. (Found: M.wt. 202; C 70.7; H 4.97; S 15.7. Calc. for C<sub>12</sub>H<sub>10</sub>OS (202.3): C 71.26; H 4.98; S 15.85.)

*Reaction between 3-bromo-2-phenylthiophene, ethyllithium and N,N-dimethylacetamide* was carried out in the same manner as described above for the 4-bromo-2-phenylthiophene, and 1.90 g of a crude liquid was obtained, starting from 3.00 g (12.6 mmol) of 3-bromo-2-phenylthiophene, 20 ml of 0.94 N ethyllithium and 3.20 g (37 mmol) of *N,N*-dimethylacetamide. Chromatography on silica gel yielded 1.49 g (9.3 mmol) of 2-phenylthiophene using hexane as eluent, and continued elution with benzene yielded 0.22 g of a mixture of about 85 % 3-acetyl-2-phenylthiophene and 15 % 3-bromo-2-phenylthiophene.

*3-(1-Hydroxyethyl)-2-phenylthiophene.* To 1.00 g (4.2 mmol) of 3-bromo-2-phenylthiophene in 20 ml of anhydrous ether cooled to –70°C, 10 ml of 0.79 N ethyllithium was added dropwise with stirring. After 15 min 0.31 g (7.0 mmol) of acetaldehyde in 5 ml of ether was added, the mixture was stirred for an additional 0.5 h at –70°C and then for 2 h at room temperature. 25 ml of 3 N ammonium chloride solution was then added, the ether layer separated, the water layer extracted with ether and the combined ether phases were washed with N hydrochloric acid, sodium carbonate solution and water and dried over magnesium sulphate. Evaporation of the ether left 0.80 g of a red oil which was chromatographed on silica gel. Elution with hexane yielded 0.16 g of a 1 : 1 mixture of 2-phenylthiophene and 3-bromo-2-phenylthiophene, and continued elution with benzene yielded 0.58 g (68 %) of 3-(1-hydroxyethyl)-2-phenylthiophene as a white solid, m.p. 58–60°C after recrystallization from petroleum ether (40–60°C). NMR (CDCl<sub>3</sub>):  $\tau_{\text{Ph}} = 2.63$  ppm,  $\tau_{\text{TH}} = 2.81$  ppm,  $\tau_{\text{CH}} = 5.04$  ppm,  $\tau_{\text{OH}} = 7.58$  ppm,  $\tau_{\text{CH}_3} = 8.71$  ppm,  $J_{\text{CH},\text{CH}_3} = 6.6$  Hz. (Found: M.wt. 204; C 70.7; H 6.03; S 15.7. Calc. for C<sub>12</sub>H<sub>12</sub>OS (204.3): C 70.56; H 5.92; S 15.69.) Hydrolysis of the reaction product from 5.00 g (21 mmol) of 3-bromo-2-phenylthiophene, 30 ml 0.98 N ethyllithium and 1.15 g (26 mmol) of acetaldehyde with 3 N hydrochloric acid yielded after chromatography on silica gel using benzene as eluent, 2.98 g of somewhat impure 3-(1-hydroxyethyl)-2-phenylthiophene since the mass spectrum showed a peak at *m/e* 390. Besides, a fore-fraction of a mixture of 2-phenylthiophene and 3-bromo-2-phenylthiophene was obtained using hexane as eluent. The main fraction was recrystallized from petroleum ether (b.p. 40–60°C) to yield 1.32 g pure 3-(1-hydroxyethyl)-2-phenylthiophene, and the residue, after evaporation of the mother liquor, was chromatographed on silica gel. Elution with a mixture of 80 % hexane and 20 % benzene yielded 0.33 g (0.86 mmol) of bis-(1-(3-(2-phenylthienyl))-ethyl) ether, colourless crystals, m.p. 108–110°C after recrystallization from petroleum ether. NMR (CDCl<sub>3</sub>):  $\tau_{\text{Ph},\text{TH}} = 2.6$ –3.0 ppm,  $\tau_{\text{CH}} = 5.44$  ppm,  $\tau_{\text{CH}_3} = 8.64$  and 8.67 ppm,  $J_{\text{CH},\text{CH}_3} = 6.5$  Hz. (Found: M.wt. 390; C 73.4; H 5.80; S 16.3. Calc. for C<sub>24</sub>H<sub>22</sub>OS<sub>2</sub> (390.6): C 73.81; H 5.68; S 16.42.)

*3-Acetyl-2-phenylthiophene.* 1.67 g (16.7 mmol) of chromium(VI) oxide was added during 15 min with ice cooling and stirring to 20 ml of pyridine.<sup>19</sup> 1.10 g (5.4 mmol) of 3-(1-hydroxyethyl)-2-phenylthiophene in 5 ml of pyridine was then added, the mixture stirred for 0.5 h at room temperature and then allowed to stand for 21 h. 200 ml of ether was added and the dark precipitate filtered off. 100 ml of water was then added to the



filtrate, the ether layer separated and the water layer extracted with ether. The combined ether phases were washed several times with N hydrochloric acid, and then with sodium bicarbonate solution and water, and dried over magnesium sulphate. The ether was distilled off, leaving 0.84 g (77 %) of 3-acetyl-2-phenylthiophene, which was dried in vacuum over sulphuric acid to remove traces of pyridine. Recrystallization from aqueous ethanol gave white crystals with m.p. 56–57°C. NMR (CDCl<sub>3</sub>):  $\tau_4$  = 2.53 ppm,  $\tau_5$  = 2.78 ppm,  $J_{45}$  = 5.3 Hz,  $\tau_{\text{C}_6\text{H}_5}$  = 2.56 ppm,  $\tau_{\text{CH}_3}$  = 7.80 ppm. (Found: M.wt. 202; C 70.9; H 4.94; S 15.8. Calc. for C<sub>15</sub>H<sub>10</sub>OS (202.3): C 71.26; H 4.98; S 15.85.)

*Metalation of 2-phenylthiophene.* 30 ml of 0.95 N butyllithium was added dropwise with stirring and under nitrogen to 3.2 g (20 mmol) of 2-phenylthiophene in 50 ml of anhydrous ether, and the mixture was stirred for 0.5 h. The solution was then poured onto powdered carbon dioxide in ether, and when the temperature had risen to 0°C, water and then hydrochloric acid was added. The ether layer was separated and extracted with N sodium hydroxide, and a grey solid, the sodium salt of the carboxylic acid, was then precipitated. The mixture was then acidified with hydrochloric acid, and the precipitated solid was filtered off, yielding 3.5 g (86 %) of 2-phenyl-5-thiophenecarboxylic acid, m.p. 190–194°C after recrystallization from aqueous ethanol; literature value<sup>19</sup> m.p. 186–188°C. NMR ((CH<sub>3</sub>)<sub>2</sub>CO):  $\tau_4$  = 2.27 ppm,  $\tau_5$  = 2.69 ppm,  $J_{34}$  = 3.9 Hz,  $\tau_{\text{C}_6\text{H}_5}$  = 2.2–2.7 ppm. Part of the crude acid was esterified with diazomethane, and GLC investigations (3 % OV 17, 190°C) showed only one peak (retention time 4.8 min).

NMR spectra were recorded on a Varian A 60 NMR spectrometer. GLC analyses were carried out with a Perkin-Elmer 900 gas chromatograph and the mass spectrometric work on an LKB A-9000 mass spectrometer. The elemental analyses were carried out at the Analytical Department of the Chemical Institute, University of Lund.

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