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On the Nitration of 2- and 3-Phenylthiophene

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The nitration of 2- and 3-phenylthiophene with cupric nitrate in acetic anhydride has been reinvestigated. It was found that 2-phenylthiophene gave two mono-nitro isomers, namely 5-nitro-2-phenylthiophene (I) and 3-nitro-2-phenylthiophene (II). NMR-spectroscopy shows that these products are formed in the ratio of 3:2. Four dinitro derivatives were also formed. These were separated by preparative thin-layer chromatography and their structures determined by NMR-spectroscopy, oxidative degradation, and by nitration of I and II. The four dinitro isomers were 3,5-dinitro-2-phenylthiophene (III), 5-nitro-2-(*o*-nitrophenyl)thiophene (IV), 3-nitro-2-(*p*-nitrophenyl)thiophene (V) and 5-nitro-2-(*p*-nitrophenyl)thiophene (VI).

Nitration of 3-phenylthiophene under the same conditions yielded a mixture consisting of 90 % of 2-nitro-3-phenylthiophene (VII), and 10 % of 5-nitro-3-phenylthiophene (VIII). No 3-(*p*-nitrophenyl)-thiophene (IX) could be found, although the main dinitro isomer is 2-nitro-3-(*p*-nitrophenyl)thiophene (X).

The directing effect of aromatic, carbocyclic, or heterocyclic rings as substituents has been very little investigated. The main reason for this is the difficulties involved in determining the structures of the isomers formed. In many cases structures were not proven, but were assigned on more or less reasonable guesses on the directing effects and steric requirements of the cyclic substituents. Thus Ivanova,[1] who nitrated 2-phenylthiophene with cupric nitrate, obtained two mononitrated phenylthiophenes, the major component of which she claimed to be 5-nitro-2-phenylthiophene, the minor 4-nitro-2-phenylthiophene. Experimental evidence only showed that the nitro groups were positioned in the thiophenic ring, as oxidation of both isomers gave benzoic acid.

Through the advancement of NMR-spectroscopy, routine structure-determination of substituted mixed biaryls should now be possible, and by applying modern separation techniques such as thin-layer chromatography and preparative gas chromatography the different isomers are readily isolated. Many aspects of the directing effect of π-excessive or π-deficient rings upon electrophilic substitution in another ring are not well understood and even the

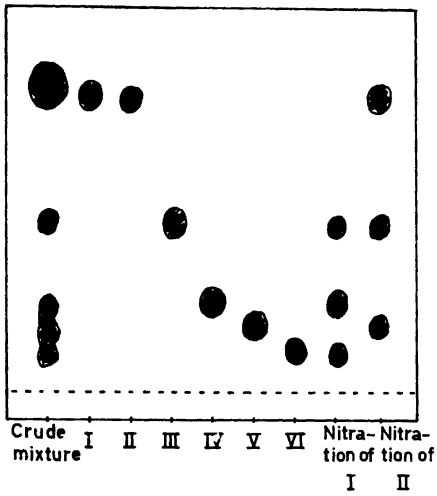


Fig. 1. Thin-layer chromatogram (silica gel, CCl_4) of the nitration products of 2-phenylthiophene.

electrophilic substitution of biphenyl offers some as yet unresolved problems. It does not, for instance, follow the selectivity relationship,[2] the reason for this being a matter of controversy.

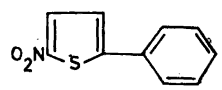
Many factors influence the substitution patterns of biaryls. It was recently found that bromination of 3-phenylthiophene with bromine in acetic acid yielded a mixture consisting of 70 % of 5-bromo-3-phenylthiophene and 30 % of 2-bromo-3-phenylthiophene, while substitution in carbon tetrachloride with N-bromosuccinimide yielded exclusively the 2-isomer.[3] We have now found that the different solvents and not the different brominating agents are responsible for the different isomer distribution.

As we for theoretical reasons considered it very unlikely that 4-nitro-2-phenylthiophene could be formed in the nitration of 2-phenylthiophene, as claimed by Ivanova, we have repeated her experiments. Thin-layer chromatography of the reaction product on silica gel using carbon tetrachloride as eluent indicated that at least six products were formed upon nitration with cupric nitrate in acetic anhydride at 10—12°C. The chromatogram of the reaction product together with that of the isolated components is shown in Fig. 1. Through preparative TLC chromatography, compounds III to VI could be separated. The most rapidly moving spot, which contained two mononitrophenylthiophenes, could not be separated into its components by TLC. However, fractional crystallization from aqueous ethanol as described by Ivanova, yielded with great losses pure samples of both isomers. The more difficultly soluble component (m.p. 125—126°C) was 5-nitro-2-phenylthiophene (I), as assigned by Ivanova. Oxidation with potassium permanganate yielded benzoic acid, proving that the nitro group is located in the thiophene ring. Its NMR-spectrum ($DCCl_3$) showed two doublets at 2.07 τ and 2.74 τ with a coupling of 4.4 c/s characteristic for 2,5-disubstituted thiophenes.[4] From the known strong deshielding effect of the nitro group on its *ortho* hydrogen [5] the 2.07 τ doublet is assigned to hydrogen 4. The resonances of

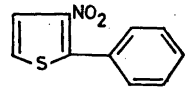
the five phenyl hydrogens occur between 2.3—2.6 τ. The more soluble mono-nitro derivative (m.p. 101.5—102.5°C) also yielded benzoic acid upon oxidation. However, its NMR-spectrum shows two doublets at 2.31 τ and 2.71 τ with a coupling constant of 5.6 c/s proving that this isomer is 3-nitro-2-phenylthiophene (II) and not the 4-isomer as claimed by Ivanova. The low-field band is assigned to hydrogen 4.

The composition of the mono-nitro phenylthiophene fraction was determined by NMR-analysis. It consisted of 60 % of I and 40 % of II.

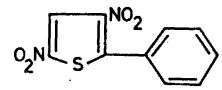
Spot III consisted of a compound, m.p. 166—167°C, which gave a correct analysis for a dinitrophenylthiophene. Oxidation yielded only benzoic acid. It was also obtained upon further nitration of both I and II (Fig. 1). Its NMR-spectrum showed a sharp peak at 1.59 τ and a somewhat broadened peak at 2.46 τ, with relative intensities of 1:5. All these facts are only consistent with III being 3,5-dinitro-2-phenylthiophene.



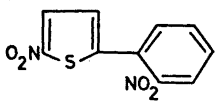
I



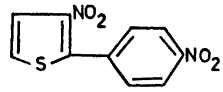
II



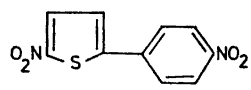
III



IV



V



VI

The compound giving spot IV, m.p. 104°C, also gave a correct analysis for a dinitrophenylthiophene. The compound is also formed upon nitration of I, but not of II, and gives *o*-nitrobenzoic acid upon oxidation with potassium permanganate. Its NMR-spectrum shows two doublets at 2.12 τ and 2.97 τ with a coupling constant of 4.2 c/s, characteristic of J_{34} in thiophenes. These combined results show unequivocally that this isomer is 5-nitro-2-(*o*-nitrophenyl)thiophene.

It was difficult to obtain a rigorously correct analysis for compound V, (m.p. 146—148°C) but it is most likely another dinitrophenylthiophene. Oxidation yielded *p*-nitrobenzoic acid. The compound was also formed upon nitration of II but not in the nitration of I. Its NMR-spectrum shows two doublets at 2.27 τ and 2.60 τ with a coupling constant of 5.8 c/s, while the benzenic hydrogens show the typical pattern for *p*-disubstituted benzenes having large shifts between the two groups of non-equivalent hydrogens. The main spectral feature is two doublets with a splitting of 9.1 c/s centered at 1.66 τ and 2.33 τ. These results show that this compound is 3-nitro-2-(*p*-nitrophenyl)thiophene.

Finally, the fourth dinitrophenylthiophene (VI), m.p. 177—179°C, which was isolated from the reaction mixture, was shown to be 5-nitro-2-(*p*-nitrophenyl)thiophene. It yielded *p*-nitrobenzoic acid upon oxidation. It was also formed in the nitration of I but not of II and its NMR-spectrum shows two thiophenic resonances at 2.02 τ (hydrogen 4) and 2.58 τ (hydrogen 3) with the coupling constant of 4.4 c/s. The main features of the A_2B_2 spectrum of the benzenic hydrogen resonances again are two doublets centered at 1.63 τ and 2.18 τ with splittings of 9.1 c/s.

The proportion between mono- and dinitro compounds formed is about 7:3, determined by isolating the components by preparative TLC. The dinitro derivatives are formed when two equivalents of cupric nitrate are used in Ivanova's method. When we used equivalent amounts of cupric nitrate and substrate, only traces of the dinitrated compounds were obtained. The main products were I and II, formed in the proportion of 3:2.

As mentioned above, some experiments were carried out on the further nitration of 5-nitro-2-phenylthiophene and of 3-nitro-2-phenylthiophene. Nitration of I in acetic acid—sulphuric acid with fuming nitric acid in acetic anhydride gave a mixture of the dinitro derivatives III, IV, and VI in the relative proportions of 3:4:4. Nitration of II under the same conditions yielded, besides recovered starting material, the dinitro derivatives III and V in the relative proportions of 4:1.

It is obvious that the phenyl group acts as an *ortho-para* directing group on substitution in the thiophenic ring. The quite large proportion of 3-nitro isomer (II) is rather unexpected. Östman [6] found in the nitration of thiophene that 85 % of the 2-isomer and 15 % of the 3-isomer are formed, while Markovitz [7] found that nitration of 2-methylthiophene gave a mixture of 80 % of 2-methyl-5-nitrothiophene, 19 % of 2-methyl-3-nitrothiophene and 1 % of 2-methyl-4-nitrothiophene. Although these nitrations were not carried out under conditions strictly comparable with ours, it is obvious that the phenyl group directs to the 3-(*ortho*) position to a larger extent than to the 5-(*para*) position. However, there might be some relation with the fact that nitration of biphenyl with nitric acid in acetic anhydride also gives large amounts of *ortho*-substitution. The partial rate-factors, f_2, f_3, f_4 have been found to be 41, <0.6, and 38, respectively,[8] while in most other electrophilic substitution reactions of biphenyl the 4-position is strongly favoured. The partial rate-factors also demonstrate that the phenyl group acts as an activating +M-substituent on the *ortho* and *para* positions, while its $-I$-effect deactivates the *meta* position.

In 5-nitro-2-phenylthiophene, because of the deactivating effect of the nitro group, the reactivities of the 3-position and of the *ortho* and *para* positions are approximately the same. One can also notice that the 5-nitro-2-thienyl group acts as an *ortho-para* directing group on the benzene ring.

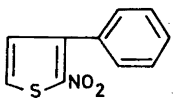
In 3-nitro-2-phenylthiophene, the thiophenic 5-position still is the most reactive one in spite of the deactivating effect of the nitro group. It can also be noted that one of the dinitrophenylthiophenes expected to be formed, namely 3-nitro-2-(*o*-nitrophenyl)thiophene, was not found, which of course could be a steric effect.

The large amount of 3-substituted products formed when thiophene and 2-substituted thiophenes such as 2-methyl- and 2-phenylthiophene are nitrated is in accordance with the relatively low selectivity factor of the nitration reaction.[2]

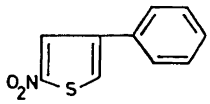
However, upon bromination of 2-phenylthiophene with bromine in acetic acid,[9] upon Vilsmeyer formylation with N,N'-dimethylformamide and $POCl_3$,[10] or upon acetylation with acetic anhydride and phosphoric acid,[11] we obtained only 5-substituted compounds, as shown by GLC analysis of the products. Besides the greater selectivity of these reactions also steric factors could be of great importance. Very little *ortho* isomers are formed in the acylation or bromination of biphenyl.[12]

Ivanova[1] also nitrated 3-phenylthiophene with cupric nitrate and claimed that a mixture of 5-nitro-3-phenylthiophene (VIII) and 3-(*p*-nitrophenyl)-thiophene (IX) was obtained, as oxidation of the nitrated mixture afforded benzoic acid (about 70 % of the total yield) and *p*-nitrobenzoic acid (about 30 % of the total yield).

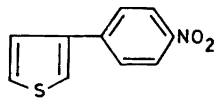
Since these structure assignments appeared improbable to us, we repeated her experiments. Using one equivalent of cupric nitrate, a mixture consisting of 90 % of 2-nitro-3-phenylthiophene (VII), m.p. 141.5—142.5°C and 10 % of 5-nitro-3-phenylthiophene (VIII), m.p. 93—95°C was obtained, in addition to small amounts of dinitro derivatives. The components were separated by preparative TLC.



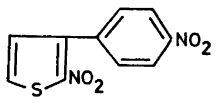
VII



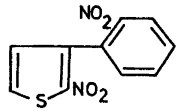
VIII



IX



X



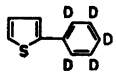
XI

The NMR-spectrum showed beyond doubt that the main product was VII, as it showed two doublets with a coupling constant of 5.5 c/s at 2.30 τ and 2.93 τ, which are assigned to the 5- and 4-hydrogen, respectively, of the thiophenic ring. The resonances of the phenyl hydrogens occur as a rather sharp peak at 2.54 τ. The NMR-spectrum of VIII shows two thiophenic doublets at 1.71 τ and at 2.11 τ, assigned to hydrogen 4 and hydrogen 2, respectively, with a coupling of 2.0 c/s, characteristic for 2,4-disubstituted thiophenes. The phenyl resonances occur as a complex multiplet. It is thus

obvious that the nitro isomer described by Ivanova as 5-nitro-3-phenylthiophene is in fact 2-nitro-3-phenylthiophene. In addition, her product was most probably contaminated with 2-nitro-(*p*-nitrophenyl)thiophene, which would explain the formation of *p*-nitrobenzoic acid upon oxidation with potassium permanganate.

When we carried out the nitration with two equivalents of cupric nitrate, as described by Ivanova, the dinitro fraction increased to about 10 % and was easily separated from the mono-nitro fraction by TLC. While the crude reaction product gave both benzoic acid and *p*-nitrobenzoic acid, oxidation of the mono-nitro fraction yielded only benzoic acid. Further nitration of VII was more difficult and could not be achieved with cupric nitrate. Instead, more forced conditions (fuming nitric acid—sulphuric acid in acetic acid—acetic anhydride) had to be used. A mixture of dinitro derivatives was obtained, which we could not separate into pure products. The main dinitro derivative (about 90 % of the dinitro compounds formed) is 2-nitro-3-(*p*-nitrophenyl)-thiophene (X) as is evident from its NMR-spectrum, which showed two doublets at 2.17 τ and 2.82 τ assigned to the 5- and 4-hydrogens of X, as they show a splitting of 5.5 c/s. In addition, also the characteristic pattern

Table 1. Chemical shifts (τ-values) and coupling constants of nitro-2-phenylthiophene. Solvent: $DCCl_3$.

Compound	Chemical shifts						Coupling constants c/s			
	Thiophene			Phenyl						
	H-3	H-4	H-5	*o*	*m*	*p*	J_{34}	J_{45}	J_{35}	$J_{o,m}$
	2.78[a]	3.02	2.87				3.6	5.0	1.5	—
	2.75[b]	2.99	2.80	—			3.4	5.1	1.25	—
I (5-NO_2)	2.74	2.07	—	complex multiplet 2.3—2.6			4.4	—	—	—
II (3-NO_2)	—	2.31	2.71	sharp peak 2.50			—	5.6	—	—
III (3,5-NO_2)	—	1.59	—	sharp peak 2.46			—	—	—	—
IV (5,*ortho*-NO_2)	2.97	2.12	—	complex multiplet 2.0—2.5			4.2	—	—	—
V (3,*para*-NO_2)	—	2.27	2.60	2.33	1.66	—	—	5.8	—	9.1
VI (5,*para*-NO_2)	2.58	2.02	—	2.18	1.63	—	4.4	—	—	9.1

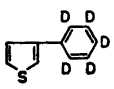
[a] According to H. Wynberg and R. M. Kellogg.
[b] According to S. Forsén.

of a *para* substituted benzene derivative appeared (two doublets at 1.65 τ and 2.25 τ with a splitting of 9.0 c/s). Oxidation with potassium permanganate yielded *p*-nitrobenzoic acid. The more soluble fraction contained a second dinitro derivative, possibly 2-nitro-3-(*o*-nitrophenyl)thiophene or less probably 2-nitro-3-(*m*-nitrophenyl)thiophene, as the NMR-spectrum contained, besides the bands of X, two doublets at 2.16 τ and 2.87 τ with a coupling constant of 5.6 c/s. Thin-layer chromatography of the oxidation products also indicated that *ortho*- or *meta*-nitrobenzoic acid had been formed.

It is interesting to compare the further nitration of VII with that of II, in which the two substituents are interchanged. In II the 5-position is activated by the +M-effect of the phenyl group and only indirectly deactivated by the nitro group, which is "*meta*-positioned". In VII, on the other hand, the nitro group (*para*) directly deactivates the 5-position and also the phenyl group should act deactivating through its $-I$-effect, as is observed for the 3-position of biphenyl in electrophilic substitution reactions.[2] It is therefore understandable why II is nitrated predominantly in the 5-position of the thiophenic ring, while VII is nitrated in the *para* position of the benzenic ring.

The chemical shifts and coupling constants of the nitrated 2-phenylthiophenes obtained from chloroform solutions are given in Table 1. For comparison, the chemical shifts and the coupling constants obtained by Wynberg and Kellogg[13] for 2-pentadeuterophenylthiophene and by Forsén,[14] who also analysed its complex ABC-spectrum, are also given. The chemical shifts of the nitrated 3-phenylthiophenes are given in Table 2. Acetonitrile solutions were used, as the phenyl resonance does not overlap the thiophenic hydrogen resonances in this solvent. For comparison the chemical shifts for 3-pentadeuterophenylthiophene, which gives an ABB'-spectrum, are also given. An

Table 2. Chemical shifts (τ-values) and coupling constants of nitro-3-phenylthiophene. Solvent: CH_3CN.

Compound	Chemical shifts						Coupling constants c/s		
	Thiophene			Phenyl					
	H-2	H-4	H-5	*o*	*m*	*p*	J_{24}	J_{45}	$J_{o,m}$
	2.42	2.55	2.55	—			—	—	—
VII (2-NO_2)	—	2.93	2.30	sharp peak 2.54			—	5.5	—
VIII (5-NO_2)	2.11	1.71		complex multiplet 2.2—2.6			2.0	—	—
X (2-*para*-NO_2)	—	2.82	2.17	2.25	1.65	—	—	5.5	9.0
XI (2,*ortho*-NO_2)	—	2.87	2.16	complex multiplet 2.1—2.5			—	5.6	—

interesting feature of the spectra of the compounds having nitro groups in the thiophenic ring *ortho* to the pivot bond is the sharp phenyl resonance, indicating that all five phenyl hydrogens have similar shifts. If this is a general property of such compounds, it would be of some use for structure determinations.

The shifts of the thiophenic hydrogens caused by the substituents are of a magnitude predictable from our knowledge of monosubstituted thiophenes,[5] as long as the substituent is not at the pivot bond. Thus the *ortho* nitro group of IV shifts the 3-hydrogen resonance 0.23 ppm towards higher field as compared to I. The *up-field shift* caused by the nitro group is even stronger noticeable in the 3-phenylthiophene series. The 4 hydrogen resonance of VII and X is shifted about 0.30 ppm up-field compared with 3-pentadeuterophenylthiophene. A similar effect has been observed when comparing 2,5-dinitro-3-(4-pyrimidyl)thiophene with 5-nitro-3-(4-pyrimidyl)thiophene.[15] Several factors contribute to this effect. The introduction of the nitro group at the pivot bond increases the angle between the rings, which changes the ring-current effect of the benzene ring on the thiophenic hydrogens, causing an up-field shift.[16] In addition, the steric interaction between the phenyl group and the nitro group could force the latter group out of coplanarity with the thiophene ring and thus diminishing the resonance effects on the chemical shifts. For IV also the anisotropy effect of the *ortho*-nitro group could be of importance in determining the shift of the 3 hydrogen.

2-Phenylthiophene was prepared according to Kosak *et al.* through the reaction of 2-thienyllithium with cyclohexanone followed by aromatization of the intermediate 2-cyclohexenylthiophene with chloranil.[9] This method was also applied to the preparation of 3-phenylthiophene from 3-thienyllithium. When this experimental work was completed, several new and possibly more convenient methods for the preparation of the phenylthiophenes have appeared in the literature.[17,18] The discovery by Wynberg *et al.* of an interesting photochemical rearrangement with phenylthiophenes has also led to renewed interest in these compounds.[17]

The mass spectra of the phenylthiophenes and of their nitro derivatives are of some interest in this connection, although in this work they were run mainly in order to ascertain the structures of the nitrated derivatives.

EXPERIMENTAL

Nitration of 2-phenylthiophene according to Ivanova.[1] 15.0 g (0.094 mole) of 2-phenylthiophene [9] in 150 ml of acetic anhydride was added dropwise with stirring to an ice-cooled solution of 22.5 g (0.093 mole) of cupric nitrate trihydrate in 150 ml of acetic anhydride. The temperature was kept between 10—12°C during the addition. The mixture was then allowed to stand at room temperature for 2 h, filtered and poured onto ice. A yellow crystalline mass separated, which was filtered off next day. After drying, 12.2 g of a mixture of mono- and dinitrophenylthiophene was obtained. A few mg of the mixture was dissolved in chloroform and thin-layer chromatographed on 1/4 mm layer of silica gel (Kieselgel G nach Stahl). The plates were activated for 1 h at 110°C. Carbon tetrachloride was used as eluent. When the solvent front had advanced over the plate, it was dried and again eluated with carbon tetrachloride. After repeating this procedure seven times, five yellow spots (Fig. 1) could be discerned on the plates, which could be developed with iodine and clearly seen in UV-light. The R_S values relative to the fastest moving spot (1.00) were 0.53, 0.28, 0.22, and 0.12.

By using 20 × 20 cm plates with a 2 mm thick layer of silica gel, and activating the plates for 3 h at 110°C, it was possible to apply 100 mg of the reaction product as a long strip on each plate. The elution with CCl_4 was repeated about 25 times, as the components moved more slowly on the thicker plate. In order to isolate the different compounds, the different strips were removed from the plates and extracted with chloroform in a Soxhlet extraction apparatus. The chloroform solutions were evaporated to dryness and the different compounds recrystallized from aqueous ethanol.

The fastest moving spot consisted of two compounds, which were separated by fractional crystallization from aqueous ethanol. The more difficultly soluble compound was 5-nitro-2-phenylthiophene, yellow crystals, m.p. 125—126°C. (Found: C 58.4; H 3.07; N 6.88; S 16.0; mol.wt. 205. Calc. for $C_{10}H_7NO_2S$ (205.2): C 58.52; H 3.44; N 6.82; S 15.62). Literature value,[1] m.p. 123—124°C.

From the mother liquor, yellow crystals of 3-nitro-2-phenylthiophene, 101.5—102.5°C after recrystallization from aqueous ethanol, was isolated. Literature value,[1] m.p. 98—100°C. (Found: C 58.2; H 3.52; N 6.78; S 15.9; mol.wt. 205. Calc. for $C_{10}H_7NO_2S$ (205.2): C 58.52; H 3.44; N 6.82; S 15.62).

From the second band (R_S = 0.58) pale yellow crystals of 3,5-dinitro-2-phenylthiophene, m.p. 166—167°C after recrystallization from aqueous ethanol, were obtained. (Found: C 47.95; H 2.45; N 10.90; S 12.63; mol.wt. 250. Calc. for $C_{10}H_6N_2O_4S$ (250.2): C 48.00; H 2.42; N 11.19; S 12.81).

The next band (R_S = 0.28) yielded 5-nitro-2-(*o*-nitrophenyl)thiophene, m.p. 104°C after recrystallization from aqueous ethanol. (Found: C 48.26; H 2.55; N 10.98; S 12.85; mol.wt. 250. Calc. for $C_{10}H_6N_2O_4S$ (250.2): C 48.00; H 2.42; N 11.19; S 12.81).

The band with R_S = 0.22 yielded 3-nitro-2-(*p*-nitrophenyl)thiophene, m.p. 146—148°C, which was not entirely pure after recrystallization from aqueous ethanol. (Found: C 48.94; H 3.44; N 10.85; S 12.09. Calc. for $C_{10}H_6N_2O_4S$ (250.2): C 48.00; H 2.42; N 11.19; S 12.81).

Finally, the band with R_S = 0.12 yielded 5-nitro-2-(*p*-nitrophenyl)thiophene, m.p. 177—179°C after recrystallization from aqueous ethanol. (Found: C 48.13; H 2.71; N 11.58; S 12.94; mol.wt. 250. Calc. for $C_{10}H_6O_4N_2S$ (250.2): C 48.00; H 2.42; N 11.19; S 12.81).

Nitration of 2-phenylthiophene with one equivalent of cupric nitrate. To 7.5 g (0.031 mole) of cupric nitrate trihydrate in 100 ml of acetic anhydride cooled with ice was added drop-wise 10.0 g (0.062 mole) of 2-phenylthiophene in 100 ml of acetic anhydride, the temperature being kept between 10—12°C. The mixture was then stirred for 2 h at room temperature, the copper salts were filtered off and the filtrate was poured onto ice. A dark-brown precipitate (9.8 g) was filtered off after standing overnight, and dried. The filtrate was extracted several times with ether, the ethereal extract dried and evaporated, yielding additional 0.2 g of material, giving a total yield of 10.0 g (79 %) of a crude mixture of 5-nitro-2-phenylthiophene and 3-nitro-2-phenylthiophene in the proportion 3:2 as found by NMR analysis. Recrystallization from aqueous ethanol yielded 2.25 g of 5-nitro-2-phenylthiophene containing traces of the 3-isomer. Upon renewed recrystallization 1.0 g of pure 5-nitro-2-phenylthiophene, m.p. 125—126°C, was obtained.

Cooling the first filtrate in the refrigerator caused 1.7 g of a fraction consisting of equal amounts of the 5- and 3-nitro-isomer to separate. The filtrate was diluted with water and cooled, giving 1.1 g of almost pure 3-nitro-2-phenylthiophene, which upon two recrystallizations from aqueous ethanol yielded 0.40 g of pure 3-nitro-2-phenylthiophene, m.p. 101.5—102.5°C.

Nitration of 5-nitro-2-phenylthiophene. To a solution of 100 mg (0.49 mmole) of 5-nitro-2-phenylthiophene in 25 ml of acetic acid and 2 ml of conc. sulphuric acid was added a solution of 0.30 ml of fuming nitric acid in 10 ml of acetic anhydride. The mixture was stirred for 4 h at room temperature and then poured onto ice. After standing overnight, the yellow precipitate (85 mg) was filtered off and dried. TLC (Fig. 1) showed that this consisted, besides traces of starting material, of 3,5-dinitro-2-phenylthiophene, 5-nitro-2-(*o*-nitrophenyl)thiophene and 5-nitro-2-(*p*-nitrophenyl)thiophene. NMR-analysis indicated the proportions of these components to be 27:36.5:36.5, respectively.

Nitration of 3-nitro-2-phenylthiophene. 100 mg (0.49 mmole) of 3-nitro-2-phenylthiophene was nitrated in the same manner as the 5-nitro-isomer described above, yielding 76 mg of product. TLC (Fig. 1) showed that it consisted, besides starting material, of 3,5-dinitro-2-phenylthiophene and 3-nitro-2-(*p*-nitrophenyl)thiophene. Weighing the

pure compounds after separation by TLC showed that these components occurred in the ratio of 4:1.

3-(1-Cyclohexenyl)thiophene. To 400 ml of 1.4 N butyllithium cooled to −70°C was added in a slow stream 70.3 g (0.43 mole) of 3-bromothiophene in 200 ml of anhydrous ether. After 5 min, 42 g (0.43 mole) of anhydrous cyclohexanone in 50 ml of ether was added dropwise with vigorous stirring. After 1 h, the cooling-bath was removed and the mixture allowed to stand overnight. The mixture was cooled to −10°C and hydrolysed by dropwise addition of 6 N hydrochloric acid. After being stirred for 0.5 h, the ether layer was separated, washed with water, dried over $MgSO_4$ and fractionated, giving 47.4 g (67 %) of 3-(1-cyclohexenyl)thiophene, b.p. 120°C/9 mm Hg.

3-Phenylthiophene. A mixture of 46 g (0.28 mole) of 3-(1-cyclohexenyl)thiophene, 138 g (0.56 mole) of chloranil and 800 ml of chlorobenzene was refluxed for 2 h. After standing overnight, the black precipitate was filtered off and most of the chlorobenzene was distilled off. The residue was taken up in ether, the ether phase washed several times with small portions of 2 N sodium hydroxide solution and the precipitate that fell out was filtered off. The ether phase was washed with water, dried over $MgSO_4$ and fractionated, giving 23.5 g (53 %) of 3-phenylthiophene, b.p. 121°C/9 mm Hg, m.p. 89.5—90.5°C after recrystallization from ethanol. Literature value,[19] m.p.91°C.

Nitration of 3-phenylthiophene with one equivalent of cupric nitrate. 8.0 g (0.033 mole) of cupric nitrate trihydrate and 10.0 g (0.062 mole) of 3-phenylthiophene were reacted as described for the 2-isomer, giving 7.4 g of a product (fraction A) which was filtered off after standing overnight. After some hours, an additional fraction of 1.7 g (B) separated from the filtrate. Finally, extraction of the filtrate with ether and evaporation of the extract yielded 0.7 g of an oil (C). Preparative TLC (silica gel, CCl_4) of 100 mg of fraction A carried out as described above yielded only one band consisting of 85 mg of 2-nitro-3-phenylthiophene, m.p. 141.5—142.5°C. 5.0 g of fraction A was then recrystallized from aqueous ethanol, yielding the analytically pure compound in yellow needles, m.p. 141.5—142.5°C. NMR: *cf.* Table 2. (Found: C 58.62; H 3.81; N 6.81; S 15.77; mol.wt. 205. Calc. for $C_{10}H_7NO_2S$ (205.2): C 58.52; H 3.44; N 6.82; S 15.62). Analytical TLC of fraction B on 0.25 mm thick silica gel plates showed three spots at 9.1 cm, 7.5 cm, and 1.5 cm, when the eluent front had moved three times over the plates. 228 mg of fraction B were placed on two preparative plates and chromatographed as described above, giving four bands. The fastest moving band, which was not detected in the analytical TLC, contained 12 mg of 3-phenylthiophene. The next band contained 97 mg of 5-nitro-3-phenylthiophene, m.p. 93—95°C after recrystallization from aqueous ethanol. NMR: *cf.* Table 2. (Found: C 58.90; H 3.34; N 7.02; S 15.44; mol.wt. 205. Calc. for $C_{10}H_7NO_2S$ (205.2): C 58.52; H 3.44; N 6.82; S 15.62). The third strip contained 42 mg of 2-nitro-3-phenylthiophene having the same IR-spectrum as the sample described above. The last band contained 5 mg of dinitrated phenylthiophenes (*cf.* below).

Nitration of 2-nitro-3-phenylthiophene. To 1.00 g (4.9 mmole) of 2-nitro-3-phenylthiophene in 100 ml of acetic acid and 5 ml of conc. sulphuric acid was added dropwise with stirring 1.2 ml of fuming nitric acid in 40 ml of acetic anhydride. The mixture was stirred for 4 h and then poured onto ice. After standing overnight, 870 mg (fraction A) of dinitro-3-phenylthiophenes were filtered off. After standing for some hours, 83 mg (fraction B) were deposited from the filtrate and filtered off. After standing overnight, additional 69 mg (fraction C) were obtained, making a total yield of 1.022 g (84 %) of crude dinitro-3-phenylthiophene.

NMR-analysis (Table 2) indicated fraction A to consist mainly of 2-nitro-3-(*p*-nitrophenyl)thiophene and trace amounts of another component, which most probably is 2-nitro-3-(*o*-nitrophenyl)thiophene. Recrystallization from aqueous ethanol did not remove the minor component, and gave a product melting at 146—160°C. Also TLC could not affect separation of the components. (Found: C 47.91; H 2.31; N 11.25; S 12.51; mol.wt. 250. Calc. for $C_{10}H_6N_2O_4S$ (250.2): C 48.00; H 2.42; N 11.19; S 12.81). NMR-analysis of fraction B indicated it to consist of about 35 % of 2-nitro-3-(*p*-nitrophenyl)-thiophene, 65 % of a component which probably is 2-nitro-3-(*o*-nitrophenyl)-thiophene. Mol.wt. 250. NMR-data: see Table 2. NMR-analysis of fraction C indicated it to consist of 15 % of 2-nitro-3-(*p*-nitrophenyl)thiophene and 60 % of 2-nitro-3-(*o*-nitrophenyl)-thiophene and 25 % of 2-nitro-3-phenylthiophene.

Oxidation of nitrophenylthiophene. General procedure. 200 mg of the nitro compound and 20 ml of an 1 % aqueous solution of potassium permanganate were heated on a

water-bath. When the permanganate colour had disappeared additional 20 ml of permanganate solution were added. After a few hours, the solution was again discoloured and another 20 ml portion was added. After discolouration, the manganese dioxide was filtered off and the filtrate acidified with dilute hydrochloric acid. The aqueous phase was extracted several times with ether and the combined ether phase was extracted with 2 N sodium hydroxide solution. The combined aqueous phase was acidified and extracted with ether. The dried ether phase was evaporated to dryness and the residual acids obtained were identified by IR-spectra or by TLC, using C_2H_5OH/conc. NH_3 in the proportion of 9:1 as eluent. The yields were in most cases between 40—60 %, although in a few cases, yields as low as 15 % were obtained.

NMR-spectra were recorded with a Varian A 60 NMR-spectrometer. The chemical shifts are given as τ-values, tetramethyl silane serving as internal standard. Mass-spectra were obtained using an LKB 9000 mass spectrometer. IR-spectra were recorded on a Beckman IR 5 A infrared spectrophotometer. The elementary analysis were carried out by Miss Ilse Beetz, Mikroanalytisches Laboratorium, Kronach, and at the Analytical Department of the Chemical Institute, University of Lund.

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