

## Nitration of 2,3'-Bithienyl

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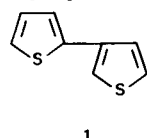
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The nitration of 2,3'-bithienyl (**1**) with fuming nitric acid in acetic anhydride at 0° gives a mixture of 3-nitro- (**2**), 2'-nitro- (**3**) and 5-nitro-2,3'-bithienyl (**4**) with relative percentages of 38.7%, 34.8% and 26.5%. When the nitration of **1** was carried out with fuming nitric acid in acetic acid at 20°, the same compounds **2**, **3** and **4** were obtained, but with different relative percentages: 20.4%, 36.5% and 43.1% respectively. The results of the mononitration of **1** are compared with those obtained in other electrophilic substitutions and with the theoretical predictions. The further nitrations of **2**, **3** and **4** with nitric acid in acetic anhydride at room temperature lead to the formation of five dinitro-2,3'-bithienyl isomers. Compound **2** gives a mixture of 2',3-dinitro- (**5**) and 3,5'-dinitro-2,3'-bithienyl (**6**); compound **3** gives a mixture of **5**, 2',5-dinitro- (**7**) and 2',4-dinitro-2,3'-bithienyl (**8**); compound **4** gives **7** and 5,5'-dinitro-2,3'-bithienyl (**9**). The possible reasons of the formation of the various dinitro-2,3'-bithienyl isomers are discussed.

There has been in the recent years a renewal of interest in the chemistry of biaryls. The research concern the behaviour of these compounds or their derivatives toward electrophilic (1-4) as well as toward nucleophilic reagents (5,6).

Data on the orienting effect of a ring as a substituent upon aromatic substitutions and on the electronic transmission of polar substituent effects in these systems have been collected (1-7). Continuing our research in this field, we report here the results obtained on the nitration of 2,3'-bithienyl (**1**). The purpose of this research is to com-



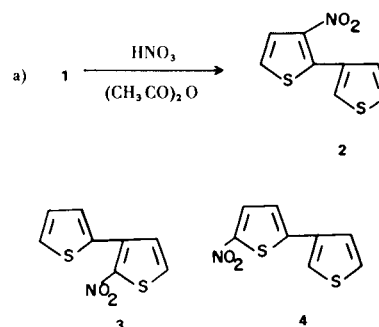
plete our study on the behaviour of the bithienyl isomers in the nitration reaction (**8**) and to compare the results of the nitration of **1** with those of other electrophilic substitutions carried out on the same substrate (1,3). It must be observed that previous investigations concerning electrophilic substitutions on **1** are confined to acetylation (1), bromination with *N*-bromosuccinimide (3), and deuterium-hydrogen exchange (3), which furnish 2',5-disubstituted derivatives.

The reaction of mononitration has been studied using as nitrating reagent both nitric acid in acetic anhydride

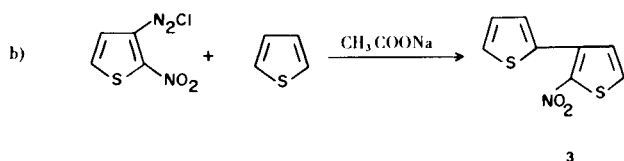
and nitric acid in acetic acid with the purpose to determine the influence of the changing nitrating reagent on the reactivity order of the various available positions of **1**. The further nitration with nitric acid in acetic anhydride of the mononitro derivatives obtained has been also examined.

## Results.

The 2,3'-bithienyl (**1**) reacted with fuming nitric acid in acetic anhydride at 0° yielding a mixture of three mononitro derivatives (scheme a). The compounds **2**, **3**



and **4** have been separated by preparative vpc and the structures assigned by analysis of the nmr spectra. The structure of **3** has been confirmed by comparison with an authentic sample prepared by decomposition of the 3-(2-nitro)thienyldiazonium chloride with sodium acetate in thiophene (scheme b). The structures of the isomers **2**,

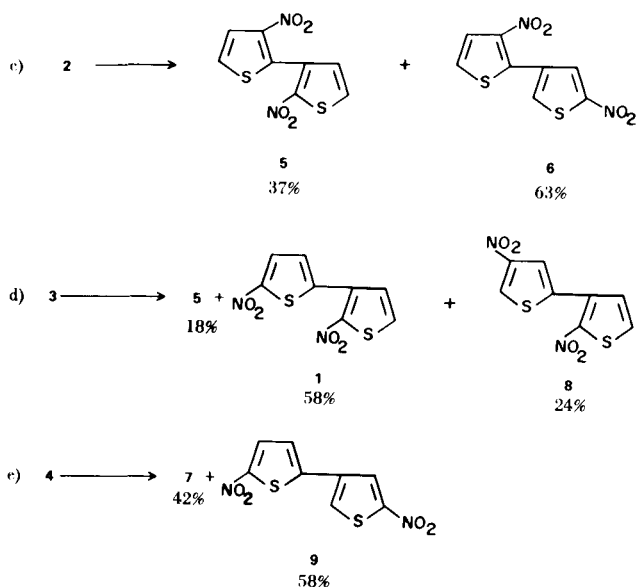


**3** and **4** have been also indirectly confirmed by structures of the dinitro derivatives obtained through their further nitration (see below scheme c, d, e). By vpc analysis the relative percentages of the various mononitro derivatives have been also determined. These were: 38.7% ( $\pm 0.3$ ) for **2**, 34.8% ( $\pm 0.3$ ) for **3** and 26.5% ( $\pm 0.2$ ) for **4**.

The mononitration of 2,3'-bithienyl has been carried out also with fuming nitric acid in acetic acid at 20°. In the reaction mixture the same compounds **2**, **3** and **4** were present, but in different relative percentages: 20.4% ( $\pm 0.2$ ) for **2**, 26.5% ( $\pm 0.3$ ) for **3** and 43.1% ( $\pm 0.3$ ) for **4**.

Under the conditions described, absence of significant dinitration products has been observed in the reaction mixtures obtained with both the nitrating reagents.

In the schemes c, d and e are reported the results obtained in the dinitration of mononitro derivatives **2**, **3** and **4** carried out with fuming nitric acid in acetic anhydride at room temperature. The various isomers present



in the reaction mixtures were separated by chromatography on column and the relative percentages are reported in the schemes. The structures of the compounds **5** and **7** have no necessity of other proofs. The structures of the isomers **6**, **8** and **9** have been determined by analysis of nmr spectra.

#### Discussion.

Electrophilic substitution in thiophenes is expected generally to be favored at positions adjacent to sulfur

atom (13); the situation appears, however, interesting in **1** where three different  $\alpha$ -positions are available. The mononitration of **1** proceeds with high selectivity at 2', 3 and 5 positions giving respectively the compounds **3**, **2** and **4**. No other substitution product has been observed.

The most notable result is the formation of compound **2** in which the nitro group has attacked the position 3 of the 2,3'-bithienyl ( $\beta$ -position with respect to the sulfur atom of the 2-thienyl ring). As mentioned above, no monosubstitution product at this position has been isolated in other electrophilic reactions studied on **1** (acetylation, bromination and deuteration) (1,3). Practically the observed positions of substitution indicate that both the 2- and the 3-thienyl residues present in **1** act as "ortho" "para" directing groups on the other thiophenic ring (14). The absence of the 4'-substituted product (other "ortho"-like substituted thiophenic isomer) must be attributed to the modest double-bond character (13) between the  $\beta$ -positions of the thiophenic ring which determines a low contribution of the conjugative effect of the 2-thienyl group from position 3' on position 4'. The lack of substitution at the 4- and particularly at the 5'-positions (15) confirms that in this reaction, as well as in the acetylation, bromination and deuteration, limiting structures involving electron +M shifts from the "other" ring contribute with a great extent at the stability of the transition state.

The previous results agree with the extended Pariser-Parr-Pople molecular orbital calculations applied on **1** (3), which predict the electrophilic substitutions at positions 2', 3 and 5 favored with respect to those at positions 4, 4' and 5'. The calculated activation energies involved in electrophilic substitutions indicate the following reactivity order: position 2' > position 5  $\geq$  position 3  $\gg$  other positions. The reactivity order observed in the nitration of **1** with nitric acid in acetic anhydride is 3  $\geq$  2' > 5. The higher reactivity of the "ortho" positions with respect to the "para" position agrees with the results obtained with the same reagent in the nitration of 2,2'-bithienyl (12) (enhanced 3-substitution with respect to 5-substitution) and of the biphenyl (4) (enhanced *ortho* substitution). It could be therefore explained with the Taylor hypothesis (4, 12) of a special mechanism of *ortho*-substitution operating in acetic anhydride which is superimposed to the normal pathway involving performance of nitronium ions followed by nitration (16). The inversion of the reactivity order of the positions when the reaction was carried out with nitric acid in acetic acid (5 > 2' > 3) confirms the previous hypothesis and furthermore suggests, when this order is compared with that expected from the calculated activation energies, steric factors play an important role in mononitration reaction of **1**. However, the relative percentage of 3-substituted product is rather large: a similar result was found also in the nitration of 2-phenylthiophene

TABLE  
Chemical Shift ( $\tau$ ) and Coupling Constants of Mono-(a) and Dinitro-2,3'-bithienyls (b)

Compound	Chemical shift ( $\tau$ )						Coupling constants (cps)					
	H <sub>3</sub>	H <sub>4</sub>	H <sub>5</sub>	H <sub>2'</sub>	H <sub>4'</sub>	H <sub>5'</sub>	J <sub>34</sub>	J <sub>35</sub>	J <sub>45</sub>	J <sub>2'4'</sub>	J <sub>2'5'</sub>	J <sub>4'5'</sub>
<b>2</b> (3-NO <sub>2</sub> )	-	2.87	2.42	2.36	2.72	2.66	-	-	5.76	1.63	2.73	5.12
<b>3</b> (2'-NO <sub>2</sub> )	2.37	2.03	2.58	-	2.83	2.61	3.72	1.20	5.22	-	-	5.63
<b>4</b> (5-NO <sub>2</sub> )	2.93	2.21	-	2.46	2.72	2.61	4.26	-	-	1.53	2.84	5.05
<b>6</b> (3,5'-NO <sub>2</sub> )	-	2.18	2.33	1.70	1.60	-	-	-	5.6	1.9	-	-
<b>8</b> (4,2'-NO <sub>2</sub> )	1.69	-	1.10	-	2.34	1.89	-	2	-	-	-	5.8
<b>9</b> (5,5'-NO <sub>2</sub> )	2.23	1.8	-	1.46	1.31	-	4.6	-	-	2	-	-

(a) Solvent carbon tetrachloride, reference TMS. (b) Solvent DMSO, reference TMS.

(2) and is in accordance with the relatively low selectivity factor in the nitration reaction. It is also interesting to note that in the nitration of **1** in acetic anhydride the amount of **2** and **3** are *ca.* the same (**3:2**  $\cong$  0.9) whereas a larger amount of **3** with respect to **2** was obtained nitrating **1** in acetic acid (**3:2**  $\cong$  1.8): the special mechanism operating in acetic anhydride is probably responsible for the lower selectivity between the two available *ortho*-positions in this solvent. The general features of the nitration reaction of **2**, **3** and **4** can be summarized as follows.

i) The disubstituted products obtained in the dinitration are very different from those obtained in the dibromination and deuterium hydrogen exchange (**1,3**) (substitution at the position 2' and 5). This fact can be explained with lesser selectivity (2) of the nitration compared with these last reactions.

ii) The formation of **5** and **7** (where the attack of the second nitro group has occurred at the "*ortho*" and "*para*" positions with respect to the *pivot* bond) was expected on the basis of the results obtained in the nitration of 2,2'- and 3,3'-bithienyl (9-12) and indicates that a nitrothienyl group is yet an "*ortho-para*" directing group in the nitration reaction of **2** and **3** as the unsubstituted thienyl one. In addition, the formation of **6**, **8** and **9** (in which a nitro group is in "*meta*"-position with respect to the *pivot* bond) from **2**, **3** and **4** respectively, show that the 2-(3-nitro (thienyl), 3-(2-nitro)thienyl and 2-(5-nitro)thienyl groups are less "*ortho-para*" directing substituents than the unsubstituted 2- and 3-thienyl groups. This enhanced "*meta*" orienting effect of a ring upon the other one, agrees with the higher electron-attracting character of the nitro substituted with respect to the unsubstituted thienyl residues. The formation of **8** is particularly noteworthy: in fact whereas in **6** and **9** the nitration reaction has occurred at the position 5' which is an  $\alpha$ -position of the

thiophenic ring, in **8** the introduction of a second nitro group has occurred at the position 4 which is a  $\beta$ -position. No example of this type was known in the behaviour either of the 2,2'-bithienyl and 3,3'-bithienyl in the same nitration reaction either in the other electrophilic reaction studied on **1**.

#### EXPERIMENTAL

2,3'-Bithienyl (**1**) and 2-nitro-3-amino-thiophene were prepared according to the literature (1, 3, 18). Nitric acid was purified according to the literature (19).

Nitration of **1** with Nitric Acid in Acetic anhydride.

To a solution of 2,3'-bithienyl (0.012 mole) in acetic anhydride (30 ml.), cooled to 0°, a mixture of fuming nitric acid ( $d = 1.52$ , 0.5 ml.) and acetic anhydride (6.6 ml.) was added dropwise and with stirring. The reaction mixture was stirred at 0° for 15 minutes and then poured into ice and extracted with ether. The residue obtained after removal of the solvent was dissolved in a small amount of benzene and fractionated by preparative vpc performed with a 6 m x 10 mm column packed with 10% silicon oil (SE 30) absorbed on Chromosorb W 80/100 at 230° using an Aerograph A-700 gas chromatograph (carrier Helium). The first fraction obtained was crystallized from light petroleum/ligroin as a colourless product, m.p. 77-78°.

*Anal.* Calcd. for C<sub>8</sub>H<sub>5</sub>NO<sub>2</sub>S<sub>2</sub>: C, 45.49; H, 2.37; N, 6.63; S, 30.33. Found: C, 45.11; H, 2.42; N, 6.74; S, 30.29.

This compound was assigned structure **2** on the basis of the nmr data. The second fraction was crystallized from light petroleum/ligroin as a colourless product, m.p. 50°.

*Anal.* Calcd. for C<sub>8</sub>H<sub>5</sub>NO<sub>2</sub>S<sub>2</sub>: C, 45.49; H, 2.37; N, 6.63; S, 30.33. Found: C, 45.37; H, 2.36; N, 6.65; S, 29.94.

This compound was assigned structure **3** on the basis of nmr data. The structure of **3** was confirmed by comparison with an authentic sample as prepared in scheme b.

The last fraction was crystallized from ligroin as a pale yellow product, m.p. 92-93°.

*Anal.* Calcd. for C<sub>8</sub>H<sub>5</sub>NO<sub>2</sub>S<sub>2</sub>: C, 45.49; H, 2.37; N, 6.63; S, 30.33. Found: C, 45.57; H, 2.43; N, 6.58; S, 30.54.

This compound was assigned structure **4** on the basis of nmr data. No other reaction product was observed. The relative per-

centages of the three mononitro isomers were calculated from the peak area.

#### Nitration of **1** with Nitric Acid in Acetic Acid.

To a solution of 2,3'-bithienyl (0.012 mole) in acetic acid (30 ml.) was added dropwise at 20° with stirring, a mixture of fuming nitric acid (d = 1.52, 0.5 ml.) and acetic acid (6.6 ml.). The reaction mixture was stirred at 20° for 1 hour and then worked-up and analyzed as previously reported.

#### 2'-Nitro-2,3'-bithienyl (**3**).

2-Nitro-3-aminothiophene (0.02 mole) in dilute hydrochloric acid (3:2, v/v, 11 ml.) was diazotized with sodium nitrite (1.5 g.) at 0-5°. The reaction mixture was stirred at 0-5° for 30 minutes and then filtered. The clear solution was rapidly added dropwise with stirring to thiophene (40 ml.) cooled at 0° and then a solution of sodium acetate trihydrate (6.4 g.) in water (16 ml.) was added dropwise. Stirring was continued for 34 hours at 0° and then for 48 hours at room temperature. The reaction mixture was extracted with ether and the residue obtained after removal of the solvent was dissolved in benzene and purified by chromatography on a silica gel column using benzene/light petroleum (2:1, v/v) as eluent. The solid obtained was crystallized from light petroleum/ligroin as a colourless product, m.p. 50°, which was shown to be identical with the compound isolated in the second fraction obtained from the nitration mixture of **1**.

#### Nitration of 3-Nitro-2,3'-bithienyl (**2**).

Compound **2** (1 g.) was added with stirring at room temperature to a mixture of nitric acid (d = 1.52, 0.4 ml.) and acetic anhydride (10 ml.). Stirring was continued for 1 hour at the same temperature and the reaction mixture was then poured into ice. The product which precipitated was collected by filtration, dissolved in benzene and chromatographed on a silica gel column using ether/light petroleum (2:1, v/v) as eluent. Two solid compounds were thus isolated; the first (0.5 g.) was crystallized from ligroin as a yellow product, m.p. 132-133°.

*Anal.* Calcd. for C<sub>8</sub>H<sub>4</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub>: N, 10.94; S, 25.00. Found: N, 10.91; S, 25.13.

This compound was assigned structure **6** on the basis of nmr data.

The second compound was crystallized from benzene/ligroin as a yellow product, m.p. 194-195°.

*Anal.* Calcd. for C<sub>8</sub>H<sub>4</sub>N<sub>2</sub>O<sub>4</sub>A<sub>2</sub>: N, 10.94; S, 25.00. Found: N, 10.99; S, 25.08.

To this compound, since it is identical to that isolated in the last fraction obtained in the nitration of 2'-nitro-2,3'-bithienyl (**3**) (see below), the structure **5** was assigned.

#### Nitration of 2'-Nitro-2,3'-bithienyl (**3**).

The reaction was carried out as previously reported for the nitration of **2**. The reaction mixture obtained in the nitration of **3** (1 g.) was chromatographed on a silica gel column using ether/light petroleum (1:1, v/v) as eluent. Three solid compounds were thus isolated; the first (0.2 g.) was crystallized from ligroin as a yellow product, m.p. 135-136°.

*Anal.* Calcd. for C<sub>8</sub>H<sub>4</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub>: N, 10.94; S, 25.00. Found: N, 10.98; S, 24.86.

This compound was assigned structure **8** on the basis of nmr data. The second compound (0.15 g.), crystallized from benzene/ligroin as a yellow product, m.p. 194-195°, was found to be 2',3'-dinitro-2,3'-bithienyl (**5**) since an identical compound was obtained in the nitration of **2**. The last fraction (0.5 g.) was crystallized from benzene/ligroin: yellow product, m.p. 163-164°.

*Anal.* Calcd. for C<sub>8</sub>H<sub>4</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub>: N, 10.94; S, 25.00. Found: N, 11.04; S, 24.95.

To this compound was assigned the structure **7**, since the same compound was obtained also in the nitration of **4**.

#### Nitration of 5-Nitro-2,3'-bithienyl (**4**).

The reaction was carried out as previously reported for the nitrations of **2** and **3**. The reaction mixture obtained from **4** (1 g.) was chromatographed on silica column using ether/light petroleum (2:1, v/v) as eluent. Two compounds were isolated: the first (0.5 g.) was crystallized from benzene/ligroin: m.p. 238-239°.

*Anal.* Calcd. for C<sub>8</sub>H<sub>4</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub>: N, 10.94; S, 25.00. Found: N, 11.01; S, 25.19.

This compound was given structure **9** on the basis of nmr data. The second compound (0.36 g.), crystallized from benzene/ligroin as a yellow product, m.p. 163-164°, was found to be 2,5'-dinitro-2,3'-bithienyl (**7**), since an identical compound was obtained in the nitration of **3**.

#### Nmr Analysis and Structure Assignment.

<sup>1</sup>H nmr spectra were recorded with a Varian XI-100 spectrometer. The chemical shifts are given as τ values, TMS serving as the internal standard. The cs and coupling constants for the various mononitro- and dinitro-2,3'-bithienyls are given in the Table. Spectral sample solutions were ca. 0.2 M. The nmr spectra of compounds **6**, **8** and **9** were all easily analyzed by direct inspection. For compounds **2** and **4** an iterative determination of the best spectral parameters by means of the LAOCN3 program (20) was performed. The probable error on computed chemical shifts and coupling constants never exceeded 0.03 Hz, while experimental error was probably restricted to within 0.2 Hz. The structures were generally assigned unambiguously from the spectral data taking into account the values of the coupling constants. These were substantiated from a large amount of literature data on mono- and disubstituted thiophene derivatives (21) and are typical and quite different from the various positioned hydrogen atoms of the thiophene ring.

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(14) Similar results (9-12) were also obtained in the nitration of 2,2'- and of 3,3'-bithienyl.

(15) In the nitration of 3-phenyl-thiophene, although under conditions not strictly comparable with ours, also 5-nitro-3-phenylthiophene was found in the reaction mixture: the absence of an isologous compound (5'-nitro-2,3'-bithienyl) in the nitration of 2,3'-bithienyl could be attributed to a "ortho-para" directing power of 2-thienyl- higher than that of phenyl group: this is in accordance with a larger negative value of  $\sigma_{p^+}$  of the former compared to the latter group (5).

(16) It must be pointed out that besides the Taylor hypo-

thesis, other factors (17) have been invoked to account for the variations in isomer proportions formed in nitration of various substrates as the reaction conditions are changed.

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