Orientation in Electrophilic Substitution of − I − M Substituted Thiophenes

I. Nitration of Thiophenealdehyde, Thiophenenitrile, and Nitrothiophene

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The isomeric compositions obtained at different temperatures in nitrations in trifluoroacetic acid of 2-thiophenealdehyde, 2-thiophenenitrile, 2-nitrothiophene, 3-thiophenealdehyde, 3-thiophenenitrile, and 3-nitrothiophene are reported. The reactivity orders for the ring positions are found to be $5 \geq 4 \gg 3$ and $5 > 2 > 4$ for 2- and 3-substituted thiophenes, respectively. The identities of the nitro products have been established with the aid of NMR and mass spectroscopy. Some results obtained in the elucidation of the mass spectra of the disubstituted thiophenes are reported.

Previous studies of isomeric compositions in nitrations of thiophenes of the present type have been limited to the 2-substituted derivatives, and only the 2,5:2,4 isomer ratios are reported.[1-3] In those studies which have been carried out with nitric acid, either alone or in acetic anhydride solution no mention has been made as to the formation of 2,3-isomers. Similarly, reports on the nitration of 3-substituted derivatives of the —I—M type seem to be concerned only with formation of the 3,5-isomer (*e.g.* Ref. 2).

These shortcomings are no doubt dependent on the difficulty of detecting and/or separating the (usually) small amounts of the "missing" isomers.

RESULTS AND DISCUSSION

Identification of the nitro-isomers. The general procedure to identify the nitro isomers and to measure the proportions in which they form has been a combination of NMR, GLC, and mass-spectral analyses of the reaction mixtures. Thus it was found that nitration of

Table 1. Experimental results (std. deviations) of nitrations of [structure: thiophene with R] in trifluoroacetic acid.

R	Isomeric compositions (%)			Ret. time (min)	Molecular ion		J_{AB} (cps)	Shifts [a] (ppm) in acetone relative solvent peak			
	25°	50°	75°		m/e	% of base peak		δ_3	δ_4	δ_6	δ_{CHO}
CHO	56 ±1	53.8±0.5	53 ±1	10.9	157	100	1.50 [a]	6.50	–	7.00	8.06
CN	37 ±2	34 ±1	32 ±1	8.5	154	90	1.50 [b]				
NO₂	50 ±1	55 ±2	52 ±2	11.9	174	100	2.00 [b]				
CHO	43 ±1	45 ±1	44.5±0.5	10.0	157	100	4.25 [a]	6.02	6.15	–	8.12
CN	63 ±2	65 ±1	66 ±2	6.5	154	75	4.25 [b]				
NO₂	49 ±1	45 ±2	47 ±2	8.4	174	99	–				
CHO	1.0±0.1	1.4±0.1	2.4±0.2	7.7	157	9					
CN	0.5±0.1	1.6±0.2	2.9±0.3	14.8	154	84					
NO₂	<1	0.3±0.1	0.4±0.1	14.4	174	61					
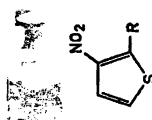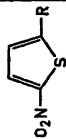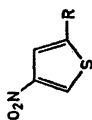
[a] Measured on GLC fractions.
[b] Coupling constants measured in reaction mixtures.

[structures: O₂N-thiophene-R; O₂N-thiophene-R; thiophene with NO₂ and R]

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Table 2. Experimental results (std. deviations) of nitrations of [structure: R-thiophene] in trifluoroacetic acid.

| R | Isomeric compositions (%) | | | Ret. time (min) | Molecular ion | | J_{AB} [a] | Shifts [a] (ppm) in acetone relative solvent peak | | | |
	25°	50°	75°		m/e	% of base peak		δ_2	δ_4	δ_6	δ_{CHO}
CHO	81 ±1	77 ±1	75 ±3	10.5	157	100	1.50	6.75	6.30	—	7.97
CN	83 ±1	83 ±1	79.2±0.1	10.0	154	100	1.75	6.68	6.37	—	—
NO₂	91 ±2	85 ±1	84.4±0.2	11.5	174	100	2.00	6.83	6.47	—	—
CHO	8 ±1	11 ±1	10 ±1	8.4	157	52					
CN	7.0±0.5	7 ±1	7.2±0.3	24.9	154	100	3.60	6.58	—	6.82	—
NO₂	3 ±1	5.3±0.3	5.4±0.1	21.7	174	92	—	6.63	—	6.63	—
CHO	10 ±1	12 ±1	15 ±2	6.3	157	3	5.40	—	5.48	5.93	8.57
CN	10 ±1	11 ±1	13.6±0.3	16.2	154	100	5.75	—	5.62	6.15	—
NO₂	6 ±1	i0 ±1	10.2±0.2	14.0	174	88	6.00	—	5.62	6.11	—
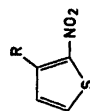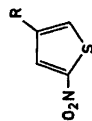
[a] Measured on GLC fractions.

with fuming nitric acid in trifluoroacetic acid solution (TFA) in each particular case gave the three possible R-nitro isomers (R=CHO, CN, NO_2) since in each case the gas chromatogram showed three peaks which according to mass-spectral analyses correspond to products with the molecular weights expected for the R-nitrothiophene isomers in question. The GLC retention times and the m/e ratios for the M^+ ions are given in Tables 1 and 2.

The isomeric compositions as measured with GLC in the reaction mixtures for three different reaction temperatures ($+25$, $+50$, and $+75°C$) are given in Tables 1 and 2. These values refer to reaction mixtures which still contain unreacted substrate.

For comparison the 2,5:2,4 isomer ratios as measured with NMR and GLC and those obtained in some previous studies are given in Table 3.

With respect to the nitrations of the 2-R thiophenes the identification of the two major peaks in the gas chromatograms could in principle be made by a comparison of the NMR and GLC intensity ratios. From Table 3 is seen, however, that the combined errors in the two methods will make such a comparison ambiguous when this particular ratio is close to unity. Thus this method of assignment of the GLC peaks was used in the 2-nitrile case only. The 2-aldehyde and 2-nitro cases are discussed below in connection with the 3-R thiophenes.

There is no question, however, that the two major GLC peaks must be the 2,5- and 2,4-nitro isomers, since the corresponding NMR coupling constants in the case of disubstituted thiophenes have been shown by Hoffman and Gronowitz [4] to offer an unambiguous characterization of the type of disubstitution irrespective of the particular substituents. The coupling constants obtained in the present cases are given in Table 1.

Consequently the third, and always minor, GLC peak has been assigned to correspond to the 2,3-R-nitro isomer chiefly because of the information of the molecular weight obtained from its mass spectrum (cf. Table 1).

From Table 2 is seen that the composition of the isomeric mixtures obtained in the nitration of 3-R thiophenes is such that the major GLC peak

Table 3. 2,5:2,4 isomer ratios in nitrations of

	Trifluoroacetic acid solution						Other media
	25°		50°		75°		
R	NMR	GLC	NMR	GLC	NMR	GLC	
CHO	0.9 ±0.1	0.77±0.03	1.1 ±0.1	0.84±0.02	1.2 ±0.1	0.84±0.02	0.33[1]
CN	2.0 ±0.3	1.70±0.06	2.0 ±0.5	1.91±0.03	2.2 ±0.4	2.06±0.04	1.33[1], 0.25[3]
NO_2	0.91±0.03	0.98±0.03	0.97±0.12	0.82±0.06	0.97±0.05	0.90±0.06	0.8±0.1[2]

must be assigned to the 3,5-isomer (according to the corresponding NMR coupling constant). In order to assign the two minor peaks to the 3,4- and 3,2-isomers the gas chromatograph was used in a preparative manner and the products collected from the gas chromatographic effluent were analyzed with NMR and their mass spectra recorded (*cf.* Table 2). Due to separation difficulties the 4-nitro-3-thiophenealdehyde could not be isolated in amounts sufficient for NMR analysis, therefore no identification other than the molecular weight is available for the corresponding GLC peak.

The above procedure was also employed in the 2-aldehyde case, thus providing an unambiguous assignment of the two major GLC peaks (Table 1). With respect to the nitrations of 2-nitrothiophene one of the major isomers is identical with the 3,5-dinitrothiophene formed in the nitration of 3-nitrothiophene. Thus from the identities of the mass spectra and the GLC retention times this isomer is easily identified in the mixture obtained from nitration of 2-nitrothiophene. Similarly the 2,3-dinitrothiophene occurs in both cases and consequently the identities of the retention times and mass spectra served to establish the formation of this isomer in the nitration of 2-nitrothiophene.

NMR. The NMR spectra of the reaction aliquots (*i.e.* in TFA-nitromethane solution, *cf.* Experimental) of the 2-R cases consisted of the AB patterns of the two major disubstituted isomers and of the ABX pattern of the substrate (AMX in the 2-nitrothiophene case). The AB pattern of the 2,4-isomers was always at the lowest field well separated from the other resonances of the spectrum whereas the AB quartet from the 2,5-isomer (one signal for 2,5-dinitrothiophene) was partly obscured by the AB bands of the substrate (A band in the 2-nitrothiophene case). Thus the isomer ratio 2,5:2,4 is obtained from $(I-2I_4)/I_{24}$ where I is the sum intensity of the two protons in the 2,5-nitro-isomer and of the 3 and 5 protons in the 2-substituted starting material. I_4 is the intensity of the X-band (*i.e.* proton 4) of the substrate.

The approximate extent of reaction as given by the sum of the mole fractions of the two major nitro-isomers is also obtained from the NMR analyses. For the 2-substituted cases these varied from 10 to 60 % conversion of the substrate to nitro products.

In the 3-R cases the reaction aliquots displayed NMR spectra consisting of the AB quartet of the 3,5-isomer generally partly obscured by the bands of the ABC pattern of the substrate. Thus NMR in these cases furnishes only the approximate degree of conversion to the 3,5-isomer which varied from 14 to 58 %.

The assignment of the substrate shifts were confirmed by comparison with calculated shifts using an ABC spectrum computer program.[5] The chemical shifts relative those of the α and β protons of thiophene (in TFA-nitromethane solution) in most cases correlated well with those measured by Gronowitz and Hoffman [6] in cyclohexane solution. The assignment of the bands of the AB quartets were made on the assumption that substituent influence is additive. In the 4-nitro-2-aldehyde case the assignment is facilitated since it has been shown [4] that the aldehydic hydrogen couples only to the 5-position in 2-aldehydes. Thus since the low field part of the AB quartet of 4-nitro-2-thiophene aldehyde was a triplet (due to coupling with the aldehydic

proton, $J=1.5$ cps) this band was assigned to the 5-proton. The aldehydic proton resonances were in general too close to the acidic protons of the solvent to permit any shift determination.

The chemical shifts in acetone of the fractions collected with the aid of preparative GLC are given in Tables 1 and 2. The shifts in acetone for 4-nitro- and 5-nitro-2-thiophenealdehyde and for 5-nitro-3-thiophenealdehyde agree fairly well with those published by Hoffman and Gronowitz.[4] Similarly the shifts of the aldehydic proton resonances for these derivatives agree with the published values.[4] In the case of 2-nitro-3-thiophenealdehyde the aldehydic proton signal is considerably broadened as is the low field part of the ring proton AB spectrum. This is due to coupling of the aldehydic proton to the 5-proton (see above). The coupling constant is estimated to be less than 1 cps. For 2-bromo-3-thiophenealdehyde this side chain coupling is 0.7 cps.[4]

GLC. The GLC retention times of the disubstituted thiophenes fall (with the exception of the aldehydes) in the orders $2,5 < 2,4 < 2,3$ and $3,5 < 3,2 < 3,4$ for 2-R and 3-R cases, respectively. The aldehyde derivatives show the orders $2,3 < 2,5 < 2,4$ and $3,2 < 3,4 < 3,5$ for 2- and 3-thiophenealdehyde, respectively, (Tables 1 and 2). Since the GLC column used (Experimental) is only slightly polar, the separation of the isomers is caused mainly by the differences in vapor pressures. It is conceivable, then, that the deviation in this respect for the aldehydes could be due to the existence of intramolecular hydrogen bonds from the aldehydic proton to a neighboring nitro group, resulting in those cases in lower boiling points. The peaks were in all cases resolved satisfactorily for quantitative evaluation.

Mass spectra. From Tables 1 and 2 are seen that the molecular ions in many of the cases furnish the base peaks of the spectra. Exceptions are found among the isomers where the nitro group occupies a position *ortho* to the aldehyde group.

From a compilation of mass spectra of a number of derivatives of nitrobenzene Beynon *et al.*[7] have suggested that the occurrence of fragments corresponding to the M−30 and NO^+ ions is due to a rearrangement of the molecular ion to its nitrite form which then may fragment into the ions above. In the present work these fragments are also observed. Since the fraction of the NO^+ ion of the total ion current increases for the isomers in the sequence $CHO < CN < NO_2$ a substituent influence on this particular fragmentation could be operating. With respect to structure, the NO^+ fragment is relatively more abundant for the 2,3- and the 3,4-isomers than for those where the substituents are in the 2,4- and the 2,5-positions. The NO^+ ion is the base peak in 2,5-, 2,3-, and 3,4-dinitrothiophenes.

The fragment m/e 45 is registered in all cases. It has been found in a number of thiophene derivatives and Bowie *et al.*[8] have shown by means of high resolution techniques that it corresponds to the thioformyl cation, $HC \equiv S^+$. Thus, as also noted by these authors, the appearance of the fragment may not necessarily be taken as evidence for a hydrogen substituted α-carbon. In terms of its fraction of the total ion current there is a minimum for 2,5- and a maximum for 3,4-disubstitution. The nitro aldehydes are exceptional since the maximum occurs for 3-nitro-2-thiophenealdehyde. This behavior might be due to con-

tribution by the extracyclic hydrogen. The m/e 45 fragment is further the base peak for the 2,3-nitroaldehydes.

The aldehydic hydrogen is certainly also responsible for the occurrence of the fragment m/e 39 which is common in thiophene compounds and which has been attributed to the cyclopropenium cation.[9] However, it is clear that this ion cannot be obtained from disubstituted thiophenes other than those which contain an extracyclic hydrogen. Consequently, in the present material the m/e 39 fragment is found only in the nitroaldehydes. Its fractional occurrence of the total ion current is remarkably constant between 11 and 13 %, and it is the base peak for 4-nitro-3-thiophenealdehyde.

The fragment m/e 64 is similarly found only in the nitronitriles and is probably the nitrile substituted cyclopropenium cation. A certain regularity is observed with respect to this fragment insofar that it is the base peak for the isomers where the nitrile group occupies the 2-position, whereas it is between 15 and 17 % of the total ion current for the cases where the nitrile group is in the 3-position.

No unique fragment of the kind observed in the aldehyde and nitrile cases is found with the dinitrothiophenes.

The fragment $C_2H_2S^+$ (m/e 58) which is abundant in the mass spectrum of thiophene [9] occurs with no obvious regularity and is further of low abundance in the present compounds.

The low abundance of molecular ions in the nitroaldehydes of the *ortho* type (*cf.* Tables 1 and 2) is likely to be due to a rearrangement to the corresponding nitroso carboxylic acids suggested by Harley-Mason *et al.*[10] for *o*-nitro-benzaldehyde. The fragmentation involves the expulsion of nitric oxide from the nitroso compound to yield M−30 ions (m/e 127 in the present cases). This ion is 2−3 times more abundant in the 2,3- and the 3,4-nitroaldehydes than in the other nitroaldehydes. The M−30 ion may further lose a hydroxyl radical [10] to form a fragment m/e 110 which again is found to be 2−3 times more abundant in the 2,3- and the 3,4-nitroaldehydes than in the 2,5- and 2,4-isomers.

Side reaction. The NMR spectra of the products of nitrations of thiophene 2-aldehyde at +50°C and at +75°C showed, in addition to the resonances described above, extra signals in the region of the substrate ring proton bands. The shifts and coupling constants of these extra bands matched exactly those obtained for the MX part of the 2-nitrothiophene AMX spin coupling pattern. The 2-nitrothiophene A band will then coincide with the low field band of 2-thiophenealdehyde and with the bands of 5-nitro-2-thiophenealdehyde, thereby distorting the intensity measurement of the 2,5:2,4 isomer ratio.

In Table 3 it is seen that the NMR and GLC measurements of this ratio for the aldehyde case do not agree for the 50° and 75° experiments. If the NMR intensity ratio is corrected for the presence of 2-nitrothiophene the 2.5:2,4 ratio becomes 0.96 and 0.98 at +50° and at +75°, respectively.

The NMR spectra of the 25° experiments do not show these extra signals, thus implicating that the formation of 2-nitrothiophene under the present conditions takes place at temperatures above 25°C. It seems likely that 2-nitrothiophene is formed through decarbonylation of 2-thiophenealdehyde

and/or of 5-nitro-2-thiophenealdehyde. (Decarbonylation of thiophenealdehyde will give thiophene which would rapidly be converted to 2-nitrothiophene. The latter could also be formed in one nitrodecarbonylation step). If only the aldehyde is decarbonylated the GLC values will still give the correct measure of the isomeric composition, but if the nitrocompound is decarbonylated it is clear that the GLC values could also be in error.

It may be assumed, however, that the value for the 2,5:2,4 ratio previously reported[1] is obtained at conditions where decarbonylation does not occur (reaction temperature −10°C). Thus the GLC values of Table 3 for the nitro-aldehydes are considered sufficiently reliable since it is significant that they are less than unity. This side reaction is presently under investigation.

Relative reactivity. A rough comparison of the rates with which the 2- and 3-substituted substrates undergo nitration is possible to obtain from the NMR measurements, since the time was noted when each aliquot was taken. Thus from those cases where the concentrations of substrate and nitric acid were about equal, the approximate rate of disappearance is obtained from the expression

$$a/(1-a) = dkt$$

where a is the fraction of substrate which undergoes conversion to nitro isomers, d is the average initial concentration of the reactants and k is the second order specific rate constant. Thus in the 2-R cases the formation of the 2,3-isomers was neglected, but in the 3-R cases the NMR mole fraction of the substrate was corrected for formation of the minor isomers with the GLC values of Table 2. From the slopes of the resulting (straight) line plots the following ratios k_3/k_2 were obtained:

$$
\begin{aligned}
R &= CHO & k_3/k_2 &= 1.2 \ (25°C) \\
&= CN & &= 2.1 \ (50°C) \\
&= NO_2 & &= 1.7 \ (50°C)
\end{aligned}
$$

Thus the overall reactivity with respect to nitration is higher for 3-R derivatives. The result may then be used in such preparative work in which the starting material is a mixture of thiophene isomers of the −I−M type. It should be particularly useful for substitution reactions more selective than nitration.

Orientation. According to Brown and Wirkkala[11] nitration of toluene in trifluoroacetic acid does not show any irregularities with respect to orientation and partial rate factors. Nitrations of benzonitrile and nitrobenzene in trifluoroacetic acid[12] show that also in these cases no significant differences are found when compared to the results obtained in other media. Similarly the 5:4 ratios of the 2-substituted thiophenes previously reported agree reasonably well with those obtained in the present study (see Table 3). The only significant exception is one of the values reported for 2-thiophenenitrile.[3] The discrepancy is not due to a temperature effect since the present study shows that the temperature dependence for this particular ratio is small, but is probably due to loss of the 2,5-isomer during the work up procedure.[3] The composition of the isomeric mixtures given in Tables 1 and 2 may then be considered as representative for the nitration of the present type of sub-

stituted thiophenes. Since the conditions are such that there is always a substantial amount of unreacted substrate left in the reaction mixture the isomeric composition is taken as a measure of the relative reactivity of the positions. Thus the reactivity orders $5 \geq 4 \gg 3$ and $5 > 2 > 4$ are obtained from the data for 2-R and 3-R cases, respectively. The sensitiveness of the 5:4 ratio in the 2-R series to the particular substituent is evident from Table 3.

The MO-treatment of 2-nitrothiophene according to Melander [13] predicts, that the 5-position should be substantially more reactive than the 4-position in electrophilic substitution. From Table 1 is seen that about equal reactivity of these positions in 2-nitrothiophene is indicated. The theoretical prediction is, however, in qualitative agreement with the orientation obtained in 2-thiophenenitrile.

With respect to the 3-R series the orientation is (irrespective of R) the one predicted by MO calculations [13] for 3-nitrothiophene. The fraction 5-substitution increases according to $CHO < CN < NO_2$, which is the same order as obtained for the fraction *meta* substitution in the benzene analogues. This order is not observed with respect to the 4-position in the 2-R series (which may be considered as a *meta* position) probably due to the fact that resonance interaction between the ring and the aldehyde substituent is larger for the 2-isomer than for the 3-isomer.[14]

The very low fraction of 3-substitution in the 2-R series is hardly surprising in view of the fact that the position is β to sulfur as well as *ortho* to the substituent. One would therefore expect a corresponding low fraction of 4-substitution in the 3-R cases. As is seen from Table 2 this site, however, is about as reactive as the 2-position. Thus it seems as if the deactivating influence of the R group is more pronounced on the 2-position than on the 4-position. This may be due to the fact that in thiophene the 3−4 bond length is increased by about 4 % compared to the 3−2 bond.[15] The difference could lead to an attenuation of the inductive effect on the 4-position compared to the 2-position.

From the valence bond structures of the ground state given by Hoffman and Gronowitz [6] for 2-thiophenealdehyde and 3-thiophenealdehyde (the "good" structures I−IV and IX−XII, respectively, in Ref. 6) the reactivity orders implied for 2-R and 3-R thiophenes are $4 > 5 \sim 3$ and $5 \sim 4 > 2$, respectively. The resonance hybrids of the relevant Wheland complexes reveal the order $5 > 4 \sim 3$ for 2-R cases and $5 \sim 2 > 4$ for the 3-R cases.

Comparison with the experimental results shows that these approaches are not satisfactory. In Part II an MO description will be given of the factors which influence the relative reactivities of the positions in the thiophene derivatives of the present kind.

From Tables 1 and 2 is seen that the temperature dependence is evident only in a few cases because of the experimental uncertainty. The trend, however, is towards a randomization of the isomeric composition as the temperature increases.

Gronowitz *et al.*[16] have reported that nitration of 3-thiophenealdehyde at −10°C in sulfuric acid gives pure 5-nitro-3-thiophenealdehyde. From the temperature dependence of the nitration of 3-thiophenealdehyde (Table 2)

the isomeric composition at $-10°C$ is predicted to be $\sim$90 % 3,5-, $\sim$5 % 3,4-, and $\sim$5 % 3,2-isomer. Thus if the selectivity is assumed to be the same in the two solvents, the primary product prepared by Gronowitz *et al.* should have the isomeric composition above.

EXPERIMENTAL

The gas chromatographic analyses were made with an Aerograph model 1520 gas chromatograph equipped with a flame ionization detector. NMR spectra were recorded on a Varian A 60A Analytical NMR Spectrometer equipped with the Varian V 6057 variable temperature system. Mass spectrometrical analyses were performed with the LKB model 9000 gas chromatograph-mass spectrometer operating at 70 eV. Samples were introduced *via* the gas chromatograph.

Starting materials. 2-Thiophenealdehyde was prepared from thiophene and N-methylformanilide with phosphorus oxychloride as catalyst.[17] Yield 79 %. B.p. $73°/8$ mm Hg.

3-Thiophenealdehyde was prepared from 3-bromothiophene *via* 3-thienyllithium and N,N-dimethylformamide.[18] Yield 60 %. B.p. $77°/16$ mm Hg.

2-Thiophenenitrile was prepared from 2-thiophenealdehyde *via* its aldoxime with acetic anhydride.[3] Yield 89 %. B.p. $72°/12$ mm Hg.

3-Thiophenenitrile was prepared from 3-bromothiophene and quinoline in the presence of cuprous cyanide.[19] Yield 85 %. B.p. $77°/10$ mm Hg.

2-Nitrothiophene was prepared according to a method which gives high isomeric purity.[20] Yield 50 %. M.p. $40-41°$.

3-Nitrothiophene was obtained through the selective dechlorosulfonation of nitro-2-thiophenesulfonylchloride.[21] Yield 38 %. M.p. $70-72°$.

3-Bromothiophene used as starting material for two of the 3-substituted thiophene derivatives was prepared according to Gronowitz [22] by debromination of 2,3,5-tribromothiophene.

The isomeric purity of the above compounds was determined with the gas chromatograph. Thus, 2-thiophenealdehyde and 2-thiophenenitrile were found to be isomerically pure whereas the corresponding 3-derivatives contained 4.3 % and 1.7 % of the 2-isomers, respectively, (TCEPE 3 % on Aeropak $80-100$ mesh, $1/8'' \times 3.3$ m, 20 ml N_2/min, $100°C$). 2-Nitrothiophene contained 1.1 % of the 3-isomer and 3-nitrothiophene contained 1.3 % of the 2-isomer. (Reoplex 5 % on Aeropak $80-100$ mesh, $1/8'' \times 3$ m, 20 ml N_2/min, $145°C$).

Nitration experiments. For each experiment 1 ml of *ca.* 1 M solutions of the thiophene derivative in trifluoroacetic acid (Eastman Kodak) was kept in the constant temperature bath for about 5 min. Then 0.2 ml of a *ca.* 6 M solution of nitric acid (Merck, *p.a.*, $d = 1.52$) in TFA was added. (In some experiments *ca.* 12 M nitric acid solutions were added). Thus the reaction mixtures at start were $0.92-1.28$ M with respect to the thiophene derivatives and $0.91-2.15$ M with respect to nitric acid. Aliquots (0.2 ml) were then withdrawn at suitable intervals and transferred to a stoppered NMR tube (at $+6°$) containing 0.2 ml of nitromethane (Eastman Kodak, Spectroscopic). Control experiments showed that this procedure effectively stopped the reaction; in addition a convenient reference for the NMR measurements was obtained. In this manner at least three aliquots were withdrawn.

The aliquot was then subjected to NMR and GLC analyses. The NMR spectra were recorded at a probe temperature between $+5$ and $+10°C$. Five integral sweeps were generally made at optimum conditions with 250 cps sweep width which covered the entire aromatic region for both starting material and products.

The subsequent GLC analyses were made on a QF1 column held at $160°$ (3 % QF1 $1/8'' \times 2$ m, 20 ml N_2/min). About 1 μl of the NMR aliquot was injected. The peak areas were evaluated according to peak height $\times$ band width at half height. The detector sensitivity was assumed to be the same for the three isomers. From Table 3 is seen that the 2,5:2,4 ratios as measured with NMR and GLC agree within the errors with the exception of the nitroaldehydes.

In order to obtain reaction mixtures enriched in the products for the purpose of preparative GLC (*cf.* Results and Discussion), nitrations were carried out with 2- to 3-fold

excesses of nitric acid and during extended periods of time (about 2 h) at $+75°$. NMR and mass spectra of the mixtures were recorded and then the trifluoroacetic acid-nitric acid was evaporated in a rotary evaporator. The residue was dissolved in acetone and NMR spectra and mass spectra were recorded. About 0.5 ml was then injected on the preparative QF1 column (160°, 3/8″ × 4.5 m, 150 ml He/min), and the fractions were collected in traps cooled with ice. The trapped material was dissolved in acetone and NMR and mass-spectra were again recorded. The results of these analyses are given in Table 1 for 2-thiophenealdehyde and in Table 2 for the 3-substituted cases. The reaction mixtures were originally about 0.8 M with respect to the substrate and the volume of the reaction mixtures was 2 ml.

The mass spectral results given in Table 1 for 2-thiophenenitrile and 2-nitrothiophene were obtained from nitrations at $+75°$ carried out similarly but without preparative GLC.

The same QF1 column used for the analytical GLC measurements was also used in the gas chromatograph-mass spectrometer.

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