

## The Behaviour of 2-Nitrothiophene and of 3-Nitrothiophene with Some Nucleophiles

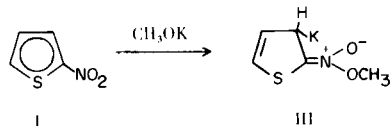
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The reactivity of 2-nitrothiophene (I) and of 3-nitrothiophene (II) with some nucleophiles has been studied. According to calculated electronic densities I can receive nucleophilic attack at C<sub>3</sub> and C<sub>5</sub> depending on the nucleophile used, but II only at C<sub>2</sub>. With *N*-lithium piperidine both I and II also give coupling products (VII and XI respectively) of the bithienyl type.

Study of the reactivity of nitrothiophenes towards alkoxides and other nucleophiles is a problem which has received little attention, whereas benzene analogues have been extensively investigated (1). Steinkopf (2) reported that 2-nitrothiophene (I) and 3-nitrothiophene (II) react with alkoxides giving coloured reaction products for which he proposed structures of alkyl ethers of the acinitro form (*e.g.*, see III).



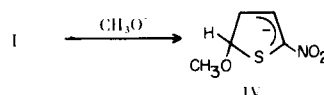
In view of recent papers on the behaviour of some methoxynitrothiophenes (3a,b) and of 2,4-dinitrothiophene (3c) with alkoxides (formation of Meisenheimer-type adducts) the previously reported structures seem incorrect. To clarify this point and also in connection with other studies (3a, 4) on direct nucleophilic substitution in nitrothiophenes, we report a chemical and nmr study of the behaviour of I and II toward sodium methoxide, *N*-lithium piperidine, *N*-lithium and *N*-sodium diphenylamine.

### Nmr Data.

Nmr spectra of I and II in cyclohexane and in deuteriochloroform have been reported by Hoffmann and Gronowitz (5), Bulman (6) and Maag and Manukian (7). For our purposes spectra in DMSO were necessary to make a comparison with the situation in the presence of sodium methoxide in the same solvent.

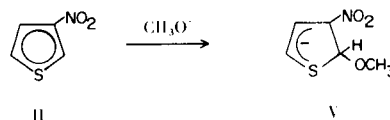
At room temperature the nmr spectrum of I presents two systems of signals [ratio of areas 1(q)/2(m)] which have been analyzed as ABX system (see Table). The

spectrum is simplified by addition of one equivalent of sodium methoxide. The signals present, because of their chemical shifts and coupling constants (see Table) compared to those of the parent compound (I), allow assign-



ment (3a,c, 8) of a Meisenheimer-type adduct at C<sub>5</sub> (IV). This behaviour, *i.e.* attack at C<sub>5</sub> ( $\alpha$ -position with respect to sulphur heteroatom that can help to accommodate negative charge), recalls that one of 2-nitro-3-methoxythiophene (3a) which furnishes a Meisenheimer-type adduct at C<sub>5</sub> with sodium methoxide. This can be related to the late position of the transition state, then largely affected by the possibility of charge dispersion on the sulphur atom.

Similar results have been obtained for II, which has a spectrum with two systems of signals [ratio of areas 1(q)/2(m)], analyzed as an ABX system (see Table). The spectrum observed after addition of one equivalent of sodium methoxide also indicates the formation of a Meisenheimer-type adduct at C<sub>2</sub> (V).



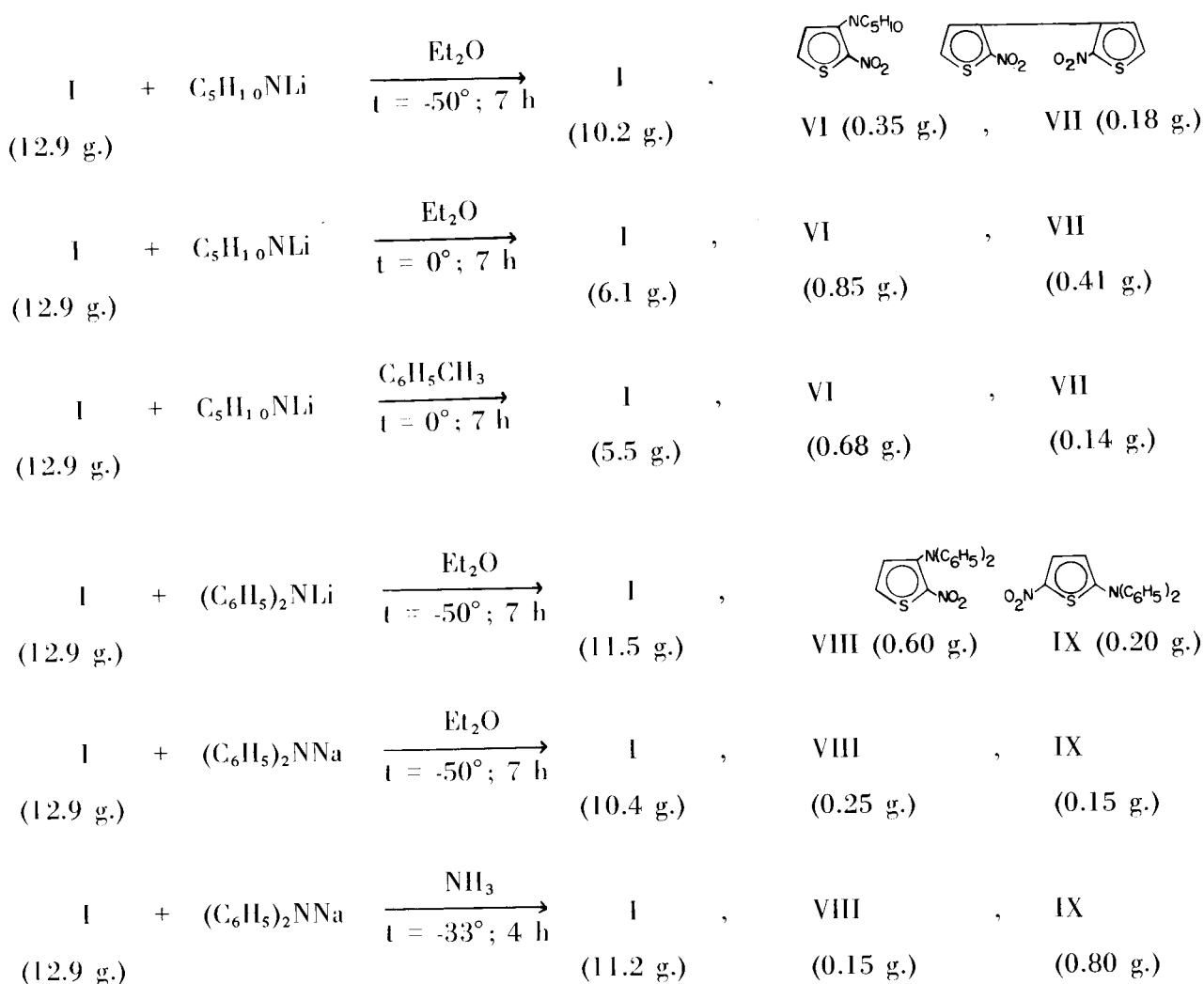
It must be pointed out that nitrothiophenes I and II represent the first examples of mononitro compounds with no other activating group (electron-accepting and/or withdrawing groups, nitrogen in the heterocycle of pyridine type, *etc.*) which gave Meisenheimer-type adducts (see 3a).

Table (a)

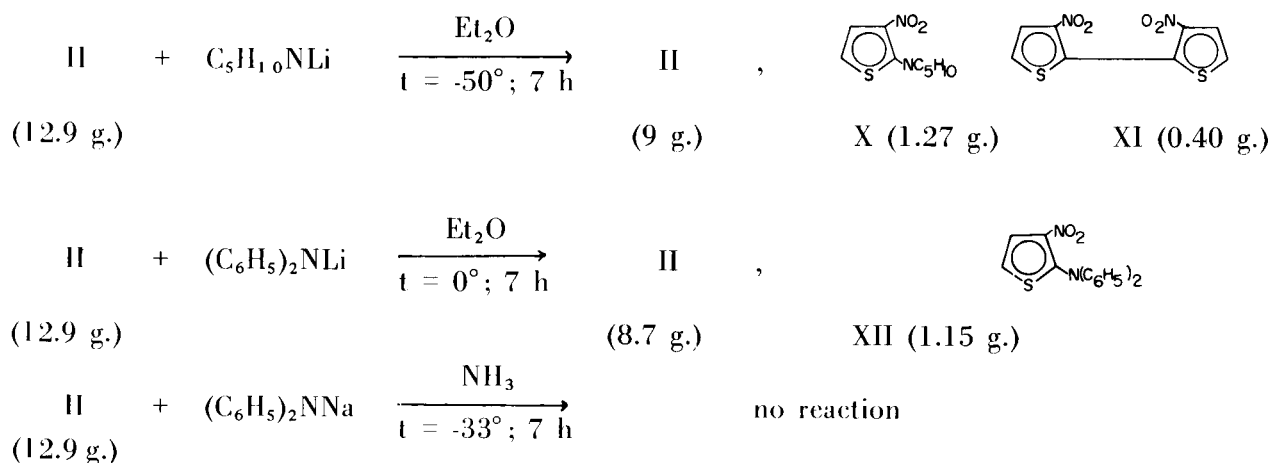
Compound	Chemical Shifts ( $\tau$ , ppm)					Coupling Constants (cps)			
	C <sub>2</sub> -H	C <sub>3</sub> -H	C <sub>4</sub> -H	C <sub>5</sub> -H	C-OCH <sub>3</sub>	J <sub>2,5</sub>	J <sub>3,4</sub>	J <sub>3,5</sub> or J <sub>2,4</sub>	J <sub>4,5</sub>
I		1.92 (b)	2.82 (1H, q)	1.99 (b)			4.0	1.5	5.7
IV (c)		3.33 (1H, d)	4.56 (1H, q)	3.94 (1H, d)	6.85 (3H, s) (d)		5.9		3.1
II	1.24 (1H, q)		2.35 (c)	2.26 (e)		3.4		1.2	5.3
V	3.88 (1H, d)		4.18 (1H, q)	3.70 (1H, d)	6.90 (3H, s) (f)			< 0.5	6.1

(a) Jeol C-60 instrument. Solutions of the nitrothiophenes (about 1.5 M) in DMSO; complex formation has been achieved by the addition of one equivalent of sodium methoxide solution in methanol (about 5 M). On standing solutions of complexes undergo exchange and/or rearrangement reactions and/or decomposition. The number in parentheses represent relative intensities of the respective lines and their multiplicity. (b) AB part of ABX system, C<sub>3</sub>-H + C<sub>5</sub>-H: 2H, m. (c) Assignment of structure has been made preparing also Meisenheimer-type adduct from 2-nitrothiophene-5-D and sodium methoxide in DMSO/deuteriomethanol. (d) C<sub>5</sub>-OCH<sub>3</sub>. (e) AB part of ABX system, C<sub>4</sub>-H + C<sub>5</sub>-H: 2H, m. (f) C<sub>2</sub>-OCH<sub>3</sub>.

Scheme I



## Scheme 2



## Chemical Data.

We have studied the behaviour of I and II with various nucleophiles in different solvents (*N*-lithium piperidine and *N*-lithium diphenylamine in ethyl ether or toluene, *N*-sodium diphenylamine in ethyl ether or in liquid ammonia). The products obtained and the relative yields are summarized in Schemes 1 and 2. In every case low yields have been obtained but by operating at low temperatures large amounts of reagents have been recovered unchanged (about 80-90% of I and 70% of II): therefore taking account of the low conversion the actual yield seems acceptable and comparable to those obtained in the case of the corresponding reactions in the benzene series (9).

## Discussion of Results.

The results observed can be rationalized considering the structures of the nitrothiophenes used, the nature of the nucleophiles with regards to the cations present and the nature of the solvents.

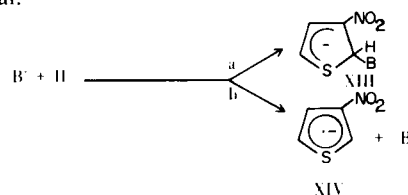
Calculated (10) electronic densities in I and in II indicate that I can receive nucleophilic attack at C<sub>3</sub> and/or C<sub>5</sub>, whereas II has a large preference for attack at C<sub>2</sub>. Therefore in the first case (I) the nature of reagents and of solvents can affect the nature of the reaction products.

In a highly polar solvent (DMSO/methanol) which favours charge-dispersion, I undergoes unique attack at C<sub>5</sub> with sodium methoxide giving a Meisenheimer-type adduct (IV). In ethyl ether or toluene (poor solvating solvents) the most powerful nucleophile (*N*-lithium piperidine) only attacks at C<sub>3</sub> (II) with low yield (VI, substitution product, and VII, coupling product), whereas the diphenylamine derivatives (lithium and sodium) give the two possible substitution products at C<sub>3</sub> and C<sub>5</sub> (VIII and IX) with different yields and ratios as a function of

cation (12), lithium favouring attack at C<sub>3</sub> more than sodium. In a more polar solvent (ammonia, able to solvate ionic species) *N*-sodium diphenylamine gives predominantly an attack at C<sub>5</sub>, probably the less hindered position.

Because of the foreseen minor sensitivity of II to variation in the experimental conditions we have studied the reactions of II with sodium methoxide and with amines and for amines we chose only the experimental conditions which gave striking differences of reactivity with I; *i.e.* reactions with *N*-lithium piperidine and diphenylamine in ethyl ether and with *N*-sodium diphenylamine in ammonia. According to calculated (10) electronic density in II we have observed attack at C<sub>2</sub> with sodium methoxide (V) in DMSO and with *N*-lithium piperidine (X and XI) and diphenylamine (XII) in ethyl ether. On the contrary II, with the same experimental conditions used for I, gives no reaction with *N*-sodium diphenylamine in ammonia, perhaps because of the fact that C<sub>2</sub> is a position hindered for a highly solvated reagent by a nitrogroup and annular sulphur, according to the previous reported interpretation of data related to the behaviour of I.

Russell hypothesis (13) can be useful to visualize the reaction pattern, *e.g.* with II. The electron transfer from an anion to an aromatic nitro compound can proceed in two main directions giving a Meisenheimer-type complex (XIII) or a radical anion (XIV) (14) together with a free radical.



Formation of XIII (pathway *a*) observed when  $B^{\cdot-} = CH_3O^{\cdot-}$  can also be responsible for substitution products (X and XII) whereas XIV (pathway *b*) seems to be intermediate for the coupling product (XI).

It is interesting to remark that this represents the first case observed of formation of coupling products which are absent, *e.g.*, in the corresponding reactions with nitrobenzene (9c). The different behaviour seems to us linked to the nature of the intermediate radical anions more stable in the case of thiophene.

Formation of coupling products has been observed with *N*-lithium piperidine (in ethyl ether and in toluene) with I as well as with II and has not been observed with other nucleophiles, indicating that the choice between pathway *a* or *b* is affected by the ability of the nucleophile to give an electron, furnishing a radical species, and this ability is quite different in the cases examined.

The situation in I is similar to that examined with II, the only complication arising from the fact that I has two different sites for reaction ( $C_3$  and  $C_5$ ). The choice of the position seems affected by the nature of the interactions between nucleophile and solvent used which determine the true dimensions of the nucleophilic reagent: experimental results seems to indicate that the more hindered position is the  $C_3$  (and this is also the carbon at which the attack should be favoured from electronic viewpoint) adjacent to the carbon carrying the nitrogroup. In fact small reagents attack at  $C_3$ , by increasing the nucleophile dimension we have observed attack at  $C_3$  and  $C_5$ , while with the largest reagent used by us (*N*-sodium diphenylamine in ammonia) attack at  $C_5$  becomes predominant.

## EXPERIMENTAL

### Synthesis and Purification of Compounds.

2-Nitrothiophene (I) (15), 3-nitrothiophene (II) (16), 2-nitro-3-*N*-piperidylthiophene (VI) (17), 2,2'-dinitro-3,3'-bithienyl (VII) (18), 2-*N*-piperidyl-3-nitrothiophene (X) (19), 3,3'-dinitro-2,2'-bithienyl (XI) (20) were prepared according to the methods reported. The other model compounds (VIII, IX and XII) were prepared as below.

### 2-Nitro-3-*N*-diphenylaminothiophene (VIII).

This compound was prepared from 2-nitro-3-bromothiophene according to the method used (21) for the synthesis of the benzene analogue, m.p. 154°, from methanol; pmr (carbon tetrachloride and deuteriochloroform): coupling constant between thiophene protons,  $J_{4,5} = 5.8$  cps.

*Anal.* Calcd. for  $C_{16}H_{12}N_2O_2S$ : C, 64.9; H, 4.1; N, 9.5; S, 10.8. Found: C, 65.1; H, 4.2; N, 9.6; S, 10.8.

### 2-*N*-Diphenylamino-5-nitrothiophene (IX).

This compound was prepared from 2-iodo-5-nitrothiophene as for the previous compound, m.p. 120°, from methanol; pmr (deuteriochloroform): coupling constant between thiophene

protons,  $J_{3,4} = 4.5$  cps.

*Anal.* Calcd. for  $C_{16}H_{12}N_2O_2S$ : C, 64.9; H, 4.1; N, 9.5; S, 10.8. Found: C, 65.0; H, 4.2; N, 9.5; S, 10.8.

### 2-*N*-Diphenylamino-3-nitrothiophene (XII).

This compound was prepared from 2-bromo-3-nitrothiophene as for the previous compound, m.p. 121°, from methanol.

*Anal.* Calcd. for  $C_{16}H_{12}N_2O_2S$ : C, 64.9; H, 4.1; N, 9.5; S, 10.8. Found: C, 65.0; H, 4.2; N, 9.6; S, 10.9.

### General Procedure for Reactions between Nitrothiophenes (I or II) and Nucleophiles.

The nitrothiophene (0.1 mole) was added to the solution or suspension of nucleophile (0.12 or 0.05 mole respectively for lithium or sodium salts) and maintained at the temperature indicated in Schemes 1 or 2 for the fixed times.

Generally the reaction mixtures were decomposed with excess 5*M* hydrochloric acid and extracted with ethyl ether. The ethereal extracts were dried (sodium sulfate), decolourized with charcoal and the ethyl ether distilled off. The residue was chromatographed on silica gel using light petroleum and then benzene as eluant.

In the case of the reaction in liquid ammonia the residue obtained after evaporation of excess ammonia was treated with ethanol and water and then the vapor phase distillation removed large amounts of diphenylamine and nitrothiophene. The residue of vpd was extracted with ethyl ether and treated as previously indicated.

The products obtained were identified by comparison (mixed m.p.; uv, ir and nmr spectra; tlc) with model compounds.

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(11) In the cases studied the solvent change between two poorly solvating solvents (ethyl ether or toluene) does not seem to affect isomeric distribution of reaction products. Absence of products deriving from attack at C<sub>5</sub> can depend on formation of ring cleavage products (4b), which undergo decomposition in the experimental conditions used.

(12) Different behaviour as a function of the metal present can be related to the different radius or complexing power of the cation and to different polar structures (intimate ion-pair, ion-pair, and so on) of the various metalamines. These factors affect the results obtained as a function of solvent [see P. Haberfield and R. B. Trattner, *Chem. Commun.*, 1481 (1971) and references therein].

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(14) Considering the fact that radical anions have been proposed as the first products of reaction in some nucleophilic substitutions [see e.g. J. F. Bunnett and J. K. Kim, *J. Am. Chem. Soc.*, **92**, 7463 (1970)], in an alternative reaction pattern XIV could be the precursor also of XIII.

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