Thiophene Series. Substituent Effect on Thiophenoxy Debromination
of Various 2-Nitro-3-bromo-5-X-thiophenes (1)

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The kinetics of the reaction of a series of 2-nitro-3-bromo-5-X-thiophenes with sodium thiophenoxide in methanol were determined.

The plot of log k against σ-values gave ρ-value + 4.51 at $20°$.

Good correlation was observed pointing out the validity of the Hammett relationship for reactions occurring directly on the thiophene ring at the β-position with respect to the heteroatom.

The validity and direct application of the Hammett relation to heterocyclic compounds has been discussed at length (2) during the last several years. For 5-membered ring systems containing one heteroatom in which a -CH=CH- group of the benzene ring has been replaced by a heteroatom there is a question of the actual existence of *ortho*, *meta* and *para* relations.

Nevertheless the Hammett relation has been extended to study *meta* and *para* structural relations in the pyrrole (2,3), furan (2,4), thiophene (2,5) and selenophene (6) ring systems. With regard to thiophene, in many cases the reaction center was on the ring or at a side-chain in the α-position with respect to the heteroatom thus giving rise to relations (7) of the *meta* and *para* type (in I: 4-R-2-Y or 5-R-2-Y). The inverse meta relation (in II: 2-R-4-Y) has been studied slightly and only for cases in which the reaction center lies in a side-chain. No 2-R-4-Y relation has been studied with the reaction center at a β-carbon atom of the heterocycle, perhaps because of experimental difficulties of synthesis of compounds which fit this purpose.
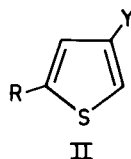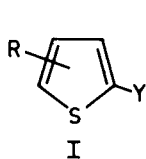

For the purpose of verifying the application of the Hammett equation to a 2-R-4-Y relation in the thiophene ring and in order to determine the sensitivity to substituent effect for a reaction occurring directly on the β-carbon, the rate constants for thiophenoxy debromination of a series of 2-nitro-3-bromo-5-X-thiophenes (in III: X=H, CONH$_2$, COOC$_2$H$_5$, COOCH$_3$, COCH$_3$, Br, CN)

were measured.

Discussion.

Thiophenoxy debromination reactions for the compounds studied appeared to proceed through a mechanistic pathway analogous to that proposed by us for piperidino and thiophenoxy dehalogenation of nitro-activated 2-halogenothiophenes (8) and generally accepted for similar reactions in the benzene series (9). This hypothesis appears to be confirmed by the absence of the element effect (10) in the reaction of thiophenoxy dehalogenation of 2-nitro-3-halogenothiophenes which favours a two-step mechanism and in which the decomposition of the intermediate complex is not rate determining.
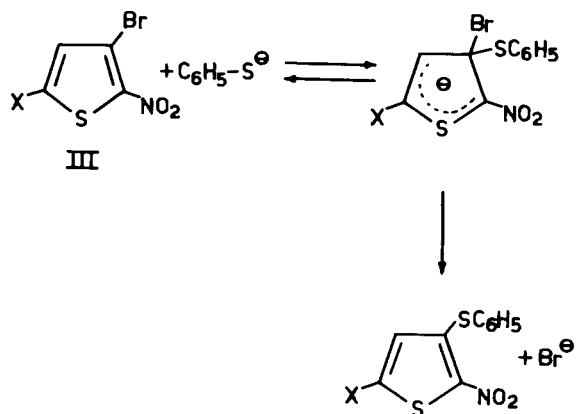
In Table I are reported the rate constants in methanol and the thermodynamic parameters for the reactions studied. The data indicates that the thiophenoxy debromination rate increases with the introduction of electron-withdrawing groups at the 5-position of the thiophene ring.

A quantitative evaluation of the electronic effect of

TABLE I

Kinetic Data for the Thiophenoxydebromination of 2-Nitro-3-bromo-5-X-thiophenes

X =	k, l mol^{-1} sec^{-1}, at various temperatures (a)				$\Delta H^{\neq}$ (b) kcal/mol	$-\Delta S^{\neq}$ (b) e.u.	σ_m (c)	λ_{max} (d) (nm)	$\log \epsilon$ (d)
	$0.00°$	$10.08°$	$20.02°$	$30.00°$					
H (e)			0.234		13.6	14.9	0.000	372	4.02
CONH$_2$		1.42	3.00	6.00	11.7	16.2	0.280	390	3.96
COOC$_2$H$_5$		3.52	7.47	14.64	11.6	14.8	0.370	392	3.96
COOCH$_3$		3.81	8.01	15.28	11.3	15.7	0.370	392	3.96
COCH$_3$		4.18	9.29	19.37	12.5	11.2	0.376	400	3.91
Br	4.61	9.56	19.34		10.8	15.7	0.391	376	4.07
CN	15.82	34.50	75.72		11.8	9.4	0.560	392	3.98

(a) The rates are accurate to better than ±4%. (b) At 20°. (c) C. D. Ritchie and W. F. Sager, "Progress in Physical Organic Chemistry", 2, 323 (1964). (d) In methanol. (e) Data from D. Spinelli, G. Guanti and C. Dell'Erba, Ric. Sci., 38, 1051 (1968).

TABLE II

Phenyl-3-(2-nitro-5-X)-thienylsulphides (a)

X =	Crystallization solvent	M.P.	Found %		Formula	Required %	
			N	S		N	S
H (b)	methanol	92°					
CONH$_2$	methanol/dioxane	272°	10.01	22.75	$C_{11}H_8N_2O_3S_2$	9.99	22.87
COOC$_2$H$_5$	ethanol	105°	4.46	20.61	$C_{13}H_{11}NO_4S_2$	4.53	20.73
COOCH$_3$	ligroin	105°	4.84	21.61	$C_{12}H_9NO_4S_2$	4.74	21.71
COCH$_3$	methanol/dioxane	143°	4.96	22.71	$C_{12}H_9NO_3S_2$	5.01	22.96
Br (c)	ligroin	122°	4.40	20.07	$C_{10}H_6BrNO_2S_2$	4.43	20.28
CN	methanol/dioxane	170°	10.80	24.32	$C_{11}H_6N_2O_2S_2$	10.68	24.45

(a) The obtained sulphides are yellow. (b) D. Spinelli, G. Guanti and C. Dell'Erba, Ric. Sci., 38, 1051 (1968). (c) Br %: Found: 25.57. Required: 25.27.

substituents is possible by means of the Hammett relation. A plot (Fig. 1) of log k (at 20°) versus σ_m gives a straight line: the ρ value is + 4.51 (r = 0.989).

The results support the following considerations: (a) the 5-position with respect to the 3-position (reaction center) is a normal meta-like benzene position in the case of reactions occurring directly on the thiophene ring. It must be pointed out that when substituents consist of single atoms of very different size (H, Br) or consist of polyatomic groups with varying van der Waals radii and different hybridization (CN, CONH$_2$, COOCH$_3$, COOC$_2$H$_5$, COCH$_3$) no deviations from the Hammett relationship are produced. This fact confirms (5) that steric or electronic interactions between substituents and the heteroatom are not present in this type of reaction at least not within the limits of the logarithmic treatment used; (b) the high positive ρ-value observed shows the

great sensitivity of the reaction to the polar substituent effects.

It should be pointed out that the ρ-value obtained by us is somewhat lower than those reported in the literature for analogous reactions in the benzene series (9). Also taking into account that in the basic hydrolysis of ethyl-4-X-thiophene-2-carboxylate (11) a ρ-value lower than that in the benzene series had been obtained ($\rho_T/\rho_B = 0.66$). it appears, on present data, that in series II for the reactions occurring both in the side-chain and directly on the thiophene ring, the influence of a polar substituent upon reactivity is lower than in the benzene series.

Of course, a more thorough study of the problem is necessary; to begin the effect of electron-repelling substituents should be determined to confirm the previous considerations.
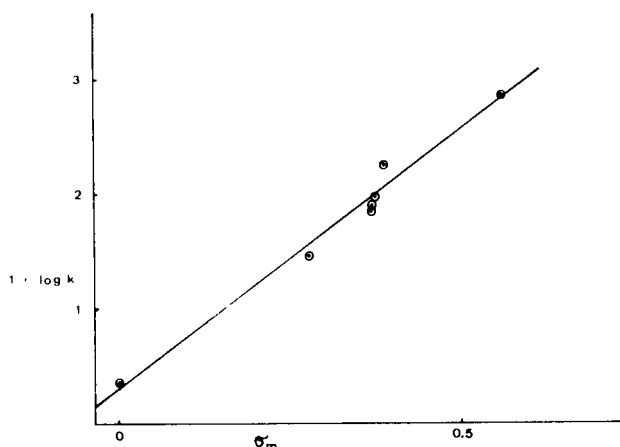
Fig. 1

EXPERIMENTAL

Synthesis and Purification of Compounds.

2-Nitro-3-bromothiophene and 2-nitro-3,5-dibromothiophene (12) were prepared and purified according to the methods reported.

Phenyl-3-(2-nitro-5-X)thienylsulphides were prepared in high yield from the corresponding 2-nitro-3-bromo-5-X-thiophenes and sodium thiophenoxide as described for phenyl-3-(2-nitro)thienyl-sulphide (13). The relevant physical and analytical data are reported in Tables I and II.

The other compounds were prepared as reported below.

2-Nitro-3-bromo-5-acetylthiophene.

The nitrating mixture (nitric acid d = 1.42, 10.2 ml.; concentrated sulphuric acid, 35 ml.) was slowly added with stirring, at -15°, to 2-acetyl-4-bromothiophene (14) (6.8 g.) dissolved in concentrated sulphuric acid (33 ml.). After being kept at -15° for 30 minutes the mixture was poured over crushed ice.

The precipitated solid was separated by filtration and crystallized from methanol, colourless crystals, m.p. 91-92°.

Anal. Calcd. for $C_6H_4BrNO_3S$: Br, 31.96: N, 5.60: S, 12.82. Found: Br, 31.71; N, 5.69; S, 12.61.

2-Nitro-3-bromo-5-thiophenecarboxylic Acid Methyl Ester.

The nitrating mixture (nitric acid d = 1.42, 1 ml.; concentrated sulphuric acid, 3 ml.) was slowly added with stirring, at -5°, -10°, to 4-bromo-2-thiophenecarboxylic acid methyl ester (15) (1 g.) dissolved in concentrated sulphuric acid (5 ml.). After being kept at -5°, -10° for 30 minutes the mixture was poured over crushed ice. The solid precipitate was separated by filtration and crystallized from ligroin, colourless crystals, m.p. 102-103°.

Anal. Calcd. for $C_6H_4BrNO_4S$: Br, 30.04; N, 5.26; S, 12.05. Found: Br, 30.09; N, 5.31; S, 12.02.

2-Nitro-3-bromo-5-thiophenecarboxylic Acid Ethyl Ester.

Using the method for the methyl ester, the corresponding ethyl ester, a colourless product, was obtained and crystallized from light petroleum, m.p. 54°.

Anal. Calcd. for $C_7H_6BrNO_4S$: Br, 28.53; N, 5.00; S, 11.45. Found: Br, 28.22; N, 4.99; S, 11.64.

2-Nitro-3-bromo-5-thiophenecarboxamide.

2-Nitro-3-bromo-5-thiophenecarboxylic acid (obtained from the above mentioned methyl ester by acid hydrolysis, colourless crystals from water/ethanol, m.p. 177°, correct analysis for Br, N and S) was converted into amide (via the acid chloride obtained by action of thionyl chloride) with aqueous ammonia. Colourless crystals from methanol, m.p. 187°.

Anal. Calcd. for $C_5H_3BrN_2O_3S$: Br, 31.83; N, 11.16; S, 12.77. Found; Br, 32.25; N, 11.24; S, 12.81.

2-Nitro-3-bromo-5-cyanothiophene.

Nitric acid (d = 1.52, 8 ml.) was slowly added with stirring, at 45°, to a solution of 2-cyano-4-bromothiophene (2 g., obtained by dehydration with phosphorus pentoxide from the corresponding carboxamide (16), colourless crystals from light petroleum, m.p. 48-49°, correct analysis for Br, N and S) in acetic anhydride (20 ml.). After being kept at 45° for 3 hours the mixture was poured onto crushed ice and extracted with ether. After removal of the solvent the product was crystallized first from ligroin and then from methanol. Colourless crystals, m.p. 85°.

Anal. Calcd. for $C_5HBrN_2O_2S$: Br, 34.29; N, 12.02; S, 13.76 Found: Br, 34.26; N, 12.17; S, 13.71.

Kinetic Measurements.

The reaction kinetics were followed as previously described (17). The infinity optical densities registered in the range 200-450 nm indicate that formation of the sulphides from the 2-nitro-3-bromo-5-X-thiophenes by action of sodium thiophenoxide is the only reaction occurring to an appreciable extent. Tlc examination of reaction mixtures confirms photometric data.

The concentrations employed were $2.5 \cdot 10^{-4}$ M for nitrobromo-thiophenes and thiophenol and $1 \cdot 10^{-3}$ M for the sodium methoxide. In the case of the reaction with 2-nitro-3-bromo-5-cyano-thiophene, in order to avoid the competitive addition of methoxide to the cyano group, a higher concentration of thiophenol ($1 \cdot 10^{-3}$ M) and a lower concentration of sodium methoxide ($2.5 \cdot 10^{-4}$ M) was used.

In the case of the reaction with 2-nitro-3,5-dibromothiophene it was possible to measure independently the rate constants related to the substitution of the two bromine atoms. Obviously the data in Table I refers to substitutions of bromine at C_3.

Acknowledgements.

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