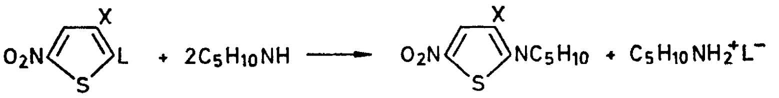
Linear Free Energy *ortho*-Correlations in the Thiophen Series. Part III.[1] The Kinetics of Piperidino-substitution of Some 3-X-5-Nitro-2-thienyl Phenyl Sulphones in Methanol

By **Domenico Spinelli,* Giovanni Consiglio,** and **Renato Noto,** Cattedra di Chimica Organica, Faculty of Pharmacy, University of Bologna, Bologna 40126, Italy, and Institute of Organic Chemistry, Via Archirafi 20, University of Palermo, Palermo 90123, Italy

To obtain information on the influence of a leaving group with high steric requirements on the possibility of obtaining *ortho*-linear free energy correlations in S_NAr reactions of five-membered ring derivatives, the rates of piperidino-substitution of some 3-X-5-nitro-2-thienyl phenyl sulphones (II; X = Me, H, Br, $CONH_2$, CO_2Me, SO_2Me, CN, and NO_2) have been measured in methanol solution. The logarithm of the rate constants gives a straight line when plotted against σ_p^- or against the logarithm of the rate constants of piperidino-substitution for the *para*-isomers (IV) except for X = Me, Br, and SO_2Me. The $\rho_{2,3}$ value (+4.60) and the ratio $\rho_{2,3}:\rho_{2,5}$ (1.15) compare well with those obtained for the corresponding piperidinodebromination reactions, thus confirming that an *ortho*-substituent affects the position of the rate-determining transition state along the reaction co-ordinate more than a *para*-substituent.

A STUDY of the piperidinodebromination reactions of some 2-bromo-3-X-5-nitrothiophens (I) has revealed a linear *ortho*-correlation of log k with σ_p^-.[2] Moreover, we have pointed out that the pK_a of a series of 3-X-thiophen-2-carboxylic acids can be linearly correlated with σ_p values.[1] We have also shown that in five-membered ring derivatives piperidino-substitution (a typical S_NAr reaction) does not suffer either primary [3] or secondary [4a,b] kinetic steric effects with bromine as leaving group but that the situation is different with phenylsulphonyl,[3,4c] a leaving group with high steric requirements. With this group we have, indeed, observed significant primary [3] and secondary [4c] steric effects.

In order to study the influence of the nature of the leaving group on the possibility of obtaining linear *ortho*-correlations, we have made kinetic measurements of the reaction rates of some 3-X-5-nitro-2-thienyl phenyl sulphones (II) with piperidine in methanol.



(I) L = Br
(II) L = SO_2Ph

(III)

a; X = Me
b; X = H
c; X = Br
d; X = $CONH_2$
e; X = CO_2Me
f; X = SO_2Me
g; X = CN
h; X = NO_2

RESULTS AND DISCUSSION

Products.—3-X-5-Nitro-2-thienyl phenyl sulphones (II) gave the corresponding 2-piperidyl-3-X-5-nitrothiophens (III) in almost quantitative yield (t.l.c. and u.v.–visible spectral analyses) on treatment with piperidine in methanol.

Kinetic Data.—Rate constants and activation parameters for the reactions studied are collected in Table 1.

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[1] Part II, D. Spinelli, R. Noto, and G. Consiglio, *J.C.S. Perkin II*, 1976, 747.

[2] D. Spinelli, G. Consiglio, R. Noto, and A. Corrao, *J.C.S. Perkin II*, 1975, 620 and references therein.

[3] D. Spinelli, G. Consiglio, and T. Monti, *J.C.S. Perkin II*, 1975, 816.

[4] (*a*) D. Spinelli, G. Guanti, and C. Dell'Erba, *J. Heterocyclic Chem.*, 1968, **5**, 323; (*b*) D. Spinelli, G. Consiglio, and A. Corrao, *J.C.S. Perkin II*, 1972, 1866; (*c*) D. Spinelli, G. Consiglio, R. Noto, and A. Corrao, *ibid.*, 1974, 1632; D. Spinelli and G. Consiglio, *ibid.*, 1975, 1388.

All the reactions were of second order, first in aromatic substrate and first in piperidine. The reactivity increases on introduction of an electron-withdrawing substituent into position 3 and diminishes on introduction of an electron repelling group. The inference that these reactions proceed *via* the addition–elimination mechanism[5] (S_NAr), with the formation of the intermediate as the rate-limiting step, is thus warranted.

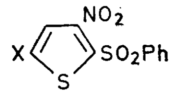
TABLE 1

Rate constants and activation parameters for the piperidino-substitution of compounds (IIa—h) in methanol

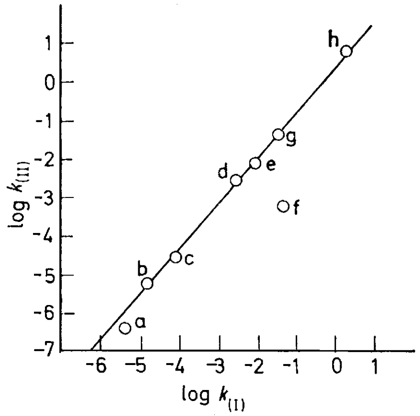
Compound	10^4k/l mol^{-1} s^{-1} [a] (t/°C)			$\Delta H^\ddagger$ [b]/ kcal mol^{-1}	$-\Delta S^\ddagger$ [c]/ kcal mol^{-1} K^{-1}	σ_p^- [d]
(Ia) [e]	0.003 64(20.04)	0.008 36(30.10)	0.014 5(40.09)	12.0	46.8	−0.10
(Ib) [e]	0.065 5(19.98)	0.146(30.30)	0.306(40.05)	13.4	36.5	0.00
(Ic)	0.276(19.98)	0.563(30.30)	0.960(40.05)	10.7	42.6	+0.35
(Id)	29.0(19.98)	58.1(30.02)	111(40.00)	11.6	30.3	+0.55
(Ie)	81.0(20.02)	150(30.02)	262(40.00)	10.1	33.5	+0.71
(If)	6.64(20.05)	12.6(30.03)	22.2(40.00)	10.4	37.4	+0.85
(Ig)	309(10.08)	482(19.95)	737(30.02)	6.8	41.1	+0.92
(Ih) [f]	24 300(0.02)	41 400(10.02)	68 000(20.03)	7.6	28.8	+1.27

[a] The rate constants are accurate to within ±3%. [b] At 20 °C, the maximum error is 0.5 kcal mol^{-1}. [c] At 20 °C. [d] See ref. 6. [e] See ref. 3. [f] See ref. 4*c*.

Linear correlations are observed when log k at 20 °C for the reactions of compounds (IIa—h) is plotted against σ_p^- (ρ +4.60, r 0.995,* s 0.27, n 5 †) and against log k at 20 °C for the reactions[6] of the corresponding 3-nitro-5-X-2-thienyl phenyl sulphones (IV) (slope 1.15, r 0.993,* s 0.08, n 5 ‡). The statistical data are in good agreement with those previously obtained for piperidinodebromination,[2,¶] the only difference being linked to the necessity for excluding the data for X = Me and SO_2Me. An inspection of molecular models[8] shows that 3-methylsulphonyl can interact with the 2-phenylsulphonyl group and piperidine in the transition state for the S_NAr reaction to such an extent as to lower greatly the reactivity of (IIf). The interaction involving 3-methyl, 2-phenylsulphonyl, and piperidine causes an analogous lowering of reactivity of (IIa). To confirm that the interaction is related to the peculiar structure of the leaving group we have made a logarithmic plot (Figure) of the reactivity of compounds (IIa—h) against that of compounds (Ia—h): § a linear correlation is observed except for X = Me and SO_2Me. Taking into account that in the linear correlation of the pK_a values of 3-substituted thiophen-2-carboxylic acids with σ_p the data for X = Me and SO_2Me fall on the straight line,[1] the peculiar behaviour of (IIa and f) supports the previously observed higher steric requirements of phenylsulphonyl as a leaving group.[3,4c]



(IV)



Logarithmic plot of kinetic constants for the piperidino-substitution of (IIa—h) *versus* the corresponding kinetic constants for the piperidino-substitution of (Ia—h) in methanol at 20 °C; slope 1.19, r 0.999, s 0.01, n 6 (t test for statistical significance indicates that the correlation is significant at the 0.1% level). Data for (Ia and f) and (IIa and f) have been excluded from the calculation

Conclusions.—The data obtained point to the possibility of obtaining linear free energy *ortho*-correlations for piperidino-substitution of *ortho*-substituted thiophen derivatives when the leaving group (SO_2Ph) has high steric requirements. Indeed, at variance with the case of bromine as leaving group, phenylsulphonyl determines the necessity of excluding Me and SO_2Me from the

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* The t test[7] for statistical significance indicates that the correlation is significant at the 0.1% level.

† Data for (IIa, c, and f) have been excluded from the calculation of ρ.

‡ Data for (IIc and f) and (IVc and f) have been excluded from the calculation.

¶ Provided that in the equation $\log k/k_H = \rho(\sigma + r_R\Delta\sigma_R^-)$ $r_R = 1$ for both bromine[6] and phenylsulphonyl, $\rho SO_2Ph : \rho Br$ ratio >1 confirms the larger effect of the variable substituent in determining the position of the rate-determining transition state along the reaction co-ordinate when L = SO_2Ph than when L = Br.

§ For piperidinodebromination of some 2-bromo-3-X-5-nitrothiophens[2] we have observed that kinetic data for X = Me and SO_2Me can be included in the calculation of ρ, *i.e.*, they obey a linear free energy relation.

[5] J. Miller, 'Aromatic Nucleophilic Substitution,' Elsevier, Amsterdam, 1968; C. F. Bernasconi, 'MTP International Review of Science; Organic Chemistry, Series 1,' Butterworths, London, 1973, vol. 3, p. 33.

[6] D. Spinelli and G. Consiglio, *J.C.S. Perkin II*, 1975, 989 and references therein.

[7] E. L. Crow, F. A. Davis, and M. W. Maxfield, 'Statistics Manual,' Dover, New York, 1960.

[8] L. N. Ferguson, 'The Modern Structural Theory of Organic Chemistry,' Prentice–Hall, New York, 1963; 'Interatomic Distances and Configurations in Molecules and Ions,' The Chemical Society, London, Special Publication No. 11, 1959, and No. 18, 1965; M. Nardelli, G. Fava, and G. Giraldi, *Acta Cryst.*, 1962, **15**, 737.

TABLE 2

Physical and analytical data for 5-nitro-3-X-2-thienyl phenyl sulphones (IIc—g) [a]

Compounds	Crystallization solvent	M.p. (°C)	Found (%)			Formula	Required (%)		
			C	H	N		C	H	N
(IIc) [b]	Ethanol–dioxan	155—156	34.6	1.8	4.0	$C_{10}H_6BrNO_4S_2$	34.5	1.7	4.0
(IId)	Methanol	180—181	42.4	2.4	8.9	$C_{11}H_8N_2O_5S_2$	42.3	2.6	9.0
(IIe)	Methanol	106—107	43.9	2.7	4.1	$C_{12}H_9NO_6S_2$	44.0	2.8	4.3
(IIf)	Methanol	155—156	37.8	2.5	3.9	$C_{11}H_9NO_6S_3$	38.0	2.6	4.0
(IIg)	Ethanol–dioxan	175	45.0	2.1	9.7	$C_{11}H_6N_2O_4S_2$	44.9	2.0	9.5

[a] Compounds (IIc—g) are colourless. [b] S, required 18.4, found 18.4%; Br, required 23.0, found 23.1%.

correlation. Our results have also confirmed that in five-membered ring derivatives a substituent in an *ortho*-like position (C-3) exerts a higher electronic effect on the reaction centre (C-2) than in a *para*-like position (C-5). This fact is reflected in the $\rho_{2,3}$ value ($\rho_o > \rho_p$) which is at variance with what happens in benzene derivatives where the observed trend is $\rho_o < \rho_p$.[2] Then, as already seen, an *ortho*-like substituent causes more variation in the position of the rate-determining transition state along the reaction co-ordinate than a *para*-like one.[6]

EXPERIMENTAL

Synthesis and Purification of Compounds.—Compounds (IIa),[3] (IIb),[9] (IIh),[10] (IIIa—h),[2] methanol,[4b] and piperidine [4b] were prepared and/or purified according to the methods reported. The other compounds were prepared as below.

5-*Nitro*-3-X-2-*thienyl Phenyl Sulphones* (IIc—g).—Compounds (IIc—g) (physical and analytical data in Table 2) were prepared from the corresponding 2-bromo-3-X-5-nitrothiophens (Ic—g) [2] and sodium benzenesulphinate according to the general method of ref. 6.

Kinetic Measurements.—The kinetics were followed spectrophotometrically as previously described [11] and carried out in the presence of piperidine hydrochloride to avoid competitive methoxy-substitution.[11,12] The concentrations used were 10^{-3}M for nitro-sulphones, 6×10^{-3}M for piperidine, and 3×10^{-2}M for piperidine hydrochloride.

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[9] G. Guanti, C. Dell'Erba, and P. Macera, *J. Heterocyclic Chem.*, 1971, **8**, 537.

[10] D. Spinelli, C. Dell'Erba, and A. Salvemini, *Ann. Chim.* (*Italy*), 1962, **52**, 1156.

[11] D. Spinelli, A. Salvemini, and C. Dell'Erba, *Ann. Chim.* (*Italy*), 1964, **54**, 869.

[12] J. F. Bunnett and R. J. Morath, *J. Amer. Chem. Soc.*, 1955, **77**, 5051; J. F. Bunnett, E. W. Garbisch, and K. M. Pruitt, *ibid.*, 1957, **79**, 385; M. Foà, A. Ricci, P. E. Todesco, and P. Vivarelli, *Boll. sci. Fac. Chim. ind. Bologna*, 1965, **23**, 65.