Application of the Hammett Relationship to a Series of Tetrasubstituted Thiophens. Kinetics of Piperidino-debromination of Some 2-Bromo-3-nitro-5-X-thiophens and 2-Bromo-4-methyl-3-nitro-5-X-thiophens in Methanol

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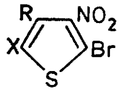
The rates of piperidino-debromination of some 2-bromo-3-nitro-5-X-thiophens and 2-bromo-4-methyl-3-nitro-5-X-thiophens in methanol have been measured. The results indicate that the Hammett relationship can be applied to the tetrasubstituted as well as to the trisubstituted compounds. The kinetic data for 2-bromo-4-methyl-3-nitro-5-X-thiophens represent the first good fit of the Hammett equation for a series of *ortho*-tetrasubstituted compounds. This is possible with fully substituted thiophens because the geometry of the 5-membered ring lowers steric interactions which in a 6-membered ring (*e.g.* benzene) are known to be very large.

The application of the Hammett relationship[1] is based on the absence of strong (primary or secondary) steric effects on the reaction centre and of strong interactions between the adjacent groups, *i.e.* the treatment cannot be applied to *ortho*-tetrasubstituted benzene derivatives which have strong steric effects.

Recently we have pointed out the absence of secondary steric effects in the nucleophilic substitution of thiophen derivatives[2] by comparing the rates of piperidino-debromination of 2-bromo-3,5-dinitrothiophen (Ig) and of 2-bromo-4-methyl-3,5-dinitrothiophen (IIg). We have observed only a small lowering of reactivity (in methanol $k_{\mathrm{H}} : k_{\mathrm{Me}}$ *ca.* 2) which has been related to the electron-repelling effect of the *meta*-methyl group ($\sigma_{m\text{-Me}} = -0{\cdot}07$).

This peculiar behaviour, very different from that of benzene derivatives,[3] induced us to explore the application of the Hammett relationship to tetrasubstituted thiophens. We measured the rates of piperidino-debromination at various temperatures in methanol of



(I; R = H)
(II; R = Me)

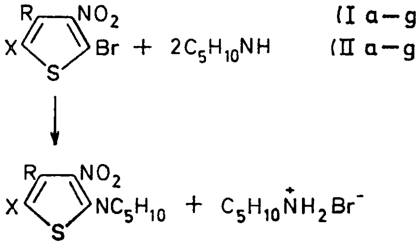
a; X = H
b; X = Br
c; X = $CONH_2$
d; X = CO_2Me
e; X = SO_2Me
f; X = CN
g; X = NO_2

seven 2-bromo-4-methyl-3-nitro-5-X-thiophens (IIa—g) and also those of the corresponding 2-bromo-3-nitro-5-X-thiophens (Ia—g), choosing 5-X-groups of different sizes.

RESULTS AND DISCUSSION

Products.—Compounds (Ia—g) and (IIa—g) in methanol gave the expected piperidino-derivatives (IIIa—g) and (IVa—g) on treatment with piperidine in almost quantitative yield as shown by t.l.c. and u.v. spectral analyses. Analytical data are in Table 1.

The reactions were carried out in the presence of piperidine hydrochloride to avoid competitive methoxy-debromination.[2,4]



Kinetic Data.—Rate constants and thermodynamic parameters for the piperidino-debromination of (Ia—g) and (IIa—g) are reported in Table 2. An increase in the rate of substitution is observed for both series on the introduction of electron-withdrawing groups. Such reactions seem to be enthalpy controlled, the only large deviation of the entropy of activation being observed for the dinitro-compounds (Ig) and (IIg).

Hammett Relationship.—The rate constants for piperidino-debromination in ethanol of several 2-bromo-3-nitro-5-X-thiophens (I; X = H, Br, $CONH_2$, CO_2Et, SO_2Me, Ac, SO_2OPh, and NO_2) have already been measured by one of us.[5] A good fit to the Hammett relationship was found with a high positive ρ value ($+3{\cdot}21$) using the σ_p^- values. The ρ value in methanol now measured was quite similar ($\rho = +3{\cdot}18$; $r = 0{\cdot}995$) as expected from the similar characteristics of the two alcohols employed as solvents. As previously pointed out[5] the *p*-$MeSO_2$ group required the use of the Bordwell and Andersen[6] $\sigma_{p\text{-MeSO}_2}^-$ value ($+0{\cdot}840$) and not that used for benzenes[7] ($+1{\cdot}049$).

The rate constants for piperidino-debromination of compounds (II) were smaller by a factor between 2 and 4 than for compounds (I). They gave a good fit to the

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[1] (*a*) L. P. Hammett, 'Physical Organic Chemistry,' McGraw-Hill, New York, 1940; (*b*) H. H. Jaffé, *Chem. Rev.*, 1953, **53**, 191; (*c*) P. R. Wells, *ibid.*, 1963, **63**, 171; (*d*) H. H. Jaffé and H. L. Jones, *Adv. Heterocyclic Chem.*, 1964, **3**, 209.

[2] D. Spinelli, G. Guanti, and C. Dell'Erba, *J. Heterocyclic Chem.*, 1968, **5**, 323.

[3] B. Capon and N. B. Chapman, *J. Chem. Soc.*, 1957, 600.

[4] 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; D. Spinelli, A. Salvemini, and C. Dell'Erba, *Ann. Chim.* (*Italy*), 1964, **54**, 869; M. Foà, A. Ricci, P. E. Todesco, and P. Vivarelli, *Boll. sci. Fac. Chim. ind. Bologna*, 1965, **23**, 65.

[5] C. Dell'Erba and D. Spinelli, *Tetrahedron*, 1965, **21**, 1061.

[6] F. G. Bordwell and H. M. Andersen, *J. Amer. Chem. Soc.*, 1953, **75**, 6019.

[7] Ref. 1*b*.

Hammett relationship with a high positive ρ value (+3·24) using the same σ_p^- parameters chosen for series (I) with an excellent correlation coefficient ($r = 0·995$). The observed ρ values for series (I) and (II) were similar indicating that the insertion of a methyl group between the activating nitro-group and the 5-X-groups produced only a slight decrease in the rate (see above) and had no influence on the transmission of substituent effects which were practically additive.* This is of interest because compounds (II) are tetrasubstituted thiophens and the same large 5-X-substituents[8] in *ortho*-tetrasubstituted benzenes cause secondary steric effects.

TABLE 1

Analytical and spectroscopic data of piperidino-derivatives (IIIa—g) and (IVa—g)

Compounds	Crystallization solvent	Colour	M.p. (°C)	Found (%) N	Found (%) S	Formula	Required (%) N	Required (%) S	$\lambda_{max.}$/nm [a]	log ε [a]
(IIIa) [b]	Ligroin	Orange	77						398	3·75
(IIIb) [b]	Ligroin	Orange	98						404	3·78
(IIIc) [b]	Ethanol	Orange	216						394	3·76
(IIId)	Ligroin	Yellow	92	10·4	11·9	$C_{11}H_{14}N_2O_4S$	10·4	11·9	390	3·76
(IIIe) [b]	Ligroin	Yellow	104						384	3·78
(IIIf) [b]	Ligroin	Yellow	118						386	3·79
(IIIg) [c]	Ethanol	Orange	103						380	4·20
(IVa)	Light petroleum	Orange	55	12·4	14·1	$C_{10}H_{14}N_2O_2S$	12·4	14·2	404	3·57
(IVb) [d]	Ethanol	Yellow	89	9·5	10·4	$C_{10}H_{13}BrN_2O_2S$	9·2	10·5	408	3·63
(IVc)	Methanol	Red	178	15·8	12·1	$C_{11}H_{15}N_3O_3S$	15·6	11·9	402	3·52
(IVd)	Ligroin	Yellow	92	10·0	11·1	$C_{12}H_{16}N_2O_4S$	9·9	11·3	400	3·50
(IVe)	Ethanol	Yellow	157	9·3	21·3	$C_{11}H_{16}N_2O_4S_2$	9·2	21·1	392	3·55
(IVf)	Methanol	Yellow	105	16·9	12·7	$C_{11}H_{13}N_3O_2S$	16·7	12·8	395	3·62
(IVg) [c]	Ethanol	Yellow	143						408	4·25

[a] In methanol. [b] See ref. 5. [c] See ref. 2. [d] Found: Br, 26·5. Required Br, 26·2%.

TABLE 2

Kinetic data and thermodynamic parameters for piperidino-debromination in methanol of 2-Br-3-NO_2-5-X-thiophens (Ia—g) and 2-Br-3-NO_2-4-Me-5-X-thiophens (IIa—g)

Compound	10^3k/l mol^{-1} s^{-1} (at various °C) [a]			$\Delta H^{\ddagger}$ [b]/ kcal mol^{-1}	$-\Delta S^{\ddagger}$ [c]/ cal mol^{-1} K^{-1}	σ_P^- [d]
(Ia)	0·114 (20·00)	0·268 (35·00)	0·958 (46·33)	14·4	27·2	0·000
(Ib)	1·80 (20·00)	3·95 (30·00)	8·34 (40·50)	13·0	26·5	0·289
(Ic)	3·61 (9·80)	7·82 (20·00)	16·7 (29·90)	12·4	25·8	0·552
(Id)	13·6 (9·80)	27·8 (20·00)	54·8 (29·90)	11·2	27·3	0·678
(Ie)	16·6 (0·16)	33·6 (9·85)	74·4 (20·00)	11·4	24·6	0·840 [e]
(If)	29·7 (0·15)	64·8 (9·90)	127 (20·00)	11·0	24·8	0·997
(Ig) [f]	1060 (10·82)	1980 (20·00)	3780 (30·02)	10·7	20·5	1·270
(IIa)	0·0584 (20·00)	0·138 (30·00)	0·306 (40·00)	14·5	28·3	0·000
(IIb)	0·667 (20·00)	1·47 (30·00)	2·99 (40·00)	13·1	28·3	0·289
(IIc)	0·907 (9·80)	1·89 (20·00)	3·90 (29·85)	11·8	30·7	0·552
(IId)	4·02 (9·80)	8·65 (20·00)	16·7 (29·95)	11·4	28·8	0·678
(IIe)	4·48 (0·16)	10·2 (9·95)	21·7 (20·00)	12·0	24·9	0·840 [e]
(IIf)	18·3 (0·15)	36·8 (9·90)	74·3 (20·00)	10·6	27·3	0·997
(IIg) [f]	563 (10·82)	987 (20·00)	2000 (30·02)	10·7	21·9	1·270

[a] The rate constants are accurate to within ±3%. [b] At 20°, the probable error is 0·5 kcal mol^{-1}. [c] At 20°. [d] Ref. 1; L. N. Fergusson, ' The Modern Structural Theory of Organic Chemistry ', Prentice-Hall, New York, 1959, p. 415. [e] Ref. 6. [f] Data from ref. 2.

Of the substituents only two (H and CN), because of their dimensions and geometry, are presumably free of steric effects. The others (*e.g.* Br, $CONH_2$, and CO_2Me) should be able to exert steric effects because of hybridization of the head-atoms of substituents and/or of their van der Waals radius. The absence of a secondary steric effect (and of variable kinetic steric effects) for these substituents, as for the nitro-group already pointed out,[2] is dependent on the geometry of the 5-membered ring which reduces the overlapping of the van der Waals spheres of the 4-methyl and 5-X-substituents with respect to the benzene series and so cancels out the kinetic steric effect.

In the case of the $MeSO_2$ group, because of the dimension of this group, the reduced overlapping (see above) of the van der Waals spheres seems to be insufficient to explain the absence of a kinetic steric effect. This result must be related to the fact[9] that in contrast to other groups (*e.g.* NO_2, CO_2Me, *etc.*) the methylsulphonyl group does not require coplanarity of the C_{Ar}–S bond with aromatic ring to exert an extra conjugative effect on the reaction centre in the intermediate.

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* Kinetic data related to piperidino-debromination of compounds (Ia—g) and (IIa—g) was used for a unique Hammett treatment for compounds (II) by adding the $\sigma_{m\text{-}CH_3}$ value (−0·07) to the single σ_p^- value. The ρ value so obtained was +3·22 with an excellent correlation coefficient ($r = 0·992$).

[8] J. Miller, ' Aromatic Nucleophilic Substitution,' Elsevier, Amsterdam, 1968, p. 95 and references therein; ' Interatomic Distances and Configuration in Molecules and Ions,' The Chemical Society, Special Publications No. 11, 1959 and No. 18, 1965.

[9] H. Kloozerstiel and H. J. Backer, *Rec. Trav. chim.*, 1953, **72**, 185.

EXPERIMENTAL

Synthesis and Purification of Compounds.—2-Bromo-3-nitro-5-X-thiophens (Ia—c, e—g),[5] 2-bromo-4-methyl-3,5-dinitrothiophen (IIg),[2] the corresponding piperidino-derivatives (IIIa—c, IIIe—g,[5] IVg [2]), methanol,[10] and piperidine [11] were prepared and/or purified according to the methods reported. The other compounds were prepared as below.

Methyl 5-*Bromo*-4-*nitrothiophen*-2-*carboxylate* (Id).—This was prepared according to the method of ref. 5. It crystallized from methanol, m.p. 99° (Found: Br, 30·7; N, 5·3; S, 12·0. $C_6H_4BrNO_4S$ requires Br, 30·1; N, 5·3; S, 12·0%).

2-*Bromo*-4-*methyl*-3-*nitrothiophen* (IIa).—The carboxamide (IIc) (1 g) was hydrolysed by boiling for 3 h in the presence of concentrated H_2SO_4 (50 ml) and water (270 ml) to give 5-*bromo*-3-*methyl*-4-*nitrothiophen*-2-*carboxylic acid*, m.p. 215° (from benzene) (correct analysis). This acid was reacted with mercury(II) acetate and the acetoxymercury compound so obtained was hydrolysed with aqueous HCl [12] to give 2-*bromo*-4-*methyl*-3-*nitrothiophen*, m.p. 88° (from light petroleum) (Found: Br, 36·0; N, 6·2; S, 14·5. $C_5H_4BrNO_2S$ requires Br, 36·0; N, 6·3; S, 14·4%).

2,5-*Dibromo*-4-*methyl*-3-*nitrothiophen* (IIb).—3-Methyl-4-nitrothiophen-2-sulphonyl chloride was obtained with 3-methyl-5-nitrothiophen-2-sulphonyl chloride by action of fuming HNO_3 on 3-methylthiophen-2-sulphonyl chloride. They were separated by high vacuum distillation, rates of formation being *ca.* 2 : 1. 3-Methyl-4-nitrothiophen-2-sulphonyl chloride and mercury(II) acetate gave the di-acetoxymercury compound which on treatment with an aqueous solution of bromine in potassium bromide [2] gave 2,5-*dibromo*-4-*methyl*-3-*nitrothiophen*, m.p. 53° (from light petroleum) (Found: Br, 53·9; N, 5·0; S, 10·7. $C_5H_3Br_2NO_2S$ requires Br, 53·1; N, 4·7; S, 10·7%).

5-*Bromo*-3-*methyl*-4-*nitrothiophen*-2-*carboxamide* (IIc).—Solid potassium nitrate (1·03 g, 0·01 mol) was slowly added with stirring to 5-bromo-3-methylthiophen-2-carboxamide (2·20 g, 0·01 mol) at 10°. After being kept at 10° for 30 min the mixture was poured over crushed ice and the precipitated solid was filtered off and crystallized from benzene to give crystals, m.p. 166° (Found: Br, 30·5; N, 10·7; S, 12·0. $C_6H_5BrN_2O_3S$ requires Br, 30·1; N, 10·6; S, 12·1%).

5-*Bromo*-3-*methylthiophen*-2-*carboxamide*.— 5-Bromo-3-methylthiophen-2-carboxylic acid was heated under reflux for 30 min with excess of thionyl chloride. After elimination of excess of thionyl chloride, the crude acid chloride was slowly poured with stirring into excess of ammonia, keeping the temperature at 5—10°. The *amide* was filtered off and crystallized from benzene and ligroin, m.p. 109° (Found: Br, 36·3; N, 6·4; S, 14·6. C_6H_6BrNOS requires Br, 36·3; N, 6·4; S, 14·6%).

5-*Bromo*-3-*methylthiophen*-2-*carboxylic Acid*.—5-Bromo-3-methylthiophen-2-carbaldehyde (8·7 g) was slowly added with stirring to a suspension of silver oxide [silver nitrate (15 g) and sodium hydroxide (7 g) in water (60 ml)]. The silver was eliminated by filtration and the filtrate acidified with concentrated HCl. Cooling (12 h at −5 to 0°) gave the *acid*, m.p. 168° (from methanol) (Found: Br, 36·4; S, 14·6. $C_6H_5BrO_2S$ requires Br, 36·2; S, 14·5%).

5-*Bromo*-3-*methylthiophen*-2-*carbaldehyde*.— 3-Methylthiophen-2-carbaldehyde (12·6 g) in chloroform was slowly added with stirring to a solution of bromine (5·1 ml) in chloroform (15 ml) at room temperature. When evolution of hydrogen bromide had stopped the solution was heated under reflux for 3 h. After cooling the solution was washed with water and aqueous sodium bicarbonate. The organic layer was dried ($MgSO_4$) and distilled under reduced pressure to give 5-*bromo*-3-*methylthiophen*-2-*carbaldehyde*, b.p. 114—116° at 4 mmHg (Found: C, 35·2; H, 2·5; Br, 39·0; S, 15·7. C_6H_5BrOS requires C, 35·1; H, 2·5; Br, 39·0; S, 15·6%).

Methyl 5-*Bromo*-3-*methyl*-4-*nitrothiophen*-2-*carboxylate* (IId).—The *methyl ester*, prepared from the acid, was crystallized from benzene–ligroin, m.p. 105° (Found: Br, 29·0; N, 5·0; S, 11·4. $C_7H_6BrNO_4S$ requires Br, 28·5; N, 5·0; S, 11·5%).

2-*Bromo*-4-*methyl*-5-*methylsulphonyl*-3-*nitrothiophen* (IIe).—This was prepared by the method for (IIg) [2] from a mixture of 3-methyl-2-methylsulphonyl-4-nitrothiophen and 3-methyl-2-methylsulphonyl-5-nitrothiophen (see later) by mercuriation and bromination. Only the 4-nitro-compound was transformed, the 5-isomer was unaltered by the mercuriation treatment. 2-*Bromo*-4-*methyl*-5-*methylsulphonyl*-3-*nitrothiophen* had m.p. 174° (from ethanol) (Found: Br, 26·7; N, 4·9; S, 21·4. $C_6H_6BrNO_4S_2$ requires Br, 26·6; N, 4·7; S, 21·4%).

3-*Methyl*-2-*methylsulphonyl*-4-*nitrothiophen*.— 3-Methyl-2-methylsulphonylthiophen (2·46 g) was added to a cooled (−10°) and stirred mixture of concentrated H_2SO_4 (6 ml) and HNO_3 (6 ml) and stirring continued for 30 min. It was then poured over crushed ice and the separated solid was filtered off and washed with water. It was a mixture of 3-methyl-2-methylsulphonyl-4-nitrothiophen and 3-methyl-2-methylsulphonyl-5-nitrothiophen.

3-*Methyl*-2-*methylsulphonylthiophen*.—This was prepared from 3-methylthiophen-2-sulphonyl chloride by reduction with Na_2SO_3 and methylation of the sulphinic acid with MeI according to the method of ref. 13. Crystals were obtained from benzene–ligroin, m.p. 62° (Found: S, 36·4. $C_6H_8O_2S_2$ requires S, 36·4%).

5-*Bromo*-3-*methyl*-4-*nitrothiophen*-2-*carbonitrile* (IIf).—Fuming HNO_3 (5 ml) was added with stirring to a solution of crude 5-bromo-3-methylthiophen-2-carbonitrile (10·5 g) in Ac_2O (10 ml) kept at 10°. The mixture was set aside at 10° for 3 h and then poured over crushed ice. The mixture was extracted with ether. The ethereal extracts were washed with aqueous sodium bicarbonate and water, dried (Na_2SO_4), and the ether was distilled off. The residue was purified by column chromatography on silica gel (eluant cyclohexane) to give the *nitrile*, m.p. 95° (from benzene–ligroin) (Found: Br, 32·5; N, 11·4; S, 12·9. $C_6H_3BrN_2O_2S$ requires Br, 32·3; N, 11·3; S, 13·0%).

5-*Bromo*-3-*methylthiophen*-2-*carbonitrile*.—This was prepared from 5-bromo-3-methylthiophen-2-carbaldehyde oxime according to the general method of ref. 14 and was nitrated after high vacuum distillation.

5-*Bromo*-3-*methylthiophen*-2-*carbaldehyde Oxime*.—This compound was prepared from the corresponding aldehyde by the general method of ref. 14 to give crystals, m.p. 139°

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[14] P. Reynaud and R. Delaby, *Bull. Soc. chim. France*, 1955, 1614.

(from benzene–ligroin) (Found: Br, 36·3; N, 6·5; S, 14·4. C_6H_6BrNOS requires Br, 36·3; N, 6·4; S, 14·6%).

Piperidino-derivatives (IIId, IVa—f).—These compounds were prepared by reacting the corresponding bromonitrothiophens (Id, IIa—f) with piperidine according to the general method of ref. 2.

Kinetic Measurements.—The kinetics were followed spectrophotometrically as previously described.[11] The concentrations employed were $1\cdot10^{-3}$M for the bromonitrothiophens (Ia—f, IIa—f), $6\cdot10^{-3}$M for piperidine, and $3\cdot10^{-2}$M for piperidine hydrochloride.

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