Steric Effects in Nucleophilic Substitution of Five-membered Rings. Influence of the Nature of the Leaving Group on Secondary Steric Effects

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Kinetic data from the substitution of piperidine into some 2-substituted 3,5-dinitro-4-methyl- (IIa—d) and 3,5-dinitro-thiophens (Ia—d) show the occurrence of a small secondary steric effect ($k_{(Id)}/k_{(IId)} = 8$) only when the leaving group is SO_2Ph. This effect seems to depend on the interaction of the groups at C-2, -3, and -4 of the thiophen ring, as the results obtained for other thiophens indicate.

We have previously studied steric effects in heteroaromatic nucleophilic substitutions in five-membered ring compounds [1,2] and in these systems we have shown the absence of secondary steric effects (which affect [3] S_NAr in the benzene series) by comparing the rates of

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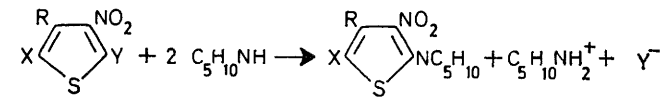
[3] B. Capon and N. B. Chapman, *J. Chem. Soc.*, 1957, 600.

piperidinodebromination of 2-bromo-3,5-dinitrothiophen (Ib) and 2-bromo-3,5-dinitro-4-methylthiophen (IIb). The presence of a methyl group between the two nitro-groups produces only a small kinetic effect ($k_{(Ib)}/k_{(IIb)}$ *ca.* 2 in methanol) related to the weak electron-repelling effect of the *m*-methyl group.

We have now extended our study to the substitution of piperidine for other leaving groups (Y = Cl, I, or SO_2Ph) to see if this variation affects the occurrence of secondary steric effect.

RESULTS AND DISCUSSION

Products.—Compounds (I)—(VI) gave the expected [1,2] piperidino-derivatives (VII)—(XII) as shown by t.l.c. and u.v. analysis. Some reactions (see Table) were carried out in the presence of piperidine hydrochloride to avoid competitive methoxy-substitution.[1,4]



(I) R=H, X=NO_2
(II) R=Me, X=NO_2
(III) R=X=H
(IV) R=Me, X=H
(V) R=H, X=Br
(VI) R=Me, X=Br

(VII) R=H, X=NO_2
(VIII) R=Me, X=NO_2
(IX) R=X=H
(X) R=Me, X=H
(XI) R=H, X=Br
(XII) R=Me, X=Br

a; Y=Cl
b; Y=Br
c; Y=I
d; Y=SO_2Ph

Kinetic Data.—Rate constants and thermodynamic parameters are reported in the Table. The observed sequence * of reactivity with piperidine for compounds (Ia—d) is I < Br < Cl < SO_2Ph (reactivity ratio 1 : 11 : 21 : 40). The absence of an element effect confirms [4b,5] that the formation of the first transition state is the rate-determining step. The sequence of reactivity for halogens seems to be affected by their dimensions [6] and effective electronegativities.

The higher reactivity of (Id) seems to depend on the higher electronegativity of the leaving group SO_2Ph, which masks the steric effects, indicated by molecular models,[7] which are probably present.

For compounds (II) we note that the observed sequence of reactivity for the halogen compounds (IIa—c) is the same, whereas (IId) has a lower reactivity than (IIb and c), *i.e.*, I < SO_2Ph < Br < Cl (reactivity ratio 1 : 7 : 8 : 15).

Kinetic data and thermodynamic parameters for substitution of piperidine of compounds (I)—(VIII) in methanol

Compound	k/l mol^{-1} s^{-1} [a] (at various temperatures)			$\Delta H^{\ddagger}$/ kcal mol^{-1} [b]	$-\Delta S^{\ddagger}$/ cal mol^{-1} K^{-1} [c]	k_H/k_{Me} [d] at 20°
(Ia) [e]	0·866 (0·03)	1·88 (9·99)	3·74 (20·03)	11·0	18·1	1·9
(IIa) [f]	0·494 (0·02)	1·05 (10·00)	1·93 (20·00)	10·2	22·2	
(Ib) [g]	1·06 (10·82)	1·99 (20·06)	3·78 (30·02)	10·7	20·6	1·9
(IIb) [g]	0·563 (10·82)	0·991 (20·06)	2·00 (30·02)	10·7	21·9	
(Ic) [e]	0·176 (20·00)	0·348 (30·03)	0·621 (39·95)	10·9	24·5	1·7
(IIc) [f]	0·103 (20·04)	0·194 (30·02)	0·356 (40·10)	10·7	26·5	
(Id) [e]	2·43 (0·02)	4·14 (10·02)	6·80 (20·03)	7·6	28·8	7·8
(IId) [f]	0·257 (0·02)	0·485 (10·00)	0·878 (20·03)	9·3	27·5	
(IIIb) [h]	0·114 × 10^{-3} (20·00)	0·268 × 10^{-3} (35·00)	0·958 × 10^{-3} (46·33)	14·4	27·2	2·0
(IVb) [h]	0·0584 × 10^{-3} (20·00)	0·138 × 10^{-3} (30·00)	0·306 × 10^{-3} (40·00)	14·5	28·3	
(IIId) [i]	0·592 × 10^{-4} (20·05)	1·48 × 10^{-4} (30·10)	2·88 × 10^{-4} (40·10)	13·8	30·5	7·7
(IVd) [j]	0·766 × 10^{-5} (20·02)	2·12 × 10^{-5} (30·00)	4·45 × 10^{-5} (40·05)	15·4	29·1	
(Vb) [h]	1·80 × 10^{-3} (20·00)	3·95 × 10^{-3} (30·00)	8·34 × 10^{-3} (40·50)	13·0	26·5	2·7
(VIb) [h]	0·667 × 10^{-3} (20·00)	1·47 × 10^{-3} (30·00)	2·99 × 10^{-3} (40·00)	13·1	28·3	
(Vd) [k]	1·32 × 10^{-3} (20·05)	2·81 × 10^{-3} (30·05)	5·60 × 10^{-3} (40·12)	12·5	28·9	8·9
(VId) [l]	1·48 × 10^{-4} (20·02)	3·43 × 10^{-4} (30·00)	6·60 × 10^{-4} (40·15)	13·0	31·6	

[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] Values recalculated from thermodynamic parameters. The probable error is ±6%. [e] The concentrations employed were 10^{-4}-substrate, 5 × 10^{-4}-piperidine, and 2 × 10^{-2}M-piperidine hydrochloride. At $\lambda_{max.}$ 380 nm (log ε 4·20). [f] Concentrations as in the previous cases. At $\lambda_{max.}$ 408 nm (log ε 4·25). [g] See ref. 1. [h] See ref. 2. [i] The concentrations used were 10^{-3}-substrate and 2 × 10^{-2}M-piperidine. At $\lambda_{max.}$ 398 nm (log ε 3·75). [j] Concentrations as in the previous case. At $\lambda_{max.}$ 404 nm (log ε 3·57). [k] The concentrations used were 10^{-3}-substrate, 6 × 10^{-3}-piperidine, and 3 × 10^{-2}M-piperidine hydrochloride. At $\lambda_{max.}$ 404 nm (log ε 3·78). [l] Concentrations as in the previous case. At $\lambda_{max.}$ 408 nm (log ε 3·63).

Examination of the values of $k_{(I)}/k_{(II)}$ (see Table) shows that in the case of the three halogens this ratio is about the same (*ca.* 2), whereas for Y = SO_2Ph it rises to 8—9, indicating a small, but significant, secondary steric effect, probably of an unusual type. The methyl group (see also below) seems to exert a buttressing effect which enhances the steric interactions [7] between the phenylsulphonyl and the adjacent nitro-group.

To clarify the nature of the interactions present in (IId) we have extended the comparison to other pairs of

* A similar pattern of reactivity has also been observed for the reaction of sodium benzenethiolate with some thiophens (G. Guantsi, C. Dell'Erba, and P. Macera, *J. Heterocyclic Chem.*, 1971, **8**, 537).

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[5] (*a*) D. Spinelli, C. Dell'Erba, and A. Salvemini, *Ann. Chim.* (*Italy*), 1962, **52**, 1156; (*b*) L. Chierici, C. Dell'Erba, A. Guareschi, and D. Spinelli, *ibid.*, 1967, **57**, 632.

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bromonitrothiophens (IIIb)—(VIb) and of nitrophenylsulphonylthiophens (IIId)—(VId). The compounds chosen are of two types: those without substituents in the 5-position [(IIIb and d) and (IVb and d)] where the steric interactions are limited to the groups linked to C-2, -3, and -4 of the thiophen ring, or those with a large substituent [bromine, (Va and d) and (VIb and d)] which does not suffer steric inhibition of resonance (S.I.R.) and can affect the reactivity ratios through an enhancement of the buttressing effect.

When the leaving group is Br, as already shown,[2] there is no indication of secondary steric effect ($k_H/k_{Me} = 2$—3). On the other hand, for Y = SO_2Ph the ratio k_H/k_{Me} rises to 8—9, *i.e.* the same value as observed for the pair (Id) and (IId), thus indicating that in all these compounds the steric interactions are limited to those possible between 2-phenylsulphonyl, 3-nitro-, and 4-methyl groups.

The values of the thermodynamic parameters support this viewpoint.[3,8] In fact, the decrease in the rate constants observed when Y = SO_2Ph in the compounds containing a methyl group at C-4 with respect to those with 4-H depends on changes in the enthalpy, the factor affected by S.I.R.[3]

EXPERIMENTAL

Synthesis and Purification of Compounds.—Compounds (Ia—d),[5a] (IIb),[1] (IIIb),[9] (IIId),[10] (IVb),[2] (Vb),[11] (VIb),[2] (VII)—(XII),[2] methanol, and piperidine [2] were prepared and/or purified according to the methods reported. The other compounds were prepared as below and gave the anticipated analyses and n.m.r. spectra.

2-*Chloro*-4-*methyl*-3,5-*dinitrothiophen* (IIa). Methyl 3-methylthiophen-2-carboxylate [12] was chlorinated at the 5-position by treatment with an equimolar amount of sulphuryl chloride at room temperature for 24 h. The reaction mixture was poured onto ice and extracted with ether. The ether extracts were washed with 5% sodium hydrogen carbonate and water, dried (Na_2SO_4), and the ether was distilled off. The crude chlorinated ester (containing *ca.* 50% starting material) was saponified by boiling with 10% potassium hydroxide for 1 h and then acidified with concentrated hydrochloric acid. The mixture was extracted with ether, the ether extracts were dried (Na_2SO_4), decolourized with charcoal, and the ether was distilled off. The crude mixture of 5-chloro-3-methyl- and 3-methyl-thiophen-2-carboxylic acid was nitrated by the method of decarboxylative nitration used [13] for other thiophen compounds to give a mixture of 2-*chloro*-4-*methyl*-3,5-*dinitro*- (IIa), m.p. 96—97° (from light petroleum), 3-methyl-2,4-dinitro-,[14] and 3-methyl-2,5-dinitro-thiophen [14] which were separated by column chromatography on silica gel (eluant light petroleum–benzene).

2-*Iodo*-4-*methyl*-3,5-*dinitrothiophen* (IIc). Compound (IIc) was obtained from 3-methyl-2,4-dinitrothiophen [14] by mercuriation and iodination (heating at 60°) according to the method [1] used for the synthesis of (IIb), m.p. 108—109° (from methanol).

4-*Methyl*-3,5-*dinitro*-2-*phenylsulphonylthiophen* (IId). A solution of 2-bromo-4-methyl-3,5-dinitrothiophen [1] (2×10^{-3} mol) in methanol was refluxed for 20 min with sodium benzenesulphinate ($2{\cdot}2 \times 10^{-3}$ mol). The precipitate obtained was filtered off and crystallized from ethanol, m.p. 161—162°.

4-*Methyl*-3-*nitro*-2-*phenylsulphonylthiophen* (IVd). Compound (IVd) was obtained from 2-bromo-4-methyl-3-nitrothiophen,[2] as for the previous compound, by boiling for several hours, m.p. 135—136° (from ethanol).

5-*Bromo*-3-*nitro*-2-*phenylsulphonylthiophen* (Vd). Compound (Vd) was obtained from 2,5-dibromo-3-nitrothiophen [11] as for the previous compound, m.p. 179—180° (from methanol–dioxan).

2-*Bromo*-3-*methyl*-4-*nitro*-5-*phenylsulphonylthiophen* (VId). Compound (VId) was obtained from 2,5-dibromo-4-methyl-3-nitrothiophen [2] as for the previous compound, m.p. 160—161° (from ethanol–dioxan).

Kinetic Measurements.—The kinetics were followed spectrophotometrically as previously described.[5a] The concentrations and wavelengths used are reported in the Table.

We thank the C.N.R. for financial support.

[4/716 *Received*, 9*th April*, 1974]

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