Kinetics of the Reactions of Some 5-Bromo-2-nitro-3-R-thiophens, 3,4-Dibromo-2-nitro-5-R-thiophens, 3-Bromo-2-nitro-5-R-thiophens, and 2-Bromo-3-nitro-5-R-thiophens with Nucleophiles in Methanol †

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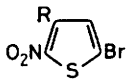
The reactivity of some 5-bromo-2-nitro-3-R-thiophens (Ia—g; R = H, Me, Et, Pr^n, n-hexyl, Pr^i, and Bu^t), 3,4-dibromo-2-nitro-5-R-thiophens (IIa and b; R = H and Me), 3-bromo-2-nitro-5-R-thiophens (IIIa and b; R = H and Me), and 2-bromo-3-nitro-5-R-thiophens (IVa and b; R = H and Me) with amines and sodium benzenethiolate has been studied in methanol at various temperatures. Piperidinodebromination of compounds (Ia and c) has also been studied in benzene, in dioxan, and in dioxan–water (60:40 and 10:90). Independent of the position of the alkyl group (*meta* or *para* with respect to the leaving bromine), an unexpected alkyl activation has been observed, which represents a further exception to the electron-releasing behaviour of alkyl groups.

SOME of our recent results [1] concerning unusual examples of weak activation of S_NAr reactions in thiophen derivatives by a *meta*-methyl group induced us to investigate the effect of the introduction of an alkyl group into the *meta*-like position (with respect to the leaving bromine) of 2-bromo-5-nitrothiophen (Ia), by studying the reactivity of some 3-alkyl-5-bromo-2-nitrothiophens (Ib—g) with piperidine and sodium benzenethiolate in methanol.



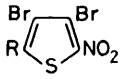
(I)

a; R = H e; R = n-hexyl
b; R = Me f; R = Pr^i
c; R = Et g; R = Bu^t
d; R = Pr^n

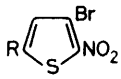
The alkyl groups chosen were those we used in a previous study of primary steric effects.[2] They have similar electronic effects, but we expected that increasing size of the alkyl group by branching at the α-carbon atom (Me, Et, Pr^i, and Bu^t) or by chain lengthening (Me, Et, Pr^n, n-hexyl) should influence the reaction rate in a different way.

Indeed, two main factors could come into play: (a) the steric hindrance to solvation of the ring and/or of the 2-nitro-group, possibly superimposed on the ponderal steric effect and (b) the kinetic secondary steric effect caused by the steric inhibition of the resonance of the 2-nitro-group.

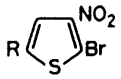
As shown below, the kinetic data could be unambiguously interpreted only if compared to those for some model compounds. To this end we have synthesized the compounds (IIa), (IIb), (IIIb), and (IVb) and studied their reactivity with nucleophiles in methanol. In addition, we have carried out some kinetic measurements of the piperidino-substitution reactions of (Ia and c) in various solvents.



(II)
a; R = H
b; R = Me



(III)
a; R = H
b; R = Me



(IV)
a; R = H
b; R = Me

Synthesis of Substrates for Nucleophilic Substitution.—The series of 3-alkyl-5-bromo-2-nitrothiophens was prepared by metallation of 3-alkylthiophens followed by bromination and nitration. It has previously been demonstrated that 3-alkylthiophens are preferentially metallated in the 5-position by butyl-lithium–tetramethylethylenediamine (TMEDA).[3] Thus, 3-methylthiophen gave 93% 4-methyl-2-thienyl-lithium and 7% 3-methyl-2-thienyl-lithium, 3-isopropylthiophen gave 99% of the 2,4-isomer, and only 1% of the 2,3-isomer, while with 3-t-butylthiophen only the 2,4-isomer could be detected.[3] The lithium compounds were characterized as methyl derivatives after reaction with dimethyl sulphate. Lithium compounds can be transformed to bromine derivatives through the reaction with bromine.[4] However, this reaction is difficult to control and often leads to further bromination. Thus, from 3-ethylthiophen, butyl-lithium–TMEDA and one equivalent of bromine a 59% yield of monobromo-derivatives, consisting of *ca.* 88% 2-bromo-4-ethylthiophen and 10% 2-bromo-3-ethylthiophen, and a 14% yield of 2,5-dibromo-3-ethylthiophen, was obtained. Wittig *et al.* have previously used the reaction of 1,2-dibromoethane [5] or methylene dibromide [6] with phenyl-lithium in a 'reverse' metal–halogen exchange to obtain bromobenzene. However, with 3-isopropyl-5-thienyl-lithium no such exchange occurred, and after hydrolysis 3-

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isopropylthiophen was recovered. Also, in the reaction of 3-methyl-5-thienyl-lithium with methylene dibromide, only 3-methylthiophen was found upon hydrolysis, even when an excess of methylene dibromide was used. It seems that due to the high stability of the thienyl-lithium derivative, the halogen–metal exchange equilibrium is still far to the left. We have previously shown that the reaction of heterocyclic lithium derivatives with hexachloroethane is very useful for the preparation of chloro-derivatives.[7] However, the price of hexabromoethane was a deterrent so instead carbon tetrabromide was tried successfully. We have not studied the reaction in more detail, but it appears that one mole of carbon tetrabromide can brominate more than one mole of thienyl-lithium, as carbon tetrabromide was always recovered, when equivalent amounts were used; in some cases CBr_4 was difficult to separate from the brominated alkylthiophen as it sublimed at 50—80 °C and 10 mmHg. In most cases, we therefore used an excess of the thienyl-lithium reagent and found it advantageous to add carbon tetrabromide very slowly at −70 °C to the thienyl-lithium reagent. An advantage with carbon tetrabromide was that it did not react at all or only to a very minor extent with the 3-alkyl-2-thienyl-lithium reagent present in minor amounts, giving almost isomer-free 4-alkyl-2-bromothiophens. The products probably contained small amounts of carbon tetrabromide, which however did not disturb the subsequent nitration. In this way, 2-bromo-4-methyl-, 2-bromo-4-ethyl-, 2-bromo-4-propyl-, 2-bromo-4-isopropyl-, 2-bromo-4-t-butyl-, and 2-bromo-4-hexyl-thiophen were obtained.

Another possible way to prepare some of the 4-alkyl-2-bromothiophens was to utilize the *meta*-directing power of carbonyl groups. Thus, 3-acetylthiophen gives 4-acetyl-2-bromothiophen [8] upon reaction with bromine and excess of $AlCl_3$ (swamping catalyst method).[9] This compound cannot be reduced by the Clemmensen or Wolff–Kishner methods, as bromine is removed under these conditions. However, reaction with $LiAlH_4$–$AlCl_3$ can usually be used successfully.[10] This was also the case with 4-acetyl-2-bromothiophen, which gave 2-bromo-4-ethylthiophen as the main product. However, *ca.* 15% of 4-bromo-2-vinylthiophen was formed as a by-product. Since the metallation procedure for 3-alkylthiophens, which we had available from other investigations, was successful, we did not try to modify the reduction procedure for the acetyl derivative in order to avoid the formation of vinyl derivatives or to apply it to other 4-acyl-2-bromothiophens. 4-Acetyl-2-bromothiophen was also used for the preparation of the isopropyl derivative. Reaction with methylmagnesium iodide gave 2-(2-bromo-4-thienyl)propan-2-ol, which could be reduced to 2-bromo-4-isopropylthiophen with tin(II) chloride and hydrochloric acid, or better in two steps *via* dehydration to 2-bromo-4-isopropenylthiophen, followed by homogeneous hydrogenation using tristriphenylphosphinechlororhodium as catalyst.[11]

All 4-alkyl-2-bromothiophens were nitrated using fuming nitric acid in acetic anhydride, giving the desired nitro-compounds in most cases in 50—60% yield. Complications were observed in the nitration of 2-bromo-4-t-butylthiophen. The main product, t-butylmaleic thioanhydride, showed a molecular ion at *m/e* 170, analysed for $C_8H_{10}O_2S$, and showed two bands at δ 1.33 (9 H) and 6.72 (1 H) in the ^1H n.m.r. Only a low yield of the nitro-derivative was obtained. In the nitration of 2-bromo-4-methylthiophen a minor by-product was isolated in crystalline form, which mass and n.m.r. spectra proved to be 4,4′-dimethyl-5,5′-dinitro-2,2′-bithienyl.

Compounds (IIb) and (IIIb) have been synthesised by nitration of 3,4-dibromo-2-methylthiophen and 4-bromo-2-methylthiophen, respectively, with a nitric acid–acetic anhydride mixture. Compound (IVb) has been prepared from 2-bromo-5-methylthiophen by chlorosulphonation followed by nitration and removal of the chlorosulphonyl group with mercury(II) acetate in acetic acid.

TABLE 1

Physical and spectroscopic data for the products of the reactions of compounds (I)—(IV) with nucleophiles [a] in methanol

Compound	Nucleophile	Crystallization solvent	Colour	M.p. (°C)	$\lambda_{max.}$/nm [b]	log ε [b]
(Ib)	P	Ligroin–benzene	Orange	162	440	4.54
	S	Methanol	Yellow	80	380	4.02
(Ic)	P	Methanol	Orange	116	442	4.54
	S		Orange	*c*	382	4.00
(Id)	P	Methanol	Orange	90	442	4.54
	S		Orange	*c*	382	4.00
(Ie)	P		Orange	*c*	442	4.53
	S		Orange	*c*	382	4.00
(If)	P	Methanol–dioxan	Orange	175	444	4.54
	S		Orange	*c*	384	4.01
(Ig)	P	Methanol	Orange	152	450	4.52
	S	Light petroleum	Yellow	50	394	3.98
(IIa)	A	Methanol	Red	114	416	4.03
(IIb)	A	Methanol–dioxan	Orange	166	416	4.03
(IIIa) [d]	A [d]	Ligroin–benzene	Orange	104	414	4.17
(IIIb)	A	Ligroin	Yellow	97	414	4.21
	S	Methanol	Yellow	118	374	4.07
(IVb)	P	Light petroleum	Yellow	56	410	3.78
	S	Light petroleum–benzene	Yellow	119	380	3.81

[a] P = piperidine, A = aniline, S = sodium benzenethiolate. All the substitution products gave correct analyses. [b] In methanol. [c] Oil. [d] *Cf.* R. G. R. Bacon and S. D. Hamilton, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1970.

Products of Nucleophilic Substitutions.—Compounds (I)—(IV), on treatment with nucleophiles, gave the corresponding substitution products in high yield, as shown by t.l.c. and u.v.–visible spectral analysis. The piperidino-derivatives, the thienylanilines, and the phenyl thienyl sulphides were prepared and purified according to the general methods reported in refs. 12—14, respectively. The relevant physical and analytical data are shown in Table 1.

TABLE 2

Kinetic data [a] and activation parameters for the reactions of compounds (I)—(IV) with piperidine (P) or aniline (A) in methanol

Compound	Nucleophile	10^5k/l mol^{-1} s^{-1} (T/°C)	$\Delta H^{\ddagger}$ [b]/kcal mol^{-1}	$-\Delta S^{\ddagger}$ [c]/cal mol^{-1} K^{-1}
(Ia) [d]	P	1.63(20.01) 3.89(30.01) 9.37(40.03)	15.3	28
(Ib)	P	2.86(19.95) 6.58(29.98) 14.3(40.02)	14.0	31
(Ic)	P	3.15(20.06) 7.25(29.95) 15.8(40.02)	14.1	31
(Id)	P	2.66(19.95) 6.08(30.00) 13.3(40.06)	14.0	32
(Ie)	P	2.96(19.95) 6.84(30.00) 15.0(40.06)	14.1	31
(If)	P	3.30(19.90) 7.62(29.95) 16.6(40.05)	14.0	31
(Ig)	P	7.69(20.05) 16.9(30.06) 34.4(40.00)	13.1	33
(IIa)	A	0.382(21.00) 0.793(30.12) 1.64(40.00)	13.4	38
(IIb)	A	0.984(20.05) 2.19(30.05) 4.35(39.95)	13.0	37
(IIIa)	A	0.069(20.04) 0.161(30.12) 0.353(40.00)	14.3	38
(IIIb)	A	0.217(19.82) 0.507(30.08) 1.04(40.00)	13.6	38
(IVa) [e]	P	11.4(20.00) 26.8(30.00) 59.8(46.33)	14.4	27
(IVb)	P	11.3(19.90) 26.0(29.92) 58.1(40.10)	14.2	28

[a] The rate constants are reproducible to within ±3%. [b] At 20 °C, the maximum error is 0.5 kcal mol^{-1}, 1 cal = 4.184 J. [c] At 20 °C. [d] D. Spinelli, C. Dell'Erba, and G. Guanti, *Ann. Chim.* (*Rome*), 1965, **55**, 1260. [e] D. Spinelli, G. Consiglio, and A. Corrao, *J. Chem. Soc., Perkin Trans. 2*, 1972, 1866.

RESULTS AND DISCUSSION

Kinetic Data.—Rate constants and activation parameters for the reactions of compounds (I)—(IV) with nucleophiles are reported in Tables 2 and 3. Some kinetic results from the reactions of compounds (Ia and c) with piperidine in various solvents are shown in Table 5.

meta-*Activation of* S_NAr *Reactions by Alkyl Groups.*—An examination of $k_R : k_H$ ratios (Table 4) for compounds (Ia—g) reveals that *meta*-alkyl substitution increases the reactivity of 2-bromo-5-nitrothiophen with both piperidine and sodium benzenethiolate. The magnitude of activation is practically independent of nucleophile and of alkyl group, the average value of $k_R : k_H$ ratios being 2.1 ± 0.5.

Thus, the acceleration by *meta*-alkyl groups is not limited to dihalogeno-*ortho*-tetra-substituted thiophen compounds (*cf.* ref. 1), but could arise by some factors connected with the 2,3,5-trisubstituted thiophen ring.

Changing hydrogen for alkyl group in an *ortho*-like position with respect to the nitro-group might hinder the orientation of solvent molecules in this region and then cause, to a certain extent, a reduction in the solvation energy. In order to cause an acceleration of the reaction, this effect should act mainly in the initial state rather than in the transition state.

As far as the ground state of substrates under investigation is concerned, the polarity features of the molecules are principally dependent on the polar interactions with the ring, as sketched in (V).

TABLE 3

Kinetic data [a] and activation parameters for the benzenethiolate substitutions of compounds (I)—(IV) in methanol

Compound	k/l mol^{-1} s^{-1} (T/°C)	$\Delta H^{\ddagger}$ [b]/kcal mol^{-1}	$-\Delta S^{\ddagger}$ [c]/cal mol^{-1} K^{-1}
(Ia) [d]	0.0573(10.06) 0.136(20.02) 0.321(30.00)	14.2	14
(Ib)	0.279(19.95) 0.586(29.98) 1.20(40.05)	12.6	18
(Ic)	0.295(19.98) 0.616(29.95) 1.21(40.05)	12.2	19
(Id)	0.228(20.05) 0.459(29.92) 0.945(40.02)	12.4	19
(Ie)	0.252(20.06) 0.521(29.92) 1.07(40.02)	12.6	18
(If)	0.168(19.95) 0.365(30.00) 0.734(40.05)	12.8	18
(Ig)	0.261(20.08) 0.547(29.96) 1.08(40.00)	12.4	19
(IIIa) [e]	0.100(10.08) 0.234(20.02) 0.524(30.00)	13.6	15
(IIIb)	0.596(20.00) 1.24(30.00) 2.50(40.00)	12.5	17
(IVa) [d]	0.0477(10.06) 0.116(20.02) 0.253(30.00)	13.8	16
(IVb)	0.205(20.02) 0.438(29.95) 0.876(40.00)	12.7	18

[a-c] As in Table 2. [d] D. Spinelli, C. Dell'Erba, and G. Guanti, *Ann. Chim.* (*Rome*), 1965, **55**, 1252. [e] D. Spinelli, G. Guanti, and C. Dell'Erba, *Ric. Sci.*, 1968, **38**, 1051.

The alkyl substituent in the 3-position is sufficiently close to the nitro-group to prevent a certain number of solvent molecules from orienting around this polar group.

Of course, this steric inhibition of solvation will be significant only when the polarity of the nitro-group is not enhanced as in the limiting structure (VI).*

In this case, the strong charge localization might cause a degree of solvation scarcely dependent on the

* The halogen mobility order in S_NAr reactions of thiophen derivatives [15] indicates that this formula does not represent a good approximation of the actual structure.

TABLE 4

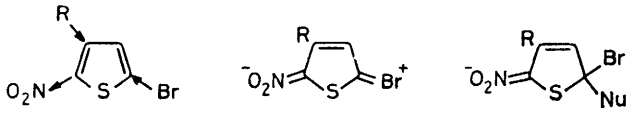
Reactivity ratios, $k_R : k_H$, for the reactions of compounds (I)—(IV) with nucleophiles in methanol

Compound	R	Nucleophile	$k_R : k_H$ at 20 °C
(I)	Me	P	1.8
		S	2.0
(I)	Et	P	2.0
		S	2.2
(I)	Pr^n	P	1.7
		S	1.6
(I)	n-Hexyl	P	1.8
		S	1.8
(I)	Pr^i	P	2.1
		S	1.2
(I)	Bu^t	P	4.8
		S	1.9
(II)	Me	A	2.8
(III)	Me	A	3.2
		S	2.5
(IV)	Me	P	1.0
		S	1.8

presence of either a hydrogen atom or an alkyl group in the 3-position.

On the other hand, as the formation of the transition state (VII) is rate determining in the reaction with both nucleophiles, it is necessary that the nitro-group is in conjugation with the ring so that the negative charge arising from the nucleophilic attack can be delocalized.

Other Examples of Alkyl Activation of S_NAr.—With the aim of confirming the above hypothesis, we studied the S_NAr reactivity of some model thiophen compounds (IIb)—(IVb) where both the leaving group (bromine)



(V) (VI) (VII)

and the kind of activation (conjugated '*ortho*'- or '*para*'-like nitro-group) remained the same, whereas the relative positions of alkyl and nitro-groups were changed.

Very surprisingly, the pairs (IIa and b) and (IIIa and b) (Table 4) behaved in the same way as 2,3-dibromo-4-R-5-nitrothiophens (R = H and Me, *cf.* ref. 1) and of the pair (Ia and b), respectively.

Moreover, the introduction of a methyl group in the *para*-like 5-position of 2-bromo-3-nitrothiophen (IVa) had no effect or once again a weakly activating effect in the reactions of this substrate with piperidine or sodium benzenethiolate (Table 4).

While confirming that the alkyl activation does not rest on *ortho*-dihalogeno-substitution these findings

TABLE 5

Kinetic data and activation parameters for the reactions of 2-bromo-5-nitro- (Ia) and 5-bromo-3-ethyl-2-nitro-thiophen (Ic) with piperidine (P) in various solvents at 20 °C

Solvent	$10^5 k_H$ [a]	$10^5 k_{Et}$ [a]	$\Delta H^\ddagger_H$ [b]	$\Delta H^\ddagger_{Et}$ [b]	$-\Delta S^\ddagger_H$ [c]	$-\Delta S^\ddagger_{Et}$ [c]	$k_{Et} : k_H$ [d]
Benzene	0.088 [e]	0.088 [f,g]	11.9 [e]	12.1 [g]	46 [e]	45 [g]	1.0
Dioxan [h]	1.17	1.37	9.9	9.8	47	47	1.2
Dioxan–water (60 : 40)	17.6 [i]	21.7 [l]	13.4 [i]	12.8 [l]	30 [i]	32 [l]	1.2
Methanol [m]	1.61	3.14	15.3	14.1	28	31	2.0
Dioxan–water [n] (10 : 90)	59.9	346	16.4	14.4	17	22	5.8

[a] The kinetic constants, l mol^{-1} s^{-1}, were reproducible to ±3%. [b] kcal mol^{-1}, the maximum error is ±0.5 kcal mol^{-1}. [c] cal mol^{-1} K^{-1}. [d] From k_{Et} and k_H values calculated at 20 °C by activation parameters. [e] Ref. 15. [f] As for (Ia) (*cf.* note *e*), the apparent kinetic constant for the piperidino-substitution of (Ic) increases linearly with increasing piperidine concentration (range 0.1—1.0M) according to the following equations: at 20 °C, $10^6k = (0.88 \pm 0.03) + (4.17 \pm 0.05)$ [P], $n = 5$, $r = 0.9998$; at 30 °C, $10^6k = (1.74 \pm 0.08) + (6.96 \pm 0.13)$ [P], $n = 5$, $r = 0.9995$; at 40 °C, $10^6k = (3.53 \pm 0.08) + (11.0 \pm 0.1)$ [P], $n = 5$, $r = 0.9998$. [g] At [P] = 0. [h] Values calculated at 20 °C from kinetics measured in the range 20—40 °C, at [P] = 1.02M. [i] Ref. 18. [l] Values calculated at 20 °C from kinetics measured in the range 20—40 °C, at [P] = 0.02M. [m] *Cf.* Tables 1, 2, and 4. [n] Values calculated at 20 °C from kinetics measured in the range 20—40 °C, at [P] = 0.02—0.1M. Probably due to interference by OH$^-$ the reactions were not 'clean'. The kinetic constants correspond to the first few percent of conversion and have to be considered 'initial' values.

The alkyl substituents might determine a different solvation of the initial state compared to the transition state, and the observed acceleration can be accounted for on these grounds.

meta-*Alkyl Activation and Influence of Solvent.*—In order to ascertain the role played by solvation effects in *meta*-alkyl activation, we investigated the reactions of compounds (1a and c) with piperidine in benzene, dioxan, and dioxan–water (Table 5).

The trend of $k_{Et} : k_H$ values seemed to support the idea of the different steric inhibition of solvation, since (Ic) shows both activation enthalpy and entropy values lower than (Ia), the alkyl-substituted substrate being less solvated and then more 'disordered'. Moreover, the difference in activation parameters increases with increasing solvent polarity, and (Ic) becomes more and more reactive compared to (Ia).

constitute compelling evidence *against* the differential solvation hypothesis.

Does an Alkyl Substituent Stabilize or Destabilize the Transition State of S_NAr *Reactions?*—In principle, alkyl groups are able to both donate and accept electrons as the charged site demands, resulting in the stabilization of both positive and negative charge through a polarization-type process. Traditionally, a methyl group is considered to be electron releasing in that it stabilizes cations and destabilizes anions. However, there are exceptions to this generalization.[16]

As far as the S_NAr reactions are concerned, there is no example of alkyl activation in the benzene series. Nevertheless, we consider the stabilization of the transition state through electron polarization by alkyl groups as a plausible hypothesis.

Conclusions.—It is very difficult to formulate clear

interpretations of the data reported in this and in the preceding paper. The reason for this is predominantly the very small range of rate coefficients and activation parameters, which we, for the most part, have been dealing with. However we feel that the facts we have brought to light are worthy of interest and hope they will stimulate further work in this area.

EXPERIMENTAL

Synthesis and Purification of Compounds.—Compound (IIa),[17] piperidine,[12] benzenethiol,[14] aniline,[13] methanol,[18] benzene,[18] and dioxan [18] were prepared and/or purified according to the methods reported.

General Procedure for Preparation of 4-Alkyl-2-bromothiophens.—Anhydrous TMEDA (64.0 g, 0.55 mol) and 1.45N-butyl-lithium (380 ml, 0.55 mol) in hexane was added dropwise under nitrogen to the 3-alkylthiophen (0.50 mol) in anhydrous ether (350 ml) at such a rate that slow reflux is obtained. After the addition is complete, the mixture was refluxed for 30 min and then cooled to −70 °C. A solution of carbon tetrabromide (110.6 g, 0.33 mol) in anhydrous ether (200 ml) was added dropwise and the mixture stirred overnight at −70 °C. The mixture was then poured into ice–water and the ether phase separated. The aqueous phase was extracted with ether and the combined ether phases washed with 6N-hydrochloric acid, sodium hydrogencarbonate solution and 20% sodium chloride solution and dried ($MgSO_4$). The ether was evaporated and the residue fractionated *in vacuo*. The results are given in Table 6.

Alternative Route to 2-Bromo-4-isopropylthiophen.—To a solution of methylmagnesium iodide prepared in the usual way from magnesium (4.8 g, 0.204 mol) in anhydrous ether (50 ml) and methyl iodide (25 g, 0.18 mol) in anhydrous ether (50 ml), 4-acetyl-2-bromothiophen (25.0 g, 0.122 mol) [8] in ether (200 ml) was added dropwise. The mixture was refluxed for 2 h and poured into ice–water. The mixture was carefully acidified with 6N-hydrochloric acid. The aqueous phase was separated and extracted with ether. The combined ether phases were washed with 6N-hydrochloric acid, sodium hydrogencarbonate solution and water, dried ($MgSO_4$), and the solvent evaporated to give 2-(2-bromo-4-thienyl)propan-2-ol (24.2 g, 90%), δ($CDCl_3$) 7.00 (d, $J_{3,5}$ 1.7 Hz, H-3 or -5), 6.95 (d, $J_{3,5}$ 1.7 Hz, H-5 or -3), 3.28 (1 H, s, OH), and 1.47 (6 H, s, CH_3).

2-(2-Bromo-4-thienyl)propan-2-ol (13.2 g) and anhydrous oxalic acid (2.0 g) were heated to reflux at 60—70 mmHg for 2 h. After cooling, the mixture was poured into water and extracted with ether. The combined ether phases were washed with sodium carbonate solution and 20% sodium chloride solution, dried ($MgSO_4$), and evaporated to give 2-bromo-4-isopropenylthiophen (10.9 g, 89%). This was added to tristriphenylphosphinechlororhodium [11] (309 mg) dissolved in degassed benzene (86 ml) and degassed hexane (32 ml). The mixture was hydrogenated in a Parr apparatus at 3—4 atm during 4 h. After filtration and evaporation, fractional distillation *in vacuo* gave 2-bromo-4-isopropylthiophen (3.9 g, 35%) having the same spectral data as the sample described above.

General Procedure for 3-Alkyl-5-bromo-2-nitrothiophens (I).—In a four-necked flask equipped with stirrer, thermometer, dropping funnel, condenser, and drying tubes, the 4-alkyl-2-bromothiophen (0.28 mol) was dissolved in acetic anhydride (90 ml). The solution was cooled to −30 °C in a carbon dioxide–ethanol bath. The nitrating reagent, prepared by careful dropwise addition of fuming nitric acid (46.2 ml; *d* 1.52) to acetic anhydride (90 ml) with cooling, was added at such a rate that the temperature was kept below −20 °C. Cooling as well as stirring was continued for 1 h, whereupon the mixture was poured into ice–water and left overnight. The product was taken up in chloroform and the aqueous phase extracted with chloroform. The combined chloroform phases were washed with sodium hydrogencarbonate solution and sodium chloride solution and dried ($MgSO_4$). After evaporation of the solvent, fractional distillation gave the products shown in Table 7.

TABLE 6

Yields and physical data for 4-alkyl-2-bromothiophens [a]

R	Yield (%)	B.p. (°C/mmHg)	δ_{H-3}	δ_{H-5}	δ_R	$J_{3,5}$/Hz	J_{R-5}/Hz	J_{CH-CH_3}/Hz
Me	68	60—62/10	6.83	6.75	2.18	1.6	1.2	
Et	76	78—82/10	6.87	6.77	1.17; 2.58	1.6		
Pr	66	85—90/10	6.82	6.73	0.90; 1.57; 2.50	1.6		
Pr^i	81	74—86/10	6.91	6.76	1.19; 2.80	1.8	1.2	6.6
Bu^t	75	84—92/9	6.98	6.78	1.25	1.6		
n-Hexyl	52	137—144/10	6.85	6.77	0.9; 1.3; 2.53	1.6		

[a] Starting materials described in Ref 3.

3,4-Dibromo-2-methyl-5-nitrothiophen (IIb).—Nitric acid (*d* 1.52; 2 ml) in acetic anhydride (6 ml) was added with stirring to a solution of 3,4-dibromo-2-methylthiophen [19] (4.4 g; prepared from 2-methyl-3,4,5-tribromothiophen [20] by debromination with butyl-lithium according to Lawesson [21]) in acetic anhydride (8 ml). The reaction mixture was cautiously heated to 60 °C and then poured into water with vigorous stirring. The resulting solid was filtered off and crystallized from methanol, m.p. 96—97 °C (Found: C, 20.0; H, 1.1; N, 4.6. $C_5H_3Br_2NO_2S$ requires C, 20.0; H, 1.0; N, 4.6%).

3-Bromo-5-methyl-2-nitrothiophen (IIIb).—Nitric acid (*d* 1.4; 4 ml) in acetic acid anhydride (10 ml) was slowly added with stirring to a solution of 4-bromo-2-methylthiophen [22] (10.4 g) in acetic anhydride (19.2 ml) at −5 to 0 °C. After being kept at 0 °C for 1 h, the mixture was poured onto crushed ice. The separated oil was extracted with ether.

The ethereal extracts were washed with aqueous sodium hydrogencarbonate (10%) and water, dried (Na_2SO_4), decolourised with charcoal, and the ether was distilled off. The residue was crystallized from ligroin, m.p. 79—80 °C (Found: C, 27.2; H, 1.9; N, 6.4. $C_5H_4BrNO_2S$ requires C, 27.0; H, 1.8; N, 6.3%).

5-Bromo-2-methylthiophen-3-sulphonyl Chloride.—2-Bromo-5-methylthiophen [23] (31.6 g) was added dropwise to a mixture of chlorosulphonic acid (29.4 ml) and phosphorus pentachloride (37.1 g) at 10 °C. The mixture was immedi-

TABLE 7

Yields and physical data for 3-alkyl-5-bromo-2-nitrothiophens

R	Yield (%)	B.p. (°C/mmHg)	M.p. (°C)	δ_{H-4}	δ_R	Found (%) C	H	S	Molecular weight	Calc. (%) C	H	S	Molecular weight
Me [a]	52	82—92/0.03—0.04	28—29	6.92	2.58	27.3	2.0	14.4	221/223	27.05	1.8	14.45	222.0
Et	57	85—89/0.050—0.065		7.05	1.28; 3.01	30.55	2.6	13.6	235/237	30.5	2.55	13.6	236.1
Pr[n]	53	89/0.03—0.04		6.98	1.00; 1.70; 3.02	33.55	3.25	12.75	249/251	33.6	3.2	12.8	250.1
Pr[i]	78	136—139/10	30.5—31.5	7.07	1.27; 3.97	33.55	3.25	12.9	249/251	33.6	3.2	12.8	250.1
But [b]	12	100/0.065—0.1		7.10	1.45	36.45	3.85	12·2		36.35	3.8	12.15	
n-Hexyl	38	121—128/0.04—0.05		7.00	0.89; 1.38; 3.03	41.15	4.85	11.05	291/293	41.1	4.85	10.95	292.2

[a] From the residue of the distillation, yellow crystals (1.5 g) of 4,4′-dimethyl-5,5′-dinitro-2,2′-bithienyl were obtained, m.p. 134—136 °C after recrystallization, δ ($CDCl_3$) 7.85 (H-4, -4′), 2.30 (H-CH_3, H-CH_3′) (Found: C 42.4; H 2.85; S 22.5%; *M*, 284. Calc. for $C_{10}H_8N_2O_4S_2$: C, 42.25; H, 2.85; S, 22.5%; *M*, 284.3). [b] The main component was t-butylmaleic thioanhydride, b.p. 41—47 °C at 0.04 mmHg, δ ($CDCl_3$) 6.72 (1H, s, CH), 1.33 (9H, s (CH_3)$_3$] (Found: C, 56.4; H, 5.9; S, 18.8%; *M*, 170. Calc. for $C_8H_{10}O_2S$: C, 56.45; H, 5.9; S, 18.85%; *M*, 170.2). Crude (1g) obtained by fractional distillation was purified by preparative t.l.c. (silica gel Merck 60 F_{254}; eluant light petroleum–$CHCl_3$ 3 : 1).

ately poured onto crushed ice, and the oil which separated was extracted with chloroform. The extracts were washed with water, dried ($CaCl_2$), and the chloroform distilled off at reduced pressure. The *residue* was purified by fractional distillation, b.p. 105—107 °C at 0.2 mmHg (Found: C, 21.9; H, 1.4; S, 23.3. $C_5H_4BrClO_2S_2$ requires C, 21.8; H, 1.5; S, 23.3%).

5-Bromo-2-methyl-4-nitrothiophen-3-sulphonyl Chloride.—5-Bromo-2-methylthiophen-3-sulphonyl chloride (12.7 g) was added in small portions to nitric acid (*d* 1.52; 33.7 ml), with stirring, at 25—30 °C. The mixture was heated to 40 °C for 1 h and then poured onto crushed ice. The oil obtained was extracted with carbon tetrachloride and the extracts were washed with water and dried ($CaCl_2$). The solvent was removed under reduced pressure and the residue was crystallized from ligroin–benzene, m.p. 103—104 °C (Found: C, 18.9; H, 0.9; N, 4.3. $C_5H_3BrClNO_4S_2$ requires C, 18.7; H, 0.9; N, 4.4%).

2-Bromo-5-methyl-3-nitrothiophen (IVb).—5-Bromo-2-methyl-4-nitrothiophen-3-sulphonyl chloride (3.9 g) was heated under reflux for 2 h in a solution of mercury(II) acetate [mercury(II) oxide (5.2 g) in acetic acid (30 ml)]. After being kept at room temperature overnight, the product of mercuriation was filtered off and washed with water, ethanol, and ether. The acetoxymercury compound was hydrolysed with aqueous HCl according to Hurd and Kreuz,[24] to give *2-bromo-5-methyl-3-nitrothiophen*, m.p. 92—93 °C (from ligroin) (Found: C, 27.3; H, 1.8; N, 6.5. $C_5H_4BrNO_2S$ requires C, 27.0; H, 1.8; N, 6.3%).

Analyses.—G.l.c. analyses were performed with a Perkin-Elmer 900 apparatus equipped with a flame ionization detector and connected to a Varian 480 digital integrator. The columns were made of stainless steel with 3 mm o.d. For the g.l.c. analyses the following columns were used: 2 m 10% butane-1,4-diol succinate (BDS) on Chromosorb W (80—100 mesh) and 2 m 3% free fatty acid phase (FFAP) on Gas-Chrom Q (100—120 mesh). ^1H N.m.r. spectra were recorded on a Varian A-60 instrument and ^{13}C n.m.r. spectra on a JEOL-FX 60 machine. Tetramethylsilane was used as internal standard and $CDCl_3$ as solvent. A Perkin-Elmer 257 i.r. spectrometer was used for i.r. spectra. Mass spectra were recorded on an LKB 9000 mass spectrometer at 70 eV. Elemental analyses were performed by the Department of Analytical Chemistry at the University of Lund, Sweden, or by the Laboratory of Microanalyses at the University of Milano, Italy.

Kinetic Measurements.—The kinetics were followed spectrophotometrically as previously described.[15] The concentrations used were 10^{-4} — 2×10^{-3}M for substrates, 0.5—1.0M for piperidine, 1.0M for aniline, and 4×10^{-4}—2×10^{-3}M for sodium benzenethiolate.

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