Thiophene Series. Note IX (1). The absence of Secondary Steric Effects in Nucleophilic Substitutions of Thiophene Derivatives: Kinetics of the Reactions of 2-Bromo-3,5-dinitrothiophene and 2-Bromo-3,5-dinitro-4-methylthiophene with Piperidine.

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The kinetics of the reactions of piperidine with 2-bromo-3,5-dinitrothiophene (IV) and 2-bromo-3,5-dinitro-4-methylthiophene (III) have been measured in methanol, ethanol and benzene.

Molecular model predictions were confirmed when the kinetic results ($k_{IV}/k_{III} \cong 2$) demonstrated, for the first time, the absence of secondary steric effects for nucleophilic substitutions in thiophene compounds.

It is known (2,3) that the halogen atom of 3-chloro-2,6-dinitrotoluene (I), in contrast to that of chloro-2,4-dinitrobenzene (II), is very difficult to remove with nucleophilic reagents (e.g., aniline and piperidine). The kinetic behavior

I   II
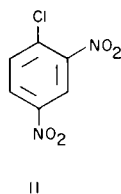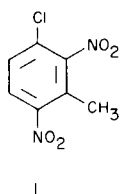
of I and II with piperidine in ethanol has been studied by Capon and Chapman (3). The much slower reactivity of I has been attributed to steric inhibition of resonance (S.I.R.) of the two nitro groups by the intervening methyl group.

Various cases of kinetic effects, derived from secondary steric effects in activated nucleophilic substitutions, have been observed in benzene derivatives (4), polycyclic compounds (5) and 6-membered heterocyclic ring compounds (6). Recently, Marino and coworkers(7) have pointed out an interesting case of steric inhibition in the solvation of the aza-group in pyrimidine compounds.

However, the influence of steric effects on nitro-activated nucleophilic substitutions in 5-membered hetero-aromatic compounds has not yet been investigated.

These compounds, having a different geometry than 6-membered rings, give rise to a different steric situation. From an inspection of scale molecular models (8) of I and

of 2-bromo-3,5-dinitro-4-methylthiophene (III) (see Fig. 1), we observed that the steric interactions between the methyl and nitro groups in III are much less than the same interactions in I. This is a result of the greater bond
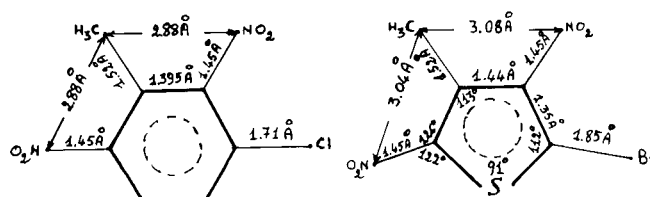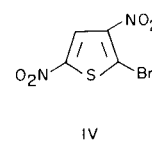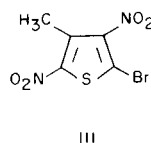

Fig. 1

III   IV

length between atoms 3 and 4 of thiophene ring and the larger external angles of the 5-membered ring (9).

Consequently, we expected the thiophene compound to have a lower S.I.R. and a lower kinetic steric effect. To confirm our expectations we have measured the reactivity of III and of 2-bromo-3,5-dinitrothiophene (IV) with piperidine (see Table I).

It is of interest to note that the insertion of a methyl group between two activating nitro groups in III produces

TABLE I

Kinetic Data of Piperidinodebromination of 2-Bromo-3,5-dinitro-4-X-thiophenes in Various Solvents.

X =	k, 1 mole^{-1} sec^{-1} (1) at various temperatures			$\Delta H \neq$ (2) kcal/mole	$-\Delta S \neq$ (3) u.e.	k_H/k_{CH_3} at 20° (4)	Solvent	λ max mμ	log ϵ
	10.82°	20.06°	30.02°						
H	1.13	2.25	4.53	11.8	16.6	2.3	ethanol	382	4.18
CH$_3$	0.438	0.95	1.85	12.3	16.4		ethanol	408	4.24
H	1.06	1.99	3.78	10.7	20.6	2.0	methanol	380	4.20
CH$_3$	0.563	0.991	2.00	10.7	21.9		methanol	408	4.25
H		8.32	13.75	8.3	26.0	1.6	benzene	386	4.18
CH$_3$		5.29	8.70	8.2	27.2		benzene	404	4.24

(1) The rate constants are accurate to better than ± 4%. (2) The probable error is 0.3 kcal/mole. (3) At 20°. (4) The probable error is ± 6%.

only a slight diminution of the rate, i.e., a factor of about 2, Table I, whereas an analogous diminution in rate by a factor of 970 (20° in ethanol), mainly related to difference in activation enthalpy, is reported for I. This latter rate diminution is explained in terms of steric inhibition of the conjugation of the nitro groups with the aromatic system and we feel that there is also an important steric hindrance to the formation of a solvated intermediate or perhaps a hindrance toward solvation of the departing halide ion.

The slight difference in reactivity between III and IV, may be related to the methyl group's weak power of repelling electrons and not to its steric effect.

In fact, considering the values of σ_{m-CH_3} (10 a) and of ρ known for nucleophilic substitutions in thiophene compounds (10 b), and supposing the additivity of electronic effects of substituents, we can expect the methyl group, because of its inductive electron release, to determine the diminution of rate by a factor of 1.7. Therefore the calculated value agrees with the experimental value (see Table I).

The absence of secondary steric effects in nucleophilic substitutions in thiophene compounds (III and IV), in contrast to what is found in similar benzene compounds (I and II), agrees with the observation that in steric interactions, small changes in "compression" (11) can determine strong kinetic effects. This is because the behavior of repulsive interactions between two groups is not linearly correlated with the distance between them (12).

The differences in rates and in thermodynamic parameters in the various solvents are similar to that already observed by us (13, 14) in the piperidine debromination of other 5-membered heteroaromatic compounds having a nitro group ortho to the reactive center.

EXPERIMENTAL

Preparation and Purification of Compounds.

2-Bromo-3,5-dinitrothiophene (15) and 2-N-piperidyl-3,5-dinitrothiophene (16) were prepared as previously described. Piperidine and the solvents were purified as previously reported (13).

2-Bromo-3,5-dinitro-4-methylthiophene.

3-Methyl-2,4-dinitrothiophene (17) (1.88 g.) in a solution of mercuric acetate in acetic acid (4.3 g. of mercuric oxide in 25 ml. of acetic acid) was refluxed for two hours. After being kept at room temperature overnight the product of mercuration was filtered off and washed with water, ethanol and ether. The filtrate on dilution with water gave more of the product. A mixture of this product of mercuration (3 g.) in water (20 ml.) was treated with bromine (0.6 ml.) dissolved in a solution of potassium bromide (4 g. in 20 ml. of water) and warmed on a steam bath for three hours. After being cooled the reaction mixture was extracted with ether. The ethereal extracts were washed with an aqueous solution of sodium sulfite, dried with sodium sulfate, and the ether distilled off. The colourless residue was recrystallized from light petroleum to give III, m.p. 89°, which gave a depression in melting point to 65-75° when admixed with an authentic sample of 3-methyl-2,4-dinitrothiophene.

Anal. Calcd. for C$_5$H$_3$BrN$_2$O$_4$S: Br, 29.96; N, 10.49; S, 11.98. Found: Br, 30.28; N, 10.51; S, 11.60.

2-N-Piperidyl-3,5-dinitro-4-methylthiophene.

A solution of III (0.54 g., 2 x 10^{-3} mole) in ethanol was treated with piperidine (0.36 g., 4.2 x 10^{-3} mole). After being kept at room temperature overnight the solvent was removed in vacuo. The residue was crystallized from ethanol to give 2-N-piperidyl-3,5-dinitro-4-methylthiophene, yellow-orange plates, melting at 143°. The structure of this compound was confirmed by means of its proton resonance spectrum.

Anal. Calcd. for C$_{10}$H$_{13}$N$_3$O$_4$S: N, 15.50; S, 11.81. Found: N, 15.61; S, 11.76.

Kinetic Measurements.

The reaction kinetics were followed as previously described (18).

The wavelength and the logarithm of the molar extinction coefficients of 2-N-piperidyl-3,5-dinitrothiophene and of 2-N-piperidyl-3,5-dinitro-4-methylthiophene are reported in Table I.

The rate constants are given in Table I. The concentrations employed were 2×10^{-5} M for the bromonitrothiophenes and 1×10^{-4} M for the piperidine. The reactions in methanol were carried out in presence of piperidine hydrochloride (1×10^{-2} M) to eliminate any competitive reaction of methoxide ion (19).

Acknowledgments.

REFERENCES

(1) Part VIII, D. Spinelli, C. Dell'Erba and G. Guanti, Ann. Chim. (Rome), 55, 1260 (1965); presented at the "Journées de Chimie Organique", Nice, March 1967.

(2) H. Lindemann and A. Pabst, Ann. Chem., 462, 24 (1928).

(3) B. Capon and N. B. Chapman, J. Chem. Soc., 600 (1957).

(4) W. C. Spitzer and G. W. Wheland, J. Am. Chem. Soc., 62, 2995 (1940); P. Van Berk, J. O. M. Van Langen, P. E. Verkade and B. M. Wepster, Rec. Trav. Chim., 75, 1137 (1956).

(5) E. Berliner, M. J. Quinn and P. J. Edgerton, J. Am. Chem. Soc., 72, 5305 (1950); M. Simonetta and G. Favini, Rend. Accad. Naz. Lincei, [8], 16, 84 (1954); G. Illuminati and F. Tarli, Ric. Sci., 28, 1464 (1958); P. Beltrame and M. Simonetta, Gazz. Chim. Ital., 91, 260 (1961); G. Illuminati, G. Marino and O. Piovesana, Ric. Sci., 34, (II-A), 437 (1964); G. Illuminati and G. Marino, Rend. Accad. Naz. Lincei, [8], 34, 407 (1963).

(6) N. B. Chapman, D. K. Chandhurg and J. Shorter, J. Chem. Soc., 1975 (1962); N. B. Chapman and C. W. Rees, J. Chem. Soc., 1190 (1954); G. Illuminati, P. Linda and G. Marino, Rend. Accad. Naz. Lincei, [8], 38, 389 (1965).

(7) M. Calligaris, P. Linda and G. Marino, Tetrahedron, 23, 813 (1967).

(8) L. N. Ferguson, "The Modern Structural Theory of Organic Chemistry," Prentice-Hall, N. Y. (1963); "Interatomic Distances and Configuration 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., 15, 737 (1962).

(9) In the models (Fig. 1), the bond angles between the nucleus and the substitutents are those known for monosubstituted compounds (8). We have not considered the change in position which the substituents undergo as a result of compression determined by the presence of substituents in the ortho positions one against the other. The V. der W. radii used for -CH₃ and -NO₂ groups are respectively 1.73 and 1.92 Å.

(10a) D. H. McDaniel and H. C. Brown, J. Org. Chem., 23, 420 (1958); (b) C. Dell'Erba and D. Spinelli, Tetrahedron, 21, 1061 (1965).

(11) Studying the reactions of certain 6-X-2-NO₂-chlorobenzenes with piperidine N. E. Sbarbati [J. Org. Chem., 30, 3365 (1965)] observed that substituents having a V. der W. radius less than 1.8 Å gave a good Hammett correlation, while substituents with a radius of 1.9-2.0 Å were not readily correlated.

(12) E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, "Conformational Analysis," Interscience Publisher, N. Y. (1965), p. 435 ff.

(13) D. Spinelli, C. Dell'Erba and G. Guanti, Ann. Chim. (Rome), 55, 1260 (1965).

(14) L. Chierici, C. Dell'Erba, A. Guareschi and D. Spinelli, ibid., 57, 632 (1967).

(15) R. Motovama, K. Sato and E. Imoto, Nippon Kagaku Zhassi, 82, 1543 (1961).

(16) D. Spinelli, C. Dell'Erba and A. Salvemini, Ann. Chim. (Rome), 52, 1156 (1962).

(17) I. J. Rinkes, Rec. Trav. Chim., 52, 1052 (1933).

(18) D. Spinelli, A. Salvemini and C. Dell'Erba, Ann. Chim. (Rome), 54, 869 (1964).

(19) J. F. Bunnett and R. J. Monath, J. Am. Chem. Soc., 77, 5051 (1955); J. F. Bunnett, E. W. Garbisch and K. M. Pruitt, ibid., 79, 385 (1957); D. Spinelli, A. Salvemini and C. Dell'Erba, loc. cit.; M. Foa, A. Ricci, P. E. Todesco and P. Vivarelli, Boll. Sc. Fac. Chim. Ind. (Bologna), 23, 65 (1965).