Reactivity of the Halogenothiazoles toward Nucleophiles. Part III.[1] Kinetics and Mechanisms of the Reaction between 4(5)-X-2-Halogenothiazoles and Substituted Thiophenols

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4(5)-X-2-Halogenothiazoles react with un-ionised thiophenol to give the normal substitution products [4(5)-X-2-phenylthiothiazoles]. The effects of structural changes in the thiazole and in the thiophenol operate in the sense opposite to that observed in normal nucleophilic substitutions and emphasise the existence and importance of a pre-equilibrium (of the acid–base type) between the thiazole and the thiophenol which precedes the substitution step. The effect of added acid is also considered.

We have reported previously [2] that 4(5)-X-2-halogenothiazoles react with sodium benzenethiolate to afford the corresponding 4(5)-X-2-phenylthiothiazoles through an S_NAr pathway. The '3-aza-group' activates the reactions.[3]

It was also observed that the thiazoles react not only with benzenethiolate ions (whose considerable nucleophilic ability is well known), but also with un-ionised thiophenol [2] as found for halogenoquinolines [4] and for halogenobenzimidazoles [5] and in some cases the rate of substitution of the thiol is comparable with that of the anion.

Therefore with the aim of extending our studies on the reactivity of the thiazole ring and of its derivatives, it seemed of interest to investigate quantitative aspects of the reaction between 2-halogeno-X-substituted thiazoles and substituted thiophenols.

RESULTS

2-Halogenothiazoles react with thiophenols in methanol at 50° according to the stoicheiometric equation (1).

$$XC_3HNS\text{–}Hal + YC_6H_4SH \longrightarrow XC_3HNSC_6H_4Y + Hal^- + H^+ \quad (1)$$

All the reactions investigated follow clean second-order kinetics, first order in both reactants (Table 1). No autocatalytic effect due to the acid released during the reaction is observed even if it is followed to high conversion.

For non-polar aprotic solvents such as benzene instead of polar protic ones (*e.g.* methanol), no appreciable reactivity is observed, and even after long reaction times, both halogenothiazole and thiophenol can be recovered unchanged.

Furthermore the analogous 2-halogenobenzothiazoles which undergo easy phenylthio–dehalogenation [3] do not react with undissociated thiols even if electron-releasing substituents (which enhance the basicity of the heterocyclic nitrogen atom) are present in the benzo-ring.

Table 2 illustrates changes in reactivity caused by substituents on the thiazole ring: a sharp decrease of reactivity is observed in going from electron-releasing to electron-withdrawing substituents, *e.g.* on passing from 2,5-dichloro- to 2-chloro-4-methylthiazole there is a difference of *ca.* 10 in rate. Table 2 also gives results obtained for the analogous reaction of thiophenol with halogenoquinolines [4] and halogenobenzimidazoles.[5] The reactivity of the thiazoles, however substituted, is lower than that of the quinoline and benzimidazole derivatives.

TABLE 1

Reaction between 2-halogeno-4-X-thiazoles and thiophenol at 50° in methanol

Halogen	Cl	Cl	Br	Br
X	H	H	H	H
10^2[Thiazole]/M	20·3	12·8	1·77	1·76
10^2[C_6H_5SH]/M	2·14	32·2	5·11	7·66
10^5k/l mol^{-1} s^{-1}	0·47	0·47	2·28	2·25
Halogen	Br	Br	Br	
X	H	H	H	
10^2[Thiazole]/M	1·78	1·75	1·78	
10^2[C_6H_5SH]/M	10·9	27·5	40·6	
10^5k/l mol^{-1} s^{-1}	2·31	2·39	2·17	
Halogen	Br	Br	Cl	
X	H	H	4-Me	
10^2[Thiazole]/M	1·79	1·81	1·59	
10^2[C_6H_5SH]/M	42·3	52·2	9·48	
10^5k/l mol^{-1} s^{-1}	2·24	2·26	1·86	
Halogen	Cl	Cl	Cl	
X	4-Me	4-Me	4-Me	
10^2[Thiazole]/M	1·59	1·61	1·86	
10^2[C_6H_5SH]/M	20·6	50·9	79·8	
10^5k/l mol^{-1} s^{-1}	1·85	1·95	1·95	

TABLE 2

Reactivities of 2-chloro-4(5)-X-thiazoles with thiophenol at 50° in methanol

X	10^5k (l mol^{-1} s^{-1})
H	0·47
5-Me	1·2
4-Me	1·9
5-Cl	0·18
4-Ph	0·28
4-Cl	0·028
5-NO_2	0·75
2-Br-thiazole	2·3
2-Cl-quinoline	74·6 [a]
2-Cl-*N*-methylbenzimidazole	339 [b]
2-Cl-imidazole	53·7 [b]
4-Cl-quinoline	8610 [a]

[a] At 30° (ref. 4). [b] Ref. 5.

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[5] A. Ricci and P. Vivarelli, *J. Chem. Soc.* (*B*), 1968, 1280.

In the case of 2,4- and 2,5-dichlorothiazoles we did not observe any displacement of the halogen ion from C-4 or -5, even at 70—80% conversion. Independent experiments carried out on 4-bromothiazole showed that C-4 is inert towards this kind of reaction, whereas similar experiments on 5-bromothiazole have shown that the halogen can be displaced, although at a lower rate than when it is at C-2 ($k_{5\text{-bromothiazole}}$ 10^{-6} l mol^{-1} s^{-1}); however the kinetic pattern for this isomer is rather complex and difficult to interpret.

The effects of structural changes (both electronic and steric) in the thiophenols have been examined. Table 3

TABLE 3

Reaction between 2-halogeno-5-X-thiazoles and Y-substituted thiophenols in methanol at 50°

Halogen = Br, X = H

Y	H	2,6-Me_2	*m*-Me	*p*-Me
10^5k/l mol^{-1} s^{-1}	2·3	1·0	1·9	3·5
Y	*p*-OMe	*m*-Cl	*m*-NO_2	*p*-NO_2
10^5k/l mol^{-1} s^{-1}	4·0	6·8	20	31

Halogen = Cl, X = NO_2

Y	H	*m*-Me	*m*-Cl
10^5k/l mol^{-1} s^{-1}	0·75	1·0	3·6

reports pertinent data for the reaction of 2-bromothiazole and, in some cases, for that of 2-chloro-5-nitrothiazole. For these two substrates the effects caused by structural modifications in the thiol on the reaction rate are strictly similar.

The effect of the changes in the acidity of the medium obtained by initial addition to the reaction mixture of suitable amounts of trifluoroacetic acid in methanol has been examined and the results are listed in Table 4 (the stability of the thiazoles was checked by control experiments carried out in methanol with trifluoroacetic acid

TABLE 4

Reaction between 2-halogeno-5-X-thiazoles (1—2 × 10^{-2}M) and thiophenol (1·5—33 × 10^{-1}M) in presence of trifluoroacetic acid at 50° in methanol,

Halogen = Br, X = H

$[CF_3CO_2H]$/M		0·051	0·102	0·205	0·237
10^5k/l mol^{-1} s^{-1}	2·3 [a]	2·27	2·38	2·70	2·60

Halogen = Cl, X = Me

$[CF_3CO_2H]$/M		0·044	0·102	0·349	0·818
10^5k/l mol^{-1} s^{-1}	1·2 [a]	1·21	1·37	1·79	1·84

Halogen = Cl, X = NO_2

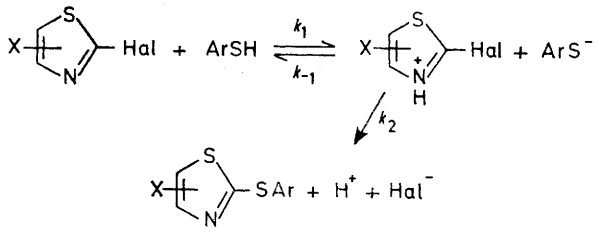
$[CF_3CO_2H]$/M		0·007	0·036	0·136	0·177	0·924
10^5k/l mol^{-1} s^{-1}	0·75 [a]	0·75	0·75	0·79	0·95	1·28

[a] Data from Table 2.

alone). As shown in Table 4, in every case the rate constants increase with increasing acid concentration.

DISCUSSION

The observed reactivity may be interpreted as in the Scheme, which is analogous to those proposed [4,5] for



SCHEME

other aza-activated substrates. The kinetic equation (2) applies if the steady state treatment is invoked.

$$\text{Rate} = [k_1k_2/(k_1 + k_2)][\text{Thiophenol}][\text{Halogenothiazole}] \quad (2)$$

Assuming that $k_{-1} \gg k_2$ and considering $K_e = k_1/k_{-1}$ equation (2) reduces to (3) in accordance with the

$$\text{Rate} = K_ek_2[\text{Thiophenol}][\text{Halogenothiazole}] \quad (3)$$

observed second-order kinetics provided $k_{obs} = K_ek_2$. The two constant K_e and k_2 are influenced in opposite ways by electronic effects both in the aza-activated substrate and in the thiol.

Changes in the aza-activated substrate which increase the basicity of the heterocyclic nitrogen atom increase the K_e value but decrease that of k_2; the resulting effect on k_{obs} may be irregular, as in the case of halogenoquinolines [4] and halogenobenzimidazoles.[5] The comparative data show that k_{obs} decreases as the basicity of heterocyclic nitrogen atom is reduced (Table 2). Thiazole, which is less basic (pK_a 2·5) [6] than both quinoline (pK_a 4·95) [7] and benzimidazole (pK_a 5·53),[8] is also the least reactive system. Thus the lack of reactivity of the benzothiazole system can be explained by its low basicity (pK_a 1·2).[8] Although the pK_a values refer to the parent heterocycles and not to the substrate actually employed in the kinetic studies, we think that the comparison is acceptable, at least from a qualitative point of view.

The fact that, in the case of the halogenothiazoles, k_1 is not the slow step is confirmed by the absence of a kinetic isotope effect. The rate constants of the reactions measured in MeOD with ArSD or in MeOH with ArSH are the same within experimental error.

In the thiazole series electron-releasing substituents (4-Me, 5-Me) increase the rate, while electron-withdrawing ones (5-Cl, 4-Cl) decrease it. (2-Chloro-5-nitrothiazole is a particular case which is treated below.) This trend is opposite to that for normal aromatic nucleophilic substitutions for which the treatment of data by the simple Hammett or more sophisticated equations derived from it given a positive value of ρ. The application of the simple Hammett relation to the reaction of 4(5)-X-2-halogenothiazoles with thiophenol (Figure 1), in which normal σ_{meta} values are used for 4-substituents and σ_{para} values for 5-substituents, although quantitatively unsatisfactory (r 0·946), gives a ρ value of *ca.* − 3.

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[8] D. D. Perrin, ' Dissociation Constants of Organic Bases in Aqueous Solution,' Butterworths, London, 1965, p. 243.

An analogous treatment of data for substitution with benzenethiolate ion showed a regular linear trend with a high positive ρ value (5·30).[2] The results not only emphasise the sensitivity or the thiazole ring to

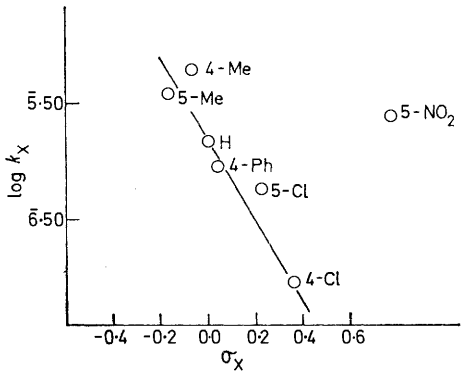

FIGURE 1 Hammett correlations for variation in thiazole substituents

substituent effects, but also demonstrate that, overall, the thiazole derivatives may be regarded as undergoing electrophilic attack. Previously we observed [9] that the oxidation of substituted 2-phenylsulphinylthiazoles with perbenzoic acid, in which the thiazole system also undergoes electrophilic attack shows a small negative ρ (−1·19). In the present case the thiazole ring interacts with the thiophenol, so that the electronic effects of substituents on the thiazole ring are more important than in oxidation, where the reaction centre is the sulphur atom in the side-chain.

The observed high negative ρ value is a new feature in this kind of reaction; in fact the reaction of the 2-halogenobenzimidazoles [5] or the halogenoquinolines [4] is scarcely influenced by the nature of the substituents on the heteroaromatic ring, so that the rate constant shows only modest and irregular variations, upon changes in the substituents on the aza-activated derivatives. This emphasises that in the thiazole system the aza-group plays a substantial role related to its basic characteristics.

The effects of substituents in the thiophenols have also been examined, and the data reported in Table 3 for the reaction of 2-bromothiazole show that the normal electronic requirements of nucleophilic attack are not observed in this case. Electron-withdrawing groups (able to reduce electron availability on the sulphur atom of the thiol and thus lowering its nucleophilicity) increase the reaction rate. This effect may be related to the increase in acidity exhibited by thiophenol when the electron-attracting power of substituents is increased, and therefore to the ability of substitited thiophenols to shift the equilibrium (Scheme) to the right.

However, a small rate increase is also observed when electron-donating substituents (*e.g.* *p*-OMe, *p*-Me) are present. This is the expected trend for a normal nucleophilic substitution. This behaviour can logically be ascribed to the enhanced role of nucleophilicity factors, which, even if less important, must be considered as competing with acidity factors in determining the observed rate.

The Hammett treatment (Figure 2) of the data is typical of a two-stage reaction pattern having opposed electronic requirements [10] (electrophilic attack of the thiol hydrogen atom on the aza-group in the first stage, nucleophilic attack of sulphur on C-2 in the second).

For the substituents investigated, structural changes in the thiol for the reaction with 2-chloro-5-nitrothiazole leads to behaviour parallel to that of 2-bromothiazole. Since for this substrate high reactivity towards nucleophilic substitution is well known it was logical to expect the normal effect of substituents on thiophenol, *i.e.* one underlining the need for nucleophilic attack in the slow step of the reaction. However, even in this case there is an electrophilic requirement, even if the reactivity of 2-chloro-5-nitrothiazole is much higher than that expected from the Hammett correlation for the effect of substituents on thiazole (see Figure 1).

2,6-Dimethylthiophenol is slightly less reactive than the unsubstituted thiol, indicating the absence of steric hindrance in the rate-determining step of the reaction. Such phenomena have been observed for attack on C-2 of benzothiazoles [11] so that in our case we can exclude attack on this centre in the rate-determining step.

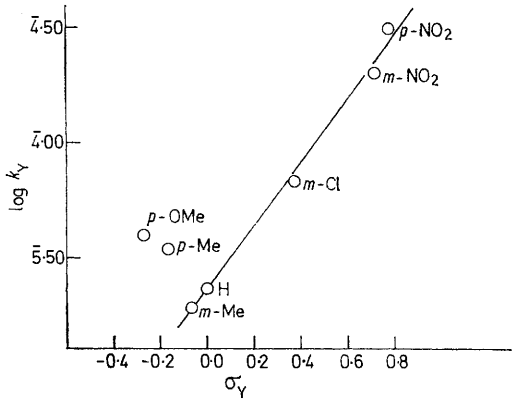

FIGURE 2 Hammett correlation for variation in thiophenol substituents

In addition, a modest ' element effect ' (Br/Cl = 4·9) emphasises that carbon–halogen bond breaking is not involved in the rate-determining step of the reaction. The sequence Br > Cl follows the respective polarisabilities of the entering and leaving groups, as already observed in reactions with benzenethiolate ion.[2,12]

Trifluoroacetic acid, when added to the reaction mixture, causes a rate increase only if present in ap-

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[12] M. Foá, A. Ricci, and P. E. Todesco, *Boll. sci. Fac. Chim. ind. Bologna*, 1965, **23**, 229.

preciable quantities (Table 4), the rate being unchanged when small quantities of the acid are present. This is in agreement with the absence of any autocatalytic phenomena derived from the acid evolved during the reaction, although in our case the acid is probably neutralised by 2-phenylthiothiazole which is certainly more basic than the corresponding 2-halogen derivative.

The effect of trifluoroacetic acid is the same both when electron-releasing and electron-withdrawing groups are present on the thiazole ring. Probably this effect is related to a simple variation in the medium polarity which can slightly modify the position of the acid–base equilibrium.

If the added acid, on the one hand, favours the reaction by increasing the concentration of protonated thiazole (presumably more reactive than the unprotonated species [13]), on the other, it slows it down, by causing reduction of the concentration of benzenethiolate ion which is clearly more reactive towards nucleophilic substitution than free thiophenol. In addition the sensitivity of the system to variation in the protic power of the medium is emphasised by the absence of reactivity in benzene.

From the results we conclude that the reactivity of halogenothiazoles with thiols can be explained by the existence of an acid–base equilibrium preceding the phenylthio–dehalogenation. Because of the low basicity of the heteroaromatic substrate, the formation of an ionic pair or of thiazolium and benzenethiolate ions, is the rate-determining step.

EXPERIMENTAL

Kinetic Measurements.—The experiments were performed as previously described.[2]

Materials.—Analytical grade methanol was purified by distillation using a standard method. Thiophenol,[14] *m*-chloro-,[15] *p*-methoxy-,[16] *m*-nitro-,[16] *p*-methoxy-,[17] *p*-nitro-,[18] *m*-methyl-,[16] and 2,6-dimethyl-thiophenol [16] were prepared and purified by standard methods. The thiazoles were prepared as previously reported.[2]

The reaction between 2-chloro-5-nitrothiazole and thiophenol is typical of the procedure. 2-Chloro-5-nitrothiazole (1·0 g, 0·006 mol) in MeOH (5 ml) was added to thiophenol (1·2 g, 0·01 mol) in MeOH (5 ml) and the mixture was heated at 50° for 20 h. The solvent was then evaporated and the crude residue chromatographed on silica gel eluting with pentane–ether (9 : 1). Two products were separated: the first was unchanged 2-chloro-5-nitrothiazole (0·5 g); the second (0·6 g, 83%), m.p. 96° (from ethanol) was identified by comparison with an authentic sample of 5-nitro-2-phenylthiothiazole.[19]

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