Reactivity of Thiazole Derivatives. IV.[1] Kinetics and Mechanisms of the Reaction of 2-Halogeno-4(5)-X-thiazoles with Methoxide Ion

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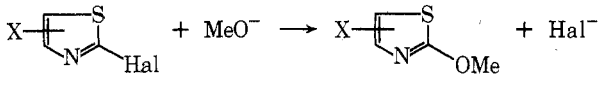
4(5)-X-2-Chlorothiazoles react with sodium methoxide in a normal aza-activated nucleophilic substitution reaction. The reactivity is influenced by substituents in positions 4 and 5. When X is 5-NO_2, the 2-methyl ether is obtained in good yields only when the amount of methoxide ion is less than that of the halo derivative; moreover, the 5-nitro-2-methoxythiazole reacts with sodium methoxide to give a mixture of two σ-anionic complexes. These Meisenheimer-like adducts rapidly decompose to a mixture of derivatives, among which the 5-nitro-2-hydroxythiazole was identified. The structural variations in comparison with those observed in thiophenoxy dehalogenation are discussed.

The reactivity of position 2 in the thiazole ring toward nucleophiles has been investigated[2,3] and the results indicate that the concept of "aza activation" can be extended to these pentatomic heterocyclic compounds, even if their peculiar structural characteristics, such as ring geometry, heterocyclic sulfur, and pronounced aza-group basicity, make their behavior different from that of the six-membered aza-activated derivatives. In fact, the reactivity of halogenothiazoles toward nucleophiles is observed also when the halogen is linked to the 4 or 5 position of the ring.[4]

With the purpose of obtaining further information on the quantitative aspects of the reactivity of chlorothiazoles, we have studied the reaction between 2-chloro-4(5)-X-substituted thiazoles (X = H, 4-CH_3, 4-Cl, 4-C_6H_5, 5-Cl, 5-CH_3, 5-NO_2) and methoxide ion in methanol at 50°.

Results and Discussion

2-Halogeno-4(5)-X-thiazoles react with sodium methoxide, quantitatively yielding the corresponding 2-methyl ethers. The stoichiometry of the reaction follows the scheme below.



In cases of 2,4-dichloro- or 2,5-dichlorothiazole, using more than 1 equiv of methoxide ion, halogen in position 4 or 5 can also be partially displaced. The displacement of the halogen atom in position 4 or 5 is also proved by independent experiments carried out on 4- and 5-halogenothiazoles;[4] nevertheless, using equimolar concentrations of thiazole and methoxide, the only product obtained is the 4(5)-chloro-2-methoxythiazole, as shown by TLC, GLC, and NMR analysis of the reaction mixture checked until 70–80% conversion: the titrimetric determinations of the halide ion coincide with appearance of 4-chloro-2-methoxythiazole (or 5-chloro-2-methoxythiazole) revealed by GLC analysis.

All reactions follow a second-order kinetic law, first order with respect to each reactant; the results are summarized in Table I.

The 5-nitro-2-methoxythiazole has been obtained (by reaction between 5-nitro-2-chlorothiazole and methoxide ion in large excess) in a poor yield (30%) as reported by Metzger,[5] who suggests preparing it by nitration of 2-methoxythiazole. However, it is possible to obtain 5-nitro-2-methoxythiazole in higher yields (85%) using the thiazole derivative and the sodium methoxide in equimolecular quantities.

Table I
Reaction between 2-Chloro-4(5)-X-thiazoles and MeO^- in MeOH at 50°

Registry no.	X	10^5 k, sec^{-1} mol^{-1} l.
	H	0.81[a]
33342-65-3	5-CH_3	0.18
26847-01-8	4-CH_3	0.24
1826-23-9	4-C_6H_5	1.3
16629-14-4	5-Cl	61
4175-76-2	4-Cl	104
3034-47-7	5-NO_2	2,960,000

[a] From ref 3.

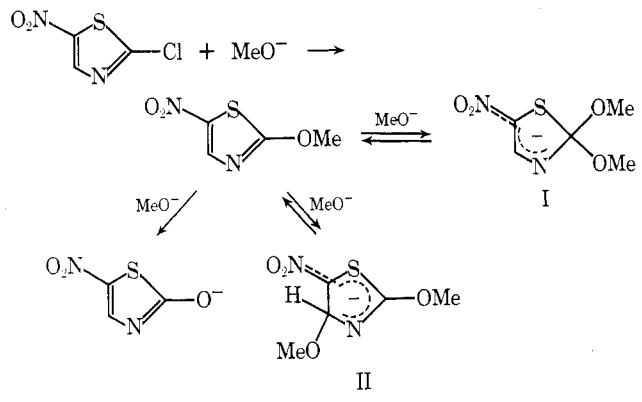
Table II
Reaction rate of the 5-Nitro-2-chlorothiazole in MeOH with MeO^-

Temp, °C	k, sec^{-1} mol^{-1} l.	$\Delta E^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
−21.0	0.031		
0.0	0.33		
10.4	1.0		
50	29.6[a]	15.7	−5.50
2-Chlorothiazole[b]			
50	0.81×10^{-5}	18.5	−27.1

[a] Extrapolated value. [b] From ref 3.

The kinetic data of Table II are obtained under these conditions. If 5-nitro-2-methoxythiazole in methanol is mixed with an equimolecular quantity (or slightly less) of sodium methoxide and the solvent is evaporated, a mixture of crystalline products, very soluble in water, but only slightly soluble in the usual organic solvents, can be obtained. By means of NMR analysis we have demonstrated the presence in this reaction mixture of two σ-like anionic complexes. These adducts are unstable and decompose into unidentified products. If the methoxydechlorination of 2-chloro-5-nitrothiazole is carried out with excess of methoxide, the 2-methoxy-5-nitrothiazole initially produced reacts with a second equivalent of methoxide ion to give complexes I and II (see Scheme I), which decompose. Also, the uv and visible spectrophotometric analysis (in the range of λ 600–250 nm) show that the first step is the methoxydehalogenation.

Scheme I



The NMR analysis (in DMSO-d_6, internal reference Me_4Si) of the mixture of I and II has been carried out and from the chemical shifts it was possible to assign structures I and II reported in Scheme I.

In both adducts the nuclear protons signals are shifted upfield with respect to 5-nitro-2-methoxythiazole [τ_{H_4} 1.48 (1 H), $\tau_{C_2OCH_3}$ 5.80 (3 H)]; the lower field signal (τ 1.92) is assigned to the ring proton of adduct I, and that at higher field (τ 4.19) is attributed to the H_4 of adduct II; this larger shift is consistent with the sp^2 to sp^3 change in the hybridization of the carbon atom[6] at position 4 of the thiazole derivative, subsequent to attack of methoxide ion on this position. Moreover, while for adduct I a singlet at τ 6.84 is found, corresponding to six equivalent methoxy protons, two peaks of three equivalent protons each are observed at τ 6.13 and 6.76, respectively, and assigned to the two nonequivalent methoxy groups of adduct II.

Adduct II has been independently observed by Illuminati and Stegel (VI Symposium of Organic Chemistry, Taormina, Italy, May 1972). In the reactions of 5-nitro-2-chlorothiazole with aliphatic amines, Ilvespää[7] found, in addition to the normal substitution products, some acyclic compounds shown by the NMR spectra in which the H-4 peak is sharply shifted downfield (τ 1.3–1.1). Such products are derived, as reported by the above-mentioned author, from a preliminary attack of the base on position 4, followed by release of halide from position 2 and by the concerted ring opening.

When NMR spectra are recorded in the presence of increasing quantities of methanol in addition to the DMSO-d_6, a slight increase of the amount of I can be observed (the intensity of the peak at τ 1.92 is increased if compared with a known quantity of benzene added as inert reference), while the amount of isomer II rapidly decreases to a value lower than that of I.

It must be emphasized that appearance of I does not quantitatively follow disappearance of II: when the DMSO/MeOH ratio is 1:1, I reaches 50%. Moreover, under these conditions the NMR spectrum is complicated by the presence of several unidentified signals, probably due to decomposition products; nevertheless it is possible to recognize a peak at τ 1.41, which has been assigned to the ring proton of 5-nitro-2-hydroxythiazole by comparison with a sample of 5-nitro-2-hydroxythiazole obtained by the method of von Babo and Prjis.[8] All attempts to isolate complexes I and II failed. The presence in methanol of isomer II to a larger extent (80%) with respect to isomer I (20%) may be justified by a kinetic control on the methoxide ion attack (more relevant steric hindrance being offered by the already alkoxy-bearing position). On the other hand, the impossibility of using resonance structures in which the negative charge is localized on the heterocyclic nitrogen

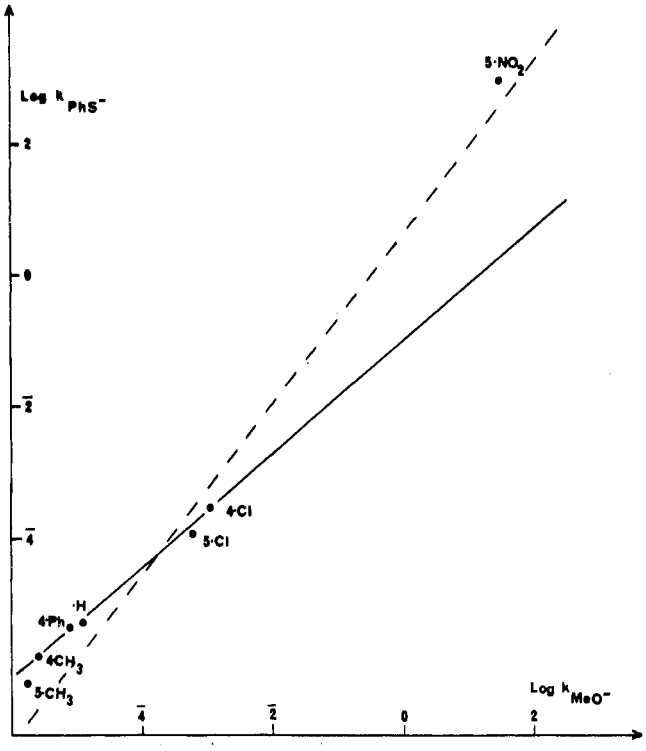


Figure 1. Dashed line, calculated by least-squares analysis for all substituted derivatives; full line, calculated only for 4-substituted derivatives.

seems to indicate that the thermodynamic stability of isomer II is due to the charge delocalization afforded by the heterocyclic sulfur atom.[9] However, the reactivity scheme of 5-nitro-2-chlorothiazole can be represented as in Scheme I.

Formation of 5-nitro-2-hydroxythiazole and instability of adducts I and II (which probably leads to the presence in the reaction medium of ring-opening products not yet identified) must be taken into account to explain the low yield in methoxydechlorination of the 5-nitro-2-chlorothiazole (at least for reactions carried out with an excess of sodium methoxide), and the incomplete conversion of adduct II to I.

The kinetic effects produced by structural variations on the methoxydechlorination of 2-chloro-X-thiazoles are very large, as the 5-nitro-2-chlorothiazole is more reactive than the 5-methyl-2-chlorothiazole by a factor of 1.6×10^7. The observed log k values of the reactions are roughly correlated with the analogous data obtained for benzenethiolate dehalogenation of the same substrates,[2] as shown in Figure 1.

The correlation coefficient is unsatisfactory (0.990). A more careful examination of the plots in Figure 1 reveals that the groups in position 4 correlate well (r = 0.998) while the groups in position 5 deviate from linearity.

Position 4 in thiazole can be thought of as "meta"-like and position 5 as "para"-like with respect to position 2. In fact, the reaction requires delocalization of negative charge in the transition state and appropriate groups in position 5 can provide strong resonance stabilization. This assumption seems reasonable, while it is not in fully agreement with the observed reactivities of 4- or 5-halogenothiazoles[4] and recent data of Noyce and Fike[10] for conjugation phenomena between position 2 and 4 in thiazole systems.

In the series of 1-halogeno-2-nitro-X-benzenes, Brieux[11] and coworkers have pointed out that the resonance contribution depends on the type of nucleophile and on the kind of substituents. Experimental σ values for substituents in

position 5 can be obtained by ρ values calculated from kinetic data of 4-X-2-chlorothiazoles. If σ(experimental) = σ_I + σ_R, σ_R can be evaluated, as reported in Table III.

Table III
Hammett-Taft Parameter Calculated for Nucleophilic Substitution Reactions of Some 2-Chloro-X-thiazoles[a]

Reaction	ρ_4	r	$(\sigma_R)_{exp}$ 5-CH_3	5-Cl	5-NO_2
Methoxy substitution	5.88	0.998	−0.06	−0.15	+0.49
Thiophenoxy substitution	5.14	0.995	−0.11	−0.19	+0.98

[a] See text.

Values of σ_R experimentally determined here for thiophenoxy or methoxy substitution do not substantially differ from the normal σ_R values for the donor groups CH_3 and Cl (respectively −0.12 and −0.24), in agreement with the normal application of Hammett-type correlation. Analogous values are also reported by Brieux for a homocyclic aromatic system.[11]

The case of the 5-nitro derivative is peculiar; in fact we found for the benzenethiolate substitution a σ_R ~1, while in the methoxy substitution, for which one can expect an analogous strong activation, the observed σ_R value is only 0.49, not different from that observed in reactions of six-membered homocyclic aromatic derivatives.[11] Therefore the exceptional nitro activation in the thiazole derivatives previously reported[2] is a specific fact of the thiophenoxy substitution. It is interesting to observe that only for 5-nitro-2-chlorothiazole is benzenethiolate more reactive than methoxide ion, while for all other substituents we observe the opposite trend. This fact can be interpreted considering that also in homocyclic aromatic systems the benzenethiolate ion is more reactive than methoxide in the strongly activated systems such as 1-halogeno-2,4-dinitrobenzenes, while with poorly activated systems, such as *p*-fluoronitrobenzene, methoxide and thiophenoxide ions react with comparable rates. We previously observed[12] that in the case of 2-halogenobenzothiazoles the benzenethiolate ion is less reactive than methoxide while the 2-halogeno-6-nitrobenzothiazoles show the opposite trend.[17]

An interesting remark can be made about the reactivity of the dichloro derivatives; previously[4] it was pointed out that the halogen at position 5 is more reactive than that at position 2. For reactions with sodium methoxide the sequence 5 > 2 > 4 was observed, so that the halogen in position 5 would be expected to be more reactive than that in position 2, at least for reaction of 2,5-dichlorothiazole. On the contrary, the experimental data show that (under our reaction conditions) the 2-methoxy dehalogenation is always favored.

This fact can be related to the different activation due to the substituent effect, less important from position 2 to 5 than from position 5 to 2.

Similarly we have observed other cases of different sensitivity to substituent effects, for example, measuring the acidity constants of 2-carboxy-6-X-benzothiazoles[13] (ρ 1.4) and 6-carboxy-2-X-benzothiazoles[14] (ρ 0.9).

Experimental Section

Physical Measurements. The NMR spectra were recorded with a Varian 100-MHz instrument, using tetramethylsilane (TMS) as internal standard. The chemical shifts are expressed in τ values and are approximated to ±0.02 ppm.

The uv spectra were recorded with a Zeiss DMR 21 spectrophotometer.

Materials. Methanol, sodium methoxide, and thiazole substrates were prepared and/or purified by methods previously described.[2] DMSO-d_6 was used without further purification (minimum deuteration 99%).

Kinetic measurements were made by usual procedures. Kinetic experiments on 2,4-dichlorothiazole and 2,5-dichlorothiazole were performed by following both the appearance of the chloride ion (Volhard) and the formation of 4(5)-chloro-2-methoxythiazole by GLC using a Hewlett-Packard instrument (6-ft column SE-30). The rate constants determined by the two analyses were within experimental error (5%).

Procedures of preparation and characterization of 2-methoxy-4(5)-chlorothiazoles and 2-methoxy-5-nitrothiazole are reported. The melting points and boiling points are uncorrected.

5-Chloro-2-methoxythiazole and 4-Chloro-2-methoxythiazole. A 20-ml portion of sodium methoxide solution in methanol (1 *N*) was added to a methanolic solution of 1.53 g of 2,5-dichlorothiazole, and the mixture was kept at 50°. After about 3 hr the titrimetrical chloride ion analysis revealed that the reaction had occurred at 74%. The mixture was poured onto ice, neutralized with HCl (1:1), and extracted with diethyl ether. The oil obtained after evaporation of the solvent was analyzed by GLC, TLC, and NMR and was found to be a mixture of two products, one of which was the starting substrate. Separation was made by silica gel column chromatography (petroleum ether–diethyl ether, 5:2). 2,5-Dichlorothiazole eluted first and then 0.91 g of an oil, bp 166–167° (760 mmHg), was obtained in 83% yield and identified by NMR analysis as 5-chloro-2-methoxythiazole.

Anal. Calcd for C_4H_4ClNSO: Cl, 23.71. Found: Cl, 23.4.

In a similar way 4-chloro-2-methoxythiazole was obtained in 86% yield as an oil, bp 185–188° (760 mmHg).

Anal. Calcd for C_4H_4ClNSO: Cl, 23.71. Found: Cl, 23.6.

Table IV reports NMR data.

Table IV
Chemical Shifts for the Reaction Product of 2,4(5)-Dichlorothiazoles and MeO^-Na^+ in MeOH at 50°[a]

Substrate	τH_4	τH_5	τ Me	Registry no.
2,5-Dichlorothiazole	2.69 (s)			
2-Methoxy-5-chlorothiazole	3.16 (1 H)		5.99 (3 H)	54166-43-7
2,4-Dichlorothiazole		3.13 (s)		
2-Methoxy-4-chlorothiazole		3.68 (1 H)	5.94 (3 H)	54166-44-8

[a] In τ values in CCl_4, internal reference Me_4Si.

5-Nitro-2-methoxythiazole. A 17.5-ml (2.0×10^{-2} mol) portion of sodium methoxide solution (1.15 *N*) was added dropwise under cooling to a solution of 3.5 g (2.1×10^{-2} mol) of 5-nitro-2-chlorothiazole in the minimum amount of anhydrous methanol. After a few minutes the reaction was practically complete. The solvent was partially removed under vacuum from the yellow solution and the crude residue was chromatographed on silica gel (hexane–diethyl ether, 4:1). After some unreacted material, a pale yellow solid, mp 56–59°, was obtained in 86% yield. After recrystallization from hexane this compound melted at 58–59°, and was identical with an authentic sample of 5-nitro-2-methoxythiazole obtained by nitration of 2-methoxythiazole with 86% nitric acid in sulfuric acid at 0°.[15]

Anal. Calcd for $C_4H_4N_2O_3S$: S, 20.02. Found: S, 19.7.

The yield of 5-nitro-2-methoxythiazole is decreased to 30% when the reaction is carried out in the presence of an excess of sodium methoxide.

Isolation and Characterization of the Adducts I and II. The reaction was carried out in a manner similar to that described by Illuminati[16] for isolation of the adduct of 2-methoxy-3,5-dinitrothiophene.

2-Methoxy-5-nitrothiazole (70 mg) was dissolved in the minimum amount of methanol; 0.42 ml (1 equiv) of methanolic sodium methoxide solution (1.07 *N*) was slowly added. The yellow solution immediately turned deep red. The solvent was removed under vac-

uum. The residue, a red, crystalline solid, was collected and washed with anhydrous benzene and dried at 0.1 mmHg (oil pump).

The adducts were characterized by their NMR spectra (Table III) as reported in the Results and Discussion. Small amounts of some other unidentified products are present. This fact and the instability of I and II give a discrepancy in the elemental analysis of the mixture.

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Registry No.—I, 54166-45-9; II, 54166-46-0; 5-nitro-2-methoxythiazole, 26245-61-4; methoxide ion, 3315-60-4.

References and Notes

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(17) Note Added in Proof. The observed lower reactivity of sodium methoxide, with regard to sodium benzenethiolate, can also be due to the formation of a σ anionic complex arising from attack of the methoxide in position 4 of the 2-chloro-5-nitrothiazole in a concurring competitive reaction, which occurs in more concentrated solutions (illuminati and coworkers, private communication). Nevertheless we have not found any evidences of such a process in our experimental conditions.

Chlorination of Disulfoxides

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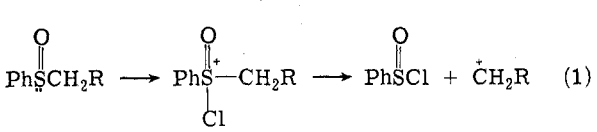
Chlorination of (±)- and *meso*-bis(phenylsulfinyl)methane (**1a** and **1b**) with sulfuryl chloride under a variety of conditions gives α-chloro sulfoxides **2a** and **2b** + **2c**, respectively, in high yield with no change in stereochemistry at the sulfur centers. With excess sulfuryl chloride, **1a** is dichlorinated to (±)-bis(phenylsulfinyl)dichloromethane (**3a**), which can be reduced, in succession, to α-chloro sulfoxide **2a** and then to **1a** with either chromous ion or tri-*n*-butylphosphine. The role of base (pyridine or sodium bicarbonate) in the chlorination of sulfoxides **1a**, **1b**, and **2a** and phenylsulfinylphenylsulfonylmethane (**4**) is fundamentally different from the role played by pyridine in the halogenation of bis(phenylsulfonyl)methane.

Recently, α-halo sulfoxides have generated a good deal of interest from both synthesis and mechanism viewpoints.[1] Earlier, we[2] reported on the syntheses and reductions of α,α-dichloro sulfoxides. We[2] as well as others[3] have commented on the problems associated with chlorination of sulfoxides where the intermediate chlorosulfoxium ion is likely to cleave and yield a relatively stable carbenium ion (eq 1). In view of this, a study has been made on the α-chlo-



(1)

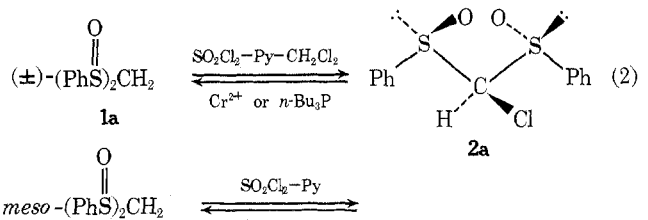
rination of sulfoxides bearing the electron-withdrawing (and carbenium ion destabilizing) sulfinyl and sulfonyl groups. Not only should cleavage (eq 1) be precluded in such systems, but with two sulfinyl groups present, the stereochemistry of the reaction at the chiral sulfur could be ascertained, since potentially one diastereomer series could be epimerized over to the other diastereomer series during the chlorination (vide infra).

Results and Discussion

Bis(phenylsulfinyl)methane was synthesized by oxidation of bis(phenylthio)methane with 2 equiv of *m*-chloroperoxybenzoic acid (MCPBA). The two diastereomers were separated by fractional crystallization and characterized by their known melting points and ^{1}H NMR spectra.[4]

Several halogenating agents were studied, but *N*-chlorosuccinimide (NCS), *N*-bromosuccinimide (NBS), and molecular bromine all proved unreactive toward **1**.[5] Chlorination with iodobenzene dichloride[6] produced α-chloro derivatives only in low yields, whereas chlorination with sulfuryl chloride took place readily and in good yields. Therefore, only the reactions of this chlorinating agent were examined in detail.

The reaction of **1a** with sulfuryl chloride in dichloromethane in the presence of either pyridine or powdered sodium bicarbonate yielded the single monochloride **2a**. Reduction of **2a** with either chromous ion[2] or tri-*n*-butylphosphine[2] gave only **1a** (eq 2). Chlorination of *meso*-**1b** gave a



(2)

(3)

50:50 mixture of **2b** and **2c**. Reduction of this mixture or reduction of the separated diastereomers with chromous ion or tri-*n*-butylphosphine gave only **1b** (eq 3). If excess