The Kinetics and Mechanism of the Electrophilic Substitution of Heteroaromatic Compounds. Part XLII.[1] The Nitration of Thiazoles and Thiazolones

By **Alan R. Katritzky** * and **Cemil Ögretir**, School of Chemical Sciences, University of East Anglia, Norwich, NR4 7TJ
H. Okan Tarhan,* Chemistry Department, Middle East Technical University, Ankara, Turkey
Henri M. Dou and **Jacques V. Metzger**, Laboratoire de Chimie Organique A, associé au C.N.R.S., Faculté des Sciences, Rue Henri Poincaré, 13013–Marseille, France

Kinetic investigations show that whereas 2,4- and 2,5-dialkylthiazoles undergo nitration as their protonated forms at all acidities studied, 2-thiazolones are nitrated *via* a free base mechanism at least at the lower acidities. The reactivities are discussed in terms of standard rates extrapolated to 25° and H_0 −6.6.

CONSIDERABLE knowledge of the quantitative aspects of thiazole chemistry is already available from one of our laboratories [2,3] including correlations of reactivity by quantum methods.[4] Hydrogen exchange under basic conditions involves nucleophilic attack on the 2-hydrogen atom.[3,5] Preparative studies show [6-8] that whereas thiazole itself is nitrated only under forcing conditions to give a poor yield of 5-nitro-together with some 4-nitrothiazole,[9] the more reactive 2-methylthiazole is nitrated more easily (although in only 12% yield) in sulphuric acid [7] to the 5-nitro- and 4-nitro-products (3.3 : 1). Predominant reaction at the 5-position reflects the *meta*-directing of the ' aza'-nitrogen and the α-directing effect of the sulphur. Other mono- and di-alkylthiazoles are nitrated at the 5- (preferably) or at the 4-position and competitive nitration studies [7,10] yielded rates relative to benzene for substitution in various compounds (see later discussion). Nitrothiazoles have also received attention as potential drugs.[11] Noyce and Fike [12] have studied the transmission of substituent effects in thiazoles.

We now present the first kinetic studies of electrophilic substitution in thiazoles: the nitration of alkylthiazoles

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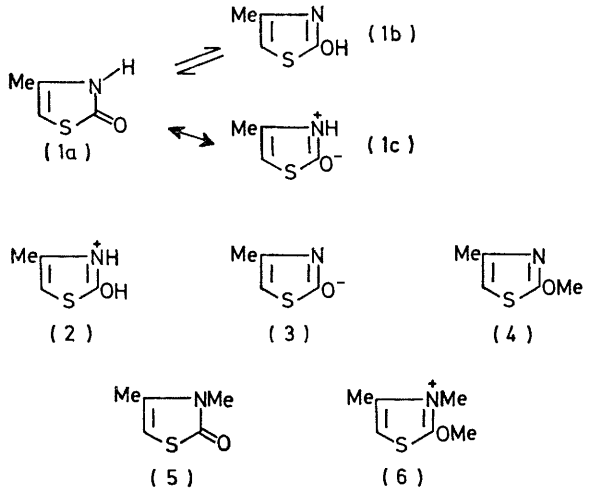
and thiazolones.* The detailed reaction mechanism, and in particular, whether the free bases or the protonated forms of thiazoles underwent nitration, was previously unknown. However, phenylthiazoles undergo nitration and sulphonation in the benzene ring [13] which points to conjugate acid reaction. Marino [14] calculated from σ constants for heteroatoms that the reactivities of azoles as free bases are greater than that of benzene. As the azolyl ring as a substituent decreases the reactivity of the phenyl group (*cf.* work on benzylthiazoles [15]), it follows that nitration in the phenyl group occurs on the conjugate acid.

2,4- and 2,5-Dimethyl-, 5-ethyl-2-t-butyl-, and 5-isopropyl-2-t-butyl-thiazole were preparatively nitrated in mixed acid by the procedure of ref. 10. Similar conditions caused nitration of 2,3,4-trimethylthiazolium trifluoromethanesulphonate. All these compounds underwent smooth nitration under kinetic conditions. We have also studied representative thiazol-2-ones. Although u.v. and i.r. studies [16] indicate that thiazol-2-ones exist predominantly in the oxo-form (1a), reactions could proceed *via* the hydroxy-form (1b) or the corresponding cation (2) or anion (3). We have now differentiated between these possibilities using the kinetic rate profiles, and the model compounds (4) and (5).



In thiazolone derivatives, the oxygen function in the 2-position activates the ring towards electrophilic substitution. Thiazole-2-one is nitrated by mixed acid [16] at −18°, exclusively at the 5-position; and 4-methylthiazol-2-one behaves similarly. If the 5-position is blocked, reaction occurs at the 4-position.[6] In our hands, 4-methylthiazol-2-one, 2-methoxy-4-methylthiazole, and 3,4-dimethylthiazol-2-one underwent smooth nitration at near room temperatures. Attempts to nitrate the quaternary 2-methoxy-3,4-dimethylthiazolium cation (6) gave only the hydrolysis product 3,4-dimethyl-5-nitro-2-thiazolone.

EXPERIMENTAL

Materials.—AnalaR grade nitric and sulphuric acids were used and their strengths determined as before.[17] The following thiazoles were prepared according to literature methods: 2,4-dimethylthiazole,[18] triply distilled under nitrogen, b.p. 144° at 689 mmHg[18] (lit., 70—73° at 50 mmHg); 2,4-dimethyl-5-nitrothiazole,[8] b.p. 87° at 0.8 mmHg (lit.,[8] 120° at 18 mmHg); 2,5-dimethylthiazole,[18] b.p. 143° at 689 mmHg (lit.,[19] 148.9—150.9° at 734 mmHg); 2,5-dimethyl-4-nitrothiazole,[8] m.p. 57—58° (lit.,[8] 56.5°); 4-methylthiazol-2-one, m.p. 103° (sublimed) (lit.,[20] m.p. 102—103°); 4-methyl-5-nitrothiazol-2-one, m.p. 155—157° (lit.,[21] m.p. 158°); 2-chloro-4-methylthiazole, b.p. 69° at 14 mmHg (lit.,[20] b.p. 69° at 14 mmHg); 5-ethyl-2-t-butylthiazole,[22] b.p. 202—203° at 760 mmHg (lit.,[22] 200—201° at 755 mmHg); 5-ethyl-4-nitro-2-t-butylthiazole (ref. 23, *cf.* ref. 8), m.p. 43—44°; 5-isopropyl-2-t-butylthiazole,[22] b.p. 154° at 100 mmHg (lit.,[22] 98—99° at 15 mmHg); 5-isopropyl-4-nitro-2-t-butylthiazole (ref. 23, *cf.* ref. 8), m.p. 48°.

2,3,4-*Trimethyl-5-nitrothiazolium Trifluoromethanesulphonate.*—Methyl trifluoromethanesulphonate (1 ml) was added slowly with cooling to 2,4-dimethyl-5-nitrothiazole (1 g) and dry benzene (5 ml), and the whole stirred at 20 ° for 12 h. The *sulphonate* was filtered off and washed with ether; it crystallised from ethanol as yellow needles (1.5 g, 75%), m.p. 109—110° (Found: C, 25.9; H, 3.2; N, 8.7. $C_7H_9F_3N_2O_5S_2$ requires C, 26.1; H, 2.8; N, 8.7%), τ (D_2O) 5.96 (3 H), 6.94 (3 H), and 7.40 (3 H).

2,3,4-*Trimethylthiazolium Perchlorate.*—2,4-Dimethylthiazole (3 g), ethanol (25 ml), and methyl iodide (10 ml) were heated under reflux during 3 h. The precipitated *methiodide* crystallised from ethanol as needles (5.5 g, 82%), m.p. 274—276° (Found: C, 28.6; H, 4.4; N, 5.8. $C_6H_{10}INS$ requires C, 28.4; H, 3.9; N, 5.5%).

The methiodide (2 g) in deionised water (20 ml) was passed through an ion-exchange column [Amberlite IRA—400 (Cl)] previously converted into the perchlorate form. The eluate was evaporated; the resultant *perchlorate* crystallised from ethanol as needles (1.8 g, 90%), m.p. 215—218° (Found: C, 31.7; H, 4.3; N, 6.4. $C_6H_{10}ClNO_4S$ requires C, 31.6; H, 4.4; N, 6.1%).

2-*Methoxy-4-methylthiazole.*—Potassium iodide (0.01 g) cupric oxide (3.73 g), 2-chloro-4-methylthiazole (10 g), and methanolic sodium methoxide [from sodium (6 g) and anhydrous methanol (75 ml)] were stirred and heated under reflux during 2 h. The cold solution was filtered, diluted with water (80 ml), and extracted with ether (3 × 40 ml).

* Preliminary nitration kinetic data for 2,4- and 2,5-dimethylthiazole (S. Ilkay and H. O. Tarhan, *Chimica Acta Turcica*, 1973, **1**, 123) are compatible with those in the present work.

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The dry ($MgSO_4$) extracts distilled to give the *methoxy-compound* (4.76 g, 50%) as an oil, b.p. 73—74° at 14 mmHg (Found: C, 44.9; H, 5.6; N, 10.5. C_5H_8NOS requires C, 46.5; H, 5.4; N, 10.9%), τ (neat liquid) 4.10 (1 H), 6.36 (3 H), and 8.12 (3 H).

2-Methoxy-4-methyl-5-nitrothiazole.—Nitric acid (*d* 1.42; 70%; 1 ml) was added dropwise at 0° to 2-methoxy-4-methylthiazole (0.5 ml) and sulphuric acid (96%, 5 ml). The mixture was stirred during 30 min at 22°, and then poured onto crushed ice. The *nitro-compound* crystallised from ethanol as needles (0.6 g, 89%), m.p. 73—74° (Found: C, 33.9; H, 3.8; N, 16.0. $C_5H_6N_2O_3S$ requires C, 34.5; H, 3.5; N, 16.1%), τ (D_2SO_4) 5.3 (3 H) and 6.90 (3 H).

3,4-Dimethylthiazol-2-one.—4-Methylthiazol-2-one (6 g), methanolic sodium methoxide [from sodium (1.15 g) and methanol (15 ml)], and methyl iodide (10.65 g) were stirred at 40° for 12 h. Solvent was evaporated off; *3,4-dimethylthiazol-2-one* sublimed at 75° and 3 mmHg to give needles (2 g, 34%), m.p. 46—47° (Found: C, 46.2; H, 5.5; N, 11.0. C_5H_7NOS requires C, 46.5; H, 5.4; N, 10.9%), τ ($CDCl_3$) 4.2 (1 H), 6.74 (3 H), and 7.85 (3 H).

3,4-Dimethyl-5-nitrothiazol-2-one.—Nitric acid (*d* 1.42; 0.1 g) and acetic anhydride (2 ml) were added to 3,4-dimethylthiazol-2-one (1 g) in acetic anhydride (25 ml) at −10°. The stirred mixture was heated at 60° for 4 h, cooled, and extracted with chloroform (3 × 25 ml). Addition of ether gave a *precipitate* which crystallised from $CHCl_3$–ether as yellow needles (1.0 g, 76%), m.p. 90—92° (Found: C, 34.8; H, 3.5; N, 13.9. $C_5H_6N_2O_3S$ requires C, 35.3; H, 3.5; N, 13.9%), τ ($CDCl_3$ 6.56 (3 H) and 7.2 (3 H).

2-Methoxy-3,4-dimethylthiazolium Trifluoromethanesulphonate.—Methyl trifluoromethanesulphonate (1 g) was added dropwise at 0° to 2-methoxy-4-methylthiazole (1 g) in dry benzene (5 ml). After 12 h the crude *product* was filtered off and recrystallised from ethanol as needles (1.3 g, 77%), m.p. 55—57° (Found: C, 28.1; H, 3.6; N, 5.1. $C_7H_9F_3NO_4S_2$ requires C, 28.7; H, 3.4; N, 4.8%), τ (D_2O) 2.92 (1 H), 5.58 (3 H), 6.30 (3 H), and 7.60 (3 H).

Kinetic Methods.—The nitration was followed at wavelengths where reactants have minimum and products have maximum absorptions (Table 1). The dilution technique [17] was applied for the nitration of alkylthiazoles and the nitration of the thiazolones and the methoxythiazoles was followed in the u.v. cell. Pseudo-first-order conditions were used for the nitration of alkylthiazoles and 2-methoxy-4-methylthiazole, but second-order conditions for the nitration of 4-methyl- and 3,4-dimethyl-thiazol-2-one. To eliminate any error arising from protonation of the nitro-compound, infinity readings were obtained for solutions of each kinetic run kept for 48 h at 25°; the infinity optical densities observed and those calculated from the known extinction coefficient of the pure nitro-derivative agreed within 5% in each case.

TABLE 1

U.v. and pK_a data for substituted thiazoles and thiazolones

	Spectral maximum (nm)			Basicity measurements			
Compound	Neutral species	Cation	λ/nm [a]	λ/nm [b]	$H_0^{1/2}$	*m*	pK_a
2,4-Dimethylthiazole	246 (3.39)	253 (3.41)	300	260	3.90	0.96	3.76
2,5-Dimethylthiazole	245 (3.71)	253 (3.74)	302				3.91 [f]
2,4-Dimethyl-5-nitrothiazole	312 (3.94)	282 (3.62)		310	0.10	1.08	−0.09
2,5-Dimethyl-4-nitrothiazole	302 (3.79)	271 (3.81)		320	−2.24	1.09	−2.44
2,3,4-Trimethylthiazolium perchlorate		252 (3.64)	285				
2,3,4-Trimethyl-5-nitrothiazolium toluene-*p*-sulphonate		300 (3.34)					
2,3,5-Trimethylthiazolium perchlorate		252 (3.84)	275				
2,2,5-Trimethyl-4-nitrothiazolium trifluromethanesulphonate		275 (3.69)					
5-Ethyl-2-t-butylthiazole	246 (3.77)	256 (3.82)	305	260	3.70	0.94	3.48
5-Isopropyl-2-t-butylthiazole	246 (3.41)	257 (3.51)	305	265	3.98	0.94	3.74
5-Ethyl-4-nitro-2-t-butylthiazole	305 (3.28)	275 (3.54)		320	−2.63	0.94	−2.45
5-Isopropyl-4-nitro-2-t-butylthiazole	275 (3.52)	305 (3.61)		315	−2.60	0.99	−2.60
4-Methylthiazol-2-one	245 (3.67)	248 (3.61)		*e*		0.50 [e]	−1.80 [e]
4-Methyl-5-nitrothiazol-2-one	350 (3.78)	300 (3.69)	300 [c] 350 [d]	310	−7.29	0.48	−3.50
2-Methoxy-4-methylthiazole	242 (3.53)	252 (3.65)		260	1.98	1.12	2.22
2-Methoxy-4-methyl-5-nitrothiazole	335 (3.56)	300 (3.70)	300	325	−1.97	1.09	−2.15
3,4-Dimethylthiazol-2-one	244 (3.00)	248 (3.62)		220	−3.21	0.53	−1.70
3,4-Dimethyl-5-nitrothiazol-2-one	357 (3.79)	305 (3.61)	300 [c] 350 [d]	310	−8.30	0.41	−3.43

[a] λ for nitration. [b] λ For pK_a. [c] λ For high acidity range. [d] λ For low acidity range. [e] Assumed value. [f] P. Goursot and I. Wadsö, *Acta Chem. Scand.*, 1966, **20**, 1314.

Rate constants are defined by equations (1)—(3) and are expressed throughout in 1 mol^{-1} s^{-1}. In these equations k_2(obs) is the observed second-order rate constant, k_2(fb) is the second-order rate constant corrected for the concentration of free base, and k_2* is the second-order rate constant corrected for the concentration of NO_2^+ ion.

The H_0 value of half protonation, $H_0^{1/2}$, was measured using the spectrophotometric method, as previously described.[24] Data for pK_a measurements are shown in Table 1.

$$-\mathrm{d[Subst.]}/\mathrm{d}t = k_2(\mathrm{obs})[\mathrm{Subst.}][\mathrm{HNO_3}] \quad (1)$$

$$\log k_2(\mathrm{fb}) = \log k_2(\mathrm{obs}) + m(H_0^{1/2} - H_0) \quad (2)$$

$$\log k_2^* = \log k_2(\mathrm{obs}) - \log \frac{[\mathrm{NO_2^+}]}{[\mathrm{HNO_3}]} \quad (3)$$

RESULTS AND DISCUSSION

Basicity Behaviour.—The data of Table 1 suggest that the alkyl- and the 2-methoxy-thiazoles, which all undergo protonation at nitrogen, are Hammett bases

[24] C. D. Johnson, A. R. Katritzky, B. J. Ridgewell, N. Shakir, and A. M. White, *Tetrahedron*, 1965, **21**, 1055.

TABLE 2

Nitration of alkyl thiazoles in the high and low acidity region

% H_2SO_4	$-H_0$ [a]	$-(H_R + \log a_{H_2O})$	$-\log k_2$(obs)
2,4-Dimethylthiazole (70°)			
97.30	9.12		1.38
95.80	8.82		1.25
94.30	8.46		1.15
91.00	8.06		1.06
88.00	7.60		1.52
85.60	7.34		2.02
85.20	7.29		2.13
84.24	7.15		2.42
84.10	7.12	15.07	2.42
82.30	6.87	14.17	2.98
80.20	6.55	13.31	3.75
79.10	6.42	12.99	4.31
75.60	5.91	11.88	4.70
73.50	5.61	11.42	5.38
69.70	5.30	10.54	6.03
2,5-Dimethylthiazole (80°)			
97.58	9.18		
94.25	8.53		1.64
93.03	8.32		1.55
89.20	7.74		1.54
86.75	7.41		1.91
84.81	7.16		2.50
83.05	6.89		2.98
2,5-Dimethylthiazole (100°)			
82.02	6.29	12.25	2.46
80.75	6.13	11.85	2.88
78.89	5.89	11.24	3.51
77.32	5.68	10.78	4.04
74.82	5.36	10.20	4.62
2,3,4-Trimethylthiazolium perchlorate (63°)			
97.88	9.43		1.59
96.52	8.98		1.54
95.03	8.87		1.63
90.40	8.12		1.42
88.23	7.82		1.63
88.00	7.79		1.74
85.20	7.43		2.75
84.24	7.27		3.23
2,3,4-Trimethylthiazolium perchlorate (80°)			
86.59	7.28	15.38	1.75
85.20	7.10	14.95	2.27
83.80	6.90	14.38	2.73
80.65	6.46	12.89	3.88
76.70	5.88	11.10	5.40
5-Ethyl-2-t-butylthiazole (60°)			
97.86	9.48		2.01
95.80	9.08		1.85
94.85	8.92		1.85
93.00	8.63		1.75
90.90	8.18		1.53
89.50	8.10		1.47
87.30	7.82		1.96
85.50	7.56		2.14
5-Ethyl-2-t-butylthiazole (108°)			
82.00	6.19	11.93	2.03
81.00	6.06	11.53	2.38
79.96	5.94	11.23	2.82
78.12	5.71	10.65	3.17
74.40	5.22	9.81	3.94
5-Isopropyl-2-t-butylthiazole (75°)			
97.86	9.15		2.23
94.55	8.50		1.95
92.90	8.23		1.83
91.70	8.05		1.70
89.25	7.71		1.75
88.23	7.57		1.99
86.92	7.42		2.35
5-Isopropyl-2-t-butylthiazole (132°)			
82.00	5.88	10.83	1.98
81.00	5.75	10.44	2.30
79.96	5.64	10.16	2.58
79.50	5.57	10.10	2.68
76.60	5.22	9.28	3.28
2,3,5-Trimethylthiazolium perchlorate (80°)			
97.60	9.20		−1.94
96.03	8.84		−1.94
93.00	8.32		−1.80
90.00	8.02		−1.80
88.98	7.70		−1.72
87.52	7.50		−2.01
86.69	7.40		−2.16
85.80	7.30	15.13	−2.27
84.03	7.04	14.53	−2.68
79.96	6.20	12.07	− 4.48
77.86	6.14	11.98	−4.77
76.26	5.91	11.52	−5.07

[a] Corrected for temperature.

with m values near unity. However the two thiazolones, which are protonated on oxygen, possess low m values (0.41—0.53), behaviour analogous to that of the pyridones.[25]

The pK_a of 4-methylthiazol-2-one could not be measured. The absorption spectra of the protonated and the neutral form were similar; the n.m.r. technique also failed, since H_2SO_4 obliterated the spectrum and the base underwent H–D exchange in D_2SO_4.

Alkylthiazole Nitrations.—The kinetic data are given in Table 2. The rate profile slopes d[log k_2(obs)]/d $[-H_0]$ in the 92—98% H_2SO_4 region (Table 2 and Figure 1) are 0.13—0.49, within the usual range 0.1—0.5 for nitration as majority species.[26]

At lower acidities, the Moodie–Schofield criterion [27] of d[log k_2 (obs)]/d$[-(H_R + \log a_{H_2O})]$ gives slopes 0.78—0.87 sufficiently close to unity (Table 2, Figure 2), to indicate nitration as majority species at lower acidities. Further evidence to support this conclusion is high (1.93—2.58) d[log k_2]/d$[-H_0]$ values (Table 3). We recently showed [28] that conjugate acid reactions have d[log k_2]/d$[-H_0]$ values near or greater than 2.

Thiazolone Nitration.—The kinetic data (Table 4) provide the high and low acidity rate profiles of Figures 1 and 2. The slopes (Table 5) of the low acidity rate profiles suggest reaction as free bases for 4-methyl- and 3,4-dimethylthiazol-2-one (*ca.* 0.5) but a conjugate acid mechanism for 2-methoxy-4-methylthiazole (1.01). The d[log k_2]/d$[-H_0]$ value (Table 3) for 2-methoxy-4-methylthiazole (2.31) and those for 4-methyl- (1.30) and 3,4-dimethyl-thiazol-2-one (1.03) show conjugate acid and free base reactions respectively.

The high acidity rate profiles show clearly the conjugate

[25] A. Gordon, A. R. Katritzky, and S. K. Roy, *J. Chem. Soc.*, 1968, 556.

[26] (*a*) A. G. Burton, P. J. Halls, and A. R. Katritzky, *J.C.S. Perkin II*, 1972, 1953; (*b*) E. V. Scriven, Ph.D. Thesis, University of East Anglia, 1969.

[27] R. B. Moodie, K. Schofield, and M. J. Williamson, *Tetrahedron*, 1964, **20**, Suppl. 1, 89.

[28] A. R. Katritzky, B. Terem, E. V. Scriven, S. Clementi, and H. O. Tarhan, *J.C.S. Perkin II*, 1975, 1600.

acid mechanism for 2-methoxy-4-methylthiazole, as expected. However, for the two thiazolones studied, the slopes of *ca.* 0.5 (Table 5) are ambiguous, lying in the range intermediate between conjugate acid and free base.[26a] This may indicate a change of mechanism from free base to conjugate acid within this region.

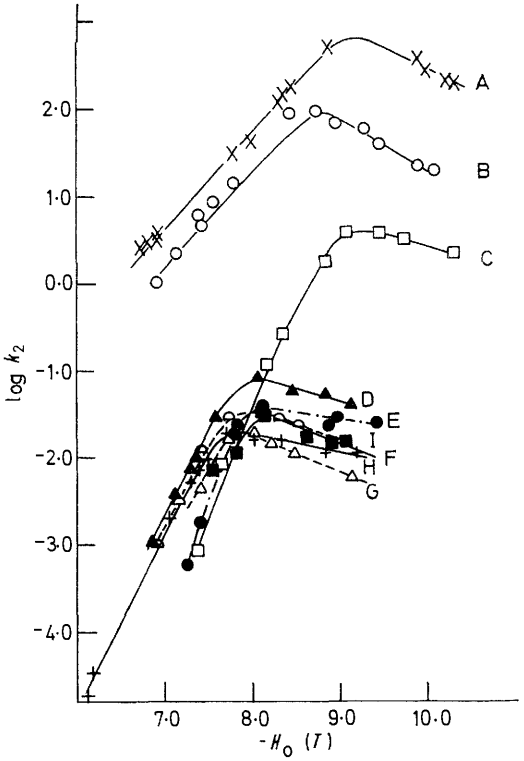


FIGURE 1 The high acidity rate profiles for the nitration of A, 3,4-dimethylthiazol-2-one (×, 25°); B, 4-methylthiazol-2-one (○, 25°); C, 2-methoxy-4-methylthiazole (□, 25°); D, 2,4-dimethylthiazole (▲, 70°); E, 2,3,4-trimethylthiazolium perchlorate (●, 70°); F, 5-ethyl-2-t-butylthiazole (■, 60°); G, 5-isopropyl-2-t-butylthiazole (△, 75°); H, 2,3,5-trimethylthiazolium perchlorate (+, 80°); I, 2,5-dimethylthiazole (⊡, 80°)

ternary cation occurs as a competing reaction before and after nitration.

The Reactivity of Thiazoles and 2-Thiazolones.—Standard log k_2 values (Table 3) were calculated at H_0 −6.60 from the least square plots of log k_2(obs) against H_0 (T), extrapolated to 25° using $\Delta\bar{H}^{\ddagger}$ 35 kcal mol^{-1} (see ref. 28), and corrected for minority species where necessary.

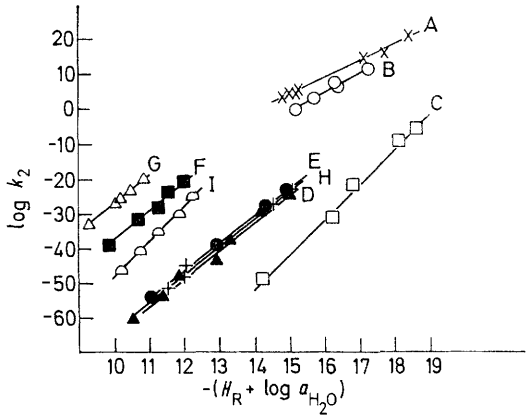


FIGURE 2 The low acidity rate profiles for the nitration of A, 3,4-dimethylthiazol-2-one (×, 25°); B, 4-methylthiazol-2-one (○, 25°); C, 2-methoxy-4-methylthiazole (□, 25°); D, 2,4-dimethylthiazole (▲, 70°); E, 2,3,4-trimethylthiazolium perchlorate (●, 80°); F, 5-ethyl-2-t-butylthiazole (■, 108°); G, 5-isopropyl-2-t-butylthiazole (△, 132°); H, 2,3,5-trimethylthiazolium perchlorate (+, 80°); I, 2,5-dimethylthiazole (, 100°)

All the alkylthiazoles investigated, and the corresponding quaternary salts, show log k_0 values in the range −6.9 to −7.5 for reaction both at the 4- and the 5-position; thus these cations are considerably less reactive than benzene. A 2-methoxy-group has a significant rate-enhancing effect on nitration at the 5-position (*ca.* 3 log units), and the negatively charged 2-oxido-substituent [*cf.* (1c)] in the 2-thiazolones increases the rate by another 6 log units. These substituent effects, and those of the ring heteroatoms are discussed in the accompanying paper.[29]

TABLE 3

Standard rate constants for thiazoles and 2-thiazolones

Compound	Range %	T/°C	Range (H_0)	$\frac{d[\log k_2]}{d[-H_0]}$	log k_2 (at H_0 6.6)	log k_2 (25°)	Species	pK_a	m	log k_2°
2,4-Dimethylthiazole	70—88	70	5.3—7.6	−1.96	−3.53	−6.90	+			−6.90
2,5-Dimethylthiazole	83—87	80	6.9—7.4	−2.05	−3.60	−7.60				−7.60
2,3,4-Trimethylthiazolium	81—87	80	6.5—7.3	−2.58	−3.52	−7.52	+			−7.52
2,3,5-Trimethylthiazolium	76—88	80	5.3—7.5	−2.00	−3.72	−7.72	+			−7.72
5-Ethyl-2-t-butylthiazole	74—82	108	5.2—6.3	−1.94	−1.37	−6.96	+			−6.96
5-Isopropyl-2-t-butylthiazole	77—82	132	5.2—5.9	−1.93	−0.65	−7.43	+			−7.43
4-Methylthiazol-2-one	77—82	25	6.9—7.8	−1.3	−0.38	−0.38	0	−1.8[a]	0.5[a]	+1.12
3,4-Dimethylthiazol-2-one	76—86	25	6.7—8.3	−1.05	+0.22	+0.22	0	−1.70	0.53	+1.82
2-Methoxy-4-methylthiazole	74—86	25	6.4—8.4	−2.31	−4.62	−4.62	+			−4.62

[a] Assumed value.

Attempts to nitrate the model compound 2-methoxy-3,4-dimethylthiazolium cation failed. The complex u.v. and n.m.r. data indicate that hydrolysis of the qua-

Comparisons of nitration rates for the polymethyl derivatives show that the thiazole 5-position is more reactive than the 4-position by a factor of *ca.* 2. This agrees well with competitive experiments in one of our laboratories,[7] revealing the relative reactivities of 2,4-

[29] A. R. Katritzky, S. Clementi, and H. O. Tarhan, *J.C.S. Perkin II*, 1975, 1624.

TABLE 4

Nitration of substituted thiazolones in the high and low acidity region

% H_2SO_4	$-H_0$ (25°)	$-(H_R + \log a_{H_2O})$	$-\log k_2$(obs)	$\log k_2$(fb) [a]	$\log k_2$*(obs)
4-Methylthiazol-2-one (25°)					
96.63	10.10		−1.26	5.01	1.26
95.36	9.90		−1.33	4.98	1.33
92.69	9.44		−1.56	4.96	1.56
91.70	9.28		−1.75	5.07	1.77
89.71	8.96		−1.81	4.96	1.91
88.15	8.72		−1.95	4.97	2.25
86.34	8.42		−1.92	4.78	2.82
82.45	7.80	17.30	−1.13	3.66	3.53
80.80	7.56	16.65	−0.90	3.31	3.90
80.20	7.43	16.40	−0.64	2.98	4.01
79.92	7.40	16.30	−0.76	3.08	4.02
78.30	7.15	15.70	−0.32	2.51	4.20
76.80	6.90	15.20	+0.02	2.04	4.42
2-Methoxy-4-methylthiazole (25°)					
97.86	10.32		−0.34		0.34
94.40	9.74		−0.50		0.50
92.50	9.45		−0.57		0.57
90.45	9.10		−0.60		0.66
88.80	8.85		−0.26		0.44
85.84	8.36	18.65	+0.59		0.45
84.60	8.17	18.15	+0.92		0.32
81.44	7.64	16.85	+2.08		0.72
79.66	7.35	16.25	+3.07		0.39
74.00	6.45	14.25	+4.92		0.37
3,4-Dimethylthiazol-2-one (25°)					
97.50	10.30		−2.29	6.05	
97.40	10.26		−2.31	6.05	
96.52	10.08		−2.42	6.06	
95.03	9.84		−2.52	5.84	
88.98	8.85		−2.69	5.68	2.71
86.20	8.42		−2.23	4.99	3.13
85.80	8.37		−2.15	4.89	3.15
85.50	8.30	18.50	−2.06	4.76	3.22
83.50	7.98	17.75	−1.60	4.13	3.50
82.20	7.78	17.15	−1.46	3.88	3.86
77.00	6.93	15.75	−0.57	2.54	4.93
76.80	6.90	15.20	−0.47	2.43	4.71
76.25	6.80	15.00	−0.45	2.35	5.07
75.75	6.72	14.80	−0.39	2.25	5.17

[a] Taking pK_a −1.6 and slope 0.53.

TABLE 5

Rate profile slopes for nitration of thiazoles and thiazolones

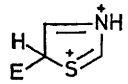
		Low acidity				High acidity		
Compound	Position of nitration	T/°C	Slope [a]	Corr. coeff.	Species reacting	T/°C	Slope [b]	Species reacting
2,4-Dimethylthiazole	5	70	0.80	0.992	C.A.	70	0.29	C.A.
2,5-Dimethylthiazole	4	100	1.06	0.999	C.A.	80	0.28	C.A.
2,3,4-Trimethylthiazolium perchlorate	5	80	0.83	0.996	C.A.	70	0.13	C.A.
2,3,5-Trimethylthiazolium perchlorate	4	80	0.77	0.998	C.A.	80	0.15	C.A.
5-Ethyl-2-t-butylthiazole	4	108	0.89	0.995	C.A.	60	0.33	C.A.
5-Isopropyl-2-t-butylthiazole	4	132	0.84	1.000	C.A.	75	0.43	C.A.
2-Methoxy-4-methylthiazole	5	25	1.00	0.997	C.A.	25	0.27	C.A.
4-Methylthiazol-2-one	5	25	0.54 [c]	0.993	F.B.	25	0.50	F.B.
3,4-Dimethylthiazol-2-one	5	25	0.45 [d]	0.997	F.B.	25	0.51	F.B.

[a] $d[\log k_2]/d[-(H_R + \log a_{H_2O})]$. [b] $d[\log k_2]/d[-H_0]$, $H_0 > 9.0$. [c] Corrected slope for the minority species is 0.75 (0.992). Corrected slope for the minority species is 0.70 (0.999).

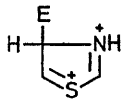
dimethyl- and 2,5-dimethyl-thiazole as 2 : 1. Calculations indicate that the 5-position possesses the highest electron density.[30]

The relative reactivities of the 5- and 4-positions in thiazoles are the opposite of those in 1-substituted imidazoles. The nitration of 1-methylimidazole with mixed acids gave 4-nitro- and 5-nitro-derivatives in the ratio 2.7 : 1.[31] The only pertinent data on oxazoles concern the base-catalysed deuteriation [32] which proceeds by a deprotonation mechanism. Brown and Ghosh [32] conclude that in oxazoles the order of positional reactivity towards electrophilic substitution is 4 > 5.

The intermediate (7), with terminal sulphonium and immonium atoms, evidently provides better resonance stabilisation than (8). Pyrrole likewise shows a greater preference for 2-substitution than does thiophen, in electrophilic substitution.[14]



(7)



(8)

We thank NATO and TBTAK for financial assistance, and also the Turkish Ministry of Education, for a Scholarship (to C. Ö.).

[5/361 *Received*, 20*th February*, 1975]

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