The Kinetics and Mechanism of the Electrophilic Substitution of Heteroaromatic Compounds. Part XLIII.[1] The Nitration of Isothiazoles

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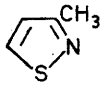
Whereas isothiazole and its 3- and 5-methyl derivatives are all nitrated solely as free bases, the 3,5-dimethyl analogue shows a mechanistic changeover to nitration as conjugate acid. The effects of methyl groups on the reactivity are discussed in comparison with hydrogen exchange.

FOLLOWING the first synthesis of the mononuclear isothiazole [2] in 1956, this ring system has attracted considerable interest. The reactivity of the 4-position towards electrophiles is indicated by electron density calculations.[3] The nitration of isothiazole in mixed acid gives the 4-nitro-product (>90%),[4] and various alkyl-, bromo-, and acetamido-[4,5] isothiazoles behave similarly. Isothiazoles are sulphonated by oleum,[6] and undergo both base and acid catalysed hydrogen exchange of the ring protons.[7,8] Our recent investigation clarifies the mechanism of the acid-catalysed exchange.[9] Previous kinetic studies of the nitration of 3,5-dimethylisothiazole are discussed below together with further data on the nitration of this and other methylisothiazoles made to facilitate comparisons with other systems.

Isothiazole (1), 3-methylisothiazole (2), and 5-methylisothiazole (3) underwent nitration at the 4-position as previously reported.[4] Kinetic nitrations of (1)—(3) were carried out at 120, 140, and 150°, respectively.

Isothiazole and its 3- and 5-methyl derivatives were converted into the corresponding 2-metho-quaternary salts by reaction with methyl tosylate: the salts were


(1)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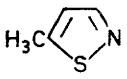
(3)

isolated and analysed as perchlorates. Each of the corresponding 4-nitroisothiazoles also reacted with methyl trifluoromethanesulphonate (or fluorosulphonate) to yield a quaternary salt, but those derived from isothiazole and 5-methylisothiazole rapidly decomposed and could not be purified. Attempts at preparative nitration on these quaternary salts failed: this was not surprising in view of the expected difficulty in isolation of the products. Attempted nitration under kinetic conditions of the quaternary salts derived from isothiazole and 5-methylisothiazole led to the gradual disappearance of the initial u.v. absorption, to give products transparent in the

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[3] R. Phan-Tan-Luu, L. Bouscasse, E. J. Vincent, and J. Metzger, *Bull. Soc. chim. France*, 1967, 3283.
[4] von. F. Hübenett, F. H. Flock, W. Hansel, H. Heinze, and Hd. Hofmann, *Angew. Chem.*, 1963, **75**, 1189.
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[7] J. A. White and R. C. Anderson, *J. Heterocyclic Chem.*, 1969, **6**, 199.
[8] A. G. Burton, P. P. Forsythe, C. D. Johnson, and A. R. Katritzky, *J. Chem. Soc.* (*B*), 1971, 2365.
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u.v. This could have been due to initial nitration followed by decomposition of the nitro-quaternary salts, known to be unstable. The results for the 3-methyl and 3,5-dimethyl quaternary salts indicate a more complex situation: both these compounds are nitrated under kinetic conditions with gradual disappearance of the initial u.v. spectrum and appearance of new absorption analogous to that expected for the nitro-product. However, although straight line pseudo-first-order rate plots for 2,3,5-trimethylisothiazolium ion were obtained (as before [8]), for the 2,3-dimethyl analogue, the reaction did not reach apparent completion and curved plots were obtained. The n.m.r. spectrum of 2,3,5-trimethylisothiazolium cation in H_2SO_4–H_2O was invariant with time; but at low acidity the addition of one equivalent of nitric acid to the trimethyl salt in H_2SO_4 rapidly changed both the *N*-methyl singlet and the *C*-methyl doublets into multiplets, indicating complex reactions. However, in 90% sulphuric acid, the n.m.r. of the 2,3,5-trimethyl-cation does not change appreciably with addition of nitric acid, except for decrease in the 4-position peak. The chemical shifts of the *C*- and *N*-methyl groups in 4-nitro and parent cations are very similar.

EXPERIMENTAL

Acids.—Nitric and sulphuric acids were AnalaR grade. For kinetic measurements, the percentages of acids were determined by titration with standard N-NaOH solution using Methyl Orange–Xylene Cyanol as internal indicator. Sulphuric acid used for basicity measurements was prepared by dilution of the acid by weight with deionised water and the final density determined using an ASE torsion-type balance.

Materials.—The following were prepared by the literature methods quoted: 4-nitroisothiazole, m.p. 86° (lit.,[4] 87°), 5-methylisothiazole, b.p. 44—47° at 18 mmHg (lit.,[10] 44—46° at 18 mmHg), m.p. 36—39° (lit.,[4] 36°), 3-methyl-4-nitroisothiazole, b.p. 108° at 14 mmHg (lit.,[5] 108° at 14 mmHg). Isothiazole and 3-methylisothiazole were kindly supplied by Dr. E. Lunt (May and Baker).

2-Methylisothiazolium Perchlorate.—Isothiazole (1.5 g) and methyl toluene-4-sulphonate (4.7 g) were heated for 12 h at 90°. On cooling, a solid separated and was recrystallized from ethanol to give the crude methotosylate (3.9 g), m.p. 136—140°. A Dowex 1-X8 ion exchange column was converted from the chloride to the perchlorate form (until the eluant gave no further precipitate with $AgNO_3$). Excess of sodium perchlorate solution was eliminated by washing the column with deionised water (500 ml). The methotosylate (3.9 g) in deionised water (25 ml) was passed. Evaporation of the eluate gave the *perchlorate* (2.3 g, 65%), from ethanol as needles, m.p. 197—198° (Found: C, 24.0; H, 3.2; N, 7.3. $C_4H_6ClNO_4S$ requires C, 24.0; H, 3.0; N, 7.0%); τ (D_2O) 0.60—0.80 (1H, d), 1.07—1.15 (1H, d), 2.30—2.47 (1H, q), and 5.75 (3H, s).

The following were prepared similarly: *2,3-dimethylisothiazolium perchlorate*, from ethanol as needles (83%), m.p. 193—194° (Found: C, 27.8; H, 3.7; N, 6.3. $C_5H_8ClNO_4S$ requires C, 28.1; H, 3.8; N, 6.6%); τ (D_2O) 0.75—0.85 (1H, d), 2.40—2.60 (1H, m), 5.90 (3H, s), and 7.30 (3H, s); *2,5-dimethylisothiazolium perchlorate*, (0.52 g, 48%), as needles, m.p. 170—172° (from ethanol) (Found: C, 27.8; H, 4.0; N, 6.3. $C_5H_8ClNO_4S$ requires C, 28.1; H, 3.8; N, 6.6%); τ (D_2O) 1.32 (1H, s), 2.50—2.60 (1H, d), 5.90 (3H, s), and 7.20 (3H, s); *2,3-dimethyl-4-nitroisothiazolium perchlorate* (methyl fluorosulphonate was used in the quaternisation) (62.8%), as needles, m.p. 145° (from ethanol) (Found: C, 23.1; H, 2.8; N, 10.7. $C_5H_7N_2ClO_6S$ requires C, 23.2; H, 2.7; N, 10.8%); τ (D_2O) −0.22 (1H, s), 5.85 (3H, s), 7.20 (3H, s).

Spectroscopy.—N.m.r. spectra were recorded at 60 MHz on a Perkin-Elmer R12 spectrometer and tetramethylammonium sulphate used as internal standard. The pK_a determinations (Table 1) and kinetics were followed by a

[10] M. P. L. Caton, D. H. Jones, R. Slack, and K. R. H. Wooldridge, *J. Chem. Soc.*, 1964, 446.

TABLE 1

Proton chemical shifts (τ) for isothiazolium cations [a]

	Isothiazole ring positions							
	2		3		4		5	
Substituents								
2-Methyl	CH_3	5.75	H	1.07—1.15	H	2.30—2.47	H	0.60—0.80
2,3-Dimethyl	CH_3	5.90	CH_3	7.30	H	2.40—2.60	H	0.75—0.85
2,5-Dimethyl	CH_3	5.90	H	1.32	H	2.50—2.60	CH_3	7.20
2,3-Dimethyl-4-nitro	CH_3	5.85	CH_3	7.20	NO_2		H	−0.22
2,3,5-Trimethyl	CH_3	5.85	CH_3	7.33	H	2.25	CH_3	7.26
2,3,5-Trimethyl-4-nitro	CH_3	5.95	CH_3	7.33	NO_2		CH_3	7.26

[a] Relative to internal standard tetramethylammonium sulphate in D_2O as solvent.

TABLE 2

U.v. data for isothiazoles

Compound	Neutral species λ/nm ($\log_{10}\varepsilon$)	Cationic species λ/nm ($\log_{10}\varepsilon$)	H_0 (1/2)	*m*	pK_a
Isothiazole	255 (3.136)	255 (3.803)	−0.52	0.94	−0.52
3-Methylisothiazole	260 (2.753)	260 (3.846)	0.48	1.00	0.48
5-Methylisothiazole	260 (2.968)	260 (3.728)	0.02	0.99	0.02
3,5-Dimethylisothiazole [a]	218.5 (3.62)	220 (3.64)	1.12	1.02	1.12
4-Nitroisothiazole	255 (3.738)	255 (3.887)	−4.10	1.01	−4.10
3-Methyl-4-nitroisothiazole	265 (3.716)	265 (3.919)	−3.04	1.19	−3.04
5-Methyl-4-nitroisothiazole	265 (3.710)	265 (3.895)	−3.47	1.01	−3.47

[a] See ref. 8.

Unicam SP 800 self-recording spectrometer and by an SP 500 manual instrument.

Kinetic Procedure.—Each of the neutral isothiazoles was stable at the acidities and temperatures at which the kinetics were carried out.

The reaction solutions were prepared by dissolving substrate (*ca.* 10—25 mg) in sulphuric acid (*ca.* 10 ml) of known strengths. Nitric acid was added and mixed. Aliquot portions (*ca.* 2 ml) were placed into Pyrex tubes (internal diameter 6 mm, wall thickness 1 mm) which were then sealed and placed in electrically controlled heating blocks. Tubes taken out at various intervals were cooled in ice and diluted to 25 ml with water. The optical densities were measured at those wavelengths which gave a large difference in the extinction coefficients of the substrate and product (Table 2). The difference between the calculated infinity optical densities and those of experimental was not more than 4% which indicates no side-product formation.

The nitrations were carried out under pseudo-first-order conditions for all compounds. The observed rate constants, corrected for the free base concentration and nitronium ion concentration were calculated from equations (1)—(3) respectively. Results are recorded in Table 3.

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

$$\log k_2(\text{fb}) = \log k_2(\text{obs}) + m(H_0^{\frac{1}{2}} - H_0)_T \quad (2)$$

$$\log k_2^* = \log k_2(\text{obs}) - \log\{[NO_2^+]/[HNO_3]_{\text{stoich}}\} \quad (3)$$

TABLE 3

Rate constants for the nitration of isothiazoles

Isothiazole at 120°

% H_2SO_4	$-H_0$ (120°)	$-[H_{R(120)} + \log a_m]$	$-\log k_2$ (obs)	$\log k_2$ (fb)
96.75	8.02		4.83	
95.36	7.75		4.25	
94.06	7.53		4.18	
92.32	7.26		3.98	
90.77	7.07		3.84	
88.78	6.84		3.73	
86.35	6.56		3.87	
82.13	6.05	11.37	4.21	1.32
79.56	5.70	10.54	4.69	0.49
77.59	5.49	9.98	5.16	−0.19
75.58	5.24	9.56	5.39	−0.67
73.44	4.97	9.12	5.70	−1.25

% H_2SO_4	$-H_0$ (140°)	$-\log k_2$ (obs)
97.80	7.94	3.31
96.00	7.55	3.07
95.00	7.39	2.96
94.00	7.21	2.79
93.00	7.06	2.78
92.00	6.91	2.62
91.00	6.80	2.70
89.00	6.55	2.73

3-Methylisothiazole at 140°

% H_2SO_4	$-H_0$ (140°)	$-[H_{R(140)} + \log a_{H_2O}]$	$-\log k_2$ (obs)	$\log k_2$ (fb)
87.00	6.35		2.88	
86.00	6.24		2.98	
84.67	6.08		3.16	
83.00	5.86		3.40	
82.00	5.77	10.45	3.59	2.66
80.00	5.54	9.77	3.84	2.18
79.00	5.43	9.51	4.11	1.80
78.00	5.29	9.24	4.21	1.56
77.00	5.18	9.04	4.38	1.28
76.00	5.05	8.84	4.34	1.19
75.00	4.94	8.72	4.50	0.92
74.00	4.82	8.49	4.73	0.57

5-Methylisothiazole at 150°

% H_2SO_4	$-H_0$ (150°)	$-\log k_2$ (obs)
96 05	7.41	2.67
94.65	7.13	2.38
91.57	6.70	2.10
90.00	6.52	2.21
87.88	6.30	2.32
86.92	6.20	2.34
85.65	6.07	2.40

% H_2SO_4	$-H_0$ (150°)	$-[H_{R(150)} + \log a_{H_2O}]$	$-\log k_2$ (obs)	$\log k_2$ (fb)
81.29	7.32	11.13	3.20	2.39
79.96	7.07	9.76	3.35	2.12
78.73	6.89	9.35	3.44	1.86
76.70	6.69	8.60	3.67	1.38

TABLE 3 (*Continued*)

3,5-Dimethylisothiazole at 130°

% H_2SO_4	$-H_0$ (130°)	$-\log k_2$ (obs)
97.80	8.16	2.09
95.99	7.71	2.10
93.95	7.37	1.92
93.01	7.25	2.01
92.00	7.07	1.83
90.00	6.81	1.85
88.00	6.60	2.11
87.01	6.45	2.23
84.00	6.13	2.83
81.98	5.89	3.24

% H_2SO_4	$-H_0$ (130°)	$-[H_{R(130)} + \log a_{H_2O}]$	$-\log k_2$ (obs)	$-\log k_2$ (fb)
80.01	5.66	10.20	3.81	2.97
78.00	5.41	9.63	4.12	2.41
76.00	5.16	9.23	4.44	1.84
74.00	4.92	8.87	4.82	1.22

2,3,5-Trimethylisothiazolium perchlorate at 130°

% H_2SO_4	$-H_0$ (130°)	$-\log k_2$ (obs)
97.80	8.16	2.14
95.99	7.71	1.99
93.95	7.37	1.82
93.01	7.25	1.96
92.00	7.07	1.75
90.00	6.81	1.80
88.00	6.60	1.93
87.01	6.45	2.30
84.00	6.13	2.64

RESULTS AND DISCUSSION

Mechanisms at Low Acidities.—The rate profile slopes cover a range of values: $\mathrm{d}\log k_2/\mathrm{d}[-(H_R + \log a_{H_2O})]$ varies from 0.40 to 0.80 (Table 4). Isothiazoles behave as Hammett bases (*cf.* m values in Table 2); applying the appropriate correction gives Moodie–Schofield slopes of 0.87—1.27. Whereas the values for 3,5-dimethylisothiazole are indecisive; overall reaction of the remaining compounds as free bases is indicated.

We consider that $\mathrm{d}\log(k_2)/\mathrm{d}[-H_0]$ values provide a better criterion for mechanism, especially at elevated temperatures. That is because the range of $\mathrm{d}(\log k_2)/\mathrm{d}[-(H_R + \log a_{H_2O})]$ is restricted to below 84% H_2SO_4, whereas the $\mathrm{d}(\log k_2)/\mathrm{d}[-H_0]$ values can be carried to considerably higher acidity (see Figure). Whereas for isothiazole and the 3- and 5-methyl derivatives, reaction is only occurring on the free-base species (expected slope

1.23 ± 0.24),[11] the slope for 3,5-dimethylisothiazole of 1.67 is not clear cut. We believe that a change-over in mechanism occurs for the nitration of this compound near H_0 −5.

Mechanism at High Acidity.—The slope of d log k_2/d[−H_0] (Table 4) indicates that 3,5-dimethylisothiazole undergoes nitration as the conjugate acid in the high acidity region, but that the parent and monomethyl analogues continue to be nitrated as the free base forms: a survey has shown [8] that majority and minority species show slopes in the ranges 0.2—0.6 and 0.8—1.5, respectively. Evidence was previously reported [8] for a change-over in mechanism of the hydrogen-exchange of 3,5-dimethylisothiazole from free base to conjugate acid on raising the acidity.

Standard Rates.—The log k_0 values of Table 5 show that isothiazoles are nitrated at the 4-position some four powers of ten less readily than benzene.[12] The effects of a 3- and of a 5-methyl group on the standard rates are 1.1 and 0.9 units respectively, *i.e.* identical to within experimental precision. The combined effect of 3,5-dimethylation cannot be ascertained experimentally with much accuracy because of the mechanistic change-over already mentioned; however, the extrapolation of the lower portion (−H_0 4.9—5.5) of the rate profile to −H_0 = 6.6, followed by temperature extrapolation to 25° and free base correction, gives log k_0 for free base reaction as 1.5. The combined activating effect of the two 3,5-dimethyl groups is hence 2.3 log units which is close to the sum of their individual effects. The deactivation due to the protonation of the isothiazole ring is *ca.* 8 log units, similar to the deactivation factor for the corresponding hydrogen exchange reactions.[8]

The reactivity order for nitration rates of five-membered heterocycles containing two adjacent hetero-atoms is pyrazole ≫ isothiazole ≫ isoxazole. This is in contrast to the order of reactivity of five-membered heterocycles containing one heteroatom which for trifluoroacetylation is pyrrole ≫ furan ≫ thiophen.[13] The

TABLE 4

The slopes of the rate profiles for the nitration of isothiazoles

Substituents	T/°C	Low acidity range [a] m_1 (corr) [b]	m_2 (corr) [c]	Species [d]	High acidity range m_3 [e]	Species
	120	0.67 (0.998)	1.14 (0.998)	FB	1.01	FB
3-Methyl	140	0.56 (0.982)	1.06 (0.990)	FB	0.76	FB
5-Methyl	150	0.40 (0.990)	0.87 (0.990)	FB	1.11	FB
3,5-Dimethyl	80	0.70 (0.995) [f]	1.21 (0.999) [f]	CA	0.39	CA
3,5-Dimethyl	130	0.77 (0.995)	1.27 (0.996)	FB–CA	0.45	CA

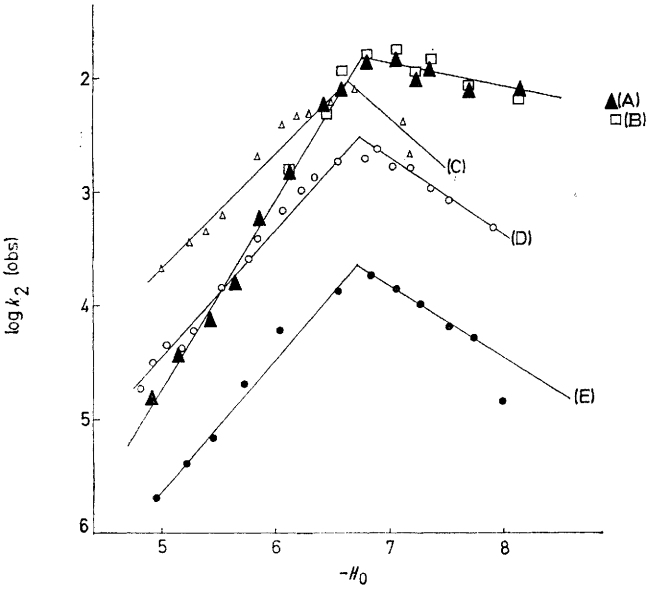
[a] The range covered is given in Table 2. [b] m_1 = d log k_2/d[−(H_R + log a_{H_2O})]. [c] m_2 = d log k_2(fb)/d[−(H_R + log a_{H_2O})]. [d] FB = Free base, CA = conjugate acid. [e] m_3 (−H_0 >6.5) = d log k_2/d[−H_0]. [f] Taken from ref. 8; temperature corrected.

TABLE 5

Standard rate constants for the nitration of isothiazoles

Substituents	T/°C	Range % H_2SO_4	Range H_0	d log k_2/d[−H_0]	Reactive species	−log k [a]	−log k_{25}	−log k (fb)	−log k^0
	120	73—82	4.9—6.1	1.22	FB	3.70	9.90	3.82	3.8
3-Methyl	140	74—89	4.8—6.6	1.20	FB	2.60	9.74	2.66	2.7
5-Methyl	150	76—90	5.0—6.6	1.08	FB	1.98	9.56	2.94	2.9
3,5-Dimethyl	130	80—88	5.5—6.6	1.67	CA	2.07	8.75		8.7
	130	74—80	4.9—5.5	1.35	FB	2.52	9.20	1.48	1.5
2,3,5-Trimethyl	130	84—88	6.1—6.6	1.44	CA	1.99	8.67		8.7

[a] log k_2 at 6.6 H_0.



Rate profiles for (A) 3,5-dimethylisothiazole at 130°, (B) 2,3,5-trimethylisothiazolium cation at 130°, (C) 5-methylisothiazole at 150°, (D) 3-methylisothiazole at 140°, (E) isothiazole at 120°

[11] A. R. Katritzky, B. Terem, E. V. Scriven, S. Clementi, and H. O. Tarhan, *J.C.S. Perkin II*, 1975, 1600.
[12] R. G. Coombes, R. B. Moodie, and K. Schofield, *J. Chem. Soc.* (*B*), 1968, 800.
[13] S. Clementi and G. Marino, *Tetrahedron*, 1969, **25**, 4599.

comparison for the two heteroatom compounds is derived from the 3,5-dimethyl compounds, since the nitration kinetics of 3(5)-methyl and unsubstituted isoxazoles have not been carried out. However, comparison of the present results with those for 1-methyl and 1,3(5)-dimethyl pyrazoles [14] is in agreement with the above order of reactivity.

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[14] *H. O. Tarhan*, personal communication.

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