The Kinetics and Mechanism of the Electrophilic Substitution of Heteroaromatic Compounds. Part XXIX.[1] The Nitration of the 1-Methyl Cations of 2-Methylamino-, 2-Methylamino-5-nitro-, and 4-Dimethylamino-pyridine

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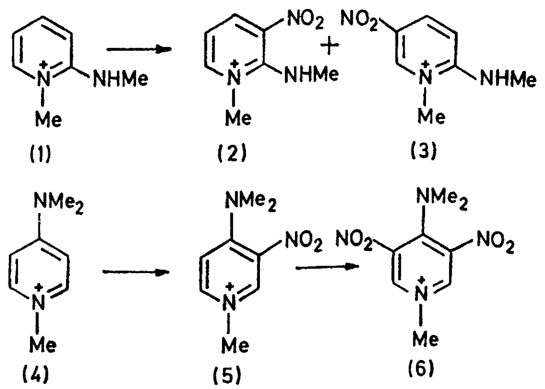
Rate constants for the nitration of the title compounds have been determined and compared with those for 2-dimethylamino-, 2-dimethylamino-5-nitro-, and 4-dimethylamino-pyridine. The mechanisms of nitration of these substituted pyridines is discussed with particular reference to the occurrence of the ' proton loss ' mechanism.

THE preceding paper describes the nitration of 2- and 4-dimethylaminopyridines. The present work was undertaken to provide kinetic models to help elucidate details of the reaction mechanisms. The 1-methyl-2-methylaminopyridinium cation (1) was nitrated in sulphuric acid, at concentrations in the range 10^{-4}M, to yield a mixture of the corresponding 3- (2) and 5-nitro-cations (3). The cation (1) was prepared as the perchlorate *via* the iodide, which was itself obtained by reaction of 2-iodo-1-methylpyridinium iodide with methylamine. The cations (2) and (3) were synthesised independently as trifluoromethanesulphonates by reaction of 2-methylamino-3-nitro- and 2-methylamino-5-nitro-pyridine with methyl trifluoromethanesulphonate (methyl triflate). Similar nitrations of 1-methyl-4-dimethylaminopyridinium cation (4) were attempted; the nitro-cations (5) and (6) were synthesised independently by quaternisation.



(1) (2) (3)

(4) (5) (6)

EXPERIMENTAL

1-*Methyl-2-methylaminopyridinium Perchlorate*.—2-Chloropyridine (25 g) and methyl iodide (40 g) were heated under reflux for 8 h in acetone (100 ml). The resulting 2-iodo-1-methylpyridinium iodide (70 g, 92%) crystallised from ethanol as pale yellow needles, m.p. 207—207·5° (lit.,[2] 207°). The iodide (10 g), ethanol (20 ml), and ethanolic methylamine (33% w/v; 30 ml) were heated under reflux for 1 h. Evaporation of volatile material and repeated recrystallisation from ethanol–ethyl acetate gave 1-methyl-2-methylaminopyridinium iodide (6·5 g, 94%) as prisms, m.p. 159—160° (lit.,[3] 160°). Anion exchange[4] gave the *perchlorate* as needles, m.p. 121—122°, from ethanol (Found: C, 37·6; H, 4·9; N, 12·7. $C_7H_{11}ClN_2O_4$ requires C, 37·8; H, 4·9; N, 12·6%); τ (D_2O) 6·97 (s, 3H), 6·22 (s, 3H), and 2·0—3·2 (m, 4H); $\lambda_{max.}$ (ε) (H_2O) 233 (13,700) and 312 (8600); (98% H_2SO_4) 259 nm (5860).

2-*Methylamino-3-nitropyridine*.— 2-Chloro-3-nitropyridine (5 g) was heated under reflux for 2 h with ethanolic methylamine (33% w/v; 20 ml). Evaporation of the solvent gave the product which crystallised from light petroleum (b.p. 60—80°) as orange plates (4·6 g, 95%), m.p. 63—65° (lit.,[5] 63—64°). 2-Methylamino-5-nitropyridine, similarly prepared from 2-chloro-5-nitropyridine, crystallised from water as yellow prisms, m.p. 181—182° (lit.,[5] 181°).

1-*Methyl-2-methylamino-5-nitropyridinium Perchlorate*.—2-Methylamino-5-nitropyridine (1 g) and methyl trifluoromethanesulphonate (1·0 ml) were heated at 50° for 15 min. The cooled crude methotriflate was washed with anhydrous ether and dried to give a colourless solid (1·95 g, 94%), m.p. 124—126°. Anion exchange as previously described[4] gave the *perchlorate* (100%) as prisms, m.p. 161—163°, from ethanol (Found: C, 31·3; H, 3·8; N, 15·8. $C_7H_{10}ClN_3O_6$ requires C, 31·4; H, 3·7; N, 15·7%); τ (D_2O) 6·77 (s, 3H), 6·04 (s, 3H), 2·72 (d, 1H), 1·34 (dd, 1H), and 0·77 (d); $\lambda_{max.}$ (ε) (H_2O) 216·5 (6880), and 317 nm (13,380).

1-*Methyl-2-methylamino-3-nitropyridinium Perchlorate*.—2-Methylamino-3-nitropyridine (1·0 g), anhydrous benzene (5 ml), and methyl trifluoromethanesulphonate (1·0 ml) were kept for 12 h under nitrogen to give the methotriflate (1·8 g, 87%), which was washed with anhydrous benzene and then anhydrous ether. Anion exchange[4] gave the *perchlorate* as cream prisms, m.p. 144—146°, from ethanol (Found: C, 31·7; H, 3·8; N, 15·7. $C_7H_{10}ClN_3O_6$ requires C, 31·4; H, 3·7; N, 15·7%); τ (D_2O) 6·93 (s, 3H), 5·96 (s, 3H), 2·94 (t, 1H), 1·78 (dd, 1H), and 1·43 (dd, 1H); $\lambda_{max.}$ (ε) (H_2O) 213 (13,040), 284 (3870), and 360 nm (4530).

1-*Methyl-4-dimethylaminopyridinium Perchlorate*.—1-Methyl-4-dimethylaminopyridinium iodide (3·96 g), ethanol (20 ml), and sodium perchlorate monohydrate (4·2 g) were heated until dissolution was complete. The *perchlorate* crystallised from the cooled solution as needles, m.p. 190° (Found: C, 41·2; H, 5·5; Cl, 15·4. $C_8H_{13}ClN_2O_4$ requires C, 40·6; H, 5·5; Cl, 15·0%); $\lambda_{max.}$ (ε) (H_2O) 214 (9800) and 287 (20,500); (98% H_2SO_4) 261 (4440) and 266 nm (3760).

1-*Methyl-4-dimethylamino-3-nitropyridinium Perchlorate*.—4-Dimethylamino-3-nitropyridine[1] (3·34 g), methyl iodide (8·5 g) and ethanol (15 ml) were left at room temperature for 12 h, to give the *methiodide* (5·7 g, 92%) as plates, m.p.

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[1] Part XXVIII, A. G. Burton, R. D. Frampton, C. D. Johnson, and A. R. Katritzky, preceding paper.

[2] A. Michaelis and A. Hölken, *Annalen*, 1904, **331**, 245.

[3] L. C. King and F. J. Ozog, *J. Org. Chem.*, 1955, **20**, 448.

[4] A. G. Burton, P. P. Forsythe, C. D. Johnson, and A. R. Katritzky, *J. Chem. Soc.* (*B*), 1971, 2365.

[5] A. E. Tschitschibabin and A. W. Kirssanow, *Ber.*, 1928, **61B**, 1229.

200—202°, from ethanol (Found: C, 12·9; H, 31·4; N, 3·9. $C_8H_{12}IN_3O_2$ requires C, 13·6; H, 31·1; N, 3·9%). The iodide (3·09 g), ethanol (15 ml), and sodium perchlorate monohydrate (2·1 g) were heated until all solids had dissolved. The *perchlorate* separated from the cooled solution as prisms, m.p. 91° after recrystallisation from water (Found: C, 34·5; H, 4·0; N, 14·8; Cl, 12·8. $C_8H_{12}ClN_3O_6$ requires C, 34·1; H, 4·3; N, 14·9; Cl, 12·6%); $\lambda_{max.}$ (ε) (H_2O) 219 (8950), 287 (12,430), and 260 (2650); (98% H_2SO_4) 271 (3870) and 278 nm (3480).

1-*Methyl*-4-*dimethylamino*-3,5-*dinitropyridinium Perchlorate*.—4-Dimethylamino-3,5-dinitropyridine[1] (2·12 g) and methyl iodide (30 ml) were heated for 30 h at 95° (sealed tube). Evaporation of volatile material gave the *methiodide* (3 g, 85%) which formed needles, m.p. 198° from ethanol. The iodide (1·75 g), ethanol (10 ml), and sodium perchlorate monohydrate (1·4 g) were heated until all solids had dissolved. The *perchlorate* crystallised from the cooled solution and was purified as needles, m.p. 220°, from ethanol (Found: C, 29·9; H, 17·1; N, 3·4. $C_8H_{11}ClN_4O_8$ requires C, 29·4; H, 17·2; N, 3·4%); $\lambda_{max.}$ (ε) (H_2O) 200 (13,590), 226 (9940), 305 (19,270), and 357 (17,040), (98% H_2SO_4) 212 (13,000), 292 (8620), and 355 nm (4310).

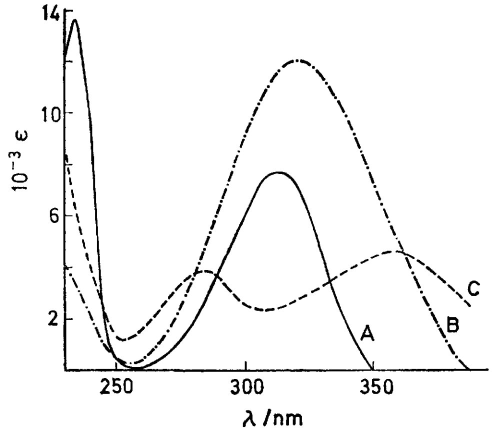


FIGURE 1 U.v. absorption spectra in water of (A) 1-methyl-2-methylaminopyridinium cation and its 5-nitro- (B) and 3-nitro- (C) derivatives

Kinetic Procedures.—(See ref. 1 for general details of procedures used and accuracies obtained.) 1-Methyl-2-methylaminopyridinium perchlorate (1) was nitrated in sulphuric acid of known strength. The proportions of the 3- and 5-nitro-products were calculated by equation (1) from the extinction coefficients at 363 and 390 nm. At

$$\% \text{ 3-Nitro} = \frac{\text{OD (390 nm)}}{\text{OD (363 nm)}} \cdot \frac{4350}{2200} \cdot 100 \qquad (1)$$

363 nm, the 3- and 5-nitro-products have equal extinction coefficients (ε 4350), whereas at 390 nm only the 3-nitro-derivative has significant absorption (ε 2200); at both wavelengths the substrate is transparent (see Figure 1). There is no significant medium dependence of the isomer proportions (Table 1). The aliquot technique for measuring rate constants was used; the fastest runs had a half-life of 1—2 min, causing errors of +5—10%. The addition of urea to the reaction mixtures produced no significant change in the observed rate constants, although the 'infinity' optical densities then observed were 10—15% lower than those calculated for complete reaction. Reaction was followed at 352 nm. Aliquots (1 ml) of reaction mixture were extracted at intervals and diluted to 20 ml with water (as the acidity of each diluted aliquot was *ca.* H_0 0·0, the substrate and products were present only as monocations). Calculated 'infinity' optical densities were used to calculate rate constants. Use of 363 nm as analytical wavelength gave results consistent with those obtained at 352 nm. Rate constants are recorded in Table 2, and the rate profile is shown, with that for 2-dimethylaminopyridine, in Figure 2.

TABLE 1

Acidity dependence of the product composition from the nitration of 1-methyl-2-methylaminopyridinium cation

$\%H_2SO_4$	Wt. substrate / mg	Reaction time / min	OD (363 nm)	OD (390 nm)	%3-Nitro
98·2	12·5	1·0	0·294	0·044	29·6
86·7	8·0	44	0·103	0·015	28·8
81·8	11·0	1200	0·203	0·032	31·2

TABLE 2

The nitration of 1-methyl-2-methylaminopyridinium ion at 25°

$\%H_2SO_4$	$-H_0$	$-(H_R + \log a_{H_2O})$	$\log k_2$ (obs)[a]	$\log k_2'$[b]
98·54	10·57		0·438	1·45
96·13	10·03		1·000	1·69
94·37	9·72		1·132	1·65
			1·147	1·67
91·96	9·32		0·973	1·28
			0·865	1·18
90·42	9·04		0·854	1·07
			0·682	0·90
88·78	8·80		−0·008	0·12
			−0·100	0·03
85·98	8·42		−1·071	−1·03
83·81	8·08	17·80	−1·772	−1·76
82·04	7·80	17·12	−2·111	−2·11
80·28	7·50	16·41	−3·453	−3·45
78·37	7·20	15·74	−3·997	−4·00

[a] k_2 in l mol s^{-1}. [b] Rate constant corrected for diprotonation of substrate; $k_2' = k_2/F$ where F = fraction of substrate in the monocation form, *i.e.* $\log k_2' = \log k_2 \text{ (obs)} + \log (1 + I)$.

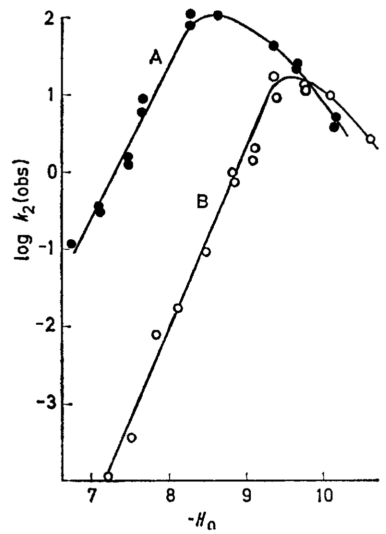


FIGURE 2 Rate profiles [log k_2 (obs)] for the nitration of (A) 2-dimethylaminopyridine at 30° and (B) model at 25°

The 2-methylamino-5-nitro-cation (3) was nitrated at 60° and the reaction was followed at 390—400 nm, in which wavelength region cation (3) is transparent (Figure 1). The increase in optical density at 390 nm, under pseudo-first-order kinetic nitrating conditions, during which aliquots of reaction mixture were quenched with an excess of 98% H_2SO_4, was recorded. Use of an ' infinity ' optical density calculated for complete reaction using the extinction coefficient at 390 nm for the cation of 2-methylamino-3,5-dinitropyridine (ε 2440), gave the results of Table 3.

TABLE 3

Comparison of nitration rates of 2-dimethylamino-5-nitropyridine and 4-dimethylaminopyridine with their model compounds

Dimethylaminopyridine	t [a]	$\%H_2SO_4$	$\log k_2$ (obs) [b]	Model compounds	t [a]	$\%H_2SO_4$	$\log k_2$ (obs) [c]
2-Dimethylamino-5-nitro	30	97·43	−3·66	(3)	60	97·7	−4·21
		82·8	−2·53			82·3	−4·81
4-Dimethylamino	50	96·96	−0·16	(4)	24	95·92	−0·55 [d]
		94·90	0·45			94·22	0·23 [d]
		85·84	0·93			85·57	−0·75 [d]
		80·30	0·05			79·81	−0·98 [d]
		75·56	−0·94			75·90	−1·66 [d]

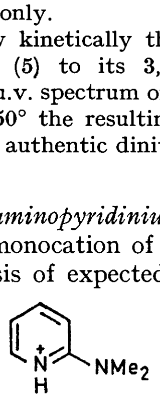
[a] Reaction temperature (°C). [b] Taken from ref. 1. [c] This work. [d] Approximate value, see text.

The 4-dimethylamino-cation (4) was nitrated at 24°, and the reaction followed at 280 nm by the aliquot technique. ' Infinity ' optical densities were 10—30% lower than those calculated for complete conversion into the 3-nitro-derivative (5). Rate constants were deduced from ' infinity ' optical densities calculated for complete reaction and are approximate only.

Attempts to follow kinetically the nitration of the 3-mononitro-derivative (5) to its 3,5-dinitro-analogue (6) failed; although the u.v. spectrum of (5) changed in nitric–sulphuric acid at >50° the resulting spectrum was dissimilar to that of the authentic dinitro-compound (6).

DISCUSSION

1-*Methyl*-2-*methylaminopyridinium Cation* (1).—This is a model for the monocation of 2-dimethylaminopyridine (7) on the basis of expected similar steric interaction between substituents on the ring N atom and in the 2-position for (1) and (7). However, the considerably weaker acidity of (1) compared to (7) makes proton loss during the nitration of (1) very unlikely.



(7)

For the low acidity region, the Moodie–Schofield plot for the nitration of (1) [$\log k_2$ (obs)] has a slope of 1·10, which indicates reaction *via* majority species. In the high-acidity region ($-H_0 \geqslant 9{\cdot}5$) both 2-dimethylaminopyridine and the model compound (1) are significantly converted into dications (see Table 4). Rate profiles corrected to allow for dication formation are shown in Figure 3. The acidities at which the nitration rate is at a maximum are normal for both compounds.

The methylamino-compound (1) is nitrated over the entire acidity range at a much lower rate than is 2-dimethylaminopyridine. The difference in rate at lower acidities (*ca.* 3·6 log units, allowing for the difference of 5° in reaction temperatures) is more pronounced than at high acidities (*ca.* 0·7 log units, again allowing for the temperature difference). The difference in activation of the two 2-substituents [$\sigma_p^+(NMe_2) = -1{\cdot}7$; $\sigma_p^+(NHMe)$ estimated at $-1{\cdot}5$ since $\sigma_p^+(NH_2) = -1{\cdot}3$ (ref. 6)] does not account for this, nor does the small difference in the H_0 values for half protonation of the two compounds. Possibly steric effects are involved (see later).

1-*Methyl*-2-*methylamino*-5-*nitropyridinium Cation* (3).—1-Methyl-2-methylamino-5-nitropyridinium perchlorate (3) underwent nitration immeasurably slowly at 30° under conditions sufficient to convert 2-dimethylamino-5-nitropyridine into its dinitro-derivative. The metho-cation (3) does undergo nitration at 60° (Table 3).

TABLE 4

pK_a Values for formation of mono- and di-cations

Compound	Mono-cation pK_a	Di-cation H_0 (½)	m	Ref.
2-Dimethylaminopyridine	6·94	−8·59	1·19	*b*
2-Dimethylamino-5-nitropyridine	3·11	<−10·5		*b*, *c*
2-Dimethylamino-3-nitropyridine	2·5 ± 0·3	−10·33	1·30	*b*
1-Methyl-2-methylamino-pyridinium cation		−9·29	1·01	*d*
1-Methyl-2-methylamino-5-nitropyridinium cation		<−10·5		*d*
1-Methyl-2-methylamino-3-nitropyridinium cation		<−10·5		*d*
4-Dimethylaminopyridine	9·70 [a]	−6·91	1·34	*b*
4-Dimethylamino-3-nitropyridine	5·23	−8·76	1·13	*b*

[a] D. D. Perrin, ' Dissociation Constants of Organic Bases in Aqueous Solution,' Butterworth, London, 1965, p. 156. [b] R. D. Frampton, Ph.D. Thesis, University of East Anglia, 1970. [c] P. J. Brignell, P. E. Jones, and A. R. Katritzky, *J. Chem. Soc.* (*B*), 1970, 117. [d] This work.

The rate profile for 2-dimethylamino-5-nitropyridine, which reacts at 30° to form the 3,5-dinitro-derivative,[1] indicated minority species nitration for both low and high acidity regions. However, the large $\log A$ and $\Delta S^{\ddagger}$ values, and the proximity of the calculated $\log k_2^*$ (fb) values to the calculated encounter rates, suggested [1]

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[6] C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, Interscience, John Wiley and Sons, New York, 1964, vol. 2, p. 335.

that the proton loss mechanism is operative at least for the high acidity reaction. If the nitration were proceeding *via* the free base, then the conjugate acid is, by definition, less reactive. The experimental result that in 82% H_2SO_4 the nitration proceeds faster by a factor >100 than that of cation (3) (Table 3) hence suggests that the proton loss mechanism is indeed operative for 2-dimethylamino-5-nitropyridine.

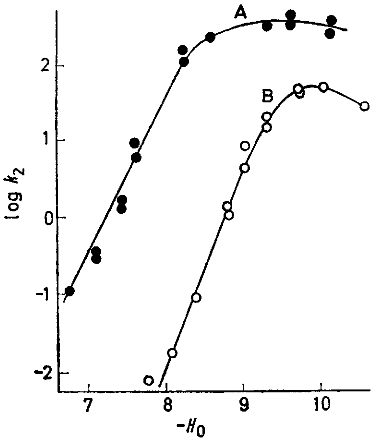

FIGURE 3 'Corrected' rate profiles (log k_2') for the nitration of (A) 2-dimethylaminopyridine at 30° and (B) 1-methyl-2-methylaminopyridinium cation at 25°

1-*Methyl-4-dimethylaminopyridinium Cation* (4).—Approximate rate constants for the nitration of cation (4) are compared with those for 4-dimethylaminopyridine in Table 3. These two substrates undergo nitration at comparable rates over the entire acidity range; this suggests strongly that 4-dimethylaminopyridine is nitrated *via* its monocation in all acidities.

Conclusions.—We now summarise the conclusions of this and the preceding paper.[1] For the 3-nitration of 2-dimethylamino-5-nitropyridine, the evidence taken as a whole suggests that the proton-loss mechanism [7] occurs throughout the acidity range in view of the similarity of the k_2* (fb) rate constants with the rate constants calculated for encounter-controlled reactions and the similarity in rate found for the model compound (3). The proton-loss mechanism probably also occurs for the 5-nitration of 2-dimethylamino-3-nitropyridine in the low acidity region; but at high acidities the reaction involves the conjugate acid.

For the nitrations of 2-dimethylamino- and 4-dimethylamino-pyridine, the evidence suggests reaction as the first conjugate acids throughout the range. However, it is curious that the model compound (1) reacts much less quickly than (7); possibly this is due to steric differences between the cations (1) and (7) which results in greater twisting of the NHMe-group in (1) out of the ring plane than the NMe_2-group in (7).

For the nitration of 4-dimethylamino-3-nitropyridine the evidence is less clear-cut; reaction probably occurs on the first conjugate acid at high acidities, but at low acidities the rate-profile slope is indeterminate.

[2/294 *Received, 10th February,* 1972]

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[7] S. R. Hartshorn and J. H. Ridd, *J. Chem. Soc.* (*B*), 1968, 1068.