The Kinetics and Mechanism of the Electrophilic Substitution of Heteroaromatic Compounds. Part XXVIII.[1] The Preparation and Kinetic Nitration of 2-, 3-, and 4-Dimethylaminopyridines and their 1-Oxides in Sulphuric Acid

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Preparative nitration of the title compounds in sulphuric acid affords products nitrated *ortho* or *para* to the dimethylamino-group in good yields for 2- and 4-dimethylaminopyridines and in poor yields for 3-dimethylaminopyridine and the 2- and 4-dimethylaminopyridine 1-oxides: a variety of demethylated and nitrosated by-products are also formed. The preparative results are rationalised from a qualitative viewpoint, and the conclusions confirmed in part by kinetic measurements at various acidities. Well established criteria show that nitration of 2- and 4-dimethylaminopyridine is occurring on the mono-protonated forms. The substitution of base-weakening nitro-groups into the aminopyridine nuclei favours free-base nitration, and the extent to which this happens is discussed.

THE present work was initiated at a time when the nitration of pyridine 1-oxide appeared [2] to possess an anomalous pre-exponential factor for free-base reaction, which could have been due to proton loss near the transition state.[3] Moodie and Schofield and their co-workers have demonstrated convincingly that the rate of nitration of aromatic compounds in sulphuric and perchloric acids,[4] as well as in sulpholan and nitromethane,[5] reaches a maximum threshold dictated by the encounter rate between nitronium ions and the aromatic substrate; this threshold is attained by those aromatic compounds more reactive than benzene itself. We sought a heteroaromatic substrate which would react at the encounter rate *on a minority species*; if proton loss near the transition state were important the pre-exponential factor should be anomalously high. Dimethylaminopyridines were selected as suitable substrates, for reasons detailed below, and, although the nitration of pyridine 1-oxide is no longer considered to be anomalous,[6] the present results have intrinsic interest: Ridd [7] has since demonstrated that proton loss near the transition state occurs in the nitration of certain nitroanilines.

Previous papers have described the protonation behaviour of the three dimethylaminopyridines [8] and their qualitative behaviour on oxidation to form *N*-oxides, and on quaternisation with methyl iodide.[9] Consideration of the relevant pK_a values [8] and application of previously substantiated [10] 'rules' indicated that while nitration of the three dimethylaminopyridines should occur *via* the first conjugate acid, reduction of the basicity of the protonation site by the introduction of the electron-withdrawing nitro-group should, at least at low acidities, induce reaction *via* the free-base species. Reaction of the free-base forms of nitrodimethylaminopyridines, in which the deactivating influences of the aza- (σ_p^+ *ca.* 0·9 [11]) and nitro-substituents ($\sigma_p^+ = 0{\cdot}79$) are more than compensated for by the activating effect of the powerful resonance donor dimethylamino- ($\sigma_p^+ = -1{\cdot}7$), should occur at the diffusion-controlled threshold rate.

Preparative Nitration of Dimethylaminopyridines.—Tschitschibabin and Knunyanz [12,13] nitrated 2-dimethylaminopyridine in sulphuric acid and reported a quantitative yield of 10% of the 3-nitro- and 90% of the 5-nitro-derivative. By nitration under similar conditions, we obtained the 3- (11%) and 5-nitro-derivatives (80%) together with a trace of an oil, b.p. 52—56°/0·3 mm, which was probably 2-nitrosomethylaminopyridine as it gave a positive Liebermann test. Further nitration readily converted both 2-dimethylamino-3-nitro- and

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[3] C. D. Johnson and A. R. Katritzky in informal discussions with K. Schofield.
[4] R. G. Coombes, R. B. Moodie, and K. Schofield, *J. Chem. Soc.* (*B*), 1968, 800.
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-5-nitro-pyridine into 2-dimethylamino-3,5-dinitropyridine, in 98 and 91% yield, respectively.

Nitration of 3-dimethylaminopyridine in sulphuric acid gave (in the presence of urea) a complex mixture which was separated by t.l.c. into 3-dimethylamino-2-nitropyridine (8%), 3-nitrosomethylamino-2-nitropyridine (14%), recovered starting material (26%), and an unidentified nitroso-compound (*ca.* 12%). The derivative (70%). We carried out the reaction in sulphuric acid, using 1·5 mol of nitric acid; a demethylated product, 2-methylamino-5-nitropyridine 1-oxide (22%) was isolated from the reaction and both starting material and 2-dimethylamino-5-nitropyridine were also shown to be present by t.l.c.[15]

Treatment of 2-dimethylamino-5-nitropyridine 1-oxide[14] with 1·4 mol of nitric acid in sulphuric acid gave

TABLE 1

N.m.r. chemical shifts (p.p.m. on scale [a]) and coupling constants (Hz) at 60 MHz of substituted pyridines.[b]

	Substituent, chemical shift and integral (*A*) [c] at ring position shown															*J* values			
	1	2			3			4			5			6						
Solvent			τ	*A*													3 : 4	4 : 5	5 : 6	4 : 6
CCl_4		NMe_2	7·02	6 *	H	3·6	(4·2)	H	2·7	(4·2)	H	3·6	(4·2)	H	1·9	(4·2)				
$CDCl_3$		NMe_2	6·72	6 *	H	3·50	1·0	H	1·68	1·0	NO_2			H	0·90	1·1	9			3
CCl_4		NMe_2	6·95	6 *	NO_2			H	1·92	1·1	H	3·33	1·0	H	1·71	1·0		7	5	2
$CDCl_3$		NMe_2	6·81	6 *	NO_2			H	1·09	1·0	NO_2			H	0·92	1·1				4
CCl_4		NMeNO	6·47	3 *	H	1·73	1·0	H	1·34	1·0	NO_2			H	0·64	1·0	9			2
D_2O		H	2·1	(2·0)	NMe_2	7·27	6 *	H	2·9	(2·0)	H	2·9	(2·0)	H	2·1	(2·0)				
CCl_4		NO_2			NMe_2	7·10	6 *	H	2·7	(2·0)	H	2·7	(2·0)	H	2·24	1·0				
$CDCl_3$		H	1·97	1·0	NMe_2	6·81	6 *	H	2·94	1·0	H	1·78	1·1	NO_2			3 [d]	9		
$CDCl_3$		NO_2			NMeNO	6·47	3 *	H	1·6	(2·0)	H	1·6	(2·0)	H	1·03	1·0				
CCl_4		Me	7·73	3 *	NMe_2	7·50	5·8	H	3·34	1·0	H	2·48	1·1	Me	7·69	3·0		12		
CCl_4		Me	7·62	3 *	NMeNO	6·73	3·0	H		(2·1)	H		(2·1)	Me	7·49	3·1		9		
CCl_4		H	1·85	1·9	H	3·59	2·0	NMe_2	7·04	6 *	H	*e*		H		*f*			10	
CCl_4		H	1·38	2·1	H	2·50	1·9	NMeNO	6·63	3 *	H	*e*		H	*f*				6	
CCl_4		H	1·40	1·0	NO_2			NMe_2	7·03	6 *	H	3·24	1·0	H	1·83	1·0			6	
$CDCl_3$		H	1·11	2·0	NO_2			NMe_2	7·03	6 *	NO_2			H	*f*					
D_2O	O^-	NMe_2	7·10	6 *	H	2·7	(2·9)	H	2·7	(2·9)	H	2·7	(2·9)	H	1·95	1·0				
D_2O	O^-	NMe_2	6·80	6 *	H	1·90	1·1	NO_2			H	2·04	1·1	H	1·50	1·0			7	3 [g]
D_2O	O^-	NMe_2	6·60	6 *	H	2·66	1·0	H	1·60	1·1	NO_2			H	0·85	1·1	10			3
TFA	OH	NMe_2 [h]	6·61	3	H	2·65	1·1	H	1·28	0·9	NO_2			H	0·66	1·0	10			3
D_2O	O^-	H	(2·6)	(3·9)	NMe_2	7·13	6 *	H	(2·6)	(3·9)	H	(2·6)	(3·9)	H	(2·6)	(3·9)				
D_2O	O^-	H	1·71	1·9	H	3·02	2·1	NMe_2	6·71	6 *	H	*e*		H	*f*				9	
D_2O	O^-	H	1·07	1·0	NO_2			NMe_2	6·79	6 *	H	2·58	1·1	H	1·78	1·0			8	2 [i]

[a] Relative to internal Me_4Si = 10 for solutions in CCl_4 and $CDCl_3$ and to HOD = 5·2 for solution in D_2O. For the spectra in TFA, an external Me_4Si reference was used. [b] Spectra were obtained of solutions *ca.* 10% (w/v). Spectral analyses were first order, and the '*J* values' quoted as peak separations. [c] Peak taken as standard designated by asterisk. Areas shown in parentheses are the sum of all the overlapping peaks in parentheses. [d] 2 : 4 Coupling constant. [e] Same environment as 3-position. [f] Same environment as 2-position. [g] 3 : 5 Coupling constant. [h] NH signal at τ 1·90, broad, area 1·1. [i] 2 : 6 Coupling constant.

nitration of 3-dimethylaminopyridine in acetic acid gave 3-nitrosomethylamino-2-nitropyridine (6%), and 3-dimethylamino-6-nitropyridine (8%). The orientation of all these products was confirmed by their n.m.r. spectra (see later). In an attempt to direct nitration into the 4-position of the pyridine ring, the behaviour of 3-dimethylamino-2,6-dimethylpyridine was also studied. Nitration in acetic acid gave 3-nitrosomethylamino-2,6-dimethylpyridine (characterised by the n.m.r. spectrum) in 76% yield; in sulphuric acid this was also the only product isolated (56%).

Nitration of 4-dimethylaminopyridine in sulphuric acid with 1·2 mol of nitric acid gave the 3-nitro-derivative (81%) and 4-nitrosomethylaminopyridine (10%). Using 2·1 mol of nitric acid, 4-dimethylamino-3,5-dinitropyridine (19%) was the only product isolated. Further nitration converted 4-dimethylamino-3-nitropyridine into 4-dimethylamino-3,5-dinitropyridine in good yield.

Preparative Nitration of Dimethylaminopyridine 1-Oxides.—The 2-isomer is reported by Polish authors[14] to undergo nitration in acetic acid to yield the 5-nitro-2-nitrosomethylamino-5-nitropyridine (30%), and t.l.c. showed the presence of starting material and another unidentified compound in the reaction mixture. However, when 2·8 mol of purified[16] nitric acid was used for this nitration, the product contained much less of the 2-nitrosomethylamino-5-nitropyridine together with starting material and two other compounds.[15]

Attempted nitration of 3-dimethylaminopyridine 1-oxide (itself prepared from 3-chloropyridine 1-oxide and dimethylamine) in sulphuric acid yielded no well defined product, and considerable starting material was reisolated.[15] 4-Dimethylaminopyridine 1-oxide was converted into the 3-nitro-derivative (27%) together with 4-dimethylamino-3,5-dinitropyridine 1-oxide (2%) and an unidentified nitroso-compound.

We also report the preparation of 2,3-dihydro-1*H*-imidazo[1,2-*a*]pyridinium bromide and its 1-methyl derivative, for model compound studies. However, they did not undergo smooth nitration. The previously reported[9] *N*-(2-pyridyl)-*NNN*-trimethylammonium

[14] J. S. Wieczorek and E. Plazek, *Rec. Trav. chim.*, 1964, **83**, 249.

[15] For full details see R. D. Frampton, Ph.D. Thesis, University of East Anglia, 1970.

[16] E. D. Hughes, C. K. Ingold, and R. I. Reed, *J. Chem. Soc.*, 1950, 2438.

iodide was converted into the hydrogen sulphate by ion-exchange.

N.m.r. Spectra and Orientation of Reaction Products.—The orientation of the reaction products is largely based on the n.m.r. spectral data collected in Table 1. The characteristic NMe_2 peak was found in the range τ 6·60—7·50; it lies at higher field in the 3-substituted compounds, especially the 2,6-dimethyl derivative, and is usually shifted to lower field by nitro-substituents (though not appreciably in the 4-series). The NMeNO group (in the range τ 6·47—6·73) is most readily distinguished by area measurement. The aromatic proton chemical shifts and coupling constants (measured as peak separations) are in line with previous work.[8,17]

EXPERIMENTAL

Preparation of Materials.—The following were prepared by the Eschweiler–Clarke method [18] and/or by deoxygenation of the corresponding *N*-oxides: [15] 2-dimethylaminopyridine, b.p. 40—42°/0·2 mm (lit.,[12] b.p. 88°/15 mm); 3-dimethylaminopyridine, b.p. 75—77°/0·4 mm (lit.,[19] b.p. 108—110°/12 mm); 4-dimethylaminopyridine, m.p. 109—110·5° (lit.,[20] m.p. 114°).

The following were made by the literature methods indicated: 2-dimethylaminopyridine 1-oxide,[21] oil [homogeneous by g.l.c. and t.l.c., characterised as the picrate, m.p. 142—143° (lit.,[21] m.p. 142·5—144°)]; 4-dimethylaminopyridine 1-oxide,[22] m.p. 213—215° (lit.,[22] two polymorphs, m.p. 97—99° and 223—225°) (Found: C, 60·8; H, 7·3; N, 20·4. Calc. for $C_7H_{10}N_2O$: C, 60·9; H, 7·3; N, 20·3%).

These compounds, and other substrates and products were characterised by their n.m.r. spectra (Table 1).

2,6-Dimethyl-3-dimethylaminopyridine.— 3-Amino-2,6-dimethylpyridine [23] (11·0 g), m.p. 133—135° (lit.,[23] m.p. 124°) was heated to 40° in 10N-H_2SO_4 (250 ml) and aqueous formaldehyde (0·32 mol) was added followed by mossy zinc (75 g) in portions during 15 min. The whole was stirred for 30 min and then heated to 100° for 2 h. The cooled solution was treated until basic with NaOH and the solution and gelatinous precipitate were extracted with $CHCl_3$ (2 × 200 ml). The extracts were distilled to give the *dimethylamino-compound* (2·91 g, 22%) as an oil, b.p. 81°/15 mm, characterised by its n.m.r. spectrum; τ (CCl_4) 7·61 (s, 3H), 7·55 (s, 3H), 7·36 (s, 6H), and 3·25 and 2·93 (AB quartet centres, 2H, *J* 9 Hz); $\lambda_{max.}$ (C_6H_{12}) 251 (ε 5000) and 291 (2000) nm.

3-Dimethylaminopyridine 1-Oxide.—3-Chloropyridine 1-oxide (18 g) and aqueous Me_2NH (30% w/w; 150 ml) were heated at 100° for 2 days in a sealed tube. Potassium carbonate (16 g) was added to the contents of the tube, and the solution was evaporated to dryness. The residue was extracted with $CHCl_3$ and the extracts were evaporated to yield the 1-*oxide*, which crystallised from benzene as needles (5·4 g, 28%), m.p. 88—90° (Found: C, 60·6; H, 7·4; N, 20·3. $C_7H_{10}N_2O$ requires C, 60·9; H, 7·3; N, 20·3%).

The picrate was prepared in and crystallised from EtOH; it formed needles m.p. 164·5—166° (Found: C, 42·7; H, 3·6; N, 19·0. $C_{13}H_{13}N_5O_8$ requires C, 42·5; H, 3·6; N, 19·1%).

2-Dimethylamino-4-nitropyridine 1-Oxide (cf. *ref.* 24).—2-Chloro-4-nitropyridine 1-oxide (8·0 g) [25] was heated under reflux for 2 h with aqueous Me_2NH (30% w/w; 50 ml). After cooling, the solution was treated with potassium carbonate (10 g) and evaporated to dryness. Ethanol extraction of the residue gave the product (6·7 g, 80%), which after crystallisation from benzene had m.p. 124—125° (lit.,[24,26] m.p. 126°) (Found: C, 46·1; H, 5·0; N, 23·0. Calc. for $C_7H_9N_3O_3$: C, 46·0, H, 5·0; N, 23·0%).

2-Chloro-3-nitropyridine (cf. *ref.* 27).—A slurry of 3-amino-2-chloropyridine (25 g) in conc. H_2SO_4 (50 ml) was slowly added to a mixture of oleum (250 ml) and aqueous hydrogen peroxide (30% w/w; 200 ml), with stirring and cooling. After 4 h at 0°, and 4 days at 20°, the solution was poured onto ice and neutralised with sodium carbonate; $CHCl_3$ extraction gave 2-chloro-3-nitropyridine (16 g, 52%), m.p. 98—100° (lit.,[28] m.p. 103—104°).

2-Dimethylamino-3-nitropyridine.— 2-Chloro-3-nitropyridine (15 g) and aqueous Me_2NH (30% w/w, 100 ml) were kept at 20° for 1 h, and then gradually heated during 1 h to boiling; this was maintained for a further 30 min. Evaporation at 100°/14 mm gave a residue (18 g), which crystallised from ethanol as yellow needles, m.p. and mixed m.p. with the sample from the nitration of 2-dimethylaminopyridine, 30—31° (lit.,[13] m.p. 31°).

Nitric Acid.—AnalaR nitric acid was distilled twice from cold H_2SO_4 by the method of Hughes, Ingold, and Reed.[16] It was condensed in a container immersed in liquid nitrogen, and kept there stoppered.

Nitration of 2-Dimethylaminopyridine (cf. *ref.* 12).—2-Dimethylaminopyridine (10·2 g) was slowly added to H_2SO_4 (27 ml) in ice. To this was added, with stirring, HNO_3 (*d* 1·5; 5·9 g) in H_2SO_4 (3·5 ml). After 3 h the mixture was poured onto ice and treated until basic with sodium carbonate to give solution A and a precipitate of 2-dimethylamino-5-nitropyridine (7·1 g, 51%), m.p. 153—154°, raised by crystallisation from ethanol to 154—155° (lit.,[12] m.p. 154—155°) (Found: C, 50·1; H, 5·5; N, 25·0. Calc. for $C_7H_9N_3O_2$: C, 50·4; H, 5·4; N, 25·2%).

The alkaline solution A (see above) was steam-distilled; the distillate yielded a brown oil (2·0 g). Preparative t.l.c. using silica and $CHCl_3$ gave a yellow band and a colourless band. Extraction of the yellow band with $CHCl_3$ yielded 2-dimethylamino-3-nitropyridine (1·5 g, 11%) as a yellow oil, which solidified after distillation, m.p. 30—31° (lit.,[13] m.p. 31°) (Found: C, 50·1; H, 5·1; N, 25·0. Calc. for $C_7H_9N_3O_2$: C, 50·4; H, 5·4; N, 25·2%).

Extraction of the colourless band gave an oil (0·3 g), b.p. 52—56°/0·3 mm, which gave a positive nitroso-test. Extraction with $CHCl_3$ of the residue from the steam distillation followed by evaporation of the dried extracts,

[17] See, *e.g.*, A. R. Katritzky and J. M. Lagowski, *J. Chem. Soc.*, 1961, 43.
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[20] E. Koenigs, H. Friedrich, and H. Jurany, *Chem. Ber.*, 1925, **58**, 2571.
[21] A. R. Katritzky, *J. Chem. Soc.*, 1957, 191.
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[27] O. von Schickh, A. Binz, and A. Schulz, *Chem. Ber.*, 1936, **69**, 2593.
[28] E. C. Taylor and J. S. Driscoll, *J. Org. Chem.*, 1960, **25**, 1716.

yielded further 2-dimethylamino-5-nitropyridine (4·0 g, 29%), m.p. 152—155°, after recrystallisation from EtOH, m.p. and mixed m.p. 154—155°.

Nitration of 2-Dimethylamino-3-nitropyridine.—HNO_3 (70%, 8 g) in H_2SO_4 (30 ml) was slowly added to 2-dimethylamino-3-nitropyridine (4·2 g) in H_2SO_4 (40 ml). The mixture was kept at 20° for 24 h, and then poured onto ice. The yellow precipitate was dried, and the acid solution extracted with $CHCl_3$ to give further 2-dimethylamino-3,5-dinitropyridine (total: 5·2 g, 98%), which after recrystallisation from EtOH had m.p. 126—127° (lit.,[12] m.p. 125—126°) (Found: C, 39·5; H, 3·8; N, 26·5. Calc. for $C_7H_8N_4O_4$: C, 39·6; H, 3·8; N, 26·4%).

Nitration of 2-Dimethylamino-5-nitropyridine.—This nitration was carried out essentially as for 2-dimethylamino-3-nitropyridine. After 2 days at 20° the mixture was worked up as before to give 2-dimethylamino-3,5-dinitropyridine (0·58 g, 91%), after recrystallisation from EtOH, m.p. and mixed m.p. with the nitration product from 2-dimethylamino-3-nitropyridine, 126—127°.

Nitration of 3-Dimethylaminopyridine.—(*a*) HNO_3 (70%, 3·6 g), urea (1·2 g), and H_2SO_4 (86%, 40 ml) were kept at 20° for 24 h and then added at 0° to 3-dimethylaminopyridine (3·8 g) in sulphuric acid (86%, 40 ml). After 24 h at 0—5° the mixture was poured onto ice and neutralised with sodium carbonate. Extraction with $CHCl_3$ gave a red oil (3·8 g). T.l.c. using silica and $CHCl_3$, gave four main bands whose R_F values decreased in the order (I) > (II) > (III) > (IV). Extraction of band (I) gave *3-dimethylamino-2-nitropyridine* (0·32 g, 8%), which distilled at 125°/0·6 mm as an oil that solidified on cooling, m.p. 15° (negative nitroso-test) (Found: C, 49·9; H, 4·8; N, 25·6. $C_7H_9N_3O_2$ requires C, 50·4; H, 5·4; N, 25·2%).

Extraction of band (II) with $CHCl_3$, evaporation of the extracts, and recrystallisation of the residue from EtOH gave *3-nitrosomethylamino-2-nitropyridine* (0·8 g, 14%) as yellow prisms, m.p. 124—125° (nitroso-test positive) (Found: C, 39·8; H, 3·3; N, 31·0. $C_6H_6N_4O_3$ requires C, 39·6; H, 3·4; N, 30·8%).

Extraction of band (III) gave a pale yellow liquid (0·5 g) (nitroso-test positive), and extraction of band (IV) gave recovered 3-dimethylaminopyridine (1·0 g, 26%).

(*b*) HNO_3 (70%, 4·1 g) in glacial acetic acid (15 ml) was added dropwise to 3-dimethylaminopyridine (4·6 g) in glacial acetic acid (30 ml) at 20°. The reaction was followed by u.v. spectroscopy. After 56 h the acetic acid was distilled off to give a red liquid which partially crystallised. The crystals were filtered off, washed with water, and dried (1·0 g): preparative t.l.c. using silica and $CHCl_3$ gave two close bands. On extraction with $CHCl_3$ the band of lower R_F value yielded 3-nitrosomethylamino-2-nitropyridine (0·4 g, 6%), m.p. and mixed m.p. 123—124°. Extraction of the band of higher R_F value with $CHCl_3$, evaporation of the extracts, and crystallisation of the residue from EtOH produced *3-dimethylamino-6-nitropyridine* (0·5 g, 8%), as needles, m.p. 202—204° (negative nitroso-test) (Found: C, 49·8; H, 5·4; N, 25·1. $C_7H_9N_3O_2$ requires C, 50·4; H, 5·4; N, 25·2%).

Nitration of 4-Dimethylaminopyridine.—(*a*) HNO_3 (70%; 1·6 g) in H_2SO_4 (90%, 20 ml) was added dropwise to 4-dimethylaminopyridine (1·8 g) in H_2SO_4 (90%, 20 ml) at 0°. After 3 h at 20°, the solution was poured onto ice, neutralised with sodium carbonate, and extracted with $CHCl_3$ to give a dark oil (2·3 g). Preparative t.l.c., using silica and $CHCl_3$, gave a yellow and a colourless band; the latter had the lower R_F value. Extraction of the yellow band as before gave *4-dimethylamino-3-nitropyridine* (2·0 g, 81%), which solidified on scratching and after distillation at 0·3 mm formed yellow crystals, m.p. 49—50° (nitroso-test negative) (Found: C, 49·9; H, 5·7; N, 25·3. $C_7H_9N_3O_2$ requires C, 50·4; H, 5·4; N, 25·2%).

Extraction of the colourless band gave 4-nitrosomethylaminopyridine (0·2 g, 10%) which had m.p. 81—82° (lit.,[29] m.p. 84°) after recrystallisation from light petroleum (b.p. 60—80°) (nitroso-test positive) (Found: C, 52·1; H, 5·0; N, 30·4. Calc. for $C_6H_7N_3O$: C, 52·5; H, 5·2; N, 30·6%).

(*b*) HNO_3 (*d* 1·5; 4·3 g) in H_2SO_4 (10 ml) was added dropwise to 4-dimethylaminopyridine (4·0 g) in conc. H_2SO_4 (10 ml). After 24 h the mixture was poured onto ice and brought to pH 5 with sodium carbonate: *4-dimethylamino-3,5-dinitropyridine* (1·3 g, 19%) separated; it crystallised from EtOH as yellow prisms, m.p. 182—183·5° (Found: C, 39·8; H, 4·3; N, 26·6. $C_7H_8N_4O_4$ requires C, 39·4; H, 4·2; N, 26·3%).

Nitration of 4-Dimethylamino-3-nitropyridine.—This nitration was carried out essentially as for 2-dimethylamino-3-nitropyridine to give a yellow solid (0·24 g) preparative t.l.c. of which, using silica and $CHCl_3$, gave a main band of 4-dimethylamino-3,5-dinitropyridine and a faint band of starting material. The R_F values were identical with those of authentic specimens. Extraction of the two bands with MeOH gave the characteristic u.v. spectra; evaporation of the corresponding solution yielded 4-dimethylamino-3,5-dinitropyridine (0·19 g, 75%), m.p. and mixed m.p. 182—183°.

Nitration of 3-Dimethylamino-2,6-dimethylpyridine.—(*a*) HNO_3 (*d* 1·5, 2·85 g) was added dropwise, with stirring, to the substrate (1·35 g) in acetic acid (15 ml) at 0°. After 2 min nitrous fumes were evolved and the temperature rose to 40—50°. After 24 h the solution was neutralised with potassium carbonate and shaken with $CHCl_3$; the dried ($MgSO_4$) extracts were evaporated to an oil (1·03 g, 76%) which was purified by preparative t.l.c., using silica and $CHCl_3$ to give *2,6-dimethyl-3-nitrosomethylaminopyridine*, as an oil, b.p. 83—86°/0·2 mm, characterised by the n.m.r. spectrum (Table 1) (positive nitroso-test).

(*b*) *Using* H_2SO_4. HNO_3 (*d* 1·5; 2·44 g) in conc. H_2SO_4 (8 ml) was added dropwise to starting material (1·29 g) in H_2SO_4 (2 ml). After 2 days the usual procedure gave an oil (0·72 g, 56%), b.p. 83—86°/0·2 mm, with n.m.r. and i.r. spectra identical to those of the oil obtained above.

Nitration of 2-Dimethylaminopyridine 1-Oxide.—HNO_3 (70%, 0·72 g) in H_2SO_4 (84%, 50 ml) was added dropwise to 2-dimethylaminopyridine 1-oxide (0·74 g) in H_2SO_4 (30 ml). After 3 days, the mixture was poured onto ice and neutralised with sodium carbonate. Extraction with $CHCl_3$ yielded an oily solid (0·70 g); on washing with water (10 ml) this produced a yellow solid (0·35 g) which on preparative t.l.c., using silica and $CHCl_3$ gave one main yellow band and two faint ones. Extraction and work-up as before of the main band gave *2-methylamino-5-nitropyridine 1-oxide* (0·20 g, 22%), which crystallised from cyclohexane as yellow prisms, m.p. 223—226° (decomp.) (negative nitroso-test) (Found: C, 42·4; H, 4·2; N, 24·6. $C_6H_7N_3O_3$ requires C, 42·6; H, 4·2; N, 24·9%).

Nitration of 2-Dimethylamino-5-nitropyridine 1-Oxide.—HNO_3 (70%; 0·70 g) in H_2SO_4 (20 ml) at 0° was added dropwise to 2-dimethylamino-5-nitropyridine 1-oxide (1·00

[29] E. Kalatzis, *J. Chem. Soc.* (*B*), 1967, 273.

g) in H_2SO_4 (30 ml) at 0°. After 2 days at 20°, the solution was poured onto ice and brought to pH *ca.* 4 with sodium carbonate. A yellow solid (0·37 g) separated leaving an aqueous solution A. Preparative t.l.c. of the solid, using silica and $CHCl_3$, gave 2-nitrosomethylamino-5-nitropyridine (0·30 g, 30%), m.p. 108—109° (lit.,[30] m.p. 112—113°) (nitroso-test positive) (Found: C, 39·4; H, 3·3; N, 30·6. Calc. for $C_6H_6N_4O_3$: C, 39·6; H, 3·3; N, 30·8%). The aqueous solution A (see above) was extracted with $CHCl_3$. Evaporation of the extracts gave a red solid (0·65 g), m.p. 85—170°, which was chromatographed on silica with Me_2CO (10% v/v) and $CHCl_3$ (90% v/v) to give starting material and more 2-nitrosomethylamino-5-nitropyridine.

Nitration of 4-*Dimethylaminopyridine* 1-*Oxide*.—This nitration was carried out essentially as for 2-dimethylaminopyridine 1-oxide. Preparative t.l.c. of the solid residue (0·50 g), using silica and Me_2CO, gave two main bands. Consecutive chromatograms were run to separate the two main bands completely. The band of greater R_F value was extracted with MeOH to give a solid (0·10 g) for which a nitroso-test was positive. The other band separated into two bands on further chromatography, the main component being extracted as before to give 4-*dimethylamino*-3-*nitropyridine* 1-*oxide* (0·23 g, 27%), m.p. 153—154° (negative nitroso-test) (Found: C, 45·9; H, 5·1; N, 22·9: $C_7H_9N_3O_3$ requires C, 45·9; H, 5·0; N, 23·0%).

The minor component of the final band was extracted to give 4-*dimethylamino*-3,5-*dinitropyridine* 1-*oxide* (0·02 g, 2%), as red crystals m.p. 210—212° (decomp.) (Found: C, 36·6; H, 3·3; N, 24·5. $C_7H_8N_4O_5$ requires C, 36·8; H, 3·5; N, 24·6%).

1-(2-*Hydroxyethyl*)-2-*aminopyridinium Chloride*.—2-Aminopyridine (153 g) was heated at 100° for 2 days in 2-chloroethanol (150 g). Water was added, then sodium carbonate to pH 8; the mixture was then extracted with $CHCl_3$ (extract A). The aqueous solution was evaporated, the residue extracted with absolute EtOH, and the EtOH evaporated to give 1-(2-hydroxyethyl)-2-aminopyridinium chloride (160 g, 57%) which after recrystallisation from EtOH had m.p. 149—150° (lit.,[31] m.p. 146—147·5°) (Found: C, 48·3; H, 6·3; N, 15·7. Calc. for $C_7H_{11}ClN_2O$: C, 48·3; H, 6·3; N, 16·0%).

The $CHCl_3$ extract A was evaporated and the residual oil (13 g) was distilled to give 2-aminopyridine (b.p. 62—63°/0·4 mm) and a yellow oil, b.p. 136—140°/0·4 mm, which on column chromatography, using silica and EtOH, gave 2-(2-hydroxyethyl)aminopyridine; this crystallised from light petroleum and had m.p. 68—69° (lit.,[32] m.p. 65°) (Found: C, 61·1; H, 7·2; N, 20·6. Calc. for $C_7H_{10}N_2O$: C, 60·8; H, 7·3; N, 20·3%).

2,3-*Dihydro*-1H-*imidazo*[1,2-a]*pyridinium Bromide*.—1-(2-Hydroxyethyl)-2-aminopyridinium chloride (50 g) was heated under reflux with conc. HBr (500 ml) for 3 days. The solution was evaporated at 100°/14 mm, to give 2,3-*dihydro*-1H-*imidazo*[1,2-a]*pyridinium bromide* (52 g, 90%) which, crystallised from EtOH, had m.p. 179·5—180·5° (Found: C, 41·8; H, 4·5; N, 13·9. $C_7H_9BrN_2$ requires C, 41·7; H, 4·5; N, 13·6%).

1-*Methyl*-2,3-*dihydroimidazo*[1,2-a]*pyridinium Hydrogen Sulphate*.—Sodium methoxide (13·5 g) in absolute EtOH (50 ml) was added dropwise, with stirring, to 2,3-dihydro-1*H*-imidazo[1,2-*a*]pyridinium bromide (30 g) and methyl bromide (72 g) in EtOH (300 ml). The mixture turned yellow-green; after 15 h the colour disappeared; the sodium bromide was filtered off and the liquid evaporated. Chloroform-extraction of the residue, followed by partial evaporation, gave crystalline 1-methyl-2,3-dihydroimidazo[1,2-*a*]pyridinium bromide (28·5 g, 87%), m.p. 170—172°, which was converted without purification, by ion-exchange, into 1-*methyl*-2,3-*dihydroimidazo*[1,2-a]*pyridinium hydrogen sulphate* (8·4 g, 24%) which, crystallised from EtOH–Me_2CO, had m.p. 219—221° (decomp.) (Found: C, 41·2; H, 5·4; N, 11·8. $C_8H_{12}N_2O_4S$ requires C, 41·4; H, 5·2; N, 12·1%).

N-(2-*Pyridyl*)-NNN-*trimethylammonium Hydrogen Sulphate*.—The corresponding iodide [9] was treated on a column of Dowex 1-X8 ion-exchange resin, which had been previously exchanged from chloride to hydrogen sulphate by washing with H_2SO_4 (10%). The product crystallised from EtOH–Me_2CO to give N-(2-*pyridyl*)-NNN-*trimethylammonium hydrogen sulphate* (0·5 g), m.p. 164—165°, an aqueous solution of which gave a precipitate with aqueous barium chloride, but not with aqueous silver nitrate (Found: C, 41·1; H, 6·2; N, 11·9. $C_8H_{14}N_2O_4S$ requires C, 41·0; H, 6·0; N, 12·0%).

Kinetics of Nitration.—Nitric and sulphuric acids were AnalaR grade. For 4-dimethylamino-3-nitropyridine the reaction was carried out in a thermostatted flask from which aliquots (1·00 ml) were withdrawn at known intervals, and quenched with 50% H_2SO_4 to a volume of 50·0 ml for optical density measurements. For the very reactive 2- and 4-dimethylaminopyridine, a solution of the compound in sulphuric acid was made up in one limb of a two-limbed reaction vessel; the second limb contained nitric acid in sulphuric acid, and the whole fitted into the ground glass joint of a u.v. cell. The full details of this technique have been described elsewhere.[33]

TABLE 2

Analytical wavelengths for measurement of kinetics of nitration of substituted pyridines

Substrate	Product	λ [a]	log ε (substrate) [b]	log ε (product) [b]
2-Dimethylamino-	5-Nitro- + 3 nitro-	333 [c] 242 [d]	<0·01 3·96	3·95 3·73
4-Dimethylamino-	3-Nitro-	295	2·64—0·0	3·98—2·79
2-Dimethylamino-5-nitro-	3,5-Dinitro-	260	2·94	3·34
2-Dimethylamino-3-nitro-	3,5-Dinitro-	333	3·33—2·95	4·01
4-Dimethylamino-3-nitro	3,5-Dinitro-	286	4·12	3·92

[a] Wavelength for kinetic measurements. [b] Where a range is given, this is due to diprotonation of substrate or product. The first figure refers to *ca.* 75% H_2SO_4 solutions, the latter to *ca.* 97% H_2SO_4 solutions. [c] For runs in 88—98% H_2SO_4. [d] For runs in 76—87% H_2SO_4.

For 2-dimethylamino-3- and -5-nitropyridine the thermostatted nitric acid solution (5 ml) was added to a solution of the substrate in a 100 ml flask. The solution was shaken and then a portion was poured into the u.v. cell, which was quickly placed in the spectrophotometer. Many of these runs were slow; a few were followed to completion

[30] A. E. Tschitschibabin and A. W. Kirssanow, *Chem. Ber.*, 1928, **61**, 1223.
[31] Ya L. Gold'farb and M. A. Pryanishnikova, *Zhur. obshchei Khim.*, 1955, **25**, 1003 (*Chem. Abs.*, 1956, **50**, 3433g).
[32] O. Bremer, *Annalen*, 1936, **521**, 286.
[33] K. Bowden and A. F. Cockerill, *J. Chem. Soc.* (*B*), 1970, 173.

whereupon an optical density reading of close to the calculated infinity reading was found, but in general only 10—15% of reaction was followed.

TABLE 3

Nitration of 2- and 4-dimethylaminopyridine

Compound (temp.)	% H_2SO_4	$-H_0$ [a]	3 + log k_2 (obs)	3 + log k_2'	$-(H_R + \log a_{H_2O})$ [b]
2-Dimethylamino-pyridine (30°)	76·12	6·73	2·053	2·053	14·96
	78·10	7·05	2·481	2·488	15·61
			1·551	2·557	
	80·34	7·39	3·124	3·140	16·47
			3·214	3·230	
	81·70	7·61	3·758	3·787	17·00
			3·931	3·960	
	85·60	8·22	4·918	5·052	18·56
	85·68	8·23	5·018	5·155	18·59
	87·80	8·56	5·068	5·354	
	92·86	9·30	4·657	5·530	
	94·64	9·60	4·387	5·613	
			4·331	5·558	
	97·40	10·12	3·718	5·534	
			3·615	5·431	
4-Dimethylamino-pyridine (50°)	71·82	5·70	0·828	0·833	13·48
	75·56	6·30	2·061	2·122	14·85
	77·85	6·59	2·102	2·239	15·54
	80·30	6·96	3·069	3·406	16·45
			3·020	3·357	
	81·90	7·19	3·299	3·830	17·09
			3·296	3·828	
	83·87	7·49	3·553	4·400	17·83
			3·574	4·421	
	85·84	7·78	3·941	5·140	18·66
			3·921	5·119	
	87·88	8·07	3·955	5·527	19·47
			3·968	5·540	
	88·90	8·20	3·979	5·717	
			3·962	5·700	
	89·88	8·34	4·008	5·933	
			4·026	5·951	
	90·88	8·48	3·718	5·832	
	91·90	8·63	3·536	5·848	
			3·786	6·098	
	92·91	8·78	3·582	6·094	
			3·660	6·171	
	94·90	9·12	3·451	6·411	
			3·457	6·418	
	96·93	9·49	2·837	6·297	
			2·826	6·286	

[a] See ref. 6. [b] Values at 25°.

TABLE 4

Temperature dependence of nitration rate for 2-dimethylaminopyridine

(*a*) in 97·40% H_2SO_4		(*b*) in 76·16% H_2SO_4	
t/°C	log k_2'	t/°C	log k_2'
23·0	2·284	24·0	−1·442
	2·151		−1·452
30·0	2·431	35·0	−0·919
	2·534		−1·041
35·0	2·606	40·0	−0·839
	2·589		−0·763
40·0	2·828	45·0	−0·552
	2·840		−0·566
45·0	2·846	50·0	−0·461
	3·007		−0·411
50·0	3·064		

The stabilities of all substrates and products were checked in 90% sulphuric acid. Except for some of the 2-dimethylaminopyridine runs, all the kinetic reactions were carried out under first-order conditions. Analytical wavelengths are given in Table 2, and the kinetic results are recorded in Tables 3—6. The precision of the kinetic measurements and the Arrhenius parameters subsequently calculated corresponded to those detailed in previous papers of this series.[1]

The following notation is used: k_2 (obs) is the uncorrected rate constant defined by equation (1), in which the concentration terms refer to stoicheiometric quantities; k_2' is the second-order rate constant corrected for diprotonation by equation (2); k_2' (fb) is defined by equation (3); k_2^* is related to k_2' by equation (4). The pK_a values used are from ref. 8: no allowance was made for temperature variation of pK_a, but all H_0 values were corrected for temperature variation.[6]

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

$$\log k_2' = \log k_2(\text{obs}) + \log(1 + [BH_2^{2+}]/[BH^+]) \quad (2)$$

$$\log k_2'(\text{fb}) = \log k_2' + \mathrm{p}K_a - H_0 \quad (3)$$

$$k_2^* = k_2'[HNO_3]/[NO_2^+] \quad (4)$$

In common with previously published work, rate constants for an individual substrate at various elevated temperatures were measured using the same wt. % H_2SO_4 solution. From consideration of the temperature variation of H_0 [6] and the shape of rate profiles, it follows that activation energies measured in this way using acid solutions of strength greater than *ca.* 92% H_2SO_4 will be larger than their true value; those measured using *ca.* 88—92% H_2SO_4 will be essentially correct, and those measured in acidities below 88% will be lower than their true value. The relative magnitudes of activation energies for nitrations *via* the free base and *via* the conjugate acid should still allow meaningful conclusions to be drawn from these apparent activation parameters.

Arrhenius parameters were initially calculated using log k_2' values. For the nitrations of 2-dimethylamino-3-nitropyridine and 2-dimethylamino-5-nitropyridine, additional Arrhenius parameters were calculated using log k_2' (fb) values. The results are recorded in Table 7. For the comparison of log k_2^* (fb) values and log k (enc) values at various acidities, rate constants were taken from the relevant rate profile of log k_2' (fb) against temperature-corrected H_0 [H_0 (corr.)] at the required acidity, and extrapolated to 25° using the appropriate activation energy measured in the nearest acidity to that required and then applying equation (4). Log k (enc) at 25° for that acidity was calculated using the appropriate equation,[34] using sulphuric acid viscosities at 25° interpolated from literature data.[35]

To compare rate constants and therefore reactivities of various substrates, the rates of nitration under standard conditions of acidity and temperature are required. We choose the conditions 75% H_2SO_4 and 25° [*i.e.* H_0 (corr.) −6·60]; in this way only a short extrapolation of the rate-profile for benzene [4] is required; moreover, either no extrapolation or only a small one is needed for the rate profile of the relevant substrate, particularly if the reaction temperature is higher than 25°. In this paper we denote standard rates as k_0; they are calculated from the rate profile of log k_2 against H_0 (corr.), taking the log k_2 value at H_0 −6·60 and extrapolating this value to 25° using the appropriate Arrhenius parameters. There are two intrinsic errors in this treatment; all pK_a values are assumed

[34] P. J. Brignell, A. R. Katritzky, and H. O. Tarhan, *J. Chem. Soc.* (*B*), 1968, 1477.

[35] 'International Critical Tables,' vol. V, McGraw-Hill, New York, 1929, p. 13.

to have the same temperature-dependence, and activation energies used for extapolation are rarely known at the required acidity.

Moodie–Schofield plots were initially drawn for each substrate by plotting $\log k_2'$ against $-(H_R + \log a_{H_2O})$. Where appropriate, additional plots were drawn using $\log k_2'$ (fb) values, and these will be referred to as 'corrected for free base nitration.'

DISCUSSION

Products of Preparative Nitration in Sulphuric Acid.—2- and 4-Dimethylaminopyridine give products of mono-nitration at the 3- and 5-positions in good yield, with small amounts of nitrosomethylaminonitro-compounds as by-products, but 3-dimethylaminopyridine affords only a small yield of the corresponding 2-nitro-derivative with the major reaction involving demethylation. For the corresponding *N*-oxides a far greater tendency for demethylation and by-product formation is found: the 2- and 4-derivative do yield small quantities of simple nitro-substitution products but no simple nitration product could be isolated in the 3-series. There is ample precedent for the nitroso-demethylations encountered in the present work. In particular, Ingold *et al.*[36] found that six intermediates were encountered in the conversion of 2,4-dinitrodimethylaniline into 2,4,6-*N*-tetranitromethylaniline; a detailed discussion is given of the mechanism of demethylation. It was concluded [36] that dealkylation probably occurs by an oxidative mechanism involving the formation of intermediates of type ArN^+Me_2NO, requiring nitrous acid, but autocatalytic in that the subsequent steps release additional amounts of nitrous acid.

TABLE 5

Nitration of 4-dimethylamino-3-nitropyridine, 2-dimethylamino-3-nitropyridine, and 2-dimethylamino-5-nitropyridine

Compound (temp.)	% H_2SO_4	$-H_0$ [a]	$4 + \log k_2$ (obs)	$4 + \log k_2'$	$4 + \log k_2'$ (fb)	$-(H_R + \log a_{H_2O})$ [b]
4-Dimethylamino-3-nitro-pyridine (50°)	82·05	7·22	0·110	0·119	12·569	17·15
	83·35	7·41	0·600	0·615	13·255	17·66
	85·61	7·75	1·046	1·080	14·060	18·56
	86·75	7·92	1·429	1·481	14·631	19·02
	89·07	8·23	1·747	1·855	15·315	
	89·92	8·34	1·825	1·962	15·532	
	90·30	8·40	1·759	1·918	15·547	
	90·82	8·47	1·817	2·000	15·700	
	92·01	8·65	1·736	2·008	15·888	
	92·85	8·77	1·440	1·772	15·772	
	94·82	9·10	1·163	1·730	16·060	
	96·90	9·48	0·614	1·521	16·231	
2-Dimethylamino-3-nitro-pyridine (30°)	78·92	7·17	0·014	0·014	9·944	15·91
	79·63	7·28	0·213	0·213	10·253	16·17
	79·95	7·34	0·276	0·276	10·376	16·30
	80·80	7·48	0·454	0·454	10·694	16·65
	82·20	7·69	0·792	0·792	11·242	17·20
	82·66	7·76	0·929	0·929	11·449	17·40
	83·75	7·96	1·245	1·245	11·965	17·83
	84·71	8·09	1·518	1·518	12·368	18·21
	85·76	8·24	1·848	1·848	12·848	18·62
	87·78	8·56	2·297	2·297	13·617	
	88·71	8·70	2·671	2·671	14·131	
	89·73	8·85	2·615	2·615	14·225	
	90·72	8·99	2·417	2·417	14·167	
	91·64	9·12	2·308	2·308	14·188	
	93·77	9·45	2·082	2·112	14·322	
	94·70	9·61	1·925	1·974	14·344	
	97·22	10·08	1·536	1·722	14·562	
	97·51	10·15	1·522	1·743	14·653	
2-Dimethylamino-5-nitro-pyridine (30°)	77·48	6·95	0·134	0·134	10·194	15·41
	78·01	7·03	0·342	0·342	10·482	15·60
	79·40	7·25	0·530	0·530	10·890	16·09
	79·75	7·30	0·691	0·691	11·101	16·23
	79·90	7·33	0·718	0·718	11·158	16·29
	81·10	7·57	0·942	0·942	11·562	16·77
			0·977	0·977	11·597	
	81·91	7·64	1·255	1·255	12·005	17·10
			1·348	1·348	12·098	
	82·80	7·78	1·467	1·467	12·357	17·45
	84·20	8·00	1·843	1·843	12·953	18·00
	86·69	8·37	2·041	2·041	13·521	
	87·55	8·52	2·189	2·189	13·819	
	88·20	8·63	2·195	2·195	13·935	
	90·43	8·95	1·964	1·964	14·024	
	91·72	9·13	1·690	1·690	13·930	
	93·31	9·38	1·342	1·342	13·832	
	97·43	10·14	0·341	0·341	13·591	

[a] At temperature of the experiment. [b] As Table 3.

[36] J. Glazer, E. D. Hughes, C. K. Ingold, A. T. James, G. T. Jones, and E. Roberts, *J. Chem. Soc.*, 1950, 2657.

TABLE 6

Temperature dependence of nitration rate for 4-dimethylamino-3-nitropyridine and 2-dimethylamino-3- and -5-nitropyridine

(*a*) 4-Dimethylamino-3-nitropyridine in 90·30% H_2SO_4

t/°C	log k_2'	log k_2' (fb)
20·2	−3·434	10·196
30·0	−2·902	10·648
40·9	−2·561	11·069
50·0	−2·083	11·547
50·2	−2·147	11·483
60·2	−1·797	11·832

(*b*) 2-Dimethylamino-5-nitropyridine in 79·80% H_2SO_4

t/°C	log k_2'	log k_2' (fb)
30·0	−3·310	5·991
30·0	−3·309	5·990
38·0	−2·757	6·543
38·0	−2·721	6·571
44·0	−2·414	6·887
50·0	−2·215	7·085
56·0	−1·810	7·490

(*c*) 2-Dimethylamino-3-nitropyridine

in 97·51% H_2SO_4

t/°C	log k_2'	log k_2' (fb)
25·1	−2·362	10·248
30·0	−2·257	10·353
35·0	−2·058	10·552
40·0	−1·916	10·694
45·0	−1·792	10·818
50·0	−1·499	11·111

in 79·63% H_2SO_4

t/°C	log k_2'	log k_2' (fb)
25·1	−4·039	5·701
30·0	−3·787	5·953
35·0	−3·600	6·140
40·0	−3·358	6·382
45·0	−3·101	6·640
50·0	−2·833	6·908

The varying amounts of demethylation and simple nitration found in the present work are governed by two generalisations. Increasing amounts of demethylation occur: (i) as the reactivity of the ring towards electrophilic substitution decreases and (ii) as the basicity of the dimethylamino-group increases (resulting in increased amounts of unreactive dication). These explain why the good yields of dimethylaminonitro-products found for the 2- and 4-dimethylaminopyridines are much reduced in the 3-series, for which the second pK_a is considerably higher,[8] and become zero for 2,6-dimethyl-3-dimethylaminopyridine: electrophilic substitution is known to be particularly difficult at the 4-position of a pyridine ring. A protonated *N*-oxide group reduces the rate of electrophilic substitution in the 3- and 5-positions of a pyridine ring, *e.g.* nitration of the cation of 2,6-dimethoxypyridine [37,38] is faster by a factor of 10 than 2,6-dimethoxy-1-hydroxypyridinium cation. It is at first sight peculiar that 3-dimethylaminopyridine 1-oxide does not nitrate readily in the 4-position, but this behaviour is almost certainly due to the relatively high second pK_a of this compound. The good yields of 3,5-dinitro-compound obtained by the nitration of the 3- and 5-mononitro-2-dimethylaminopyridines are noteworthy: although the first nitro-group decreases the susceptibility of the ring towards electrophilic attack, it also decreases the basicity at the dimethylamino-group and therefore increases the concentration of reactive monocations.

These qualitative conclusions are supported by the quantitative kinetic results next reported.

Kinetic Nitration of 2- and 4-Dimethylaminopyridine.—The high first pK_a values (6·94 and 9·70, respectively) are expected [10] to preclude nitration in sulphuric acid on the free-base species, while the second pK_a values (−10·21 and −9·28 respectively) ensure that the second conjugate acids are not the majority species over much of the range studied; these two compounds thus provide models for testing previously discussed criteria [39] particularly as the reactions were carried out at or near room temperature. (Kinetic measurements were not carried out for 3-dimethylaminopyridine owing to the complexity of the preparative nitration.)

Rate measurements are recorded in Table 2. Plots of log k_2' (corrected for the presence of diprotonated species) against H_0 show the typical shape for reaction *via* a majority species (Figure 1).

The rate profile slopes (−d log k_2'/d H_0) at high acidities (Table 8) do not show the typical behaviour of rate profiles for nitration *via* a majority species. There is undoubtediy an over-correction for the decrease in concentration of reactive species [equation (2)]; the acidity function H_+''' described by the protonation of dialkylaminopyridinium cations was assumed to be proportional to H_0 over the entire acidity range to an extent of $H_+''' : H_0 = 1{\cdot}2$, and although this is true for the region $-1 < \log([BH^{2+}]/[BH^+]) < 1$, it may not be true at higher acidities [correction of log k_2 (obs) using equation (2) with a value of $H_+''' : H_0 = 0{\cdot}8$—1·0 does give a rate profile of the expected shape]. Because of the uncertainty in the log k_2' values for 2- and 4-dimethylaminopyridine, no mechanistic conclusions can be drawn from the high-acidity rate-profile slopes.

Moodie–Schofield plots, log k_2' *vs.* $-(H_R + \log a_{H_2O})$, the significance of which has been discussed elsewhere,[40]

TABLE 7

Arrhenius parameters

Substituted pyridine	% H_2SO_4 [a]	$\Delta H^‡$ (kcal mol^{-1})	$\Delta S^‡$ (e.u.)	$\Delta G^‡$ at 25° (kcal mol^{-1})	log A	$\Delta S^‡$ (fb) [b] (e.u.)	$\Delta G^‡$ (fb) (kcal mol^{-1})	og A (fb)
4-Dimethylamino-3-nitro-	90·30	17·6	−14·0	21·8	10·2	49·6	3·3	24·1
2-Dimethylamino-3-nitro-	97·51	14·1	−21·9	20·6	8·5	35·8	3·5	21·1
	79·63	20·4	−8·5	22·9	11·4	36·1	9·6	21·1
2-Dimethylamino-5-nitro-	79·80	24·9	8·5	22·4	15·1	51·1	9·7	24·4
2-Dimethylamino-	97·40	13·3	−3·5	14·3	12·4	53·9	0·7	25·0
	76·16	16·8	−8·7	19·4	11·4	74·5	−8·9	29·5

[a] Wt. % H_2SO_4 used at each temperature. [b] Calculated using the following pK_a values: 2-dimethylamino-3-nitro-, 2·5; 2-dimethylamino-5-nitro-, 3·11 (P. J. Brignell, P. E. Jones, and A. R. Katritzky, *J. Chem. Soc.* (*B*), 1970, 117. The latter value is measured in 60% EtOH).

[37] C. D. Johnson, A. R. Katritzky, B. J. Ridgewell, and M. Viney, *J. Chem. Soc.* (*B*), 1967, 1204.

[38] C. D. Johnson, A. R. Katritzky, N. Shakir, and M. Viney, *J. Chem. Soc.* (*B*), 1967, 1213.

[39] A. R. Katritzky, C. D. Johnson, G. P. Bean, P. Bellingham, P. J. Brignell, B. J. Ridgewell, N. Shakir, O. Tarhan, M. Viney, and A. M. White, *Angew. Chem. Internat. Edn.*, 1967, **6**, 608.

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

TABLE 8

pK_a Values and rate-profile slopes

Pyridine substituents	pK_a values: 1st Protonation	pK_a values: 2nd Protonation [a]	Moodie-Schofield slopes: t [b]	Moodie-Schofield slopes: $-\frac{d \log k_2'}{d[H_R + \log a_{H_2O}]}$	Moodie-Schofield slopes: $-\frac{d \log k_2'}{d[H_R + \log a_{H_2O}]}$ (fb)	High-acidity rate-profile slopes: $-\frac{d \log k_2 (obs)}{d H_0}$	High-acidity rate-profile slopes: $-\frac{d \log k_2'}{d H_0}$	High-acidity rate-profile slopes: $-\frac{d \log k_2'}{d H_0}$ (fb)
2-Dimethylamino-	6·94	−8·59	30·0	0·89 (0·92)[c]		1·24	0·10	
4-Dimethylamino-	9·70	−6·91	50·0	0·83 (1·01)		0·87	−0·45	
2-Dimethylamino-5-nitro-	3·11		30·0	0·65 (0·68)	(1·05) [c]	1·35	1·35	0·35
2-Dimethylamino-3-nitro-	2·5	−10·30	30·0	0·62 (0·66)	(1·02)	0·82	0·65	−0·43
4-Dimethylamino-3-nitro-	5·23	−8·76	50·0	0·66 (0·84)	(1·04)	1·21	0·50	−0·50

[a] H_0 for half protonation are shown. [b] Temperature of rate profile determination. [c] Values in parentheses have been corrected. For H_R and log a_{H_2O} temperature dependence.

give good straight lines for both compounds. The slopes are somewhat less than unity, 0·86 ($r = 0·986$) for 2-dimethylaminopyridine at 50° and 0·81 ($r = 0·991$) for the 4-isomer at 30° Slopes of less than unity have previously been found at elevated temperatures;[41] however the recently-established temperature variation of H_R [42] allows calculation of these slopes corrected for the effect of temperature on H_R and log a_{H_2O};[43] the

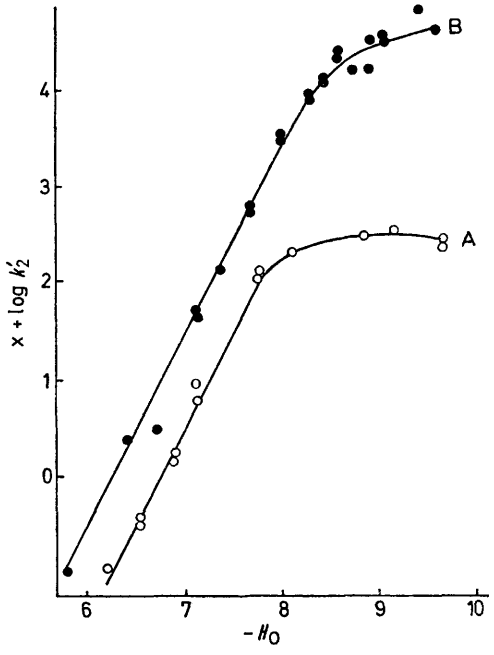

FIGURE 1 Rate profiles [log k_2'] for nitration of (A) 2-dimethylaminopyridine at 30° (x = 0) and (B) 4-dimethylaminopyridine at 50° (x = 1)

slopes for 2- and 4-dimethylaminopyridine become 0·94 and 0·93 respectively, indicating that both substrates are nitrated predominantly *via* their monocations.

Variable-temperature measurements for the rate of nitration of 2-dimethylaminopyridine at two acidities afforded activation parameters (Table 4), and in both cases the $\Delta H^{\ddagger}$ values fell within the range 12·5 to 20·2 kcal mol^{-1} generally reported for conjugate acid nitrations.[41]

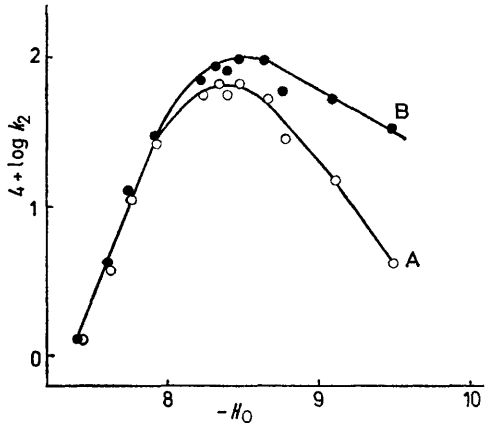

FIGURE 2 Rate profiles for the nitration of 4-dimethylamino-3-nitropyridine at 50°, (A) log k_2 (obs), (B) log k_2'

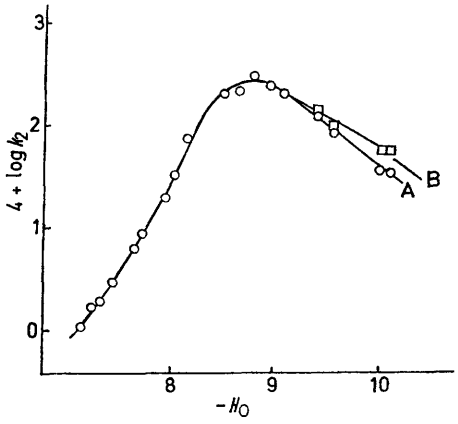

FIGURE 3 Rate profiles for the nitration of 2-dimethylamino-3-nitropyridine at 30°, (A) log k_2 (obs) and (B) log k_2'

Kinetic Nitration of 4-Dimethylamino-3-nitropyridine and 2-Dimethylamino-3- and -5-nitropyridine.—Rate profiles, corrected for any diprotonation, are shown in Figures 2—4.

For both 2-dimethylamino-compounds the slopes of

[41] Summarised in E. F. V. Scriven, Ph.D. Thesis, University of East Anglia, 1969.

[42] Work in progress with T. W. Toone.

[43] A. R. Katritzky and B. J. Ridgewell, *J. Chem. Soc.*, 1963, 3753.

the Moodie–Schofield plots (Table 8) indicate reaction is proceeding on the free-base species in the low-acidity region, but the encounter rates are close to or less than the k_0 (fb) observed. This indicates that a proton-loss mechanism, as previously mentioned, may indeed be occurring. However, for 4-dimethylamino-3-nitropyridine the Moodie–Schofield slope is indeterminate.

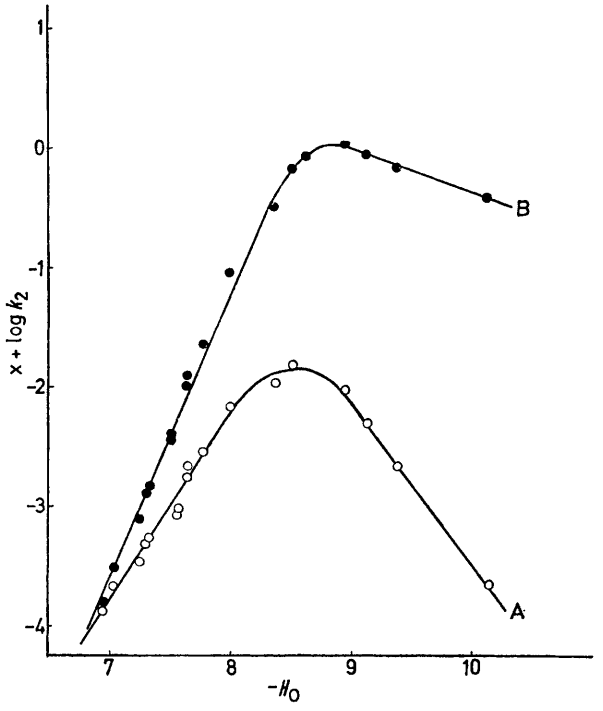

FIGURE 4 Rate profiles for the nitration of 2-dimethylamino-5-nitropyridine at 30°, (A) log k_2 (obs) (x = 0), and (B) log k_2' (fb) (x = −10)

The rate-profile slope in the high acidity region for 2-dimethylamino-5-nitropyridine (Table 8) indicates that reaction is proceeding on the free-base species in this acidity range also; correction of the rate constants for the concentration of free base (Figure 4) gives a 'corrected' rate-profile slope expected for a majority species reaction. This conclusion is supported by the Arrhenius parameters (Table 7) obtained in 79·80% H_2SO_4 for this compound. The free-base rate constants do not greatly exceed the calculated encounter rates (Table 9); the close correspondence does not allow distinction without model compound studies between normal free-base nitration and a proton-loss mechanism in the high-acidity region. The high-acidity rate-profile slope for 2-dimethylamino-3-nitropyridine indicates reaction *via* the first conjugate acid, a conclusion supported by the slope of the rate profile when rate constants are corrected for diprotonation, by the Arrhenius parameters determined in 97·51% H_2SO_4, and further by the calculated high acidity log k_2' (fb) values which significantly exceed the calculated encounter rates.

4-Dimethylamino-3-nitropyridine by virtue of its relatively high first pK_a might have been expected to undergo nitration on the first conjugate acid over the entire acidity range. This is certainly the case for the high-acidity region. A mechanistic changeover may occur between H_0 −7 and −8 [from the comparison of log k_2' (fb) and log k (enc)] whereas for 2-dimethylamino-3-nitropyridine, the changeover occurs between H_0 −8 and −9.

TABLE 9

Comparison of k_2* (fb) and k (enc)

Pyridine substituents	log k_2* (fb) [a]			
	H_0 −7	H_0 −8	H_0 −9	H_0 −10
2-Dimethylamino-	17·27	18·01	18·25	19·35
4-Dimethylamino- [b]	20·19	20·95	20·91	22·13
2-Dimethylamino-5-nitro-	9·07	9·24	8·70	8·37
2-Dimethylamino-3-nitro-	9·16	9·93	10·01	10·34
4-Dimethylamino-3-nitro-	11·04	11·39	11·00	11·54
log k (enc) [c]	8·59	8·45	8·45	8·48

[a] Extrapolated to 25°; see text. [b] Calculated using an estimated activation energy of 17 kcal mol^{-1}. [c] For calculation of k (enc), see text.

Finally, we must consider the proton-loss mechanism, as proposed by Hartshorn and Ridd [7] for the nitration of 4-nitroaniline (pK_a 0·99) and 2-chloro-4-nitroaniline (pK_a 0·85). For this mechanism, the rate profile for nitration should have a similar shape to one for a minority species reaction, whereas $\Delta S^{\ddagger}$ and log A values are typically greater (more positive) than those generally found for free-base nitrations. The mechanism is conclusively demonstrated if the calculated free-base rate constants are greater than the calculated encounter rates for the free-base species. The following paper discusses model compound studies, designed to delineate the extent of the proton-loss mechanism for these compounds and for 2-dimethylamino-5-nitropyridine. Rate constants for nitration at 25° and H_0 −6·60 and partial rate factors are compared in Table 10: discussion is reserved for a later stage.

TABLE 10

Rate constants for nitration at 25° and H_0 −6·60 [a]

Pyridine substituents	log k_0'	log k_0' (fb)	Partial rate factor (cation) [b]	Partial rate factor (neutral species) [b]
2-Dimethylamino-	−1·49	12·19	$9·3 \times 10^{-3}$	$4·5 \times 10^{11}$
4-Dimethylamino- [c]	−1·23	14·88	$1·7 \times 10^{-2}$	$2·2 \times 10^{14}$
2-Dimethylamino-3-nitro-	−5·53	4·09	$8·5 \times 10^{-7}$	$3·5 \times 10^{3}$
2-Dimethylamino-5-nitro-	−4·69	4·07	$5·9 \times 10^{-6}$	$3·4 \times 10^{3}$
4-Dimethylamino-3-nitro- [c]	−7·04	5·90	$2·6 \times 10^{-8}$	$2·3 \times 10^{5}$

[a] For method of calculation, see text. [b] Calculated taking log k_2 = 0·54 for one position of benzene in 75% H_2SO_4 at 25°; see ref. 4. [c] Calculated using an estimated activation energy of 17 kcal mol^{-1}.

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