Kinetics of Reactions in Heterocycles. Part X.[1] Reactions of Substituted *N*-Methylpyridinium Salts with Hydroxide Ions

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Kinetics of the reactions of halogeno-, methoxy-, methylthio-, and methylsulphonyl-substituted *N*-methylpyridinium salts with hydroxide ions have been determined. The salts with the leaving group in the 2-position were the most reactive: *e.g.* the k_2 values for 2-, 3-, and 4-methoxypyridine methiodides at 20° were $2{\cdot}9 \times 10^{-2}$, $5{\cdot}0 \times 10^{-9}$, and $7{\cdot}6 \times 10^{-4}$ l mol^{-1} s^{-1}, respectively. Quaternisation of 4-methylsulphonylpyridine by methylation increased its reactivity to hydroxide ions by $7{\cdot}3 \times 10^{8}$-fold at 20°, owing to a decrease in energy of activation of 7·1 kcal mol^{-1}, and an increase in log *A* 3·5 units.

U.v. and ^{1}H n.m.r. spectra are recorded and discussed.

THE quantitative effect of protonation or *N*-methylation on the nucleophilic displacement of substituents from nitrogenous heterocycles has not been studied extensively.[2] The reactivities of 2-, 3-, and 4-chloro-*N*-methylpyridinium salts with sodium *p*-nitrophenoxide in absolute methanol have been measured,[3] and quantitative estimates have been made of their reactivities with sodium methoxide in methanol;[4] the reactions of 2-, 3-, and 4-cyano-*N*-methylpyridinium salts with hydroxide ions have also been examined.[5] O'Leary and Stach,[6] in a paper which appeared after the commencement of our work, have reported kinetic

[1] Part IX, G. B. Barlin and A. C. Young, *J. Chem. Soc.* (*B*), 1971, 2323.

[2] R. G. Shepherd and J. L. Fedrick, *Adv. Heterocyclic Chem.*, 1965, **4**, 145.

[3] M. Liveris and J. Miller, *Austral. J. Chem.*, 1958, **11**, 297.

[4] M. Liveris and J. Miller, *J. Chem. Soc.*, 1963, 3486.

[5] J. W. Patton, Ph.D. Thesis, University of Wisconsin, 1961 (*Diss. Abs.*, 1961, **22**, 745).

[6] M. H. O'Leary and R. W. Stach, *J. Org. Chem.*, 1972, **37**, 1491.

results for the reactions of 4-halogeno- and 4-methoxy-*N*-methylpyridinium salts with hydroxide ions.

We have now commenced a detailed examination of the reactivity of quaternised heterocycles to obtain a quantitative measure of activation by quaternisation, and also its effect on relative positional reactivities. In this paper we augment the existing data in the pyridine series by a kinetic study of replacements in 2-, 3-, and 4-substituted-*N*-methylpyridinium salts using hydroxide ions in water to give the *N*-methylpyridone or 3-hydroxy-*N*-methylpyridinium salt. This reagent was chosen as nucleophile instead of the very reactive alkoxide ions because it gave measurable rates with the more reactive pyridinium salts, and because of the possibility [3] of solvolysis or demethylation with the latter.

The required pyridinium salts were prepared by direct methylation of the substituted pyridines with methyl iodide. Mild conditions of temperature were generally required so that exchange of the substituent [3,7] did not take place. The products were purified by recrystallisation where possible, but where high reactivity prevented this the crystalline solid was washed well with a solvent and dried. Particular care was required with 2-methoxypyridine methiodide as it decomposed readily at room temperature in air. Attempted methylations of 2-methylsulphonyl- [8] and 2- and 4-nitro-pyridines [9] were unsuccessful.

Results of the kinetic studies are given in Tables 1—3. Typical runs (Table 1) revealed that each reaction followed regular kinetics. For the reactions of the

TABLE 1

Reactions with hydroxide ions

2-Fluoropyridine methiodide at 10·7°
Hydroxide ion 0·00030M; methiodide 0·000098M

Time (s)	2·5	3·9	5·6	7·2	9·3	11·7	14·4	17·5	20·6
Reaction (%)	17·8	26·6	35·4	42·4	49·6	55·9	61·7	67·1	71·6
k/l mol^{-1} s^{-1}	282	291	301	304	305	299	296	294	293

Mean k = 296 ± 7·2

2-Chloropyridine methiodide at 55·3°
Hydroxide ion 0·000987M; methiodide 0·0000987M

Time (s)	11·5	18·8	26·2	36·6	50·3	66·0	83·8	104·7	130·9	167·5	209·4
Reaction (%)	11·4	18·0	23·9	31·6	40·1	49·1	57·0	64·3	72·5	80·1	86·4
k/l mol^{-1} s^{-1}	10·7	10·9	10·9	10·9	10·8	11·0	10·9	10·8	11·0	10·9	10·9

Mean k = 10·9 ± 0·07

2-Methoxypyridine methiodide at 47·5°
Hydroxide ion 0·000988M; methiodide 0·000131M

Time (s)	375	650	945	1275	1920	2370	2800	4005	5115
Reaction (%)	13·4	21·8	30·0	37·7	51·7	58·8	65·3	77·2	84·3
$10k$/l mol^{-1} s^{-1}	3·91	3·88	3·90	3·86	3·99	3·97	4·03	3·99	3·95

Mean $10k$ = 3·94 ± 0·06

3-Methoxypyridine methiodide at 141·5°
Hydroxide ion 0·0463M; methiodide 0·00474M

Time (s)	600	1149	1860	2567	3480	4813	5251	8411
Reaction (%)	9·3	18·2	28·2	35·4	45·6	56·6	59·5	74·1
10^3k/l mol^{-1} s^{-1}	3·52	3·81	3·91	3·75	3·88	3·88	3·85	3·63

Mean 10^3k = 3·78 ± 0·14

2-Methylthiopyridine methiodide at 34·9°
Hydroxide ion 0·0164M; methiodide 0·00166M

Time (s)	509	1090	1647	2228	3049	4002	5328	7431	11,089
Reaction (%)	12·1	24·7	33·1	42·3	52·3	61·5	71·5	81·6	92·1
k/l mol^{-1} s^{-1}	0·0157	0·0163	0·0154	0·0157	0·0157	0·0157	0·0158	0·0155	0·0160

Mean k = 0·0157 ± 0·00026

4-Methylsulphonylpyridine methiodide at 19·0°
Hydroxide ion 0·000501M; methiodide 0·0000496M

Time (s)	3·0	6·0	9·7	14·9	21·8	29·8	40·7	53·6	69·5
Reaction (%)	8·7	16·9	25·7	36·2	47·5	57·6	68·2	77·3	85·1
k/l mol^{-1} s^{-1}	61·2	63·0	62·6	62·6	62·2	61·6	61·2	61·1	61·6

Mean k = 61·9 ± 0·7

4-Methylsulphonylpyridine at 110·5°
Hydroxide ion 0·0950M; methylsulphonyl compound 0·00303M

Time (s)	1620	3000	4200	5760	8640	12,060	15,360	16,200
Reaction (%)	19·5	34·0	43·4	52·8	68·5	80·2	85·8	87·8
10^3k/l mol^{-1} s^{-1}	1·42	1·47	1·44	1·38	1·43	1·44	1·36	1·39

Mean 10^3k = 1·42 ± 0·03

[7] H. L. Bradlow and C. A. Vanderwerf, *J. Org. Chem.*, 1951, **16**, 1143.

[8] W. Markwald, W. Klemm, and H. Trabert, *Ber.*, 1900, **33**, 1556.

[9] A. Kirpal and W. Böhm, *Ber.*, 1932, **65**, 680.

TABLE 2

Kinetic results for the reactions of substituted pyridine methohalides and 4-methylsulphonylpyridine with hydroxide ion

Temp.[a] (°C)	10^4[OH^-]/M	10^5[$\overset{+}{N}$Me]/M	k_2 [b,c]	$t_{\frac{1}{2}}$ [d]	$t_{\frac{1}{2}}/t_{\frac{1}{2}}'$ [e]	$(t_{\frac{1}{2}}/t_{\frac{1}{2}}')_{calc.}$ [f]	Analyt. λ/nm [g]
			2-Fluoropyridine methiodide *				
22·0	3·0	8·81	655·4				297
16·6	3·0	9·91	464·9	5·5			297
16·6	1·5	5·34	409·0	14·3	2·61	2·02	297
10·7	3·0	9·82	296·2				297
			2-Chloropyridine methiodide *				
55·3	9·87	9·87	10·9	68·4			297
55·3	4·94	4·94	11·27	132·0	1·93	2·00	297
47·1	9·91	9·86	6·37				297
38·0	9·95	10·1	3·07				297
			2-Bromopyridine methiodide *				
55·3	9·87	9·87	7·24	102·8			297
55·3	4·94	4·94	7·27	204·7	1·99	2·00	297
47·3	9·92	10·4	4·11				297
38·1	9·95	10·1	1·86				297
			2-Bromopyridine methobromide *				
55·3	9·87	9·87	7·57	98·4			297
55·3	4·94	4·94	7·51	198·1	2·01	2·00	297
47·3	9·91	9·96	4·23				297
38·0	9·95	10·0	1·96				297
			2-Iodopyridine methiodide †				
20·2	62·5	65·0	0·0886				293
13·2	125·0	129·0	0·0412	1430			293
13·2	63·0	64·3	0·0439	2658	1·86	1·99	293
5·7	125·2	129·5	0·0195				293
			2-Methoxypyridine methiodide *				
52·2	9·85	12·6	0·585				297
47·5	9·88	13·1	0·394	1849			297
47·5	4·94	6·52	0·363	4014	2·17	1·98	297
40·0	9·92	12·7	0·204				197
			3-Methoxypyridine methiodide †				
150·9	456	470	0·00776	2017			318
149·5	230	235	0·00792	3919	1·94	1·98	318
147·0	461	472	0·00635				318
141·5	463	474	0·00378				318
128·6	469	480	0·00143				318
			2-Methylthiopyridine methiodide †				
34·9	328·6	351·2	0·0164	1367			318
34·9	164·3	166·0	0·0157	2841	2·08	2·00	318
24·8	329·6	331·4	0·00490				318
14·6	330·3	331·9	0·00174				318
			4-Methylthiopyridine methiodide †				
75·0	243·7	245·7	0·00631	4780			262
75·0	121·9	122·8	0·00620	9727	2·03	2·00	262
64·6	245·6	247·6	0·00232				262
55·2	246·4	248·4	0·00108				262
			4-Methylsulphonylpyridine methiodide *				
29·5	4·99	4·94	161·7				260
20·0	5·01	4·94	74·1	19·8			260
20·0	2·50	2·47	69·1	42·4	2·14	2·00	260
19·0	5·01	4·96	61·9				260
15·4	5·01	4·96	43·5				260
			4-Methylsulphonylpyridine †				
113·3	950	423	0·00172				255
110·5	950	303	0·00142	5200			255
110·5	476	159	0·00135	10,883	2·09	2·00	255
103·2	960	307	0·000775				255
90·7	970	323	0·000255				255

[a] ±0·2° for the rapid reaction experiments; otherwise ±0·1° for temperatures less than 90°, and ±0·3° for temperatures greater than 90°. [b] In 1 mol^{-1} s^{-1}; the standard deviation was usually within ±3%. [c] Corrected for solvent expansion or contraction. [d] Time for 50% reaction in s. [e] The ratio of $t_{\frac{1}{2}}$ values for two experiments at different concentrations. [f] Calculated values from the concentrations of reactants employed. [g] Analytical wavelength for the determination of percentage reaction.

* Rapid reaction ' stopped-flow ' technique (ref. 18) used to study this reaction. † pH 7 buffer solution used to stop the reactions and for spectroscopic measurements.

halogeno-, methylthio-, and methylsulphonyl compounds the second-order rate equation (Experimental section), which allowed for the consumption of 2 moles of sodium hydroxide per mole of heterocycle, was used, but for the methoxy-*N*-methylpyridinium iodides, due allowance for the consumption of 1 mole only of sodium hydroxide was made in the calculations. (The rate coefficients determined for 4-methoxy-*N*-methylpyridinium iodide were consistent with those later published by O'Leary and Stach,[6] who used pseudo-first-order conditions.) The reactions were shown to be essentially bimolecular and followed second-order kinetics as indicated by the $t_{\frac{1}{2}}$ values. The greatest variation in the results was shown by 2-fluoropyridine methiodide, owing to the comparison (Table 4) of the reactivities (at 20°) of the 2-halogeno-*N*-methylpyridinium salts with the data for the 4-isomers [6] revealed that the former were appreciably more reactive, by 43 to 330 times (the ratio for the chloro-compounds was higher than that reported by Liveris and Miller [3] for their reactions with sodium *p*-nitrophenoxide in methanol). The higher reactivity of the 2-series was reflected, in general, in significantly lower values of E (contrast with the results in ref. 3) and larger values of log A.

The greater reactivity of the 2-isomers is due to the stronger attraction between the cationic substrate and the anionic nucleophile. Amongst the halogeno-compounds, the greater positional difference in reactivity of

TABLE 3

Rate coefficients and Arrhenius parameters for reactions with hydroxide ion

Compound		k_2 20° [a]	E/ kJ mol^{-1} [b] (kcal mol^{-1})	log A [c]	$\Delta H^{\ddagger}$/ kJ mol^{-1} [b] (kcal mol^{-1})	$-\Delta S^{\ddagger}$/ kJ mol^{-1} deg^{-1} [d] (kcal mol^{-1} deg^{-1})
N-Methylpyridinium salt						
2-F	I^-	$5{\cdot}72 \times 10^{2}$	48·6 (11·6)	11·4	46·0 (11·0)	34·7 (8·3)
2-Cl	I^-	$6{\cdot}92 \times 10^{-1}$	62·8 (15·0)	11·0	60·3 (14·4)	43·1 (10·3)
2-Br	I^-	$3{\cdot}70 \times 10^{-1}$	67·6 (16·15)	11·6	64·9 (15·5)	31·8 (7·6)
2-Br	Br^-	$4{\cdot}10 \times 10^{-1}$	65·9 (15·75)	11·4	63·2 (15·1)	35·6 (8·5)
2-I	I^-	$8{\cdot}69 \times 10^{-2}$	71·1 (17·0)	11·6	68·6 (16·4)	31·0 (7·4)
4-F	I^- [e]	1·74	56·9 (13·6)	10·4	54·4 (13·0)	54·4 (13·0)
4-Cl	I^- [e]	$5{\cdot}96 \times 10^{-3}$	72·0 (17·2)	10·6	69·5 (16·6)	50·6 (12·1)
4-Br	BF_4^- [e]	$4{\cdot}81 \times 10^{-3}$	72·8 (17·4)	10·6	70·3 (16·8)	49·4 (11·8)
4-I	BF_4^- [e]	$2{\cdot}00 \times 10^{-3}$	71·1 (17·0)	9·9	68·6 (16·4)	62·8 (15·0)
2-OMe	I^-	$2{\cdot}90 \times 10^{-2}$	74·5 (17·8)	11·7	72·0 (17·2)	29·7 (7·1)
3-OMe	I^-	$5{\cdot}0 \times 10^{-9}$ [f]	113·4 (27·1)	11·9	110·1 (26·3)	28·0 (6·7)
4-OMe	BF_4^- [e]	$7{\cdot}59 \times 10^{-4}$	76·6 (18·3)	10·5	74·1 (17·7)	52·7 (12·6)
2-MeS	I^-	$2{\cdot}87 \times 10^{-3}$	80·8 (19·3)	11·9	78·3 (18·7)	25·3 (6·05)
4-MeS	I^-	$2{\cdot}21 \times 10^{-5}$ [f]	86·2 (20·6)	10·7	83·3 (19·9)	49·4 (11·8)
4-$MeSO_2$	I^-	$7{\cdot}41 \times 10^{1}$	69·1 (16·5)	14·1	66·5 (15·9)	−16·7 (−4·0)
Pyridine						
4-$MeSO_2$		$1{\cdot}02 \times 10^{-7}$ [f]	98·8 (23·6)	10·6	95·8 (22·9)	52·1 (12·45)

[a] Rate coefficient at 20·0° in 1 mol^{-1} s^{-1}. Experimental result or calculated from the rate coefficient at a nearby temperature unless otherwise stated. [b] Accurate to 5·0 kJ mol^{-1}; based on standard deviations. [c] Accurate to ±0·8 units. [d] Accurate to 4·0 kJ mol^{-1} deg^{-1}. [e] Ref. 6. [f] Calculated from E and A values.

very small $t_{\frac{1}{2}}$ values (5·5 s) and low concentrations of hydroxide ions. Although hydrolysis rates in similar reactions have been claimed [6] to be sensitive to ionic strength, we worked at lower concentrations, without further examination of this effect.

At 20°, the rate coefficients for the halogeno-*N*-methylpyridinium salts were in the expected order (F > Cl ≃ Br > I) and the rate variations were due principally to significant changes in the energy of activation (Table 3; that for the fluoro-compound being least), with small variations in log A. A small difference only was found in the reactivities of 2-bromopyridine

TABLE 4

Comparison of reactivity of 2- and 4-substituted *N*-methylpyridinium salts with hydroxide ion at 20°

Substituent	F	Cl	Br	I	MeO	MeS
Ratio of rate coeffts. of 2- and 4-isomers	329	116	77	43·5	38·2	130

methiodide and methobromide, and was neglected as in earlier work with chloro-*N*-methylpyridinium salts.[3] A

[10] N. B. Chapman and D. Q. Russell-Hill, *J. Chem. Soc.*, 1956, 1563.

the fluoro-compounds is probably due to the stronger electron withdrawal by the fluoro-substituent, which weakens the F–C bond most at the 2-position, near to the positive charge.

This order of positional reactivity contrasts with that of the unquaternised 4- and 2-chloropyridines, which with ethoxide ion [10] at 20° and methoxide ion [4] at 50° had relative reactivities of *ca.* 40 and 27, respectively; the 4-isomer being the most reactive and possessing the lower energy of activation.

Of the isomeric methoxy- and methylthio-*N*-methylpyridinium salts, the 2-isomers again were the more reactive and the positional reactivity ratios were similar to those of the halogeno-compounds.

At 20° the methoxy-*N*-methylpyridinium salts were more reactive than the methylthio-analogues and this was consistent with the reactivities of unquaternised methoxy- and methylthio-pyrimidines towards aminolysis.[11] As the reactions of the methylthio-compounds were conducted with a *ca.* ten molar excess of hydroxide

[11] G. B. Barlin and D. J. Brown, *Topics Heterocyclic Chem.*, 1969, 122; D. J. Brown and R. V. Foster, *Austral. J. Chem.*, 1966, **19**, 1487.

ions, and under relatively mild conditions, the rate equation used in the calculations was not varied to allow for possible regeneration of hydroxide ions [12] by oxidation of the thiolate ions to disulphide.

A comparison of the reactivities of 2-, 3-, and 4-methoxypyridine methiodides with hydroxide ions at 20° revealed rate ratios of $0{\cdot}58 \times 10^7 : 1 : 1{\cdot}52 \times 10^5$, as compared with ratios of $4{\cdot}89 \times 10^7 : 1 : 1{\cdot}62 \times 10^6$ for the reactions of chloro-*N*-methylpyridinium salts with *p*-nitrophenoxide anion in methanol at 50°.[3]

Detailed kinetic data for the reactions of 3-methylthio- and 3-bromo-*N*-methylpyridinium iodides could not be determined because reaction with an excess of hydroxide ion gave partial conversion only into the hydroxy-compound (as shown by the absorption at 320 nm).[13]

3-Nitro- and 3-methylsulphonyl-pyridine methiodides reacted with 10^{-3} and 10^{-1}M-sodium hydroxide respectively at *ca.* 50°, but the spectra of the resulting mixtures differed significantly from those of 3-hydroxy-*N*-methylpyridinium salts.

The first direct quantitative comparison of the reactivities of quaternised and unquaternised heterocycles has been made in the case of the reactions of hydroxide ion with 4-methylsulphonylpyridine and its methiodide. At 20°, the methiodide was $7{\cdot}3 \times 10^8$ times more reactive, its energy of activation was 7·1 kcal mol^{-1} lower, and its log *A* factor was 3·5 units higher than for 4-methylsulphonylpyridine.

Accurate kinetic data could not be determined for the reactions of 2- and 4-chloropyridine with hydroxide ion, owing to the occurrence of competing reactions at the high temperatures required, but approximate rate coefficients were determined for reactions at *ca.* 140° in sealed glass tubes (Table 5). Comparison of these rate

TABLE 5

Comparison of rate coefficients (l mol^{-1} s^{-1}) for the reactions of substituted *N*-methylpyridinium salts (N^+Me) and their unquaternised analogues (N) with hydroxide ion

Substituent	Temp. (°C)	Rate coefficient N^+Me compound	Rate coefficient N compound	Ratio N^+Me : N
2-Cl	142·8	$1{\cdot}32 \times 10^3$ [a]	5×10^{-6} [b]	$2{\cdot}6 \times 10^8 : 1$
4-Cl	144·6	$4{\cdot}01 \times 10^1$ [a]	2×10^{-5} [b]	$2{\cdot}0 \times 10^6 : 1$
4-SO_2Me	20·0	$7{\cdot}41 \times 10^1$	$1{\cdot}02 \times 10^{-7}$ [a]	$7{\cdot}3 \times 10^8 : 1$

[a] Calculated from *E* and *A* values; current work. [b] Approximate value only, obtained for partial reaction in glass vessels.

coefficients with values obtained for the methiodides by extrapolation revealed relative reactivities similar to those obtained for the methylsulphonyl compounds.

The difference in reactivity (*ca.* $3{\cdot}4 \times 10^6$) between 4-methylsulphonyl- and 4-methylthio-pyridine methiodides in reactions with hydroxide ions at 20° (Table 3) was greater than that found generally for methylsulphonyl- and methylthio-heterocycles with methoxide ions.[12] This is probably due to weakening of the S–C(4) bond by the powerfully electron-withdrawing methylsulphonyl group [14] in the cation.

3-Methylsulphonylpyridine did not react when treated with 5M-sodium hydroxide at 149° for 52 h.

U.v. and ^{1}H *N.m.r. Spectra.*—The u.v. spectra of the substituted *N*-methylpyridinium salts (Table 6) showed

TABLE 6

U.v. spectra

Compound	Species [a]	$\lambda_{max.}$/nm [b]	log ε [b]	pH
N-Methylpyridinium iodide [c]				
2-F [d]	+	263	3·71	7·0
2-Cl	+	213, 274	3·66, 3·86	7·0
2-Br	+	*214*, 277, *280*	*3·66*, 3·91, *3·90*	7·0
2-I [d]	+	230, 295	3·66, 3·94	7·0
2-OMe	+	226, 281	3·73, 3·79	7·0
2-SMe	+	248, 315	3·92, 3·97	7·0
3-Br	+	*224*, 279	*3·69*, 3·64	7·0
3-I	+	221, *239*, 295	3·94, *3·76*, 3·49	7·0
3-OMe	+	227, 289	3·67, 3·77	7·0
3-SMe	+	231, 270, 330	4·02, 3·96, 3·45,	7·0
3-SO_2Me	+	<210, *258*, 263, *268—269*	>3·71, *3·55*, 3·64, *3·55*	7·0
3-NO_2 [e]	+	234, 269, *274*	3·71, 3·65, *3·59*	7·0
4-OMe	+	242, *249*	4·13, *4·06*	7·0
4-SMe	+	232·5, 304	3·94, 4·34	7·0
4-SO_2Me	+	213, 271, *277*	3·83, 3·74, *3·63*	7·0
3-OH [f]	±	249, 320	3·91, 3·76	7·0
Pyridine				
1-Me 2=O [f]	0	224, 293	3·86, 3·77	6·0
1-Me 4=O [f]	0	253	4·17	7·0
3-SO_2Me	0	208, 255, 260, *265*	3·87, 3·39, 3·41, *3·30*	7·0
	+	260, *265*	3·70, *3·64*	−1·2 [g]

[a] 0, Neutral species; +, cation; ± zwitterion. [b] Shoulders and inflexions in italics. [c] Reference cell compensated with iodide ion. [d] Ref. 7 gives the spectral curves for this compound in water. [e] Ref. 31 gives $\lambda_{max.}$ 266 nm. [f] Ref. 13. [g] Hammett acidity function (*cf.* M. A. Paul and F. A. Long, *Chem. Rev.*, 1957, **57**, 1) in aqueous hydrochloric acid.

bathochromic shifts relative to the corresponding pyridines,[14-17] similar in magnitude to those observed on protonation of the latter. These shifts were greatest for the methylthio-compounds (22—40 nm) and least for the fluoro-, methylsulphonyl and nitro-compounds (3—6 nm); they were most marked in the 4-substituted series, and increased in the series I > Br > Cl > F.

The ^{1}H n.m.r. spectra (Table 7) of the substituted pyridines and their methiodides revealed significant downfield shifts on quaternisation, the protons at the 6- and 2-positions being, in general, least affected. The *N*-methyl signal was in the range δ 4·05—4·60.

EXPERIMENTAL

Solids for analysis were dried at 100° unless otherwise stated. M.p.s were taken for samples in Pyrex capillaries. All compounds were recrystallised to constant m.p. where possible and were further examined for the presence of impurities by paper chromatography on Whatman No. 1 paper in (*a*) aqueous 3% ammonium chloride, and (*b*) butan-2-ol–5M-acetic acid (7 : 3), and by t.l.c.

For kinetic studies, the fast reactions were examined by use of a Shimadzu R27 recording spectrophotometer fitted

[12] G. B. Barlin and W. V. Brown, *J. Chem. Soc.* (*B*), 1968, 1435.
[13] S. F. Mason, *J. Chem. Soc.*, 1959, 1253.
[14] G. B. Barlin and W. V. Brown, *J. Chem. Soc.* (*B*), 1967, 648.
[15] H. C. Brown and D. H. McDaniel, *J. Amer. Chem. Soc.*, 1955, **77**, 3752.
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TABLE 7

^{1}H N.m.r. spectra (δ values) [a]

Compound	Species	2-H	3-H	4-H	5-H	6-H	N+Me	Other Me
N-Methylpyridinium iodide								
2-F	+		8·55—8·88	7·70—8·10	7·70—8·10	8·55—8·88	4·30d	
2-Cl	+		7·97—8·77	7·97—8·77	7·97—8·77	9·02m	4·44	
2-Br	+		8·40—8·56	8·40—8·56	7·95—8·32	9·06m	4·49	
2-I	+		7·90—9·20	7·90—9·20	7·90—9·20	7·90—9·20	4·48	
2-OMe	+		8·35—8·48	7·48—7·73	7·48—7·73	8·35—8·48	4·05 [g]	4·31 [g]
2-SMe	+		8·27—8·56	7·58—8·05	7·58—8·05	8·78m	4·22	2·86
3-Br	+	9·22m		8·75—8·98	7·94—8·20	8·75—8·98	4·45	
3-I	+	9·28m		8·80—9·10	7·70—8·20	8·80—9·10	4·40	
3-OMe	+	8·46—8·65		8·14m	8·14m	8·46—8·65	4·44	4·10
3-SMe	+	8·71m		8·33—8·42	7·87—8·12	8·52—8·59	4·44	2·72
3-SO_2Me	+	9·69m		9·11—9·31	8·38—8·60	9·11—9·31	4·58	3·50
3-NO_2	+	10·03m		9·27—9·53	8·34—8·60	9·27—9·53	4·62	
4-OMe	+	8·63m	7·56m		7·56m	8·63m	4·28 [g]	4·19 [g]
4-SMe	+	8·48m	7·81m		7·81m	8·48m	4·26	2·71
4-SO_2Me	+	9·34m	8·73m		8·73m	9·34m	4·60	3·53
Pyridine								
2-F [b]	0		6·80—7·40	7·87m	6·80—7·40	8·25m		
2-Cl [b]	0		7·07—7·80	7·07—7·80	7·07—7·80	8·39m		
2-Br [b]	0		7·16—7·80	7·16—7·80	7·16—7·80	8·43m		
2-OMe [c]	0		6·63—6·92	7·36—7·67	6·63—6·92	8·19m		3·90
2-OMe [d]	+		8·40—8·90	7·52—7·84	7·52—7·84	8·40—8·90		4·34
2-SMe [c]	0		7·25m	7·6m	7·1m	8·58m		2·61
2-NO_2 [b]	0		8·04—8·47	8·04—8·47	7·74—7·98	8·77m		
3-Br [b]	0	8·75		7·83m	7·08—7·45	8·58m		
3-I	0	8·92		8·09m	7·16m	8·63m		
3-SMe	0	8·52m		7·60m	7·10—7·35	8·39m		2·48
3-SO_2Me	0	9·22m		8·35m	7·72m	8·97m		3·25
3-NO_2	0	9·54d		8·64m	7·68m	9·04m		
4-OMe [b,f]	0	8·46m	6·82m		6·82m	8·46m		3·77
4-OMe [d]	+	8·78m	7·65m		7·65m	8·78m		4·23
4-SMe [e]	0	8·54q	7·21q		7·21q	8·54q		2·51
4-SO_2Me [e]	0	9·09q	7·94q		7·94q	9·09q		3·14
4-NO_2	0	9·07m	8·16m		8·16m	9·07m		

[a] Spectra of the cations (+) were determined in D_2O with sodium 3-trimethylsilylpropane-1-sulphonate as internal standard, and neutral species (0) in $CDCl_3$ with tetramethylsilane. [b] T. J. Batterham (NMR Spectra of Simple Heterocycles, Wiley, New York, 1973), and W. Brügel (*Z. Electrochem.*, 1962, **66**, 159) give the n.m.r. spectrum in other solvent systems. [c] R. H. Cox and A. A. Bothner-By (*J. Phys. Chem.*, 1969, **73**, 2465) give the n.m.r. spectrum in CCl_4, and E. Spinner and G. B. Yeoh [*J. Chem. Soc.* (*B*), 1971, 279] in MeOD–D_2O. [d] In N-DCl. [e] Ref. 14. [f] P. Bellingham, C. D. Johnson, and A. R. Katritzky [*J. Chem. Soc.* (*B*), 1967, 1226] give the n.m.r. spectrum in 10% D_2SO_4. [g] Tentative assignment.

with a rapid reaction apparatus; [18] otherwise absorptions of buffered solutions [19] were measured with manual instruments.

U.v. spectra were recorded with a Unicam SP 800 spectrophotometer and $\lambda_{max.}$ and ε values were checked with a Unicam SP 500 manual instrument. ^{1}H N.m.r. spectra were recorded at 60 MHz and 33·5° with a Perkin-Elmer R10 spectrometer.

2-*Fluoropyridine Methiodide*.—The procedure of Bradlow and Vanderwerf [7] was modified in that a lower temperature was used. 2-Fluoropyridine (7·9 g) and methyl iodide (40 ml) were heated in a sealed tube at 50° for 8 h. The precipitate was filtered off and washed well with acetone to give white crystals of 2-fluoropyridine methiodide (2·1 g), m.p. 177—178° (decomp.) (lit.,[7] 71·1—72·0°) (Found, for material dried at 20° and 710 mmHg: C, 30·1; H, 3·1; N, 6·1. Calc. for C_6H_7FIN: C, 30·15; H, 2·95; N, 5·9%).

2-*Chloropyridine Methiodide*.—2-Chloropyridine (11·3 g) and methyl iodide (6·2 ml) were treated at −10° for 4 weeks essentially as described by Liveris and Miller.[3] The pale yellow crystals were filtered off, washed well with acetone, and dried at 20° and 0·35 mmHg, to give 2-chloropyridine methiodide (2·8 g), m.p. 205—206° (decomp.) (lit.,[3] 207°) (Found: C, 28·55; H, 3·05; N, 5·3. Calc. for C_6H_7ClIN: C, 28·2; H, 2·8; N, 5·5%). Attempted recrystallisation from acetone–ethanol–light petroleum (b.p. 40—60°) caused some exchange of the chloro-substituent.

2-*Bromopyridine Methiodide*.—2-Bromopyridine (15·8 g) and methyl iodide (6·2 ml) were mixed and kept at −10° for 2 weeks. The precipitate was collected, washed well with acetone and dried at the pump at 4° to give 2-*bromopyridine methiodide* (5·06 g), m.p. 208·5—209° (decomp.) (Found: C, 24·0; H, 2·5; N, 4·6. C_6H_7BrIN requires C, 24·0; H, 2·35; N, 4·7%). Attempted recrystallisation from acetone–ethanol appeared to cause some exchange of the bromo-substituent.

2-*Bromopyridine Methobromide*.—2-Bromopyridine (3·1 g) and methyl bromide (2·0 ml) were heated in a sealed tube at 92° for 21 h. The grey precipitate was collected and recrystallised twice from ethanol–acetone to give 2-*bromopyridine methobromide* (2·5 g), m.p. 225—226° (decomp.) (Found, for material dried at 20° and 20 mmHg: C, 27·9; H, 3·5; N, 5·2. $C_6H_7Br_2N$ requires C, 28·5; H, 2·8; N, 5·5%). It gave one spot only on thin-layer (silica; ethanol) and paper chromatography.

2-*Iodopyridine Methiodide*.—This compound was prepared from 2-chloropyridine and methyl iodide by heating at 91° for 12 h.[7] It was recrystallised from ethanol to give white crystals (51%), m.p. 207·5—208·5° (lit.,[7] 209·5—210·1°) (Found: C, 21·0; H, 2·0; N, 3·9. Calc. for $C_6H_7I_2N$: C, 20·8; H, 2·0; N, 4·0%).

3-*Bromopyridine Methiodide*.—This compound, prepared [7]

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from 3-bromopyridine and methyl iodide (90°; 12 h), had m.p. 163—165° (lit.,[7] 159·1—159·9°) (Found: C, 24·15; H, 2·2; N, 4·4. Calc. for C_6H_7BrIN: C, 24·0; H, 2·35; N, 4·7%).

3-*Iodopyridine Methiodide*.—A mixture of 3-iodopyridine (4·1 g), methyl iodide (6·2 ml), and ethanol (20 ml) was heated in a sealed tube at 92° for 21 h. The product was collected and recrystallised from ethanol to give 3-*iodopyridine methiodide* (4·65 g), m.p. 184—186° (Found, for material dried at 20° and 0·2 mmHg: C, 20·9; H, 3·8; N, 2·15. $C_6H_7I_2N$ requires C, 20·8; H, 4·0; N, 2·0%).

2-*Methoxypyridine Methiodide*.—2-Methoxypyridine (10·9 g) and methyl iodide (6·2 ml) were precooled, mixed, and kept at −10° for 4 weeks. The light yellow crystals were filtered off (at 4°), washed with methyl iodide, and dried over P_2O_5 at 4° at atmospheric pressure to give 2-*methoxypyridine methiodide* (9·3 g), m.p. 75° (decomp.) (Found: C, 33·8; H, 3·9; N, 5·7. $C_7H_{10}INO$ requires C, 33·5; H, 4·0; N, 5·6%). This product decomposed on attempted recrystallisation from acetone, and also when stored at room temperature (over potassium hydroxide or phosphorus pentaoxide) to give 1-methyl-2-pyridone,[20] identified by comparison of its n.m.r. spectrum and picrate [m.p. and mixed m.p. 146—148° (from ethanol) (lit.,[21] 145°)] with those of an authentic specimen [21] (Found, for sample dried at 20° over P_2O_5: C, 42·8; H, 2·95; N, 16·5. Calc. for $C_{12}H_{10}N_4O_8$: C, 42·6; H, 3·0; N, 16·6%).

3-*Methoxypyridine Methiodide*.—A mixture of 3-methoxypyridine [22,23] [1·38 g; picrate, m.p. 137—138° (lit.,[24] 136—139°)], methyl iodide (1·0 ml), and methanol (10·0 ml) was kept at room temperature for 2 days, then evaporated to dryness. The product was recrystallised from propan-2-ol to give light yellow crystals of 3-*methoxypyridine methiodide* (2·76 g), m.p. 155—156° (Found: C, 33·75; H, 4·2; N, 5·5. $C_7H_{10}INO$ requires C, 33·5; H, 4·0; N, 5·6%).

4-*Methoxypyridine Methiodide*.—4-Methoxypyridine [25] (2·2 g), methyl iodide (4·6 g), and methanol (30 ml) were kept at 25° for 24 h. The mixture was then evaporated to dryness and the product recrystallised from propan-2-ol–ethyl acetate to give 4-methoxypyridine methiodide (4·8 g), m.p. 145—147° (lit.,[26] 145°).

2-*Methylthiopyridine Methiodide*.—2-Methylthiopyridine [17] (2·6 g), methyl iodide (4·6 g), and methanol (20 ml) were heated in a sealed tube at 100° for 4 h. The mixture was evaporated and the product recrystallised from acetone to give pale yellow needles of 2-methylthiopyridine methiodide (4·7 g), m.p. 155—157° (lit.,[27,28] 156°) (Found: C, 31·5; H, 3·95; N, 5·1. Calc. for $C_7H_{10}INS$: C, 31·5; H, 3·8; N, 5·2%).

3-*Methylthiopyridine Methiodide*.—3-Methylthiopyridine [17] (5·0 g) [*picrate* (from ethanol), m.p. 136—137° (Found: C, 40·8; H, 2·9; N, 15·6. $C_{12}H_{10}N_4O_7S$ requires C, 40·7; H, 2·8; N, 15·8%)], methyl iodide (2·4 ml), and ethanol (50 ml) were refluxed for 40 min. After chilling the precipitate was collected and recrystallised from ethanol to give light yellow crystals of 3-*methylthiopyridine methiodide* (7·96 g), m.p. 122—125·5° (Found: C, 31·6; H, 4·1; N, 5·1. $C_7H_{10}INS$ requires C, 31·5; H, 3·8; N, 5·2%).

4-*Methylthiopyridine Methiodide*.—4-Methylthiopyridine [17] (1·5 g), methyl iodide (2·3 g), and methanol (15 ml) were heated in a sealed tube at 100° for 4 h, and the mixture was evaporated to dryness. The product was recrystallised from ethanol–ethyl acetate to give 4-methylthiopyridine methiodide (2·76 g) as pale yellow needles, m.p. 185—186° (lit.,[29] 177°) (Found: C, 31·6; N, 4·1; N, 5·1. Calc. for $C_7H_{10}INS$: C, 31·5; H, 3·8; N, 5·2%).

3-*Methylsulphonylpyridine*.—To a stirred solution of 3-methylthiopyridine [17] (4·0 g) in acetic acid (60 ml; 8N) at room temperature was added a solution of potassium permanganate (10 g) in water (100 ml) during 0·5 h. This mixture was stirred for 2 h, decolourised by passing sulphur dioxide, adjusted to pH 7 with ammonia, and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated to an oil (4·7 g) which solidified on cooling. It crystallised from diethyl ether to give 3-*methylsulphonylpyridine*, m.p. 54·5—56·5° (Found, for material dried in air: C, 45·9; H, 4·4; N, 8·8. $C_6H_7NO_2S$ requires C, 45·85; H, 4·5; N, 8·9%). The *picrate*, prepared in and recrystallised from ethanol, had m.p. 166—168° (Found: C, 37·7; H, 2·5; N, 14·5. $C_{12}H_{10}N_4O_9S$ requires C, 37·3; H, 2·6; N, 14·5%).

3-*Methylsulphonylpyridine Methiodide*.—A mixture of 3-methylsulphonylpyridine (4·05 g), methyl iodide (3·0 ml), and acetone (20 ml) was kept at 20° for 5 days. The precipitate (5·8 g) was collected and recrystallised from ethanol to give orange crystals of 3-*methylsulphonylpyridine methiodide* (4·21 g), m.p. 211—212° (Found: C, 28·1; H, 3·5; N, 4·6. $C_7H_{10}INO_2S$ requires C, 28·1; H, 3·4; N, 4·7%).

4-*Methylsulphonylpyridine Methiodide*.—4-*Methylsulphonylpyridine* [29] [2·16 g; m.p. 82·5—83·5° (lit.,[14] 82°)] and methyl iodide (10 ml) were kept at room temperature for 4 days. The yellow solid was collected and recrystallised from methanol to give 4-*methylsulphonylpyridine methiodide* (3·83 g), m.p. 160° (Found, for compound dried at 20° and 0·2 mmHg: C, 28·4; H, 3·6; N, 4·3. $C_7H_{10}INO_2S$ requires C, 28·1; H, 3·4; N, 4·7%).

3-*Nitropyridine Methiodide*.—3-Nitropyridine [30] was methylated with methyl iodide in methanol at 100° for 3 h by a procedure similar to that previously described.[31] The 3-nitropyridine methiodide had m.p. 212° (lit.,[31] 215°) (Found: C, 27·25; H, 2·8; N, 10·7. Calc. for $C_6H_7IN_2O_2$: C, 27·1; H, 2·65; N, 10·5%).

Chloropyridines.—Commercial 2-chloropyridine was redistilled under reduced pressure. It has b.p. 163—164° at 713 mmHg (lit.,[32] 167·3—167·5° at 744 mmHg). 4-Chloropyridine hydrochloride (commercial) was sublimed (Found: C, 40·3; H, 3·5; N, 9·6. Calc. for $C_5H_5Cl_2N$: C, 40·0; H, 3·4; N, 9·3%).

3-*Hydroxypyridine Methiodide*.—Prepared by refluxing 3-hydroxypyridine with methyl iodide in acetone,[24] this

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had m.p. 117·5—118·5° (lit.,[33] 115—117°) (Found, for material dried at 20° over P_2O_5–KOH: C, 30·6; H, 3·55; N, 5·85. Calc. for C_6H_8INO: C, 30·4; H, 3·4; N, 5·9%).

Kinetic Procedure.—Depending on the reactivity, a rapid reaction 'stopped-flow'[18] or a conventional sampling technique was employed. For practical reasons the upper limit for use of the rapid reaction technique was *ca.* 55°, and cell temperatures were determined by insertion of a thermocouple.

In the conventional technique, at temperatures greater than *ca.* 70°, aqueous solutions containing known quantities of the pyridinium salt and sodium hydroxide were heated in stoppered (to 100°) or sealed tubes in a thermostat. The tubes were then chilled and the contents diluted with buffer[19] to the required concentration for spectroscopic measurements. At temperatures less than *ca.* 50°, a weighed quantity or solution of the pyridinium salt was added to a known volume of aqueous sodium hydroxide in the thermostat, and samples were withdrawn at specified times and quenched. The u.v. absorption at the predetermined wavelength was then measured for each sample.

Rate coefficients were calculated from the expression (i)

$$\text{(i)}\quad k = [2{\cdot}303/t(a - 2b)] \log [b(a - 2x)/a(b - x)]$$

where a and b are the initial concentrations of hydroxide ion and pyridinium salt, x is the concentration of pyridinium salt consumed at time t (s), and k is the second-order rate coefficient in l mol^{-1} s^{-1}. However for the methoxy-compounds, 1 mole only of hydroxide ion was consumed for each mole of pyridinium salt, and the expression (i) was modified by inserting for (a — 2b) and (a — $2x$), the terms (a — b) and (a — x), respectively.

Where necessary, corrections were made for expansion (or contraction) of the solvent. For each run, about nine samples covering the range 10—80% reaction, and those corresponding to t_0 and t_∞ (*ca.* 15 times $t_{\frac{1}{2}}$ for the reaction and covering 98—100% conversion into the expected product as shown by the u.v. spectrum), were examined. Each reaction was studied at three temperatures covering a 20° range except where limitations of the rapid reaction apparatus precluded this. The molecularity was checked by halving the concentrations of both reactants in a run at one temperature.

The pyridinium salts were shown not to undergo appreciable solvolysis by water at the temperature and concentration of the hydrolysis reactions. The most reactive compound, 2-fluoro-*N*-methylpyridinium iodide, with water at 18·9° for 36 min, was less than 3% solvolysed. That demethylation to the respective hydroxy-compounds did not take place was checked by examination of the u.v. spectrum at t_∞ under conditions sufficient to produce the anions.[13]

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