Reactions of *N*-Heteroaromatic Bases with Nitrous Acid. Part 5.[1] Kinetics of the Diazotisation of Substituted 2-Aminopyridine and 2-Aminopyridine 1-Oxide

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In perchloric acid (up to 3.0M) kept at constant ionic strength the diazotisation of 2-amino-5-methylpyridine and 2-amino-5-chloropyridine 1-oxide takes place mainly by the interaction of the nitrous acidium ion with the protonated form of the former and the free form of the latter. However, the diazotisation of 2-amino-5-chloropyridine and 2-amino-5-methylpyridine 1-oxide takes place by the simultaneous interaction of the nitrous acidium ion with the protonated and the free form of both amines. The nitrous acidium ion shows a distinct discrimination in its reaction with the free amines and this is manifested in a rectilinear relationship between the rate constant for the diazotisation and the K_a values of the amines. Unlike the diazotisation of the free aromatic amines, the diazotisation of the 2- and 4-aminopyridines seems to involve an initial interaction between the nitrosating agent and most probably that part of the heteroaromatic ring system (including the 1-oxido group when appropriate) which is richer in electrons than the amino-group. The effects of substituents on the rate coefficient for the diazotisation of the protonated 2- and 4-aminopyridines support the view that the diazotisation of these amines involves an initial association of the nitrosating agent with the heteroaromatic ring. There is evidence that the hydroxy-group of the protonated amine 1-oxide molecules, when in the *para*-position with respect to the amino-group and therefore not involved in hydrogen bonding with it, accelerates the reaction by providing an additional site for the initial association with the nitrosating agent. pK_a Values of 2-amino-5-methyl- and 2-amino-5-chloro-pyridine 1-oxide are recorded.

DIAZOTISATION of 2- and 4-aminopyridine 1-oxide in 0.0025—5.00M-perchloric acid proceeds by attack of the nitrous acidium ion on the free and on the protonated amine.[1] The diazotisation of 2- and 4-aminopyridine under the same conditions, however, proceeds mainly by the attack of the nitrous acidium ion on the protonated forms of these amines.[2]

This paper examines the effect of substituents on the rate of the diazotisation of 2-aminopyridine and 2-aminopyridine 1-oxide in perchloric acid solutions maintained at constant ionic strength and correlates the reactivities of various amines in the free and in the protonated form.

RESULTS AND DISCUSSION

In perchloric acid solutions (up to 3.0M) kept at constant ionic strength of 3.0 by the addition of sodium perchlorate the diazotisation of 2-amino-5-methylpyridine, 2-amino-5-chloropyridine, and their 1-oxides follows the rate expression (1). The stoicheiometric second-order rate coefficients ($\bar{k}_2$) at a given

$$\text{Rate} = \bar{k}_2[\text{Amine}][\text{Nitrous acid}] \qquad (1)$$

acidity and with various initial concentrations of reactants were satisfactorily constant (Table 1) for >70% reaction (Table 2). Moreover, $\bar{k}_2$ increases with an increase in the acidity of the medium (Table 3).

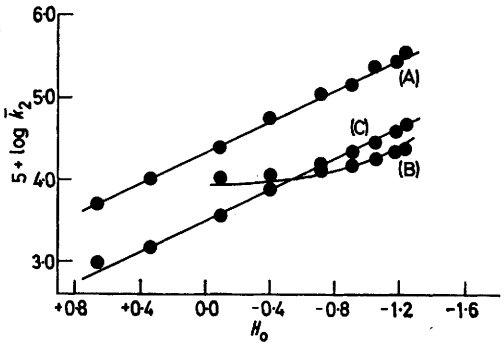


FIGURE 1 Plot of log $\bar{k}_2$ [equation (1)] against $-H_0$ for perchloric acid solutions containing sufficient sodium perchlorate to bring the ionic strength to 3.0: (A) 2-amino-5-methylpyridine; (B) 2-amino-5-chloropyridine; and (C) 2-aminopyridine.[2b] The slope is 0.94 for (A), rises for (B), and is 0.96 for (C)

For the diazotisation of 2-amino-5-methylpyridine $\bar{k}_2 \propto h_0$ since the corresponding plot of log $\bar{k}_2$ against H_0 (Table 3) is a straight line with a slope of 0.94. A similar relationship was observed for the diazotisation of 2- and 4-aminopyridine [2] (Figure 1).

[1] Part 4, E. Kalatzis and Ch. Mastrokalos, preceding paper.
[2] (*a*) E. Kalatzis, *J. Chem. Soc.* (*B*), 1967, 277; (*b*) E. Kalatzis and Ch. Mastrokalos, *J.C.S. Perkin II*, 1974, 498.

Expansion of the rate expression (1) gives equation (2) for the diazotisation of 2-amino-5-methylpyridine since

$$\text{Rate} = k_3[\text{Protonated amine}][HNO_2]h_0 \quad (2)$$

this amine (pK_a 7.22 [3]) must be present, like 2-aminopyridine,[2b] as the monocation at all acidities used in the present work. Equation (2) is similar to that obtained for the diazotisation of 2- and 4-aminopyridine [2] and, for reasons similar to those already presented,[2] it is interpreted as arising from a reaction path involving the attack of the nitrous acidium ion ($H_2^+NO_2$) on the protonated amine.

[3] F. N. Fastier and M. A. McDowell, *Austral. J. Expt. Biol.*, 1958, **36**, 491.

For the diazotisation of 2-amino-5-chloropyridine 1-oxide there is practically no dependence of $\bar{k}_2$ on h_0 since a plot of log $\bar{k}_2$ against H_0 is almost linear and horizontal, with a slightly negative slope (Figure 2). Expansion therefore of the rate expression (1) gives equation (3) since under the present conditions the stoicheiometric concentration of 2-amino-5-chloropyridine 1-oxide (pK_a 1.73) is effectively equal to the

$$\text{Rate} = k_2[\text{Protonated amine}][HNO_2] \quad (3)$$

concentration of the conjugate acid of the amine. Equation (3) can be written as (4) which for a given

$$\text{Rate} = k_3'[\text{Free amine}][HNO_2]h_0 \quad (4)$$

TABLE 1

Diazotisation at 2.0 °C; constancy of $\bar{k}_2$ [equation (1)] at a given acidity

	2-Amino-5-methylpyridine						2-Amino-5-chloropyridine					
	0.05M-$HClO_4$ + 2.95M-$NaClO_4$			1.50M-$HClO_4$ + 1.50M-$NaClO_4$			1.00M-$HClO_4$ + 2.00M-$NaClO_4$			2.50M-$HClO_4$ + 0.50M-$NaClO_4$		
10^4[Amine]$_i$/M	1.0	1.0	2.0	1.0	2.0	2.0	1.0	1.0		1.0	1.0	2.0
10^4[Nitrous acid]$_i$/M	4.0	8.0	8.0	4.0	4.0	8.0	4.0	8.0		4.0	8.0	8.0
$10\bar{k}_2$/l mol^{-1} s^{-1}	0.506	0.487	0.479	14.2	13.3	14.7	1.30	1.34		2.13	2.08	2.15
Mean $10\bar{k}_2$/l mol^{-1} s^{-1}	0.490 ± 0.014			14.1 ± 0.7			1.32 ± 0.03			2.12 ± 0.04		

	2-Amino-5-methylpyridine 1-oxide						2-Amino-5-chloropyridine 1-oxide							
	0.75M-$HClO_4$ + 2.25M-$NaClO_4$			3.00M-$HClO_4$			1.00M-$HClO_4$ + 2.00M-$NaClO_4$				2.00M-$HClO_4$ + 1.00M-$NaClO_4$			
10^4[Amine]$_i$/M	1.0	1.0	2.0	1.0	2.0	2.0	1.0	1.0	2.0	2.0	1.0	2.0	2.0	
10^4[Nitrous acid[$_i$/M	4.0	8.0	4.0	4.0	4.0	8.0	4.0	8.0	4.0	8.0	4.0	4.0	8.0	
$10\bar{k}_2$/l mol^{-1} s^{-1}	4.29	4.29	4.47	7.81	7.98	8.15	1.83	2.20	1.91	2.22	1.81	1.71	1.71	
Mean $10\bar{k}_2$/l mol^{-1} s^{-1}	4.35 ± 0.10			7.98 ± 0.17			2.04 ± 0.20				1.74 ± 0.06			

TABLE 2

Diazotisation at 2.0 °C; constancy of $\bar{k}_2$ [equation (1)] during the reaction

2-Amino-5-methylpyridine			2-Amino-5-chloropyridine 1-oxide		
[$HClO_4$] 0.10M, [$NaClO_4$] 2.90M, [Amine]$_i$ 2.0 × 10^{-4}M, [Nitrous acid]$_i$ 8.0 × 10^{-4}M			[$HClO_4$] 0.50M, [$NaClO_4$] 2.50M, [Amine]$_i$ 2.0 × 10^{-4}M, [Nitrous acid]$_i$ 8.0 × 10^{-4}M		
t/min	10^5[Product]/M *	$10\bar{k}_2$/l mol^{-1} s^{-1}	t/min	10^5[Product]/M *	$10\bar{k}_2$/l mol^{-1} s^{-1}
15	0.15	1.05	33	5.5	2.08
33	0.33	1.15	63	8.8	2.04
120	0.84	0.995	83	10.5	2.02
144	0.95	1.00	123	13.2	2.04
201	1.17	0.995	133	13.8	2.05
263	1.33	0.964	153	14.6	2.02
326	1.46	0.946			

* Taken as equivalent to the concentration of the amine reacted.

TABLE 3

Diazotisation at 2.0 °C; dependence of $\bar{k}_2$ [equation (1)] on the acidity of perchloric acid solutions maintained at constant ionic strength of 3.0 by the addition of sufficient sodium perchlorate

[$HClO_4$]/M	H_0	2-Amino-5-methylpyridine $10\bar{k}_2$/l mol^{-1} s^{-1}	2-Amino-5-chloropyridine $10\bar{k}_2$/l mol^{-1} s^{-1}	2-Amino-5-methylpyridine 1-oxide $10\bar{k}_2$/l mol^{-1} s^{-1}	2-Amino-5-chloropyridine 1-oxide $10\bar{k}_2$/l mol^{-1} s^{-1}
0.05	+0.66	0.491 ± 0.013		2.76 ± 0.03	2.15 ± 0.08
0.10	+0.34	1.00 ± 0.01		2.88 ± 0.01	2.07 ± 0.04
0.25	−0.09	2.53 ± 0.07	1.04 ± 0.06	3.27 ± 0.03	2.04 ± 0.01
0.50	−0.40	5.55 ± 0.01	1.13 ± 0.09	4.06 ± 0.01	2.08 ± 0.10
0.75	−0.56			4.35 ± 0.10	
1.00	−0.71	11.0 ± 0.5	1.32 ± 0.03		2.04 ± 0.20
1.25	−0.82			4.90 ± 0.03	
1.50	−0.90	14.1 ± 0.7	1.52 ± 0.03	5.58 ± 0.18	1.87 ± 0.11
2.00	−1.04	23.3 ± 1.0	1.75 ± 0.07	6.45 ± 0.06	1.76 ± 0.07
2.50	−1.17	27.9 ± 0.2	2.12 ± 0.04	7.52 ± 0.07	1.57 ± 0.06
3.00	−1.23	33.7 ± 0.3	2.27 ± 0.01	7.98 ± 0.17	1.55 ± 0.05

acidity can be reduced to equation (5). It follows

$$\text{Rate} = k_2'[\text{Free amine}][HNO_2] \quad (5)$$

therefore that equation (6) applies where k_2' is the

$$k_2' = k_3'h_0 \quad (6)$$

the second-order rate coefficient at a given acidity. The values of k_2' at different acidities can be calculated from the values of $\bar{k}_2$ by combining equations (1) and (5) and by determining the degree of ionisation of the conjugate acid of 2-amino-5-chloropyridine 1-oxide (pK_a 1.73) and of nitrous acid (pK_a 3.46 [4]). When the calculated values of log k_2' were plotted against H_0 a straight line with a slope of 0.94 was obtained thus showing that equation (6) is obeyed. The kinetic form described by equation (4) is therefore preferred and this is interpreted as arising from a reaction

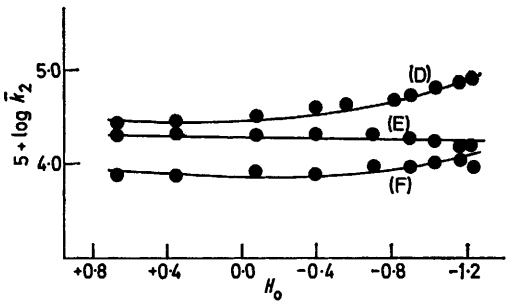


FIGURE 2 Plot of log $\bar{k}_2$ [equation (1)] against $-H_0$ for perchloric acid solutions containing sufficient sodium perchlorate to bring the ionic strength to 3.0: (D) 2-amino-5-methylpyridine 1-oxide; (E) 2-amino-5-chloropyridine 1-oxide; and (F) 2-aminopyridine 1-oxide. The slope rises for (D) and (F) and is −0.03 for (E)

between the nitrous acidium ion and the free amine. Similar kinetic forms were also obtained for the diazotisation of weakly basic aromatic amines, as for example *o*-chloroaniline [5,6a] at low acidities and *p*-nitroaniline [6] at low and even higher acidities at constant ionic strength.

The values of $\bar{k}_2$ for the diazotisation of 2-amino-5-chloropyridine 1-oxide tend to decrease at the higher acidities (Table 3). This decrease may be due to small differences between the medium effect of sodium perchlorate and that of perchloric acid on the rate of the diazotisation of the aminopyridine 1-oxides. These differences would become more manifest at the higher concentrations of sodium perchlorate or perchloric acid. Furthermore, it is unlikely that the above decrease could be due to the Hammett acidity function H_0 used in the present work because this function must represent a reasonable approximation for the protonation behaviour of the aminopyridine 1-oxides since the acidities of the kinetic solutions are less than those corresponding to the H_0 value of −3.0.[7]

For the diazotisation of 2-amino-5-chloropyridine and 2-amino-5-methylpyridine 1-oxide the dependence of $\bar{k}_2$ on h_0 is not rectilinear. A plot of log $\bar{k}_2$ (Table 3) against H_0 is in both cases a curve with a rising slope (Figures 1 and 2). Diazotisation under these conditions proceeds therefore by the attack of the same nitrosating agent on the protonated amine, as described by equation (2), and on the free amine, as described by equation (4). The contributions of equation (2) and (4) to $\bar{k}_2$ [equation (1)] are therefore given by equation (7) since [Free amine]h_0 = [Protonated amine]K_a, where K_a is the thermodynamic dissociation constant of the conjugate acid of the amine.

$$\bar{k}_2 = k_3'K_a + k_3h_0 \quad (7)$$

Plots of $\bar{k}_2$ against h_0 for the diazotisation of 2-amino-5-chloropyridine and 2-amino-5-methylpyridine 1-oxide, as in the case of 2- and 4-aminopyridine 1-oxide,[1] are straight lines with slopes equal to k_3 and intercepts equal to $k_3'K_a$ from which the values of k_3' can be calculated. Similar plots for the diazotisation of 2-aminopyridine,[2b] 2-amino-5-methylpyridine, and 4-aminopyridine [2a] are also straight lines which, as expected, pass very close to the origin of the axes because the values of $k_3'K_a$ are small. The plot of $\bar{k}_2$ against h_0 for the diazotisation of 2-amino-5-chloropyridine 1-oxide is a straight line almost parallel to the h_0 axis and has an intercept corresponding to $k_3'K_a$.

TABLE 4

Values of k_3' and k_3 [equation (6)] for the diazotisation of a number of amines in perchloric acid solutions kept at constant ionic strength of 3.0 and at 2.0 °C

Amine	pK_a	$10^2k_3'K_a$	$10^{-2}k_3'$/ l² mol⁻² s⁻¹	10^2k_3/ l² mol⁻² s⁻¹
4-Aminopyridine [a]	9.11 [e]	0.794	102 300	3.03
2-Aminopyridine [b]	6.82 [e]	0.717	474	2.54
Aniline [c]	4.60 [f]	2.50	10.0	16.1
2-Amino-5-methylpyridine	7.22 [g]	2.80	4 663	19.4
p-Methylaniline [c]	5.08 [f]	0.90	10.0	119
2-Amino-5-chloropyridine	4.83 [g]	9.23	62.4	0.78
p-Chloroaniline [c]	3.98 [f]	10.0	10.0	3.26
4-Aminopyridine 1-oxide [d]	3.69 [h]	19.5	9.55	20.6
2-Aminopyridine 1-oxide [d]	2.67 [h]	7.82	0.366	0.161
2-Amino-5-methylpyridine 1-oxide	2.77	29.7	1.75	3.07
2-Amino-5-chloropyridine 1-oxide	1.73	21.4	0.115	0.0

[a] Ref. 2a. [b] Ref. 2b. [c] Ref. 8. [d] Ref. 1. [e] A. Albert, R. Goldacre, and J. N. Phillips, *J. Chem. Soc.*, 1948, 2240. [f] A. I. Biggs and R. A. Robinson, *J. Chem. Soc.*, 1961, 388. [g] Ref. 3. [h] J. N. Gardner and A. R. Katritzky, *J. Chem. Soc.*, 1957, 4375.

The values of k_3' and k_3 (Table 4), which were determined by the method of least squares, indicate that the amines are, as expected, more reactive in the free form

[4] H. Schmid, R. Marchgraber, and F. Dunkl, *Z. Elektrochem.*, 1937, **43**, 337.

[5] E. D. Hughes, C. K. Ingold, and J. H. Ridd, *J. Chem. Soc.*, 1958 77.

[6] (*a*) L. F. Larkworthy, *J. Chem. Soc.*, 1959, 3304; (*b*) J. H. Ridd, *Quart. Rev.*, 1961, **15**, 418; (*c*) B. C. Challis, L. F. Larkworthy, and J. H. Ridd, *J. Chem. Soc.*, 1962, 5203.

[7] C. D. Johnson, A. R. Katritzky, B. J. Ridgewell, N. Shakir, and A. M. White, *Tetrahedron*, 1965, **21**, 1055; C. D. Johnson, A. R. Katritzky, and N. Shakir, *J. Chem. Soc.* (*B*), 1967, 1235.

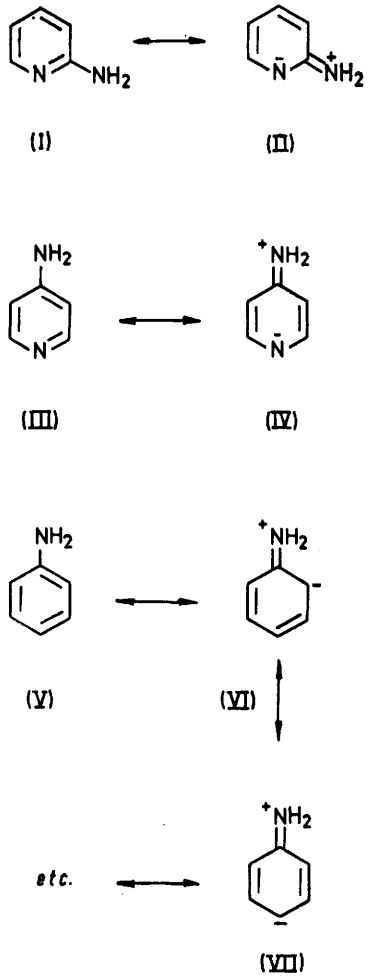
[8] E. C. R. de Fabrizio, E. Kalatzis, and J. H. Ridd, *J. Chem. Soc.* (*B*), 1966, 533.

(k_3') than in the protonated form (k_3) towards the nitrous acidium ion. This result is similar to that obtained for the diazotisation of the aromatic amines;[6a,b,8] it differs however in the fact that the nitrous acidium ion shows a distinct discrimination in its reaction with the various heteroaromatic amines studied. Thus 2- and 4-aminopyridine and substituted 2-aminopyridines are much more reactive whilst their 1-oxides are less reactive than the aromatic amines which are more basic than *p*-nitroaniline and for which k_3' appear to approach the limiting value of 1 000 l^2 mol^{-2} s^{-1} under the same experimental conditions.[6a,b,8]

It is difficult to interpret the above results for the diazotisation of the free 2- and 4-aminopyridine by accepting, as was done for the diazotisation of the free aromatic amines,[6a,b,8] as implying that the nitrosating agent directly attacks the amino-group attached to the heteroaromatic nucleus, because the values of k_3' should then have been, at the most, similar to those for the diazotisation of the aromatic amines more basic than *p*-nitroaniline.[6] The amino-group attached to the 2- or 4-position of the pyridine ring must be poorer in electrons than the heteroaromatic nucleus as a result of structures (II) and (IV) which contribute significantly to the hybrid structure of the molecules and are responsible for the enhancement of the basicity of the ring nitrogen.[9] In the aromatic series, however, structures such as (VI) and (VII) contribute less significantly to the resonance hybrid for the aniline molecule thus leaving the amino-group still richer in electrons than the rest of the molecule.

The results of the diazotisation of the free 2- and 4-aminopyridines can, therefore, be explained by accepting that the reaction involves an initial interaction between the nitrous acidium ion and that part of the molecule which is richer in electrons (heteroaromatic ring as a whole and probably more particularly the ring nitrogen) followed, as a result of electronic rearrangement in the molecule, by the migration of the nitrosating agent towards the amino-group which is thus nitrosated. This mechanism can explain the much higher values for k_3' observed in the case of the 2- and 4-aminopyridines compared with those observed in the case of the aromatic amines; it can also explain the fact that the nitrous acidium ion discriminates in its reaction with the various heteroaromatic amines included in Table 4, because molecules which are expected to have higher electron density in the heteroaromatic nucleus react faster than those which have lower electron density; for example 4-aminopyridine and 2-amino-5-methylpyridine react respectively *ca.* 215 and 10 times faster than 2-aminopyridine which in turn reacts 7.6 times faster than 2-amino-5-chloropyridine. Indeed a plot of log ($k_3'/{}_0k_3$) against log ($K_a/{}_0K_a$), where ${}_0k_3'$ and ${}_0K_a$ for 2-aminopyridine are taken as reference values, is almost rectilinear with a slope of −0.81. Thus the reaction is favoured by an increase in the electron density at the reaction centre, which again cannot be the amino-group because the K_a values of the heteroaromatic amines under study are not directly associated with the electron density of that group.

It is noteworthy that the above rectilinear relationship holds also for the diazotisation of 2- and 4-aminopyridine 1-oxides. This indicates that here also the reaction centre is not the amino-group since structures

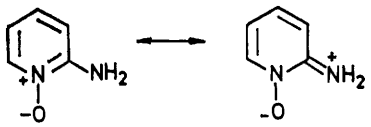


such as (IX) and (XI) make a significant contribution to the resonance hybrid for the molecules and this is responsible for leaving the amino-group poorer in electrons than the heteroaromatic ring and more particularly than the oxygen atom of the N–O group. Thus 4-aminopyridine 1-oxide and 2-amino-5-methylpyridine 1-oxide react respectively 26.1 and 4.8 times faster than 2-aminopyridine 1-oxide which in turn reacts 3.2 times faster than 2-amino-5-chloropyridine 1-oxide (Table 4).

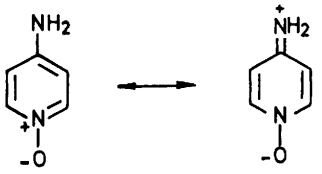
Consider now the protonated amines. It has been suggested that the diazotisation of the protonated 2- and 4-aminopyridine proceeds by an initial association between the positively charged nitrous acidium ion and the *N*-heteroaromatic nucleus followed by the nitrosation of the amino-nitrogen atom during migration of a

[9] S. J. Angyal and C. L. Angyal, *J. Chem. Soc.*, 1952, 1461; *Cf.* A. Albert, 'Heterocyclic Chemistry,' Athlone Press, London, 1968, 2nd edn., pp. 74—76.

proton to the medium.[2] The results of the present work support this view.

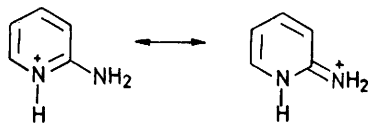


(VIII) (IX)

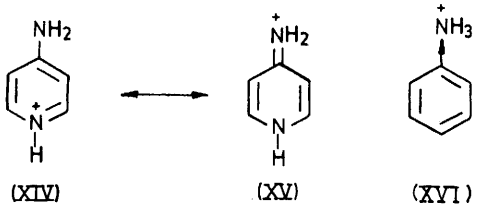


(X) (XI)

At least two properties of the protonated 2- and 4-aminopyridines are important when these amines react with the nitrous acidium ion, namely the electron donor capacity of the heteroaromatic nucleus and the acidity of the proton of the aminopyridinium ion. It is therefore noteworthy, in the first instance, that the values of k_3 for the diazotisation of the protonated *N*-heteroaromatic amines under study are smaller than those for the diazotisation of the protonated aromatic amines (Table 4). For example aniline is 6.3 or 5.3 times more reactive than 2- or 4-aminopyridine respectively, *p*-methylaniline is 6.1 times more reactive than 2-amino-5-methylpyridine, and *p*-chloroaniline 4.2 times more reactive than 2-amino-5-chloropyridine. This is in agreement with the proposed mechanism. The positive charge of the protonated ring nitrogen of 2- and 4-aminopyridine decreases the electron donor capacity of the heteroaromatic nucleus [resonance structures (XII) and (XIV)] and this decrease is expected to be greater than that suffered by the aromatic nucleus of the anilinium ion (XVI) because the protonated amino-group in this case can attract electrons from the aromatic nucleus by an inductive effect only.



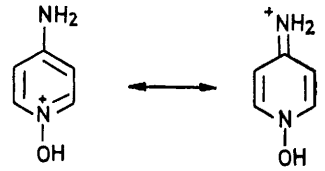
(XII) (XIII)



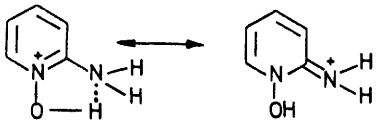
(XIV) (XV) (XVI)

As in the case of the nitrosation and diazotisation of the protonated aromatic amines,[8] electron-withdrawing substituents decrease the rate of the diazotisation of 2- and 4-aminopyridines, whilst electron-donating substituents accelerate the reaction; for example, 2-amino-5-methylpyridine reacts 7.6 times faster than 2-aminopyridine which in turn reacts 3.3 times faster than 2-amino-5-chloropyridine. A similar trend is observed for the diazotisation of the protonated 2-aminopyridine 1-oxides. These results indicate that the methyl group causes an increase in the electron donor capacity of the heteroaromatic nucleus which is more important than the decrease it causes in the acidity of the proton of the aminopyridinium ion. On the other hand, although the acidity of the proton of the aminopyridinium ion is increased by the *p*-chloro-substituent, the decrease in the donor capacity of the heteroaromatic nucleus is more important and, therefore, the reaction rate decreases.

The results of Table 4 indicate also that although the protonated 2-aminopyridine 1-oxides are less reactive than the protonated 2-aminopyridines, the protonated 4-aminopyridine 1-oxide is *ca.* 7 times more reactive than the protonated 4-aminopyridine. This greater reactivity cannot be due to the higher acidity of



(XVII) (XVIII)



(XIX) (XX)

the proton of the protonated 4-aminopyridine 1-oxide because, if that were the case, then the protonated 2-aminopyridine 1-oxide should also have been more reactive than the protonated 2-aminopyridine. It cannot also be due solely to an increase in the electron donor capacity of the heteroaromatic nucleus even if it is accepted that the positively charged aminopyridine moiety [structures (XVII) and (XVIII)] attracts to some extent electronic charge from the hydroxy-group by an inductive effect (*cf.* pK_a for 4-aminopyridinium ion -6.55 [10] and pK_a for protonated 4-aminopyridine 1-oxide -6.27 [10]). It is noteworthy that the protonated 4-aminopyridine 1-oxide is more reactive than aniline and even slightly more reactive than 2-amino-5-methylpyridine (Table 4). Furthermore, the protonated 1-oxido-group ($\overset{+}{\geqslant}$N–O–H) would

[10] H. Hirayama and T. Kubota, *J. Pharm. Soc. Japan*, 1953, **73**, 140 (*Chem. Abs.*, 1953, **47**, 4196c).

be expected to decrease the electron donor capacity of the nucleus more than the protonated ring nitrogen ($\geqslant\overset{+}{N}$–H) because of the small $-I$ effect of the hydroxy-group when attached to the positively charged ring nitrogen.[11] It is, therefore, more likely that the oxygen atom of the hydroxy-group enhances the diazotisation of the protonated 4-aminopyridine 1-oxide by providing an additional site (visualized as an extension of the heteroaromatic ring of the protonated 4-aminopyridine) which is involved in the initial interaction with the nitrous acidium ion and is further removed from the positively charged aminopyridinium moiety [compare structures (XVII) and (XVIII) with (XIV) and (XV)]. A similar explanation, *i.e.* that the oxygen atom provides a site for an initial association with the nitrosating agent, was suggested for the reaction between protonated hydroxylamine and nitrous acidium ion.[8,12]

The change of the amino-group from the 4- to the 2-position of the pyridine ring does not seem to have a great effect on the reactivity of the molecules since the value of k_3 for the diazotisation of the protonated 4-aminopyridine is only 1.2 times greater than that of 2-aminopyridine (Table 4). The much smaller reactivity of the protonated 2-aminopyridine 1-oxides compared with that of the protonated 2-aminopyridines appears, therefore, to be due to intramolecular hydrogen bond formation between the amino- and the hydroxy-group for the protonated 1-oxides, which would be responsible for resonance structure (XIX) being more stable than structure (XX) thus decreasing the electron donor capacity of the heteroaromatic ring system. Such hydrogen bonding will probably not occur to a significant extent in the case of the protonated 2-aminopyridines, as shown by structures (XII) and (XIII).

EXPERIMENTAL

Materials.—2-Amino-5-methylpyridine (Fluka; pract.) and 2-amino-5-chloropyridine (Fluka; pract.) were sublimed three times at 50 °C and 0.5 mmHg, respectively. 2-Hydroxy-5-methylpyridine was prepared by treating 2-amino-5-methylpyridine (0.01 mol) dissolved in 20% sulphuric acid (10 ml) with aqueous 50% sodium nitrite (1.4 ml) at 2 °C. The mixture was then heated to 90 °C, cooled to room temperature, and neutralised with sodium carbonate. After evaporation to dryness the solid obtained was boiled with benzene from which the extracted product was recrystallised (charcoal), yield 64%, m.p. 179—181° (lit.,[13a] 182—183°). 2-Hydroxy-5-chloropyridine (Aldrich) was sublimed at 120 °C and 0.3 mmHg, m.p. 159—161° (lit.,[13b] 163°). 2-Amino-5-methylpyridine 1-oxide and 2-amino-5-chloropyridine 1-oxide were prepared by the method [14] which was also used for the preparation of 2-aminopyridine 1-oxide [1] and the products were sublimed twice at 115 °C and 1.0 mmHg, m.p. 153—155° (lit.,[15a] 150—151°), and 145 °C and 0.6 mmHg, m.p. 197—200° (lit.,[15b] 193°), respectively. All purified products had satisfactory elemental analyses. The remaining materials used in this work were treated as described previously.[1] Microanalyses were carried out by Dr. Ch. Mantzos.

Kinetics.—The experimental procedure was that described previously.[1] Absorbances of the reaction mixtures (20.0 ml) of 2-amino-5-methylpyridine and 2-amino-5-chloropyridine were read from fully recorded spectra of a portion of these mixtures placed in the precooled Unicam cell (1.0 cm) and maintained at 2.0 °C. 5-Methyl- and 5-chloro-pyridine-2-diazonium ion, like pyridine-2-diazonium ion,[2] are unstable in the reaction mixtures and as soon as they are formed give 2-hydroxy-5-methyl- and 2-hydroxy-5-chloro-pyridine respectively. It was necessary, however, to allow for the fact that the amounts of the 2-hydroxy-derivatives obtained during the kinetic experiments were less than those expected from the initial amounts of the amines added. The decrease (up to *ca.* 25%) in the yield of the 2-hydroxy-derivatives is probably due to side reactions of the unstable 5-methyl- and 5-chloro-pyridine-2-diazonium ion formed during the diazotisation experiments, since the addition of separately prepared [16] sodium 5-methyl- and 5-chloro-pyridine-2-diazoate in perchloric acid solutions gave the corresponding 2-hydroxy-compounds in amounts which were less than those expected from the initial concentration of the diazoates.

TABLE 5

Diazotisation in perchloric acid solution maintained at constant ionic strength of 3.0 and at 2.0 °C; extinction coefficients and wavelengths at which measurements were carried out

2-Amino-5-methylpyridine

λ_1 308 nm
ε_1 6 890

H_0	ε_2	λ_2/nm	ε_3	ε_4
+0.66	1 200	289	4 500	6 000
+0.34	950	289	4 500	6 200
−0.09	600	289	4 500	6 250
−0.40	500	289	4 500	6 250
−0.71	400	290	4 600	6 000
−0.90	400	290	4 600	6 000
−1.04	400	290	4 600	6 000
−1.17	400	290	4 600	6 000
−1.23	400	290	4 600	6 000

2-Amino-5-chloropyridine

λ_1 314 nm
ε_1 5 600

H_0	ε_2	λ_2/nm	ε_3	ε_4
−0.09	1 100	294	3 450	5 250
−0.40	1 200	294	3 450	5 600
−0.71	1 300	295	3 550	5 900
−0.90	1 450	295	3 550	5 900
−1.04	1 700	295	3 550	5 900
−1.17	2 300	295	3 550	5 900
−1.23	2 900	295	3 550	6 000

The 2-hydroxy-derivatives (1.0×10^{-4}M) showed no reaction with nitrous acid (8.0×10^{-4}M) for at least 48 h in 0.01—3.0M-perchloric acid solutions. Absorbances of the reaction mixtures were read at two wavelengths (λ_1 and λ_2) and the amount of unchanged amine was thus determined

[11] A. R. Katritzky, B. J. Ridgewell, and A. M. White, *Chem. and Ind.*, 1964, 1576; G. P. Bean, P. J. Brignell, C. D. Johnson, A. R. Katritzky, and B. J. Ridgewell, *J. Chem. Soc.* (*B*), 1967, 1222.

[12] M. B. Hughes, T. D. B. Morgan, and G. Stedman, *Chem. Comm.*, 1966, 241.

[13] (*a*) F. H. Case, *J. Amer. Chem. Soc.*, 1946, **68**, 2574; (*b*) A. E. Chichibabin and A. F. Egorov, *J. Russ. Phys. Chem. Soc.*, 1928, **60**, 683 (*Chem. Abs.*, 1929, **23**, 2182).

[14] J. Delarge and L. Thunus, *Il Farmaco*, 1966, 846.

[15] (*a*) G. M. Brown, *J. Amer. Chem. Soc.*, 1957, **79**, 3565; (*b*) K. Undheim, M. A. F. El-Gendy, and T. Hurum, *Acta Chem. Scand.*, 1974, **B28**, 743.

[16] A. E. Chichibabin and M. D. Rjazancev, *J. Russ. Phys. Chem. Soc.*, 1915, **46**, 1571 (*Chem. Abs.*, 1916, 2898).

at the various time intervals from equation (8) where A and B are the absorptions at λ_1 (taken as the $\lambda_{max.}$ of the

$$[\text{Amine}] = (B\varepsilon_2 - A\varepsilon_4)/(\varepsilon_2\varepsilon_3 - \varepsilon_1\varepsilon_4) \quad (8)$$

amine) and λ_2 respectively, ε_1 and ε_2 are the extinction coefficients of amine and corresponding hydroxy-derivative respectively at λ_1, and ε_3 and ε_4 at λ_2 (Table 5).

TABLE 6

Extinction coefficients of the corresponding diazonium ions formed during the diazotisation of 2-amino-5-methyl- and 2-amino-5-chloro-pyridine 1-oxide in perchloric acid solutions maintained at a constant ionic strength of 3.0 and at 2.0 °C

H_0	5-Methyl-1-oxido-pyridine-2-diazonium ion $10^{-2}\varepsilon$ at 306 nm	5-Chloro-1-oxido-pyridine-2-diazonium ion $10^{-2}\varepsilon$ at 300 nm
+0.66	31.0	87.0
+0.34	31.0	87.0
−0.09	31.0	87.0
−0.40	29.5	78.0
−0.56	29.5	
−0.71		78.0
−0.82	28.7	
−0.90	27.5	78.0
−1.04	25.0	78.0
−1.17	25.0	78.0
−1.23	25.0	78.0

The decrease in the absorbance of a portion of the reaction mixtures (50.0 ml) of 2-amino-5-methylpyridine 1-oxide and 2-amino-5-chloropyridine 1-oxide placed in a precooled Unicam cell (1.0 cm) were measured automatically at 306 (ε 5.80 × 10^3) and 300 nm (3.90 × 10^3 for all acidities except for H_0 +0.66 when ε 3.80 × 10^3), respectively. The values of ε for 5-methyl- and 5-chloro-1-oxidopyridine-2-diazonium ion at the same wavelengths are in Table 6. The method used to calculate the amount of unchanged amine was the same as that used previously.[1] The diazonium ions were, within experimental error (5%), stable in perchloric acid solutions with and without sodium perchlorate (3.0M-$HClO_4$ and 0.5—1.5M-$HClO_4$ containing 2.5—1.5M-$NaClO_4$) for at least 3 h, as was indicated by the recorded u.v. spectra of diazotised solutions of 2-amino-5-methylpyridine 1-oxide (2.5 × 10^{-3}M) and 2-amino-5-chloropyridine 1-oxide (1.0 × 10^{-3}M) with an excess of nitrous acid (2.5 × 10^{-2} and 8.0 × 10^{-3}M, respectively). This was confirmed by extracting samples (2.0 and 5.0 ml, respectively) from these solutions, mixing them with 5.0 × 10^{-3}M-2-naphthol (10 ml) in sodium hydroxide solution, and diluting the mixture to 100 ml (final pH 12). The spectra of the diluted solutions containing the corresponding azo-oxides were recorded and absorbances were read at 500 and 530 nm respectively.

Determination of pK_a *Values*.—These were measured spectrophotometrically [17] in water at 25 °C (Table 7). Typical results of kinetic runs are in Figure 3 and Table 2.

TABLE 7

	pK_a	Spread (±)	Conc. (10^4M)	A.w.l.[a] (nm)
2-Amino-5-methylpyridine 1-oxide	2.77[b]	0.05	1.0	304
2-Amino-5-chloropyridine 1-oxide[c]	1.73[b]	0.04	1.0	305

[a] A.w.l., analytical wavelength (nm). [b] Refers to the gain of one proton. Buffers used had ionic strength 0.01 (except c).

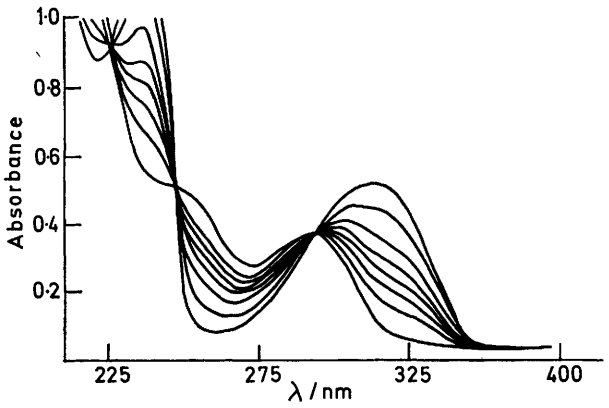


FIGURE 3 Diazotisation of 2-amino-5-chloropyridine (1.0 × 10^{-4}M) with nitrous acid (8.0 × 10^{-4}M) in 1.00M-perchloric acid solution containing 2.00M-sodium perchlorate and at 2.0 °C

[6/2348 *Received, 29th December*, 1976]

[17] A. Albert and E. P. Serjeant, ' Ionisation Constants of Acids and Bases,' Methuen, London, 1962.