# Kinetics of Reactions in Heterocycles. Part XIII.[1] Substituted *N*-Methylpyridinium and *N*-Methylquinolinium Salts with Piperidine in Water and in Ethanol

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Kinetics of the displacement reactions of some halogeno-*N*-methylpyridinium and -*N*-methylquinolinium salts towards half-neutralised piperidine in water, and unneutralised piperidine in ethanol have been determined. These revealed, for reactions in water, smaller differences in reactivity between 2- and 4-isomers than was observed with hydroxide ions. Energies of activation for the reactions with piperidine were 3.7—5.4 kcal $mol^{-1}$ lower and log *A* values were lower by 2.9—3.4 and 0.7—1.9 units for pyridinium salts with the substituent at the 2- and 4-position respectively. Displacement reactions with piperidine in ethanol were found to occur 8.0—16.75 times faster than in water. Quaternisation of 4-chloroquinoline by methylation increased its reactivity towards piperidine in ethanol at 100° by $2 \times 10^8$ fold.

RESULTS of kinetic studies of the reactions of substituted *N*-methylpyridinium, *N*-methylquinolinium, and *N*-methylisoquinolinium salts with hydroxide ions in water have been given in earlier publications.[1,2] These showed that *N*-methylation of iodoquinolines and 1-iodoisoquinoline increased their reactivity towards hydroxide ions at 114.8° by $1.2—3.4 \times 10^7$ fold for substituents at the α-positions, and $6.1 \times 10^5$ fold for substituents at the γ-position (of quinoline); and for 4-methylsulphonylpyridine at 20° by $7.3 \times 10^8$ fold. It was also shown that the salts with the leaving group in the α-position were the most reactive: 2-methoxypyridine methiodide at 20° was 38 times more reactive than its 4-isomer, and 2-iodo- and 2-methylthio-quinolinium salts at 20° were 1 440 and 1 490 times more reactive than their 4-isomers, respectively.

* Table 1 is given in Supplementary Publication No. SUP 21391 (4 pp.). For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1974, Index issue.

In this paper we report kinetic results for the reactions of substituted *N*-methylpyridinium and *N*-methylquinolinium salts with the neutral nucleophile piperidine in water, and some results for comparative purposes in ethanol. Aqueous solutions of piperidine are strongly basic but in the kinetic work described here the reagent in water was half neutralised with the calculated quantity of standardised hydrochloric acid, to minimise hydrolysis, and each reaction was thoroughly examined by u.v. spectroscopy for complete conversion to the piperidino-compound. The reactions listed in Tables 1—3 * observed regular second-order kinetics (to give the piperidino-compounds) as shown by typical kinetic runs (Table 1) and determination of $t_{\frac{1}{2}}$ values (Table 2) in selected cases. In all runs, the concentration of nucleophile was taken as that of free piperidine. Table 3 lists

[1] Part XII, G. B. Barlin and J. A. Benbow, *J.C.S. Perkin II*, 1975, 298.

[2] G. B. Barlin and J. A. Benbow, *J.C.S. Perkin II*, 1974, 790.

TABLE 2

Kinetic results for the reactions of halogeno-pyridine and -quinoline methosalts with piperidine in ethanol and in water

| Temp.[a] (°C) | [10⁴ piperidine]/ M | [10⁵N⁺Me]/ M | $k$ [b,c] | $t_{\frac{1}{2}}$ [d] | $t_{\frac{1}{2}}/t_{\frac{1}{2}}'$ [e] | $(t_{\frac{1}{2}}/t_{\frac{1}{2}}'/t_{\frac{1}{2}}')$ calc.[f] | Analyt. λ/nm[g] |
|---|---|---|---|---|---|---|---|
| (1) Piperidine in ethanol | | | | | | | |
| 4-Chloropyridine methotetrafluoroborate | | | | | | | |
| 19.3 | 58.2 | 2.45 | 10.25 | 11.68 | | | 293 |
| 19.5 | 29.1 | 2.45 | 10.16 | 23.69 | 2.03 | 2.00 | 293 |
| 28.5 | 33.9 | 2.24 | 17.80 | | | | 293 |
| 37.8 | 28.5 | 2.40 | 30.70 | | | | 293 |
| 43.1 | 33.3 | 2.20 | 42.64 | | | | 293 |
| 4-Bromopyridine methotetrafluoroborate | | | | | | | |
| 19.3 | 58.1 | 2.66 | 8.46 | 14.18 | | | 293 |
| 19.3 | 29.1 | 2.66 | 8.39 | 38.73 | 2.02 | 2.00 | 293 |
| 28.3 | 28.8 | 2.63 | 16.27 | | | | 293 |
| 37.8 | 28.5 | 2.50 | 30.27 | | | | 293 |
| 4-Iodopyridine methiodide | | | | | | | |
| 23.8 | 36.4 | 2.90 | 2.34 | | | | 293 |
| 34.7 | 35.9 | 2.66 | 5.01 | | | | 293 |
| 43.3 | 35.5 | 2.34 | 8.58 | | | | 293 |
| 4-Chloroquinoline methiodide | | | | | | | |
| 20.8 | 2.90 | 2.53 | 168.8 | | | | 369 |
| 30.0 | 2.87 | 2.51 | 269.6 | | | | 369 |
| 37.9 | 2.85 | 2.485 | 386.6 | 7.13 | | | 369 |
| 37.9 | 1.43 | 1.24 | 401.9 | 13.66 | 1.92 | 2.00 | 369 |
| (2) Piperidine in water - | | | | | | | |
| 2-Chloropyridine methiodide | | | | | | | |
| 18.1 | 523 | 10.20 | 0.613 | | | | 330 |
| 28.9 | 517 | 10.10 | 1.195 | | | | 330 |
| 38.2 | 512 | 10.02 | 2.067 | 6.56 | | | 330 |
| 38.2 | 265 | 10.02 | 1.976 | 13.30 | 1.93 | 2.03 | 330 |
| 2-Bromopyridine methiodide | | | | | | | |
| 22.0 | 515 | 12.2 | 0.619 | | | | 330 |
| 33.6 | 514 | 12.15 | 1.264 | | | | 330 |
| 43.8 | 510 | 11.7 | 2.303 | | | | 330 |
| 2-Iodopyridine methiodide | | | | | | | |
| 28.0 | 770 | 10.95 | 0.139 | | | | 330 |
| 38.4 | 766 | 10.89 | 0.276 | | | | 330 |
| 46.9 | 760 | 10.85 | 0.486 | | | | 330 |
| 56.4 | 760 | 10.8 | 0.860 | | | | 330 |
| 4-Chloropyridine methotetrafluoroborate | | | | | | | |
| 19.9 | 560 | 3.35 | 0.728 | | | | 293 |
| 29.7 | 556 | 3.33 | 1.402 | | | | 293 |
| 39.0 | 549 | 3.29 | 2.509 | | | | 293 |
| 4-Bromopyridine methotetrafluoroborate | | | | | | | |
| 11.5 | 521 | 2.96 | 0.259 | | | | 293 |
| 21.3 | 521 | 3.425 | 0.561 | | | | 293 |
| 33.6 | 519 | 3.425 | 1.313 | | | | 293 |
| 43.9 | 556 | 2.934 | 3.055 | | | | 293 |
| 4-Iodopyridine methiodide | | | | | | | |
| 22.7 | 526 | 2.67 | 0.271 | | | | 293 |
| 30.4 | 525 | 2.66 | 0.457 | | | | 293 |
| 38.2 | 523 | 2.65 | 0.755 | | | | 293 |
| 47.0 | 522 | 2.65 | 1.332 | 9.97 | | | 293 |
| 47.0 | 261 | 2.65 | 1.258 | 21.1 | 2.12 | 2.00 | 293 |
| 47.0 | 906 [i] | 2.65 | 1.236 | | | | 293 |
| 4-Chloroquinoline methiodide | | | | | | | |
| 10.5 | 517 | 2.57 | 11.5 | 1.16 | | | 367 |
| 10.5 | 259 | 2.42 | 11.8 | 2.26 | 1.95 | 2.00 | 367 |
| 14.5 | 259 | 2.72 | 15.5 | | | | 367 |
| 17.1 | 286 | 3.20 | 18.4 | | | | 367 |
| 20.0 | 259 | 2.27 | 22.5 | | | | 367 |
| 4-Iodoquinoline methiodide | | | | | | | |
| 15.8 | 514 | 2.69 | 7.08 | | | | 367 |
| 20.5 | 257 | 1.32 | 9.67 | | | | 367 |
| 27.4 | 257 | 1.31 | 14.12 | | | | 367 |
| 34.1 | 256 | 1.32 | 20.21 | | | | 367 |

[a] ±0.2°. [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 concentration of reactants employed. [g] Analytical wavelength for the determination of percentage reaction. [h] The concentrations of piperidine used in the calculations was that of the free base present in aqueous solutions half neutralised with the calculated quantity of standardised hydrochloric acid unless otherwise specified. [i] Aqueous piperidine solution 12.6% neutralised with hydrochloric acid.

the Arrhenius parameters, and rate coefficients calculated at 20°. Comparison of the rate coefficients for the reactions of the 2- and 4-halogenopyridine methiodides with piperidine in water at 20° revealed the order of reactivity Cl > Br > I; but only small differences indeed between the isomeric compounds (the greatest being three-fold for the iodo-compounds) and these were reflected in general in rather small differences in energies of activation and log $A$ values. These results contrast with our published results for the reactions of these compounds with the anionic nucleophile, hydroxide ion in water, which clearly showed that the isomeric chloro-, bromo-, and iodo-pyridine methiodides were 43.5—116 times more reactive for substituents at the 2- than at the 4-position. Energies of activation for the reactions with piperidine were also significantly less than for reactions with hydroxide ions, being 3.9—4.85 kcal mol$^{-1}$ lower for substituents at the 2-position, and 3.7—5.4 kcal mol$^{-1}$ lower for substituents at the 4-position and log $A$ values were lower also by 2.9—3.4 and 0.7—1.9 units respectively. The much diminished positional difference in reactivity exhibited by the halogenopyridine methiodides towards piperidine by comparison with hydroxide ions is attributed to the absence of the strong electrostatic attraction at the 2-position between the cationic substrate and the anionic hydroxide ion nucleophile which served to increase relatively the reactivity of 2-substituted pyridinium salts over their 4-isomers in reactions with hydroxide ions. Towards piperidine or hydroxide ions [2] in water at 20°, the 2-halogenopyridine methosalts had comparable reactivities, but the 4-isomers were significantly more reactive (by 110—122 times) towards piperidine. 4-Iodoquinoline methiodide at 20° was also 544 times more reactive towards piperidine than hydroxide ions. This was associated with a large decrease (by 6.3 units) in the energy of activation despite some compensation in log $A$.

The effect of annelation to 4-chloro- and 4-iodopyridine methiodide to give 4-chloro- and 4-iodoquinoline methiodides was to increase reactivity towards piperidine by 31 and 41 times respectively and compares with eight times for reactions with hydroxide ions. The calculated rate coefficients were relatively insensitive to variations in the degree of neutralisation. Thus no significant effect was observed on the calculated rate coefficients for the reaction of 4-iodopyridine methiodide with piperidine in water when the ratio of free piperidine to piperidine hydrochloride was increased seven fold.

It was not possible to study the kinetics of some of the reactions with partially neutralised piperidine in water. Thus spectral evidence indicated that hydrolysis was significant with 2-fluoropyridine and 4-methoxyquinoline methiodides, and was the predominant reaction with 2-methylthioquinoline methiodide.

Preliminary investigation indicated that 4-methoxy- and 4-methylthio-pyridine and the corresponding quinoline methiodides with 0.25M-piperidine in water at *ca.* 20° gave the normal piperidinolysis products. Approximate rate coefficients have been determined for 4-methoxypyridine methiodide and 4-methoxy- and 4-methylthio-quinoline methiodides as 0.000 097, 0.000 86, and 0.0058 l mol$^{-1}$ s$^{-1}$ respectively.

The reactions of the substituted pyridinium salts with piperidine in ethanol were faster than for this nucleophile in water. Thus 4-chloro-, 4-bromo-, and 4-iodo-pyridine methosalts with piperidine in ethanol at 20° were found to react 14.5, 16.75, and 8.0 times faster than for their reactions with piperidine in water, and this was associated with slightly lower energies of activation

TABLE 3

Rate coefficients and Arrhenius parameters for reactions with piperidine in ethanol and in water

| Compound | $k$ [a] 20° | $E$/kJ mol$^{-1}$ (kcal mol$^{-1}$) | log $A$ [c] | $\Delta H^{\ddagger}$/kJ mol$^{-1}$ [b] (kcal mol$^{-1}$) | $-\Delta S^{\ddagger}$/J mol$^{-1}$ K$^{-1}$ [d] (cal mol$^{-1}$ K$^{-1}$) |
|---|---|---|---|---|---|
| Reactions in ethanol | | | | | |
| *N*-Methylpyridinium salts | | | | | |
| 4-Cl | 10.6 | 46.0 (11.0) | 9.2 | 43.5 (10.4) | 77.0 (18.4) |
| 4-Br | 8.88 | 52.3 (12.5) | 10.3 | 49.8 (11.9) | 56.1 (13.4) |
| 4-I | 1.79 | 51.5 (12.3) | 9.4 | 49.0 (11.7) | 73.3 (17.5) |
| *N*-Methylquinolinium iodide | | | | | |
| 4-Cl | 162 | 36.8 (8.8) | 8.8 | 34.3 (8.2) | 84.9 (20.3) |
| Reactions in water [e] | | | | | |
| *N*-Methylpyridinium salts | | | | | |
| 2-Cl | 0.69 | 46.5 (11.1) | 8.1 | 44.0 (10.5) | 98.3 (23.5) |
| 2-Br | 0.534 | 47.3 (11.3) | 8.2 | 44.7 (10.7) | 96.5 (23.1) |
| 2-I | 0.077 | 53.6 (12.8) | 8.4 | 51.0 (12.2) | 92.8 (22.2) |
| 4-Cl | 0.73 | 49.4 (11.8) | 8.7 | 46.9 (11.2) | 86.8 (20.7) |
| 4-Br | 0.53 | 57.3 (13.7) | 9.9 | 54.9 (13.1) | 63.6 (15.2) |
| 4-I | 0.224 | 51.1 (12.2) | 8.4 | 48.6 (11.6) | 92.6 (22.1) |
| *N*-Methylquinolinium salts | | | | | |
| 4-Cl | 22.5 | 47.3 (11.3) | 9.8 | 44.8 (10.7) | 65.3 (15.6) |
| 4-I | 9.2 | 42.3 (10.1) | 8.5 | 39.9 (9.5) | 90.4 (21.6) |

[a] Rate coefficients at 20.0° in l mol$^{-1}$ s$^{-1}$. Calculated from the rate coefficient at a nearby temperature. [b] Accurate to 5.0 kJ mol$^{-1}$; based on standard deviations. [c] Accurate to ±0.8 units. [d] Accurate to 4.0 J mol$^{-1}$ K$^{-1}$. [e] Piperidine solutions half neutralised with the calculated quantity of standardised hydrochloric acid.

(except for 4-iodopyridine methiodide which was approximately the same) and higher frequency factors (compare with a ten-fold increase at 44.6° on passing *from* water to ethanol for the reaction of triethylamine with trimethylsulphonium nitrate.[3])

A measure of the effect of quaternisation by methylation was obtained from comparison of results contained in this paper with literature data. Thus the rate coefficients for the reaction of 4-chloroquinoline methiodide with piperidine in ethanol calculated at 100° ($k_{100°}$ 4 430 l mol$^{-1}$ s$^{-1}$) from this work when compared to published values for 4-chloroquinoline with piperidine in 95% ethanol,[4] revealed a rate enhancement at 100° for quaternisation by $2 \times 10^8$-fold; and is of the general order $6.1 \times 10^5$—$7.3 \times 10^8$-fold found previously for reactions of substituted pyridines, quinolines, and isoquinolines with hydroxide ions. The calculated rate coefficient for the reaction of 4-chloropyridine methiodide with piperidine in ethanol at 100° ($k_{100°}$ 572.5 l mol$^{-1}$ s$^{-1}$) when compared with that published for 4-chloropyridine with piperidine in methanol[5] revealed a $8.5 \times 10^7$-fold difference.

## EXPERIMENTAL

Solids for analysis were dried at 100° unless otherwise stated. M.p.s were taken in Pyrex capillaries. The halogeno-pyridine and -quinoline methosalts were prepared as described in Parts X[2] and XII.[1] The kinetic studies were undertaken with a Shimadzu R27 recording spectrophotometer fitted with a rapid reaction apparatus[6] as described in Part X.[2] 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, or 35° with a Varian T-60A spectrometer.

1-*Methyl*-2-*piperidinopyridinium Iodide and Picrate*.—2-Iodopyridine methiodide (0.8 g) and piperidine (0.42 g; 2 equiv.) in ethanol (30 ml) were refluxed on a steam-bath for 2 h. The mixture was evaporated to dryness, extracted with boiling ether, and the residue recrystallised from acetone to give 1-*methyl*-2-*piperidinopyridinium iodid e* (0.29 g), m.p. 161.5—163° (Found: C, 43.6; H, 5.5; N, 9.1. $C_{11}H_{17}IN_2$ requires C, 43.4; H, 5.6; N, 9.2%), $\lambda_{max.}$ ($H_2O$) 257 (log ε 3.80) and 330 nm (3.76). The *picrate*, prepared in and recrystallised from water, had m.p. 123—124° (Found: C, 50.0; H, 4.8; N, 17.0. $C_{17}H_{19}N_5O_7$ requires C, 50.4; H, 4.7; N, 17.3%).

4-*Piperidinopyridine*.—4-Methoxypyridine (1.0 g) and piperidine (3.0 ml) were heated in a sealed tube at 156° for 21 h. The mixture was diluted with water and extracted with chloroform. The product was recrystallised from light petroleum (b.p. 60—80°) to give 4-piperidinopyridine (0.52 g), m.p. 82—83° (lit.,[7] 80°).

Similarly 4-nitropyridine and piperidine gave, after 4 h at 130°, a low yield of 4-piperidinopyridine, isolated as its picrate, m.p. 144—146° (lit., [8] 142°); and 4-chloropyridine and piperidine at 156° for 21 h gave a product whose $^1$H n.m.r. spectrum was identical to that of 4-piperidinopyridine prepared above.

1-*Methyl*-4-*piperidinopyridinium Iodide and Picrate*.—The iodide was prepared from 4-piperidinopyridine and methyl iodide in methanol.[7] It had m.p. 162—164° (lit., 159°) (Found: C, 43.4; H, 5.95; N, 8.8. Calc. for $C_{11}H_{17}IN_2$: C 43.4; H, 5.6; N, 9.2%), $\lambda_{max.}$ ($H_2O$) 293 nm (log ε 4.39) (EtOH) 293—294 nm (log ε 4.36). The *picrate*, prepared in and recrystallised from water, had m.p. 141—142° (Found: C, 49.6; H, 4.7; N, 17.2. $C_{17}H_{19}N_5O_7$ requires C, 50.0; H, 4.8; N, 17.0%).

A mixture of 4-chloropyridine methiodide (0.51 g), piperidine (0.5 g), and ethanol (20 ml) was refluxed for 2 h, and the solvent evaporated. The residue was recrystallised from acetone to give crystals (0.51 g) which gave a picrate, m.p. 142.5—143.5°, not depressed on admixture with the picrate described above.

1-*Methyl*-4-*piperidinoquinolinium Iodide*.—4-Iodoquinoline methiodide (0.40 g), piperidine (0.17 g), and ethanol (7.0 ml) were refluxed on a steam-bath for 3 h. The solution was evaporated to dryness, extracted with ether, and the residue recrystallised from acetone–light petroleum (b.p. 40—60°) to give the *iodide* (0.30 g), m.p. 169—170° (Found: C, 51.2; H, 5.7; N, 7.9. $C_{15}H_{19}IN_2$ requires C, 50.9; H, 5.4; N, 7.9%), $\lambda_{max.}$ ($H_2O$) 224 (log ε 4.49), 240 (4.08), 256—275 (4.02), and 367—368 (4.31) nm; (EtOH) 224 (log ε 4.42), 241 (4.06), 257 (4.01), and 367—368 nm (4.28).

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