Electrophilic Substitution of Heteroaromatic Compounds. Part 54.[1] Intramolecular Base-catalysed Hydrogen Exchange at the 3-Position in Substituted Pyridines[1]

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Various *O*-linked substituents at the 4-position of a pyridine ring enhance the rate of base-catalysed hydrogen exchange at the 3,5-ring positions. An intramolecular proton-abstraction mechanism is proposed.

Acid-catalysed hydrogen exchange in pyridines, by the proton addition mechanism of electrophilic substitution, usually takes place at the β-position, although exchange at the α- or γ-position can be induced by suitable *o,p*-directing substituents.[2] Base-catalysed hydrogen exchange proceeds in pyridines by ring-proton abstraction, and usually occurs on a pyridinium cation or zwitterion (*e.g.* a pyridine *N*-oxide) at the α-position. Base-catalysed hydrogen exchange of neutral pyridine species is more difficult and occurs preferentially at the γ-position, followed by reaction at the β-position. Thus, pyridine itself displays the reactivity order 2(6) < 3(5) < 4 under the following conditions: (i) in MeOH–MeO^- solution[3] at 165 °C or (ii) in D_2O–OD^- at 200 °C[4] or (iii) in ND_3–$NaND_2$ at −25 °C.[5] Halogen at the 3-position accelerates exchange at the 4-position while a halogen at the 4-position accelerates exchange at the 3(5)-positions.[2a]

We now report that when a suitable substituent can act as an intramolecular H^+-abstractor, base-catalysed hydrogen exchange can occur in neutral pyridines at the β-position under quite mild conditions.

The NaOD-catalysed hydrogen–deuterium exchange of the pyridylpyridone (**1**) was followed in [$^2H_6$]dimethyl sulphoxide (DMSO). The spectrum of (**1**) showed doublets at δ 6.16 and 7.96 for the pyridone 3,5- and 2,6-H, respectively, and doublets at δ 7.10 and 8.50 for the pyridine 3,5- and 2,6-H, respectively. The disappearance of the signal at δ 7.96 at 25 °C showed replacement of H by D at the 2,6-positions of the pyridone ring, corresponding to the known[6] exchange of 1-methyl-4-pyridone at the 2,6-positions. At 30—40 °C the signal at δ 7.10 decreased in intensity indicating reaction at the 3- and 5-position of the pyridine ring. Exchange at the 3,6-positions of the pyridine ring of 4-methoxypyridine with CD_3OD–CD_3O^- is reported to occur only at 165 °C and to be accompanied by ether cleavage.[7] This suggests that the isotopic replacement might proceed by intramolecular abstraction of the proton by the anion (**10**) formed at the pyridone 2-position to give the isomeric anion (**11**) and hence the deuteriated product (**12**) *cf.* Scheme. Analogous literature precedents for such a mechanism are to be found in 1-alkoxypyridinium chemistry as illustrated in formulae (**13**)[8] and (**14**).[9]

The intramolecular proton-abstraction mechanism was confirmed by the similar exchange found in compounds (**2**) and (**3**).

The ^1H n.m.r. spectrum of 2-(4-pyridyloxy)ethanol (**2**) in [$^2H_6$]DMSO showed a multiplet at δ 3.70—4.30 for the CH_2–CH_2 protons and a broad OH signal at δ 4.35 together with a doublet at δ 7.10 and a broad peak at δ 8.55 for the pyridine 3,5- and 2,6-H, respectively. On adding CD_3ONa the CH_2–CH_2 multiplet narrowed, the δ 4.35 singlet disappeared, and the δ 8.55 signal became a doublet; in neutral solution the acidic OH proton is probably hydrogen-bonded to the nitrogen. At 85 °C, the doublet at δ 7.10 decreased in intensity, the signal at δ 8.55 changed from a doublet into a singlet indicating exchange at the 3,5-positions of the pyridine ring; simultaneously the aliphatic multiplet decreased in intensity and a new aliphatic singlet

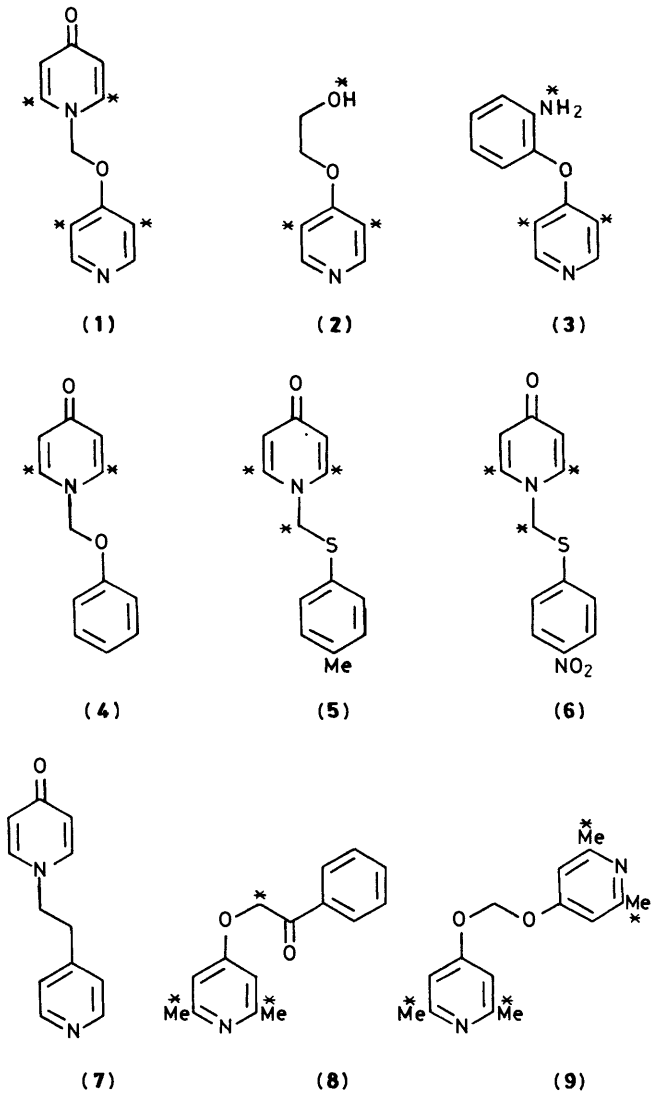
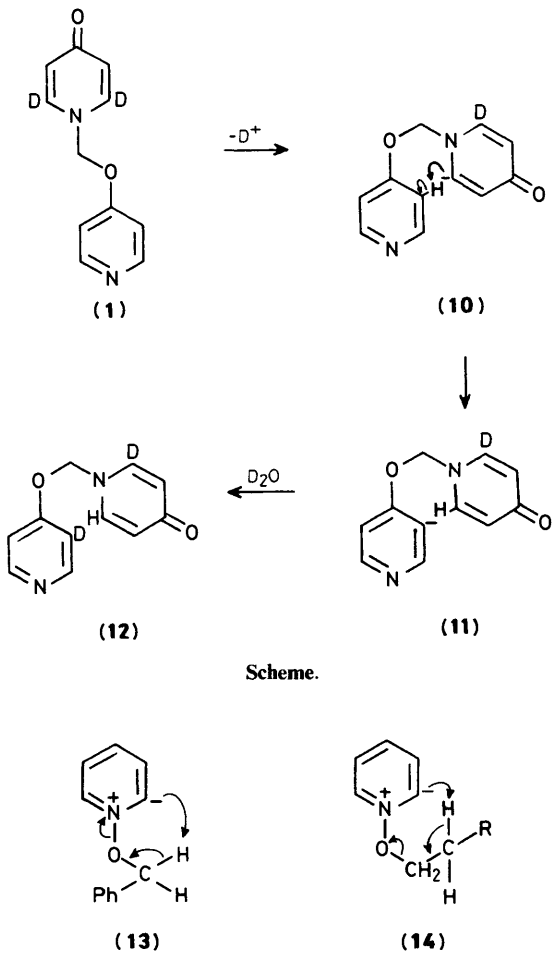


Figure. Base-catalysed hydrogen–deuterium exchange in different *N*- and *O*-substituted 4-pyridones and 4-hydroxypyridines (the positions exchanging are indicated by *)



Scheme.

peak began to appear indicating some ether cleavage and formation of ethylene glycol.

4-(2-Aminophenoxy)pyridine (**3**) in CD_3ONa–CD_3OD–[$^2H_6$]DMSO also showed a decrease in intensity of the pyridine 3,5-H signal with the signal of the pyridine 2,6-H becoming a singlet at 85 °C, indicating exchange at the pyridine 3,5-positions. Ether cleavage was also observed. In marked contrast, no exchange was found in 4-phenoxypyridine when this compound was treated similarly.

None of the other compounds in the Figure showed exchange at the pyridine 3,5-positions at temperatures up to 100 °C which further supports the mechanism. However, exchange was found at other ring positions, in accordance with expectations from literature data. Thus, exchange occurred at the 2,6-positions of the pyridone ring in compounds (**1**), (**4**), (**5**), and (**6**) at temperatures of 25, 25, 40, and 40 °C respectively. Compound (**7**) decomposed into 4-pyridone and 4-vinylpyridine on base treatment. Under identical conditions, compound (**1**) was found to exchange in [$^2H_6$]DMSO and NaOD approximately five times faster than 1-methyl-4-pyridone; this indicates enhanced inductive electron withdrawal by oxygen in compound (**1**).

Methylene groups next to sulphur in (**5**) and (**6**) and next to the carbonyl group in (**8**) [but not next to oxygen in (**1**), (**4**), (**9**), or (**2**)] also underwent exchange at 25 °C. There are numerous literature precedents[6] both for this and for the methyl-group exchange found in compounds (**8**) and (**9**).

Preparation of Compounds.—Compounds (**4**), (**5**), (**6**), and (**7**) were prepared from 4-pyridone and chloromethyl phenyl ether, chloromethyl 4-methylphenyl sulphide, chloromethyl 4-nitrophenyl sulphide, and 4-vinylpyridine, respectively.

Compounds (**8**) and (**9**) were prepared from 2,6-dimethyl-4-pyridone by reaction with bromoacetophenone and methylene dichloride, respectively. Compounds (**2**) and (**3**) were prepared from 4-chloropyridine hydrochloride by reaction with ethylene glycol and 2-aminophenol, respectively.

Conclusions.—In 1-alkyl-4-pyridones a heteroatom at the β-position of an *N*-alkyl substituent enhances the hydrogen–deuterium exchange rate at the 2,6-positions. In 4-alkoxypyridines a heteroatom at the γ-position of a 4-*O*-alkyl substituent with exchangeable hydrogen or a γ-acidic C–H enhances the hydrogen exchange rate at the 3,5-positions.

Experimental

M.p.s were recorded on a bristoline hot-stage microscope and are uncorrected. The ^1H n.m.r. spectra were recorded on a Varian 360L spectrometer using Me_4Si as the internal reference and ^{13}C n.m.r. spectra were recorded on a JEOL FX 100 spectrometer and Varian XL 200 spectrometer using the solvent ([$^2H_6$]DMSO) peak as the reference. The i.r. spectra were obtained on a Perkin-Elmer 283B spectrophotometer.

Method and Reagents.—Hydrogen–deuterium exchanges were carried out with an excess of NaOD (1M) in [$^2H_6$]DMSO as solvent unless otherwise indicated. Exchange was followed by the decrease in the peak intensity of the exchanging proton coupled with the disappearance of the coupling of the exchanging proton with the vicinal proton (^1H n.m.r.). The positions of exchange were confirmed from the ^{13}C n.m.r. spectrum which showed a decrease in signal intensity of the carbon to which the exchanging proton is attached.

General Procedure for Hydrogen–Deuterium Exchange.—The pyridone (25—30 mg) was dissolved in [$^2H_6$]DMSO (0.3 ml) in a 5 mm n.m.r. tube. NaOD or CD_3ONa (0.20—0.25 ml; 1M) was added and the ^1H n.m.r. spectra were recorded periodically. For higher-temperature exchange the n.m.r. tubes were heated in an oil-bath maintained at the required temperature.

Substrates.—The following were prepared by the literature methods indicated: chloromethyl phenyl ether, b.p. 90—95 °C (20 mmHg) [lit.,[10] b.p. 87—89 °C (16 mmHg)], chloromethyl phenyl sulphide, b.p. 85—90 °C (5 mmHg) (lit.,[11] b.p. 83 °C at 1.5 mmHg), 2,6-dimethyl-4-pyridone, m.p. 224 °C (lit.,[12] m.p. 225 °C), 1-methyl-4-pyridone, m.p. 95 °C (lit.,[6] m.p. 92—93 °C) and 4-phenoxypyridine, m.p. 45 °C (lit.,[13] m.p. 44—46 °C). 4-Methoxypyridine, b.p. 80—85 °C (20—25 mmHg) (lit.,[14] b.p. 80—82 °C at 15—20 mmHg), was prepared from 4-methoxypyridine *N*-oxide following an analogous procedure.[15]

1-(4-*Pyridyloxymethyl*)-4-*pyridone* (**1**).—4-Pyridone (4.75 g, 0.05 mol), benzyltriethylammonium chloride (0.57 g, 0.0025 mol), potassium carbonate (6.9 g, 0.05 mol), and potassium hydroxide (3.5 g; 84%) were stirred and refluxed in methylene dichloride (300 ml). After 48 h, solid was filtered off and extracted with hot CH_2Cl_2. The combined filtrate and extracts were dried (anhydrous $MgSO_4$) and the solvent evaporated to give the *pyridylpyridone* (**1**) (1.18 g, 25%), m.p. 199—201 °C (Found: C, 60.1; H, 5.6; N, 12.7. $C_{11}H_{10}N_2O_2 \cdot H_2O$ requires C, 60.0; H, 5.5; N, 12.7%); $\nu_{max.}$($CHBr_3$) 1 650 cm^{-1}; δ([$^2H_6$]DMSO) 6.00 (2 H, s), 6.16 (2 H, d, *J* 8 Hz), 7.10 (2 H, d, *J* 6 Hz), 7.96 (2 H, d, *J* 8 Hz), and 8.50 (2 H, d, *J* 6 Hz).

1-*Phenoxymethyl*-4-*pyridone* (**4**).—4-Pyridone (2.38 g, 0.025 mol), benzyltriethylammonium chloride (0.575 g, 0.0025 mol), potassium hydroxide (3.6 g; 84%), and chloromethyl phenyl ether (3.56 g, 0.025 mol) were vigorously stirred and refluxed in

methylene dichloride (300 ml). After 48 h, solid was filtered off and extracted with hot CH_2Cl_2. The combined filtrate and extracts were dried (anhydrous $MgSO_4$), the solvent evaporated, and the residue crystallized from chloroform to give the *pyridone* (**4**) (2.5 g, 50%), m.p. 149—151 °C (Found: C, 71.5; H, 5.6; N, 6.7. $C_{12}H_{11}N_2O$ requires C, 71.6; H, 5.5; N, 7.0%); $\nu_{max.}(CHBr_3)$ 1 630 cm^{-1}; δ([$^2H_6$]DMSO) 5.90 (2 H, s), 6.25 (2 H, d, *J* 7 Hz), 7.25 (5 H, m), and 7.95 (2 H, d, *J* 7 Hz).

1-(4-*Methylphenylthiomethyl*)-4-*pyridone* (**5**).—Sodium (0.58 g, 0.025 mol) was added to 4-pyridone (2.38 g, 0.025 mol) in absolute ethanol (50 ml). The mixture was then refluxed with 4-methylphenyl chloromethyl sulphide (4.31 g, 0.025 mol) for 12 h, cooled to 25 °C, poured into water, and extracted with chloroform (3 × 50 ml). The chloroform extract was dried (anhydrous $MgSO_4$), evaporated, and the residue crystallized from chloroform to give the *pyridone* (**5**) (3.5 g, 60%), m.p. 105 °C (Found: C, 67.84; H, 5.83; N, 5.96. $C_{13}H_{13}NOS$ requires C, 67.50; H, 5.66; N, 6.06%); $\nu_{max.}(CHBr_3)$ 1 620 cm^{-1}; δ($CDCl_3$) 2.32 (3 H, s), 4.98 (2 H, s), 6.33 (2 H, d, *J* 9 Hz), and 7.10—7.48 (6 H, m).

1-(4-*Nitrophenylthiomethyl*)-4-*pyridone* (**6**).—The procedure as described for (**5**), but using 4-nitrophenyl chloromethyl sulphide, gave *pyridone* (**6**) (2.6 g, 40%), m.p. 118—120 °C (Found: C, 54.50; H, 3.83; N, 10.36. $C_{12}H_{10}N_2O_3S$ requires C, 54.90; H, 3.82; N, 10.69%); $\nu_{max.}(CHBr_3)$ 1 615, 1 525, and 1 330 cm^{-1}; δ([$^2H_6$]DMSO) 5.80 (2 H, s), 6.18 (2 H, d, *J* 8 Hz), 7.75—8.10 (4 H, m), and 8.45 (2 H, d, *J* 9 Hz).

1-(4-*Pyridylethyl*)-4-*pyridone* (**7**).—4-Pyridone (0.95 g, 0.01 mol) and 4-vinylpyridine (1.05 g, 0.01 mol) were refluxed in ethanol (10 ml) for 10 h. The reaction mixture was cooled and ether was added to the mixture to give the *pyridylpyridone* (**7**) (1.8 g, 90%), m.p. 78—80 °C (Found: C, 72.12; H, 6.23; N, 13.91. $C_{12}H_{12}N_2O$ requires C, 72.00; H, 6.00; N, 14.00%); $\nu_{max.}(CHBr_3)$ 1 620 cm^{-1}; δ($CDCl_3$) 3.12 (2 H, t, *J* 7 Hz), 4.22 (2 H, t, *J* 7 Hz), 6.40 (2 H, d, *J* 7 Hz), 7.22 (2 H, d, *J* 5 Hz), 7.50 (2 H, d, *J* 7 Hz), and 8.70 (2 H, d, *J* 5 Hz).

2,6-*Dimethyl*-4-*pyridyl Phenacyl Ether* (**8**).—The procedure as described for (**5**), but using 2,6-dimethyl-4-pyridone and phenacyl bromide in place of 4-pyridone and 4-methylphenyl chloromethyl sulphide respectively, gave the *pyridine* (**8**) (75%), m.p. 225 °C (Found: C, 74.55; H, 6.48; N, 5.68. $C_{15}H_{15}NO_2$ requires C, 74.69; H, 6.22; N, 5.81%); $\nu_{max.}(CHBr_3)$ 1 690 cm^{-1}; δ([$^2H_6$]DMSO) 2.80 (6 H, s), 6.20 (2 H, s), 7.68 (2 H, s), and 7.75—8.45 (5 H, m).

Bis-(2,6-*dimethyl*-4-*pyridyloxy*)*methane* (**9**).—This compound was prepared following the same procedure as described for compound (**1**) but using 2,6-dimethyl-4-pyridone in place of 4-pyridone to give (**9**) (5.5 g, 85%), m.p. 73—75 °C (Found: C, 69.55; H, 7.15; N, 10.68. $C_{15}H_{18}N_2O_2$ requires C, 69.77; H, 6.98; N, 10.85%); $\nu_{max.}(CHBr_3)$ 1 590 cm^{-1}; δ($CDCl_3$) 2.58 (12 H, s), 5.93 (2 H, s), and 6.91 (4 H, s).

2-(4-*Pyridyloxy*)*ethanol* (**2**).—To 4-chloropyridine hydrochloride (3.0 g, 0.02 mol) dissolved in DMSO (40 ml), ethylene glycol (1.2 g, 0.02 mol), and sodium hydroxide pellets (2.0 g) were added and heated gently at 100 °C overnight. The mixture was cooled, poured into ice and water (300 g), and extracted with ether many times until the ether layer was colourless. The ether extracts were combined and dried (anhydrous $MgSO_4$), filtered, and the solvent evaporated, to give the *title compound* (**2**) (2.0 g, 72%), m.p. 118—120 °C (Found: C, 60.55; H, 6.69; N, 9.89. $C_7H_9NO_2$ requires C, 60.43; H, 6.48; N, 10.07%); $\nu_{max.}(CHBr_3)$ 3 650 cm^{-1}; δ([$^2H_6$]DMSO) 3.70—4.30 (4 H, m), 4.35 (1 H, br s), 7.10 (2 H, d, *J* 5 Hz), and 8.55 (2 H, br s).

4-(2-*Aminophenoxy*)*pyridine* (**3**).—The same procedure as described above for compound (**2**) was used except ethylene glycol was replaced by 2-aminophenol, to give the *pyridine* (**3**) (2.85 g, 72%), m.p. 98 °C (Found: C, 70.65; H, 5.52; N, 14.95. $C_{11}H_{10}N_2O$ requires C, 70.97; H, 5.38; N, 15.05%); $\nu_{max.}(CHBr_3)$ 3 365 and 3 290 cm^{-1}; δ([$^2H_6$]DMSO) 3.75 (2 H, br s), 6.50—7.20 (6 H, m), and 8.40 (2 H, d, *J* 5 Hz).

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