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The Bromination of Pyridines. IV [1]

The Bromination of Some Ethylated Pyridines

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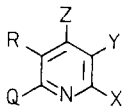
Previously [1 – 2] we described the bromination of some mono, di and trialkylated pyridines in oleum, and now conclude this study by reporting our results of the bromination of three other commercially available ethylated pyridines, namely 2-ethyl, 3-ethyl and 2,5-diethylpyridine. The reaction conditions used were those previously described by us [1], i.e. using 65 % oleum and liquid bromine at 70 – 100 °C, and isolating the reaction products by a combination of steam distillation and chromatography. When 2-ethylpyridine was treated as described above [3], the reaction proceeded as expected to yield two monobrominated products and one dibrominated product. These were assigned structures **1 – 3** by ^{1}H-n.m.r. spectroscopy where chemical shift position and coupling constants were sufficient to indicate clearly the site of bromination in the products. These results were in accord with other observations [1 – 2] i.e. that the principal site of bromination is the 3(5) position in the aromatic nucleus. By contrast, bromination of 3-ethylpyridine was more complex. Analysis of the reaction mixture resulting from the bromination of this substrate indicated that almost 80 % of the starting material remained, and that there were four monobrominated and two dibrominated products. Separation of the components of this reaction mixture was extremely tedious and required repeated column chromatography and finally preparative t.l.c., before any pure products could be obtained. The four monobrominated products were assigned structures **4 – 7** again on the basis of their ^{1}H-n.m.r. spectra. The two dibrominated products were clearly **8** and **9**, but it did not prove possible to distinguish between these two structures on n.m.r. evidence alone. In order to resolve this problem, the major dibrominated product was heated with excess morpholine to yield a monobrominated derivative **10** corresponding to the replacement of the more labile 2-bromo substituent. Reduction of the latter gave **11** whose ^{1}H-n.m.r. spectrum contained three doublets of doublets indicating the presence of three adjacent protons in the pyridine ring. This product can only be 3-ethyl-2-morpholinopyridine, and therefore **10** must be 5-bromo-3-ethyl-2-morpholinopyridine. The major dibrominated product is thus identified as 2,5-dibromo-3-ethylpyridine **8**. The results from the bromination of 3-ethylpyridine have been interpreted as follows. Since only one position 3(5) is available for substitution in the normal reaction, the reaction proceeds more slowly and as a result minor processes such as bromination at e.g. the 4 position become more important leading to a more complex reaction mixture.

Bromination of 2,5-diethylpyridine was in comparison to the first two substrates much faster. Two products only were obtained **12** and **13**. The structures of both of these com-



	X	Y	Z	R	Q
1	Et	Br	H	H	H
2	Et	H	H	Br	H
3	Et	Br	H	Br	H
4	Br	Et	H	H	H
5	H	Et	Br	H	H
6	H	Et	H	Br	H
7	H	Et	H	H	Br
8	Br	Et	H	Br	H
9	H	Et	H	Br	Br
10	morph-	Et	H	Br	H
11	morph-	Et	H	H	H
12	Et	Br	H	Et	H
13	Et	Br	H	Et	Br

morph- = morpholin-4-yl

pounds were easily established by ^{1}H-n.m.r. spectroscopy and no ambiguity exists regarding their structural assignments. In this case a faster reaction is to be expected since the pyridine nucleus is more activated, even although one of the preferred sites for bromination is already occupied.

Experimental

Distillations were carried out using a Kugelrohr (Buchi AG). Infrared spectra were measured for thin films on NaCl with a Perkin Elmer 1600 FT-IR machine, and ^{1}H-n.m.r. spectra were recorded in deuteriochloroform solution using tetramethylsilane as internal standard on a Jeol PMX 60SI instrument at 60 MHz. Mass spectra were obtained with an AEI MS 920S mass spectrometer.

Bromination of Ethylated Pyridines – General Procedure

The ethylated pyridine (0.1 mole) was dissolved with ice cooling and vigorous stirring in 65 % oleum (50 ml), and the mixture treated with liquid bromine (0.12 mole). The resulting mixtures were then heated gently on a steam bath at 70 – 100 °C either overnight or until the bromine colour had been discharged (in the case of 2,5-diethylpyridine). The mixtures were then cautiously poured onto ice, and the solutions steam distilled to afford (principally) the dibrominated products. The residue was then treated with concentrated NaOH solution until slightly basic and then treated again with steam to yield the monobrominated products and any unreacted starting material. The products were extracted from the aqueous distillates with ether, and the dried concentrated extracts purified by column chromatography and by distillation. In the case of 3-ethylpyridine all fractions were further purified by preparative thin layer chromatography. The monobrominated products (**1**) and (**2**) (previously reported [3] as a mixture) were separated on a column of tlc grade silica gel (300 g) using light petroleum/ether (85 : 15) by flash chromatography.

From 2-ethylpyridine the following products were obtained:

(a) *3-bromo-2-ethylpyridine* (**1**) (20 % yield), b.p. 40 °C/0.6 m bar.

^{1}H-n.m.r.: δ 8.34 (1H, dd); 7.58 (1H, dd); 6.88 (1H, dd); 2.94 (2H, q); 1.28 (3H, t).

C_7H_8BrN	Calcd.:	C 45.19	H 4.33	N 7.53	Br 42.95
(186.1)	Found:	C 45.00	H 4.43	N 7.52	Br 42.78

(b) *5-bromo-2-ethylpyridine* (**2**) (52 %), b.p. 35 °C/0.6 m bar.

^{1}H-n.m.r.: δ 8.38 (1H, d); 7.56 (1H, dd); 6.86 (1H, d); 2.74 (2H, q); 1.28 (3H, t).

C_7H_8BrN	Calcd.:	C 45.19	H 4.33	N 7.53	Br 42.95
(186.1)	Found:	C 45.22	H 4.33	N 7.44	Br 43.08

and (c) *3,5-dibromo-2-ethylpyridine* (**3**) (0.4 %) b.p. 55 °C/0.6 m bar.

^{1}H-n.m.r.: δ 8.41 (1H, d); 7.86 (1H, d); 2.89 (2H, q); 1.17 (3H, t).

$C_7H_7Br_2N$	Calcd.:	C 31.73	H 2.66	N 5.29	Br 60.32
(265.0)	Found:	C 31.88	H 2.51	N 5.50	Br 60.47

From 3-ethylpyridine the following products were obtained:

(a) *2-bromo-3-ethylpyridine* (**4**) (0.5 %), b.p. 40 °C/0.6 m bar.

^{1}H-n.m.r.: δ 8.08 (1H, dd); 7.42 (1H, dd); 7.11 (1H, dd); 2.72 (2H, q); 1.26 (3H, t).

C_7H_8BrN	Calcd.:	C 45.19	H 4.33	N 7.53	Br 42.95
(186.1)	Found:	C 45.32	H 4.34	N 7.77	Br 43.06

(b) *4-bromo-3-ethylpyridine* (**5**) (0.8 %), b.p. 30 °C/0.2 m bar.

^{1}H-n.m.r.: δ 8.52 (1H, s); 8.30 (1H, d, J = 4.8 Hz); 7.06 (1H, d, J = 4.8 Hz); 2.71 (2H, q); 1.24 (3H, t).

C_7H_8BrN	Calcd.:	C 45.19	H 4.33	N 7.53	Br 42.95
(186.1)	Found:	C 45.43	H 4.52	N 7.55	Br 42.78

(c) *5-bromo-3-ethylpyridine* (**6**) (3.7 %), b.p. 40 °C/0.6 m bar.

^{1}H-n.m.r.: δ 8.37 (1H, d); 7.35 (1H, complex); 2.61 (2H, q); 1.23 (3H, t).

C_7H_8BrN	Calcd.:	C 45.19	H 4.33	N 7.53	Br 42.95
(186.1)	Found:	C 45.22	H 4.43	N 7.72	Br 42.73

(d) *2-bromo-5-ethylpyridine* (**7**) (0.3 %), b.p. 35 °C/0.3 m bar.

^{1}H-n.m.r.: δ 8.39 (1H, d); 7.52 (1H, dd); 6.88 (1H, d); 2.72 (2H, q); 1.24 (3H, t).

C_7H_8BrN	Calcd.:	C 45.19	H 4.33	N 7.53	Br 42.95
(186.1)	Found:	C 45.11	H 4.56	N 7.67	Br 43.97

(e) *2,5-dibromo-3-ethylpyridine* (**8**) (4.5 %), b.p. 80 °C/0.3 m bar.

^{1}H-n.m.r.: δ 8.20 (1H, d); 7.56 (1H, d); 2.71 (2H, q); 1.24 (3H, t).

$C_7H_7Br_2N$	Calcd.:	C 31.73	H 2.66	N 5.29	Br 60.32
(265.0)	Found:	C 31.89	H 2.83	N 5.24	Br 60.55

and (f) *2,3-dibromo-5-ethylpyridine* (**9**) (0.7 %), b.p. 80 °C/0.3 m bar.

^{1}H-n.m.r.: δ 8.04 (1H, d); 7.61 (1H, d); 2.58 (2H, q); 1.24 (3H, t).

$C_7H_7Br_2N$	Calcd.:	C 31.73	H 2.66	N 5.29	Br 60.32
(265.0)	Found:	C 31.68	H 2.81	N 5.33	Br 60.09

From 2,5-diethylpyridine the following products were obtained:

(a) *3-bromo-2,5-diethylpyridine* (**12**) (26 %), b.p. 55 °C/0.3 m bar.

^{1}H-n.m.r.: δ 8.17 (1H, d); 7.48 (1H, d); 2.72 (4H, complex); 1.24 (6H, 2t).

$C_9H_{12}BrN$	Calcd.:	C 50.49	H 5.65	N 6.54	Br 37.32
(214.1)	Found:	C 50.60	H 5.66	N 6.54	Br 37.23

and (b) *2,5-dibromo-3,6-diethylpyridine* (**13**) (21 %), b.p. 85 °C/0.6 m bar.

^{1}H-n.m.r.: δ 7.48 (1H, s); 2.72 (4H, complex); 1.22 (6H, 2t).

$C_9H_{11}Br_2N$	Calcd.:	C 36.89	H 3.78	N 4.78	Br 54.54
(293.0)	Found:	C 37.03	H 3.77	N 4.76	Br 54.68

5-bromo-3-ethyl-2-morpholinopyridine (**10**)

A mixture of the dibromo derivative **8** (1.0 g) and morpholine (4 ml) was heated under reflux for 12 hours. The excess reagent was removed at reduced pressure, the residue partitioned between water and ether, and the dried concentrated ethereal extracts distilled in vacuo to afford a colourless oil (982 mg, 96 %), b.p. 110 °C/0.4 m bar.

^{1}H-n.m.r.: δ 8.19 (1H, d); 7.58 (1H, d); 3.84 (4H, t); 3.10 (4H, t); 2.63 (2H, q); 1.25 (3H, t).

i.r.: 2694, 2850, 1571, 1430 cm^{-1}.

$C_{11}H_{15}BrN_2O$	Calcd.:	C 48.73	H 5.58	N 10.33	Br 29.47
(271.2)	Found:	C 49.00	H 5.56	N 10.30	Br 29.45

3-ethyl-2-morpholinopyridine (**11**)

A mixture of **10** (0.5 g), hydrazine hydrate (0.5 g), calcium carbonate (0.2 g), palladium on charcoal (0.2 g, 5 %) and ethanol (5 ml) was heated under reflux for 4 hours. The mixture was filtered, solvents removed at reduced pressure and the residue purified by column chromatography. The major component eluted as a colourless oil (276 mg, 78 %). Distillation gave pure **11** b.p. 80 °C/0.3 m bar.

^{1}H-n.m.r.: δ 8.03 (1H, dd, J = 2.4 and 4.8 Hz); 7.38 (1H, dd, J = 2.4 and 2.4 Hz); 6.80 (1H, dd, J = 2.4 and 4.8 Hz); 3.80 (4H, t); 3.05 (4H, t); 2.65 (2H, q); 1.23 (3H, t).

IR: 3033, 2927, 2903, 1557 cm^{-1}.

MS: m/z 192 (62 %) M^+.

$C_{11}H_{16}N_2O$	Calcd.:	C 68.72	H 8.39	N 14.47
(192.3)	Found:	C 68.62	H 8.55	N 14.65

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