Preparation and Stability of 4-Fluoropyridine

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4-Fluoropyridine has been synthesised by the Balz–Schiemann method and a procedure has been evolved for its isolation and purification. Its ready transformation into *N*-(4-pyridyl)-4-pyridone is an acid-catalysed process; under conditions in which this does not occur, the base is stable.

ROE AND HAWKINS [1] used the Balz–Schiemann reaction [2] to prepare 2- and 3-fluoropyridines, but failed to obtain 4-fluoropyridine. Wibaut and Holmes-Kamminga [3] reported the preparation of 4-fluoropyridine from 4-aminopyridine, but in a 'poor and impure yield'; at room temperature this was immediately converted into *N*-(4-pyridyl)-4-fluoropyridinium fluoride. Lyle and Taft [4] have recently reported that a solution of 4-fluoropyridine in methylene chloride is stable at 0 °C. The instability of 4-fluoropyridine has been attributed to its ready polymerisation; the resulting polypyridinium salt may be hydrolysed in aqueous solutions to pyridylpyridone.[5]

[1] A. Roe and G. F. Hawkins, *J. Amer. Chem. Soc.*, 1947, **69**, 2443.
[2] G. Balz and G. Schiemann, *Ber.*, 1927, **60**, 1186.
[3] J. P. Wibaut and W. J. Holmes-Kamminga, *Bull. Soc. chim. France*, 1958, 424.
[4] J. L. Lyle and R. W. Taft, *J. Heterocyclic Chem.*, 1972, **9**, 745.
[5] R. A. Barnes, 'Heterocyclic Compounds; Pyridine and its Derivatives,' Part I, ed. E. Klingsber, Interscience, New York, 1960, p. 63.

4-Fluoropyridine has now been prepared in 22% yield by diazotization of 4-aminopyridine in fluoroboric acid with sodium nitrite, neutralization (KOH solution) at −20 °C, and distillation at room temperature under vacuum in a sealed unit. On treating the distillate with potassium hydroxide pellets at low temperature, 4-fluoropyridine separated as the upper layer. It was dried (KOH) and vacuum-distilled in the sealed unit. The pure compound was stable even at its b.p. (108°). Samples kept in sealed ampoules at 5—10° for 2 years showed no signs of decomposition. The picrate derivative could be prepared in benzene; attempts to prepare it in aqueous solution gave only the picrate of pyridylpyridone. The mass spectrum of 4-fluoropyridine (70 eV; 120° inlet temperature) showed peaks at *m/e* 97 (M^+, 100%), 78 (M − F, 20%), and 70 (M − HCN, 70%).

4-Fluoropyridine is rapidly converted into pyridylpyridone in aqueous solutions. Its stability in the absence of acids (including the weak acid water) is confirmed by its synthesis and isolation under conditions wherein the acid-catalysed dimerisation–hydrolysis is suppressed. The rate of dimerisation–hydrolysis in water increases rapidly with time owing to catalysis by liberated acid. In view of the slow decomposition of 4-fluoropyridine in alkali, it seems likely that the hydrolysis follows the quarternisation, the pyridinium nucleus facilitating the nucleophilic reaction.

EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer 257 grating spectrophotometer, u.v. spectra on a Perkin-Elmer 137 spectrophotometer, n.m.r. spectra on a Varian A60 spectrometer, and mass spectra on a double-focussing CEC 21-110B spectrometer.

4-Fluoropyridine.—4-Aminopyridine (10 g) was added to fluoroboric acid (prepared from 40% hydrofluoric acid; 42 ml). The solution was stirred and cooled in ice–salt. Sodium nitrite (7·50 g) was added in portions during 30 min and stirring was continued for 10 min more. The cold bath was removed and the diazonium salt was allowed to decompose. The solution was stirred and cooled to −20° and to it a cold solution of potassium hydroxide (70%; 20 ml) was added in one portion.

The solution was transferred to a long-necked 250 ml distillation flask carrying a cylindrical receiver flask (17 × 4·5 cm) fused through a delivery tube (30 × 1 cm). The delivery tube and the receiver of the h-shaped apparatus had been rinsed with 50% potassium hydroxide solution. The solution was cooled in an ice–salt bath, the apparatus was evacuated (2—5 mmHg), and the distillation flask was sealed. The receiver was kept in ice–salt and the distillation flask in a water-bath at 30°. Distillation for 1 h gave 4-fluoropyridine as a clear aqueous distillate.

The receiver was then cut off and the distillate stirred at −20° while potassium hydroxide pellets (30 g) were added in portions, so as not to allow the temperature to rise. The mixture was transferred to a burette and the upper layer was transferred by dropper to a tube. Potassium hydroxide pellets were added and the tube was kept stoppered overnight. The product was then transferred to an h-shaped distillation unit by dropper. The 5 ml bulb containing the product was cooled in ice–salt and a $CaCl_2$ guard-tube was placed at its open end. The unit was then evacuated and sealed. The 5 ml receiver bulb was cooled in ice–salt; distillation gave 4-fluoropyridine as a colourless liquid (2·3 g, 22%), b.p. 108° at 757 mmHg; n_D^{20} 1·4730 (Found: C, 61·65; H, 4·5; N, 14·3. Calc. for C_5H_4FN; C, 61·85; H, 4·15; N, 14·3%), $\nu_{max.}$ (film) 3040, 1590, 1580, 1480, 1405, 1245 (C–F str.), 1195, 990, 820, 765, and 725 cm^{-1}, $\lambda_{max.}$ (EtOH) 254·5 (ε 790), 249 (1164), and 243·5 nm (1104), δ_H (neat liquid, int. ref. Me_4Si) 7·12 (2H, m, 3-, 5-H), and 8·73 (2H, m, 2-, 6-H), δ_F (neat liquid, ext. ref. $CF_3{\cdot}CO_2H$; high field positive) +27·2 (m); $J_{H(3),F}$ 9·3, $J_{H(2),F}$ 8·8, $J_{H(2),H(3)}$ 5·72, $J_{H(2),H(5)}$ 0·52, $J_{H(2),H(6)}$ 0 (assumption), $J_{H(3),H(5)}$ 2·61 Hz. The *picrate*, prepared in benzene and crystallized from ethanol–benzene, melted at 241—244° (decomp.) (Found: N, 17·0. $C_{11}H_7FN_4O_7$ requires N, 17·15%).

The residue from the final distillation was 4-nitropyridine, m.p. 49—50° (lit.,[6] 50°) after distillation.

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[6] A. Kirpal and W. Bohm, *Ber.*, 1932, **65**, 680.