95. *Heterocyclic Polyfluoro-compounds. Part VI.*[1] *Preparation of Pentafluoropyridine and Chlorofluoropyridines from Pentachloropyridine.*

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Pentachloropyridine, prepared in high yield from pyridine and phosphorus pentachloride, reacts with anhydrous potassium fluoride at elevated temperatures to yield pentafluoro-, 3-chloro-2,4,5,6-tetrafluoro-, and 3,5-dichloro-2,4,6-trifluoro-pyridine. Reduction of the second of these products with lithium aluminium hydride yields 3-chloro-2,5,6-trifluoropyridine.

The preparation of pentafluoropyridine by defluorination of undecafluoropiperidine with nickel at 560°/1 atm. (*ca.* 12% yield),[2] or, preferably, iron at 580—610°/< 1 mm. (26% yield),[3] suffers from the disadvantage that undecafluoropiperidine is not readily available. A much more convenient and efficient method of synthesis of pentafluoropyridine has now been reported,[4,5] namely fluorination with anhydrous potassium fluoride of pentachloropyridine, which can be prepared in high yield by chlorination of pyridine with phosphorus pentachloride.

Pentachloropyridine was prepared by heating a mixture of pyridine and an excess of phosphorus pentachloride at 350° under pressure for 14—20 hours. When a reactant ratio of 6 : 1 molar (PCl_5 : C_5H_5N) was employed, the organic product isolated by steam distillation had to be recrystallised three times before pure pentachloropyridine was obtained, and the yield was only 28%; by contrast, use of a reactant ratio of 12 : 1 gave a product that on steam distillation immediately afforded almost pure pentachloropyridine in 97% yield, and this material gave the same results in fluorination experiments as recrystallised pentachloropyridine. This method of synthesis was reported in detail as long ago as 1898 by Sell and Dootson,[6] but since then it appears to have been neglected. Two other simple routes to pentachloropyridine are known, namely thermal chlorination of pyridine hydrochloride [7] and reaction of pyridine *N*-oxide with sulphuryl chloride at elevated temperatures,[8] but in their present states of development they afford this product in only low yield.

Replacement of chlorine by fluorine in 2-chloro-, 2,6-dichloro-, 2,3-dichloro-, 2,5-dichloro-, 2,3,5-trichloro-, and 2,3,5,6-tetrachloro-pyridine can be effected simply by heating

[1] Part V, Lee and Orrell, preceding Paper.
[2] Burdon, Gilman, Patrick, Stacey, and Tatlow, *Nature*, 1960, **186**, 231.
[3] Banks, Ginsberg, and Haszeldine, *J.*, 1961, 1740.
[4] Chambers, Hutchinson, and Musgrave, *Proc. Chem. Soc.*, 1964, 83.
[5] Banks, Haszeldine, Latham, and Young, *Chem. and Ind.*, 1964, 835.
[6] Sell and Dootson, *J.*, 1898, **73**, 432.
[7] Wibaut and Nicolaï, *Rec. Trav. chim.*, 1939, **58**, 709.
[8] Bobranski, Kochanska, and Kowalewska, *Ber.*, 1938, **71***B*, 2385.

a stirred mixture with anhydrous potassium fluoride in dimethyl sulphone at about 200°;[9] however, under these conditions only α-chlorine substituents are replaced in the last four substrates. Application of this technique to pentachloropyridine, but with 1-methyl-2-pyrrolidone as solvent, gave 3,5-dichloro-2,4,6-trifluoropyridine as the main product (up to 65% yield) together with a small amount of 3-chloro-2,4,5,6-tetrafluoropyridine (up to 9%). The extent of chlorine replacement in pentachloropyridine was increased by increasing the reaction period, using a greater excess of anhydrous potassium fluoride, and by carrying out the fluorination in an autoclave fitted with a high-speed stirrer: pentafluoropyridine (5% yield), 3-chloro-2,4,5,6-tetrafluoropyridine (17%), and 3,5-dichloro-2,4,6-trifluoropyridine (10%) were obtained; and following this, it was found that the yield of pentafluoropyridine could be increased to 83% by dispensing with the solvent and simply heating an intimate mixture of pentachloropyridine and anhydrous potassium fluoride at 500° for nearly a day. The results of a series of fluorinations in which no solvent was used are tabulated below.

C_5Cl_5N:KF (molar ratio)	1 : 9·5	1 : 24·8	1 : 26·9	1 : 20·0
Temp. (°c)	400	470	480	500
Time (hr.)	5	18	18	18
Yield (%): 2,3,4,5,6-Pentafluoropyridine	— *	40	56	83
3-Chloro-2,4,5,6-tetrafluoropyridine	19	34	27	7
3,5-Dichloro-2,4,6-trifluoropyridine	45	17	9	— *

* None detected.

The structures of the chlorofluoropyridines described above were determined by fluorine-19 n.m.r. spectroscopy. Chemical proof of structure will be presented later. Treatment of the 3-chloro-compound with lithium aluminium hydride gave a product that was shown by fluorine-19 and proton n.m.r. spectroscopy and analysis to be 3-chloro-2,5,6-trifluoropyridine; thus it appears that replacement of a β-fluorine substituent by chlorine in pentafluoropyridine does not affect the order of ease of nucleophilic displacement of fluorine ($4 > 2,6 \gg 3,5$),[10] a mechanistic discussion for which will be presented later.[11] 3-Chloro-2,4,5,6-tetrafluoro- and 3,5-dichloro-2,4,6-trifluoro-pyridine should prove to be useful precursors of 3- and 3,5-substituted polyfluoropyridines, which cannot be obtained by nucleophilic attack on pentafluoropyridine since this leads, apparently exclusively, to substitution of fluorine first in the 4 position and then in the 2 and 6 positions.[10]

Interestingly, Russian workers have reported recently that hexafluorobenzene can be prepared in 21% yield by heating hexachlorobenzene with anhydrous potassium fluoride at 450—500°;[12] this route, like the analogous one leading to pentafluoropyridine, seems well suited for commercial exploitation.

Experimental

Fluorine-19 nuclear magnetic resonance spectra were measured with either an A.E.I. RS2 spectrometer operating at 60 Mc./sec. or a Varian V4300B spectrometer operating at 40 Mc./sec.; proton n.m.r. spectra were measured with a Perkin-Elmer R10 instrument operating at 60 Mc./sec. Infrared and ultraviolet spectra were measured with a Perkin-Elmer model 21 spectrophotometer (sodium chloride optics) and a Unicam S.P. 700 spectrophotometer, respectively. Gas–liquid chromatography was carried out with a Perkin-Elmer Fraktometer model 116 (for analysis) and an Aerograph Autoprep model A-700 (for separations).

Preparation of Pentachloropyridine.—(a) *Using a* $PCl_5 : C_5H_5N$ *molar ratio of* 6 : 1. A mixture of pyridine (48·0 g., 0·6 mole) and phosphorus pentachloride (758 g., 3·6 moles) was heated in a 1-l. rocking autoclave (see Note below) at 350° for 20 hr. (a pressure of 190 atm.

Note. It is suggested that nickel-lined autoclaves be used for this reaction, since stainless steel and Hastelloy autoclaves become badly corroded.

[9] Finger, Starr, Dickerson, Gutowsky, and Hamer, *J. Org. Chem.*, 1963, **28**, 1666.
[10] Banks, Burgess, Cheng, and Haszeldine, *J.*, 1965, 575.
[11] Banks, Cheng, and Haszeldine, publication in preparation.
[12] Vorozhtsov, Platonov, and Yakobson, *Izvest. Akad. Nauk S.S.S.R., Ser. Khim.*, 1963, 1524.

developed in the autoclave). Gaseous products were vented, and the residue was poured slowly into stirred water (1 l.) cooled to 0°. The aqueous mixture so obtained was steam-distilled to yield a white solid (110 g.), m. p. 74°, which had to be recrystallised twice from ethanol and then once from light petroleum (b. p. 40—60°) before it yielded pure pentachloropyridine (42·5 g., 28%) (Found: C, 24·3; Cl, 69·8; N, 5·6. Calc. for C_5Cl_5N: C, 23·9; Cl, 70·5; N, 5·6%), m. p. 126° (lit.,[6] 123—124°), $\lambda_{max.}$ 261 mμ (ε 370) in hexane and 260 mμ (ε 340) in EtOH.

(b) *Using a* $PCl_5 : C_5H_5N$ *ratio of* 12 : 1. A mixture of pyridine (27·0 g., 0·34 mole) and phosphorus pentachloride (833 g., 4·00 moles) was heated in a 1-l. rocking autoclave at 350° for 14 hr. The hydrogen chloride formed was vented and the involatile product was poured into iced water, to yield a mixture that was steam-distilled to give crude pentachloropyridine (83·0 g., 97%) (Found: C, 24·5; N, 5·9. Calc. for C_5Cl_5N: C, 23·9; N, 5·6%), m. p. 123—125°. Crystallisation once from light petroleum (b. p. 60—80°) gave pure pentachloropyridine (78·5 g.) (Found: C, 24·1; Cl, 69·8; N, 5·6. Calc. for C_5Cl_5N: C, 23·9; Cl, 70·5; N, 5·6%), m. p. 125·5°.

Reaction of Pentachloropyridine with Potassium Fluoride.—In most of the experiments crude pentachloropyridine, m. p. 123—125°, from preparation (*b*) above was used; use of recrystallised pentachloropyridine, m. p. 125·5°, gave identical results.

(a) *With a solvent.* (i) Pentachloropyridine (10·0 g., 0·04 mole) dissolved in 1-methyl-2-pyrrolidone (100 ml.) was added slowly to a stirred slurry of anhydrous potassium fluoride (13·5 g., 0·23 mole) in 1-methyl-2-pyrrolidone (100 ml.) that was heated under reflux to 200°. After 6 hr., the mixture was cooled and filtered; the filtrate was distilled and all material that boiled below 198° was washed with water, then dried ($MgSO_4$) to yield 3,5-*dichloro*-2,4,6-*trifluoropyridine* (5·21 g., 65%) (Found: C, 29·6; F, 27·8; N, 6·7%; *M*, 202. $C_5Cl_2F_3N$ requires: C, 29·7; F, 28·2; N, 6·9%; *M*, 202), b. p. 150°, $n_D^{20.5}$ 1·4804; $\lambda_{max.}$ 265 mμ (ε 3400) in hexane and 265 mμ (ε 3300) in EtOH; $\nu_{max.}$ (cap. film) 1626, 1497, 1453, and 1417 cm.$^{-1}$ (fluorinated pyridine nucleus).

(ii) The above experiment was repeated using a higher ratio of potassium fluoride (33·4 g., 0·58 mole) to pentachloropyridine (14·8 g., 0·06 mole), and the product, after being filtered, was distilled to yield 3-*chloro*-2,4,5,6-*tetrafluoropyridine* (1·00 g., 9%), b. p. 121°, $n_D^{20.5}$ 1·4376 (Found C, 32·5; N, 7·5%; *M*, 185·5. C_5ClF_4N requires C, 32·4; N, 7·6%; *M*, 185·5); $\lambda_{max.}$ 261 mμ (ε 3200) in hexane and 260 mμ (ε 3250) in EtOH; $\nu_{max.}$ (cap. film) 1600, 1562, 1430, and 1412 cm.$^{-1}$ (fluorinated pyridine nucleus), and 3,5-dichloro-2,4,6-trifluoropyridine (5·5 g., 47%), b. p. 150°.

(iii) Pentachloropyridine (25·2 g., 0·10 mole) and anhydrous potassium fluoride (60·5 g., 1·00 mole) in 1-methyl-2-pyrrolidone (250 ml.) were heated at 200° for 24 hr. in a 1 l.-autoclave containing a high-speed magnetically-operated stirrer. The product was filtered and the filtrate was distilled; the material that distilled at temperatures below 198° was washed with water, dried (P_2O_5) and distilled to yield pentafluoropyridine (0·85 g., 5%), b. p. 83·5°, identified by infrared spectroscopy and gas–liquid chromatography, 3-chloro-2,4,5,6-tetrafluoropyridine (3·1 g., 17%), b. p. 121°, and 3,5-dichloro-2,4,6-trifluoropyridine (2·0 g., 10%), b. p. 150°.

(b) *Without a solvent at* 400° *for* 5 *hr.* An intimate mixture of finely-ground pentachloropyridine (14·8 g., 0·06 mole) and anhydrous potassium fluoride (33·0 g., 0·57 mole) was heated in a 300-ml. autoclave at 400° for 5 hr. in the absence of air. The product was extracted with ether (250 ml.), and the ethereal extract was distilled to yield 3-chloro-2,4,5,6-tetrafluoropyridine (2·11 g., 19%) and 3,5-dichloro-2,4,6-trifluoropyridine (5·30 g., 45%).

(ii) *Without a solvent at* 470° *for* 18 *hr.* An intimate mixture of pentachloropyridine (20·0 g., 0·08 mole) and anhydrous potassium fluoride (115·0 g., 1·98 mole) was heated in a sealed nickel tube (55 cm. × 4 cm. internal diam.) at 470° for 18 hr. in the absence of air. While the tube was still warm (*ca.* 100°), it was opened to a vacuum system and the volatile product (14·0 g.) was pumped out into two traps cooled to −196°. Distillation of this product gave pentafluoropyridine (5·31 g., 40%), 3-chloro-2,4,5,6-tetrafluoropyridine (5·00 g., 34%), and 3,5-dichloro-2,4,6-trifluoropyridine (2·70 g., 17%).

(iii) *Without a solvent at* 480° *for* 18 *hr.* The last experiment was repeated at 480° for 18 hr., 125 g. of anhydrous potassium fluoride being used. The products were pentafluoropyridine (7·5 g., 56%), 3-chloro-2,4,5,6-tetrafluoropyridine (3·9 g., 27%), and 3,5-dichloro-2,4,6-trifluoropyridine (1·4 g., 9%).

(iv) *Without a solvent at* 500° *for* 18 *hr.* Pentachloropyridine (29·1 g., 0·116 mole) was heated with anhydrous potassium fluoride (135·0 g., 2·33 moles), as above, at 500° for 18 hr., to give pentafluoropyridine (16·19 g., 83%) and 3-chloro-2,4,5,6-tetrafluoropyridine (1·58 g., 7%).

Preparation of 3-*Chloro*-2,5,6-*trifluoropyridine*.—An ethereal 0·12N-lithium aluminium hydride solution (7·1 ml.) was added during 15 min. to a stirred solution of 3-chloro-2,4,5,6-tetrafluoropyridine (2·2 g., 0·01 mole) in ether (40 ml.). The mixture was heated under reflux (30 min.), then cooled to 20° and treated carefully with water (5 ml.). The ethereal layer was dried ($MgSO_4$) and distilled to remove the bulk of the ether; the residue was examined by gas–liquid chromatography (2 m. silicone oil–Celite at 155°) and gave one major peak and two others, one of which was due to ether. The major peak was separated by large-scale gas–liquid chromatography (6 m. × 1 cm. internal diam. silicone oil–Celite column at 140°) and shown by infrared and fluorine-19 n.m.r. spectroscopy to be 3-*chloro*-2,5,6-*trifluoropyridine* (0·3 g.) (Found: C, 35·6; H, 0·7%; *M*, 167. C_5HClF_3 requires C, 35·8; H, 0·6%; *M*, 167·5); $\nu_{max.}$ (cap. film) 1616, 1468, and 1422 $cm.^{-1}$ (fluorinated pyridine nucleus).

Nuclear Magnetic Resonance Spectra.—(i) 3-*Chloro*-2,5,6-*trifluoropyridine*. The fluorine-19 spectrum of this compound consists of three absorption regions at −4·2, +8·8, and +64·7 p.p.m. (relative to $CF_3{\cdot}CO_2H$ as external reference; bulk-diamagnetic-susceptibility corrections were not performed). The absorption at −4·2 p.p.m., which is broad and structureless, is assigned to a fluorine nucleus in the 2-position by comparison with the spectrum of 3,5-dichloro-2,4,6-trifluoropyridine (see below); similarly, the absorption at +8·8 p.p.m., which is also broad and structureless, is assigned to a fluorine nucleus in the 6-position by comparison with the fluorine-19 spectrum of 2,3,5,6-tetrafluoropyridine.[1] The considerable broadness of these two absorptions is attributed to the quadrupolar effect of the adjacent nitrogen-14 nucleus. The absorption at +64·7 p.p.m., attributed to the fluorine nucleus in the 5-position, consisted of a doublet of doublet of doublets due to spin-spin interactions with the hydrogen nucleus in the 4-position and the other ring fluorine substituents.

The proton spectrum of 3-chloro-2,5,6-trifluoropyridine consists of a symmetrical 1 : 3 : 3 : 1 quartet centred at τ 2·22, this being interpreted as due to the hydrogen nucleus exhibiting equivalent spin coupling ($|J|$ 7 c./sec.) with the three ring fluorine substituents. The implication here that $|J_{HF}|$ (*ortho*) = $|J_{HF}|$ (*meta*) is supported by the spectrum of 2,3,5,6-tetrafluoropyridine.[1]

(ii) 3,5-*Dichloro*-2,4,6-*trifluoropyridine*. The fluorine-19 spectrum of this compound consists of two absorption regions at −7·80 (relative intensity 2) and +16·19 p.p.m. (relative intensity 1) from $CF_3{\cdot}CO_2H$ (external reference). The band at −7·80 p.p.m. is a rather broad 1 : 1 doublet ($|J| = 14{\cdot}3$ c./sec.) and is assigned to the fluorine substituents in the 2 and 6 positions; the doublet splitting is due to spin interaction with the fluorine substituent in the 4-position. The last nucleus gives rise to the band at +16·19 p.p.m., which consists of a 1 : 2 : 1 triplet ($|J| =$ 14·3 c./sec.) due to equivalent spin coupling to the fluorine nuclei in the 2 and 6 positions. The *meta*-F–F coupling of 14·3 c./sec. is in the range expected for J_{24} values in substituted tetrafluoropyridines.[1]

(iii) 3-*Chloro*-2,4,5,6-*tetrafluoropyridine*. This compound was examined as an equimolar mixture with 3,5-dichloro-2,4,6-trifluoropyridine. Its fluorine-19 consists of four absorption regions situated at −9·4, +6·3 (both structureless bands), +35·1, and +84·9 p.p.m. from $CF_3{\cdot}CO_2H$ (external reference). These bands are assigned, in order, to the fluorine substituents in the 2, 6, 4, and 5 positions. No spin-coupling constants were extracted from the spectrum.

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