691. *Polyfluoro-heterocyclic Compounds. Part I. The Preparation of Fluoro-, Chlorofluoro-, and Chlorofluorohydro-pyridines.*

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The chlorination of pyridine with phosphorus pentachloride has been developed to give good yields of tetra- and penta-chloropyridine. Reaction of these chloropyridines with potassium fluoride at elevated temperatures, without a solvent, gives high yields of highly fluorinated pyridines, *e.g.*, the synthetically important pentafluoro-, 3-chlorotetrafluoro-, and 3,5-dichlorotrifluoro-pyridines.

It has previously been shown that chlorine in polychlorobenzenes can be replaced by fluorine by using potassium fluoride in a polar solvent [1] and a similar method has also been used to replace certain chlorine atoms in some chloropyridines.[2] However, more recently it has been found that for hexachlorobenzene, conversion into a mixture of hexafluoro-, chloropentafluoro-, dichlorotetrafluoro-, and trichlorotrifluoro-benzene can be achieved by the use of potassium fluoride without a solvent at 450—500°.[3] We have now found that highly chlorinated pyridines can be converted into mixtures of fluoro-, chlorofluoro-, and chlorofluorohydro-pyridines both by the use of potassium fluoride in a solvent (sulpholane) and without a solvent at elevated temperatures. Pentafluoropyridine, 3-chlorotetrafluoropyridine, and 3,5-dichlorotrifluoropyridine in particular can now be obtained in good yield and these compounds provide a good starting point for development of the chemistry of polyfluoropyridines. The preparation of pentafluoropyridine, in low yield, by the defluorination of perfluoropiperidine, has been reported previously.[4,5]

Table 1.

Reaction of pyridine with phosphorus pentachloride.

C_5H_5N (g.)	PCl_5 (g.)	Time (hr.)	Temp. (°c)	Product (g.)	Composition of product in mole-% (% yield in parentheses)			
					$C_5H_3Cl_2N$	$C_5H_2Cl_3N$	C_5HCl_4N	C_5Cl_5N
200	2500	72	210—220	150	5 (1·5)	50 (15)	40 (13)	5 (1·5)
200	2500	50	280—285	200	—	10 (3·5)	50 (18)	40 (15)

The non-availability of highly chlorinated pyridines has led us to develop Sell and Dootson's method [6] for the chlorination of pyridine with phosphorus pentachloride. We have heated phosphorus pentachloride and pyridine in an autoclave (see Table 1). The di- and tri-chloropyridines from several reactions were further chlorinated by using

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[1] Maynard, *J. Org. Chem.*, 1963, **28**, 112.
[2] Finger, Starr, Dickerson, Gutowsky, and Hamer, *J. Org. Chem.*, 1963, **28**, 1666.
[3] Vorozhtsov, Platonov, and Yakobson, *Izvest. Akad. Nauk. S.S.S.R.*, *Ser. khim.*, 1963, **8**, 1524.
[4] Burdon, Gilman, Patrick, Stacey, and Tatlow, *Nature*, 1960, **186**, 231.
[5] Banks, Ginsberg, and Haszeldine, *Proc. Chem. Soc.*, 1960, 211.
[6] Sell and Dootson, *J.*, 1898, 432.

the same chlorinating agent at 280—285° and, overall, good yields of pentachloropyridine and (mixed) tetrachloropyridines were obtained. Of the three possible isomers of tetrachloropyridine, only those with hydrogen atoms in either the 3- or the 4-position are formed.

In a single reaction between pentachloropyridine and potassium fluoride in sulpholane at 190—210° a good yield of 3,5-dichlorotrifluoropyridine was obtained together with a small amount of 3-chlorotetrafluoropyridine. However, the reaction between pentachloropyridine and anhydrous potassium fluoride in the absence of solvent has been investigated more fully and our results are summarised in Table 2.

TABLE 2.

Reactions of pentachloropyridine with potassium fluoride in the absence of a solvent.

C_5Cl_5N (g.)	KF (g.)	Temp. (°c)	Time (hr.)	Product (g.)	Composition of product in mole-% (% yield in parentheses)		
					$C_5Cl_2F_3N$	C_5ClF_4N	C_5F_5N
15	40	480	24	7·8		10 (7·7)	90 (68·5)
20	60	480	19	13	5 (5)	25 (24)	70 (66)
20	60	450	20	13	13 (12)	44(40)	43 (39)
20	60	440	17	14	60 (53)	32 (28)	8 (15)
15	40	400	18	10	100 (84)		

The chlorine atoms in positions 2, 4, and 6 are, obviously, more easily replaced by fluorine than those in positions 3 and 5 because the dichlorotrifluoro- and the monochlorotetrafluoro-pyridines obtained each consisted of one isomer to an extent >90% (the limit of detection by n.m.r. spectroscopy). In each case also, only a single peak was obtained on analytical vapour phase chromatography (v.p.c.) with any of several stationary phases available. A considerably higher temperature is required to cause complete replacement of chlorine and this is incompatible with the use of solvent.

A single reaction between the isomeric tetrachloropyridines, prepared as described above, and potassium fluoride in sulpholane at 210—220° gave a moderate yield of an approximately equimolar mixture of 3-chloro-2,4,6-trifluoropyridine and 3,5-dichloro-2,6-difluoropyridine but again reaction in the absence of solvent has been investigated more fully and the results are summarised in Table 3. The conditions under which pentafluoropyridine is produced from pentachloropyridine caused complete decomposition of tetrachloropyridines, and this instability is probably attributable to the presence of hydrogen in the molecule.

TABLE 3.

Reactions of isomeric tetrachloropyridines with potassium fluoride in the absence of a solvent.

C_5HCl_4N (g.)	KF (g.)	Temp. (°c)	Time (hr.)	Product (g.)	Composition of product in mole-% (% yield in parentheses)			
					C_5HCl_4N	C_5HCl_3FN	$C_5HCl_2F_2N$	C_5HClF_3N
20	45	480	19		Complete decomposition			
20	45	420	19		,,	,,		
20	45	400	48	16	—	—	65 (63)	35 (34)
20	45	370	48	17	—	30 (29)	60 (59)	10 (9)
30	65	370	26	26	32	50 (67)	17 (22)	1 (6)
20	45	400	18	17·5	6·5	46 (48)	44 (45)	3·5 (2)
20	45	340	14	18	60	30 (67)	10 (20)	—

The n.m.r. spectral evidence so far available, dealing with the structures of the products shown in Table 3, indicates that we have been unable to replace chlorine atoms in positions 3 or 5 in the tetrachloropyridines, and that even chlorine atoms in positions 2, 4, and 6 are less easily replaced by fluorine than those in pentachloropyridine. This is consistent with the result of Finger and his co-workers [2] who, working mainly with lightly chlorinated pyridines, have shown that, while a chlorine atom in the 3-position activates chlorine atoms in both the positions 2 and 6, a chlorine atom in position 2 is rendered the more active.

EXPERIMENTAL

Infrared (i.r.) and ultraviolet (u.v.) spectra were recorded by using Grubb-Parsons, type G.S.2A and Optica C.F.4 spectrometers, respectively. Nuclear magnetic resonance (n.m.r.) spectra were measured on an A.E.I. R.S.2 spectrometer at 60 Mc./sec. Samples were examined as neat liquids with trichlorofluoromethane (10—20% v/v) as internal reference, except 3,5-dichloro-2,6-difluoropyridine which was dissolved in that compound. Positive shifts are to high field. Fluorine analyses were carried out by Mr. T. Holmes, using the biphenyl–sodium method of decomposition.[7]

Chlorination of Pyridine.—In a typical experiment an autoclave (3 l.) charged with dry pyridine (200 g., 2·5 mole) and phosphorus pentachloride (2,500 g., 12 mole) was heated to 280—285° for 50 hr. After allowing the autoclave to cool to room temperature the hydrogen chloride generated during the reaction was released before the vessel was opened and then the product was hydrolysed by slowly adding it to water. When this was complete, the organic product was steam distilled and the distillate extracted with methylene dichloride. The solvent was removed by distillation to yield a mixture of chloropyridines (200 g.). Removal of water was achieved by azeotropic distillation with benzene. The chloropyridines were distilled through a 20 in. column packed with Dixon gauze into two main fractions, (i) b. p. 225—256° and (ii) b. p. 256—280°. Fraction (i) was redistilled to give tetrachloropyridines, b. p. 248—252° (lit.,[8] b. p. 248·5—252°). Fraction (ii) was redistilled to give pentachloropyridine, b. p. 279—280°, m. p. 124° (from ethanol) (lit.,[8] b. p. 279—280°, m. p. 125—126°).

The composition of the original product was estimated by analytical-scale g.l.c. to be $C_5H_2Cl_3N$, 10; C_5HCl_4N, 50; C_5Cl_5N, 40 mole-%.

Replacement of Chlorine by Fluorine in Pentachloropyridine.—(a) *By using potassium fluoride without solvent.* An autoclave (120 ml.) charged with pentachloropyridine (20 g., 0·079 mole) and anhydrous potassium fluoride (60 g., 1·04 mole) was evacuated before being heated to 480° for 19 hr. While the reaction vessel was still hot the product (13 g.) was distilled under vacuum.

Distillation through a concentric tube column of the combined product from several reactions afforded three main fractions. (i) Pentafluoropyridine, b. p. 84° (lit., b. p. 84°,[4] 83·5° [5]) (Found: F, 55·9. Calc. for C_5F_5N: F, 56·2%); $\lambda_{max.}$ 2568 Å in cyclohexane; n_D^{20}, 1·3818 (lit.,[5] 1·3856); $\nu_{max.}$ 1639, 1595, 1550, 1524, 1499, 1447, 1413, 1353, 1282, 1105, 1075, 1046, 1030, 1009, 975, 733, 693, and 617 cm.$^{-1}$. The fluorine-19 n.m.r. spectrum is that of an AA′PP′X [9] system. There are three groups of chemically shifted peaks in the intensity ratios 2 : 1 : 2, the least intense of which can be assigned to the 4-fluorine. The peak due to the 2- and 6-fluorine is distinguished by the broadening effect of the nitrogen atom. The chemical shifts are 87·630 (2-F and 6-F), 162·025 (3-F and 5-F), and 134·188 (4-F) p.p.m. (ii) 3-*Chlorotetrafluoropyridine*, b. p. 119° (Found: Cl, 19·0; F, 40·7. C_5ClF_4N requires Cl, 19·1; F, 40·5%); $\lambda_{max.}$ 2617 Å in cyclohexane; n_D^{20}, 1·4307; $\nu_{max.}$ 1626, 1585, 1493, 1475, 1449, 1412, 1241, 1100, 1060, 957, 900, 893, and 738 cm.$^{-1}$. Four chemically shifted peaks of equal intensity in the fluorine-19 n.m.r. spectrum at positions (*a*) 72·122, (*b*) 85·708, (*c*) 114·307, and (*d*) 163·903 p.p.m., show that the molecule is asymmetric. Peaks (*a*) and (*b*) are broadened by nitrogen, hence they are due to fluorine atoms in the 2- and the 6-position; therefore since the molecule is asymmetric the chlorine atom must be in the 3-position. (iii) 3,5-*Dichlorotrifluoropyridine*, b. p. 159—160° (Found: Cl, 35·4; F, 28·6. $C_5Cl_2F_3N$ requires Cl, 35·1; F, 28·2%); $\lambda_{max.}$ 2662 Å in cyclohexane; $\nu_{max.}$ 1603, 1526, 1493, 1464, 1429, 1410, 1370, 1209, 1104, 1083, 1055, 1047, 821, and 740 cm.$^{-1}$. The fluorine-19 n.m.r. spectrum is that of an AX_2 system. The peak for the 2- and the 6-fluorine is broadened and that for the 4-fluorine is a triplet (1 : 2 : 1) with $J_{FF} = 14·0 \pm 0·5$ c./sec. The chemical shifts are 69·858 p.p.m. (2- and 6-fluorines) and 94·022 p.p.m. (4-fluorine).

The composition of the product from each reaction was estimated by analytical-scale g.l.c.

(b) *By using potassium fluoride in sulpholane.* Pentachloropyridine (15 g., 0·06 mole) and anhydrous potassium fluoride (37 g., 0·64 mole) in dry sulpholane (50 ml.) were vigorously

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[7] Johncock, Musgrave, and Wiper, *Analyst*, 1959, **84**, 245.

[8] Hertog, Schogt, de Bruyn, and Klerk, *Rec. Trav. chim.*, 1950, **69**, 673.

[9] Emsley, Feeney, and Sutcliffe, " High Resolution Nuclear Magnetic Resonance," Pergamon, 1964.

stirred at 190—210° for 36 hr. after which the product (9 g.) was distilled from the vessel under reduced pressure. This material was shown by analytical g.l.c. to consist of two compounds whose times were coincident with those of 3-chlorotetrafluoro- and 3,5-dichlorotrifluoropyridine (ratio of peak areas 1 : 10, respectively). They were separated by preparative-scale g.l.c. and their i.r. spectra were identical with those of authentic samples.

Replacement of Chlorine by Fluorine in Tetrachloropyridines.—(a) *By using potassium fluoride in sulpholane.* A mixture of tetrachloropyridine (20 g., 0·092 mole) and anhydrous potassium fluoride (45 g., 0·775 mole) in dry sulpholane (125 ml.) was stirred at 210—220° for 30 hr. The product (5·5 g.) was shown by analytical-scale g.l.c. to consist of two components. These were separated by preparative-scale g.l.c.: (i) 3-*chloro*-2,4,6-*trifluoropyridine*, b. p. 128—129° (Found: Cl, 21·6; F, 34·2. C_5HClF_3N requires Cl, 21·2; F, 34·0%); $\lambda_{max.}$ 2502 Å in cyclohexane; n_D^{20}, 1·4473; $\nu_{max.}$ 1634, 1613, 1582, 1468, 1416, 1399, 1152, 1055, 1011, 839, 732, and 687 cm.$^{-1}$. The fluorine-19 n.m.r. spectrum shows each fluorine to have hydrogen or chlorine neighbours but no fluorine neighbour. The structure of this compound is determined from the magnitude of the chemical shifts. The effect of introducing chlorine and hydrogen into a pyridine nucleus in place of fluorine atoms is to displace the neighbouring fluorine resonances to low fields by predictable amounts.[10] In this case the 2- and 6-fluorine chemical shifts become 68·462 and 66·547 p.p.m. and the 4-fluorine becomes 94·630 p.p.m. (ii) 3,5-dichloro-2,6-difluoropyridine, m. p. 45—46° (lit.,[2] 45—46·3°) (Found: Cl, 38·7; F, 20·8. Calc. for $C_5HCl_2F_2N$: Cl, 38·6; F, 20·65%); complex band with $\lambda_{max.}$ 2795 Å in cyclohexane; $\nu_{max.}$ 1587, 1441, 1403, 1304, 1260, 1205, 1103, 923, 928, 757, and 729 cm.$^{-1}$. The fluorine-19 n.m.r. spectrum consists of a single broad peak at 72·417 p.p.m. The proton magnetic resonance spectrum is a 1 :.2 : 1 triplet, J_{FH} = 7·5 ± 0·1 c./sec.

(b) *By using potassium fluoride without a solvent.* In a typical experiment an autoclave (120 ml.) charged with tetrachloropyridines (20 g., 0·092 mole) and anhydrous potassium fluoride (45 g., 0·775 mole) was evacuated before being heated to 370° for 48 hr. While the autoclave was still hot, the volatile product (17 g.) was distilled. The products from several reactions were combined and fractionated through a concentric-tube column. Three main fractions were collected. (i) 3-chloro-2,4,6-trifluoropyridine, b. p. 128—129°, identified by its i.r. spectrum. (ii) $C_5HCl_2F_2N$, b. p. 169° (Found: Cl, 39·0; F, 21·0. Calc. for $C_5HCl_2F_2N$: Cl, 38·6; F, 20·65%). This material on analytical-scale g.l.c. with silicone grease as the stationary phase gave a single peak which was resolved into two peaks when di-n-decyl phthalate was used. The longer retained material had a retention time coincident with that of 3,5-dichloro-2,6-difluoropyridine. (iii) C_5HClF_3N, b. p. 208—210° (Found: C, 30·1; Cl, 53·4; F, 9·7. C_5HCl_3FN requires C, 29·9; Cl, 53·1; F, 9·5%). This material also produced a simple peak with silicone grease as the stationary phase but was resolved into two components with di-n-decyl phthalate.

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[10] Boden, Emsley, Feeney, and Sutcliffe, *Mol. Phys.*, 1964, in the press.