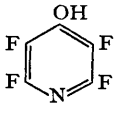
# 1079. *Polyfluoro-heterocyclic Compounds. Part III.*[1] *Hydroxy-derivatives of Pentafluoro- and Chlorofluoro-pyridines.*

By R. D. Chambers, J. Hutchinson, and W. K. R. Musgrave.

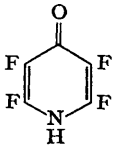
Reaction of pentafluoropyridine, 3-chlorotetrafluoropyridine, and 3,5-dichlorotrifluoropyridine with aqueous potassium hydroxide gives mainly the 4-hydroxy-compounds, but the isomer ratios are different with potassium hydroxide in t-butyl alcohol. The isomeric hydroxy-compounds are easily distinguished by their nuclear magnetic resonance spectra. In contrast to 4-hydroxypyridine, tetrafluoro-4-hydroxypyridine exists predominantly as the pyridine and not the pyridone tautomer in carbon tetrachloride solution, and is a strong acid in water. As with pentafluoropyridine, ammonia and hydrazine give with 3-chlorotetrafluoro- and 3,5-dichlorotrifluoro-pyridine exclusive replacement of the 4-fluorine. The order of reactivity, determined by competition experiments with ammonia, is 3,5-dichlorotrifluoro- > 3-chlorotetrafluoro- > pentafluoro-pyridine.

In previous Papers[1] we have described a useful route to pentafluoropyridine and perchlorofluoropyridines, and shown that the 4-position in pentafluoropyridine is the most susceptible to nucleophilic attack. We have now prepared a number of halohydroxypyridines by nucleophilic displacement of fluorine by using aqueous potassium hydroxide, or potassium hydroxide in t-butyl alcohol, and even water alone at elevated temperatures although the latter reaction is accompanied by considerable decomposition. With pentafluoropyridine, aqueous potassium hydroxide at 80—90° gave tetrafluoro-4-hydroxypyridine but no detectable amount of the 2-hydroxy-compound. However, potassium hydroxide in t-butyl alcohol gave a mixture of tetrafluoro-4-hydroxy- (90%) and tetrafluoro-2-hydroxy-pyridine (10%). This difference in isomer ratio probably arises because the t-butyl alcohol plays an active part in this substitution (see later). Tetrafluoro-4-hydroxypyridine was also obtained from tetrafluoro-4-methoxypyridine[1] by demethylation with hydriodic acid; aluminium trichloride was an unsuitable reagent for demethylation, a mixture of products of unknown identity being obtained.

The structure of tetrafluoro-4-hydroxypyridine offers the possibility of tautomerism, *i.e.*, structures (I) and (II), and it has been well established that the corresponding 2- and also




(I)




(II)

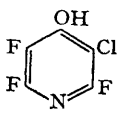
4-hydroxypyridines exist principally in the pyridone form[2,3] in the solid state and in carbon tetrachloride solution. Examination of the infrared spectrum of tetrafluoro-4-hydroxypyridine shows absorption in the O–H stretching region; a dilute solution in carbon tetrachloride gave a band of medium intensity at 3556 with a weak broad band at 3180 and a weak band at 3697 cm.$^{-1}$. The broad band was the most intense in concentrated solution but, on dilution of the solution, the intensity decreased relative to the band at 3556 cm.$^{-1}$, which is consistent with the effect of intramolecular hydrogen bonding. Absorption in this region is similar to that of pentafluorophenol,[4] not only in the shape and relative size of the

[1] Part II, R. D. Chambers, J. Hutchinson, and W. K. R. Musgrave, *J.*, 1964, 3736.
[2] J. A. Gibson, W. Kynaston, and A. S. Lindsey, *J.*, 1955, 4340.
[3] S. F. Mason, *J.*, 1957, 4874.
[4] J. M. Birchall and R. N. Haszeldine, *J.*, 1959, 13.

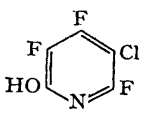
bands, but also in the position of the peak maxima, *i.e.* a dilute solution in carbon tetrachloride of pentafluorophenol gave a medium band at 3571 cm.$^{-1}$ with a weak shoulder at 3676 cm.$^{-1}$ and a broad band at 3257 cm.$^{-1}$. This similarity suggests that the absorption bands referred to are due to O–H stretch [in tautomer (I)] and not N–H stretch [in tautomer (II)]. There are no other bands of significant intensity that could be assigned to N–H stretch, and a very weak band at 1712 cm.$^{-1}$ (possibly arising from C=O stretch) is the only evidence to suggest the possible occurrence of tautomer (II). The C=O stretching frequency for a tetrafluoro-4-pyridone (II) is estimated to occur in the region 1645 cm.$^{-1}$, from a consideration of the corresponding frequencies observed in benzoquinone (1667 cm.$^{-1}$) 4-pyridone[3] (1638 cm.$^{-1}$), and tetrafluorobenzoquinone[5] (1674 cm.$^{-1}$). We conclude therefore, that, unlike 2- and 4-hydroxypyridines, tetrafluoro-4-hydroxypyridine exists principally in the pyridine (I) and not the pyridone (II) form in carbon tetrachloride solution, in the absence of added acid or base. This conclusion is consistent with the reactions of the compound; base-catalysed reaction with iodomethane or reaction of the potassium salt with dimethyl sulphate gave only the *O*-methyl derivative and none of the *N*-methyl compound. That electron availability on nitrogen in this system is considerably reduced with respect to pyridine has already been indicated by the lack of basic properties of pentafluoropyridine;[1] also, we have been unable to obtain an *N*-oxide by the reaction of pentafluoropyridine with peroxytrifluoroacetic acid. A predominance of the pyridine form (I) is then most probably due to this reduced electron availability on nitrogen. Aqueous sodium hydrogen carbonate gives an effervescence with tetrafluoro-4-hydroxypyridine, this being a strong acid with $K_a = 3{\cdot}3 \times 10^{-4}$, which is considerably stronger than pentafluorophenol[6] ($K_a = 3{\cdot}0 \times 10^{-6}$) and pentachlorophenol[7] ($K_a = 5{\cdot}5 \times 10^{-6}$). This is consistent with the enhanced reactivity of pentafluoropyridine over hexafluorobenzene towards nucleophilic attack, and is further indication of the considerably reduced electron density in the pyridine ring.

The infrared spectra of other perhalogenohydroxypyridines that we have prepared are similar, in the region of O–H stretch, to that of tetrafluoro-4-hydroxypyridine. Therefore, we suggest that the pyridine form is generally predominant in these systems.

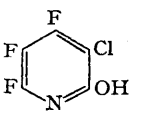
Competition experiments with ammonia have shown that the susceptibility towards nucleophilic substitution increases in the series pentafluoropyridine < 3-chlorotetrafluoropyridine < 3,5-dichlorotrifluoropyridine in the ratio 1 : 3·7 : 12·6, respectively. This trend is consistent with the known greater resultant (of inductive and mesomeric effects) electron-withdrawing capacity of chlorine over fluorine in an aromatic system. However, the 4-position is still the most reactive site in each case. Hydrazine hydrate with 3-chlorotetrafluoropyridine gave exclusively the 4-hydrazino-derivative which was converted into 4-amino-3-chlorotrifluoropyridine by treatment with hydriodic acid. The same amine was obtained directly by treating 3-chlorotetrafluoropyridine with aqueous ammonia. Whereas attack by these nitrogen bases occurs exclusively (> 95%, the limits of detection by n.m.r. spectroscopy) at the 4-position, aqueous potassium hydroxide with 3-chlorotetrafluoropyridine gave a mixture of the 4-hydroxy- (III) and 6-hydroxy-compounds (IV), the composition being 90 and 10%, respectively. In the light of the now considerable number of examples of nucleophilic displacement in polyfluoropyridines, which have all resulted in at




(III)




(IV)

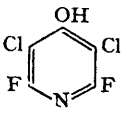



(V)

[5] E. Nield and J. C. Tatlow, *Tetrahedron*, 1960, **8**, 38.
[6] J. M. Birchall and R. N. Haszeldine, *J.*, 1959, 3653.
[7] G. J. Tiessans, *Rec. Trav. chim.*, 1931, **50**, 112.

least 90% preference for the 4-position, the reaction of 3-chlorotetrafluoropyridine with potassium hydroxide in t-butyl alcohol was surprising. Here, a mixture of isomers (III), (IV), and (V) was produced, containing 55, 35, and 10%, respectively. The considerable amount of attack at position 6, which is not reflected in other reactions, indicates participation by the t-butoxide ion, since the consequent steric requirement would make position 6 favourable to attack. This is confirmed by the fact that potassium hydroxide in t-butyl alcohol gave with 3,5-dichlorotrifluoropyridine a mixture containing a predominance of the 2-hydroxy-derivative, *i.e.* 3,5-dichloro-2-hydroxy- (70%) and 4-hydroxy-pyridine (30%), (VI) and (VII), respectively, whereas the composition of the product obtained by using aqueous potassium hydroxide was 90% (VII) and 10% (VI).


(VI)




(VII)

Although the above reactions indicate significant attack at the 2-position, reactions between 3,5-dichlorotrifluoropyridine and aqueous ammonia, hydrazine hydrate, and methoxide ion all lead to exclusive replacement of the 4-fluorine.

*Nuclear Magnetic Resonance* (*n.m.r.*) *Spectra.*—The structures of the various hydroxy-compounds were deduced from their n.m.r. spectra and, in particular, by using the known fluorine-19 chemical shifts for pentafluoro-, 3-chlorotetrafluoro-, and 3,5-dichlorotrifluoro-pyridine and applying the fact that, in polyfluorobenzenes, the fluorine-19 chemical shifts produced by the introduction of a hydroxyl group into the ring are approximately +2·0, +5·5, and +10 p.p.m. for *ortho*, *meta*, and *para* nuclei, relative to the hydroxyl group. It can be seen from the Table that, on this basis, the observed chemical shifts are completely consistent.

Fluorine-19 chemical shifts in fluoropyridines and their hydroxy-derivatives (position of the fluorine atom in brackets).

| Compound | Chemical shift from $CCl_3F$ (p.p.m.) |
|---|---|
| Pentafluoropyridine | 87·630(2,6); 162·025(3,5); 134·188(4) |
| 3-Chlorotetrafluoropyridine | 72·122(2); 85·708(6); 114·307(4); 163·903(5) |
| 3,5-Dichlorotrifluoropyridine | 69·858(2,6); 94·022(4) |
| Tetrafluoro-4-hydroxypyridine | 94·307(2,6); 164·663(3,5) |
| Tetrafluoro-2-hydroxypyridine | 91·550(6); 141·305(4); 164·663(3); 173·612(5) |
| (III) | 75·950(2); 92·492(6); 165·833(5) |
| (IV) | 75·950(2); 120·438(4); 165·833(5) |
| (V) | 90·200(6); 117·925(4); 173·567(5) |
| (VI) | 73·317(6); 99·547(4) |
| (VII) | 74·117 |

## Experimental

1. *Tetrafluorohydroxypyridines.*—(a) *Pentafluoropyridine and potassium hydroxide in t-butyl alcohol.* A mixture of pentafluoropyridine (1·0 g., 0·0059 mole), potassium hydroxide (0·70 g., 0·0125 mole), and t-butyl alcohol (10 ml.) was heated under reflux for 90 min. Water (15 ml.) was then added, the alcohol distilled off, and then the cooled solution acidified with dilute hydrochloric acid, and extracted with methylene dichloride. The methylene dichloride extract was dried and the solvent was removed by distillation, to leave a yellow solid, which on sublimation (80°/2—3 mm.) yielded a white solid (0·65 g., 65%). Resublimation and recrystallisation (twice) from light petroleum (b. p. 40—60°)–chloroform gave *tetrafluoro-4-hydroxypyridine*, m. p. 95—97° (Found: C, 35·9; F, 45·3. $C_5HF_4NO$ requires C, 35·9; F, 45·5%); $\nu_{max.}$ 3145, 1653, 1543, 1495, 1346, 1306, 1248, 1155, 1100, 1095, 964, 957, 740, 705, and 606 cm.$^{-1}$.

The fluorine-19 n.m.r. spectrum of the crude product showed that the 4-hydroxy-isomer was the major (> 90%) component. An AA "XX" spectrum was observed with chemically shifted

peaks at 94·307 and 164·663 p.p.m. relative to monofluorotrichloromethane as internal reference (10% v/v). There was also present, ~10% of another isomer, giving chemically shifted peaks at 91·550, 141·305, 164·663, and 173·612 p.p.m. These values are consistent with those expected for the 2-hydroxy-isomer and its presence was confirmed by methylation (see later).

(b) *Pentafluoropyridine and aqueous potassium hydroxide.* A Carius tube containing pentafluoropyridine (1·0 g., 0·0059 mole), potassium hydroxide (0·7 g., 0·00125 mole), and water (10 ml.) was heated to 85° for 20 hr. The cooled tube was opened and the contents extracted with methylene dichloride; when the extracts were dried and the solvent was removed, only a trace of starting material was recovered. The aqueous layer was acidified with dilute hydrochloric acid and extracted with ether; the extracts were dried and the solvent removed under reduced pressure, leaving a tacky solid from which was sublimed (80°/2—3 mm.) tetrafluoro-4-hydroxypyridine (63%) identified by its infrared spectrum. The fluorine-19 n.m.r. spectrum of the complete reaction product showed that only the 4-hydroxy-compound was present.

(c) *Tetrafluoro-4-hydroxypyridine from tetrafluoro-4-methoxypyridine.* Tetrafluoro-4-methoxypyridine[1] (0·60 g., 0·033 mole), which had been purified by gas chromatography, was heated under reflux with aqueous hydriodic acid (8 ml., 54% w/w) for 3 hr., and the cooled solution was treated with sodium pyrosulphite to remove iodine. The solution was extracted with methylene dichloride, the extract dried, and solvent removed by distillation to leave a pale yellow solid (0·39 g., 71%). Sublimation (80°/3—4 mm.) and recrystallisation from light petroleum (b. p. 40—60°)–chloroform gave tetrafluoro-4-hydroxypyridine, m. p. 95—97°, which was identified by comparison of its infrared spectrum with that of an authentic sample, prepared as described above.

*Determination of the ionisation constant of tetrafluoro-4-hydroxypyridine.* The ionisation constant was determined by measurement of the pH of a dilute aqueous solution, titrated against aqueous sodium hydroxide, at half-neutralisation point;[9] application of the Henderson equation gives $pH = pK_a$. The mean value of $K_a$, determined thus, was $3{\cdot}3 \times 10^{-4}$.

*Methylation of tetrafluorohydroxypyridines.* (*i*) The product from reaction (1a) (3·0 g., 0·018 mole), potassium hydroxide (1·1 g., 0·019 mole), iodomethane (2·6 g., 0·018 mole), and methanol (12 ml.) were sealed in a tube, which was heated to 100° for 2½ hr. The tube was cooled and opened, and its contents were washed with water into a separating funnel. The aqueous layer was made alkaline and extracted with methylene dichloride. Acid was then added to the aqueous layer, which was again extracted with methylene dichloride, and from this extract starting material (1·2 g.) was recovered. Removal of most of the solvent from the extracts from the alkaline solution gave a brownish liquid, which was shown by analytical g.l.c. to contain two compounds (ratio of peak areas 1:9). The reaction was repeated on a larger scale and the combined product was separated into its two components by preparative-scale g.l.c. (silicone grease on Celite at 95°). The minor component, which also had the shorter retention time, was found to be *tetrafluoro-2-methoxypyridine* (Found: C, 39·6; F, 41·6. $C_6H_3F_4NO$ requires C, 39·8; F, 42·0%), b. p. 135°; $n_D^{20}$, 1·4171; $\nu_{max.}$ 3012, 2994, 2950, 2857, 1692, 1653, 1639, 1578, 1562, 1527, 1495, 1443, 1425, 1393, 1357, 1279, 1203, 1167, 1155, 1105, 1092, 1037, 1002, 935, 761, 738, 700, 690, 617 cm.$^{-1}$. The fluorine-19 n.m.r. spectrum shows four groups of chemically shifted peaks at 90·75, 140·28, 163·93, and 171·28 p.p.m. from monofluorotrichloromethane as an internal reference. Only the peak at 90·75 p.p.m. corresponds to a fluorine atom in the α-position to nitrogen, hence the compound must be substituted in an α-position. The material with the longer retention time was identified by its infrared spectrum[1] as tetrafluoro-4-methoxypyridine.

(*ii*) The potassium salt prepared from tetrafluoro-4-hydroxypyridine (1 g.), dimethyl sulphate (1·4 g.), and dry methanol (2 ml.) were refluxed for 2 hr. The solution was cooled to room temperature, dilute aqueous alkali was added, and the mixture was extracted with methylene dichloride. The solvent was distilled from the dried organic layer to yield a pale yellow liquid (0·3 g.) whose retention time and infrared spectrum were identical with those of tetrafluoro-4-methoxypyridine.[1] The aqueous layer was acidified and extracted with methylene dichloride. Removal of the solvent and sublimation gave tetrafluoro-4-hydroxypyridine (0·2 g.), identified by its infrared spectrum.

2. *3-Chlorotrifluorohydroxypyridines.*—(a) *3-Chlorotetrafluoropyridine and potassium hydroxide in t-butyl alcohol.* 3-Chlorotetrafluoropyridine (1·0 g., 0·0054 mole), potassium hydroxide (0·65 g., 0·0116 mole), and t-butyl alcohol (10 ml.) were treated as described in (1a), and the solid product

[8] N. Boden, J. W. Emsley, J. Feeney, and L. M. Sutcliffe, *Mol. Phys.*, 1964, **8**, 467.
[9] G. M. Bennett, G. L. Brooks, and S. Glasstone, *J.*, 1935, 1821.

on sublimation under a vacuum gave 3-chlorotrifluorohydroxypyridines (0·78 g., 79%) (Found: Cl, 19·3; F, 30·8. Calc. for $C_6HClF_3NO$: Cl, 19·3; F, 31·1%).

The fluorine-19 n.m.r. spectrum of the complete product showed that it consisted of a mixture of three isomers. When the product was sublimed, the less volatile fraction was found to be a single isomer (within the limits of detection), giving three chemically-shifted peaks at 75·950, 92·492, and 165·833 p.p.m. These values are consistent with the expected values for the 4-hydroxy-isomer, and, in addition, the two lower-field peaks are broader than the high-field peak, showing that two of the fluorine atoms are in an α-position relative to the nitrogen. A more volatile fraction that was still a mixture of three isomers was obtained, the 4-hydroxy-compound (III) still being the most abundant. The next most prominent isomer showed peaks at 75·950, 120·438, and 165·833 p.p.m., which is consistent with the expected values for the 6-hydroxy-isomer (IV). The third isomer gave peaks at 90·200, 117·925, and 173·567 p.p.m., which is clearly only consistent with the 2-hydroxy-isomer (V). A peak at such high field as 173·5 p.p.m. can only arise from a 5-F atom (which gives a peak at 163·9 p.p.m. in the starting material)[1] that is *para* to a hydroxyl group. From the relative intensities of all the peaks in the total reaction product it was deduced that the composition of the mixture of isomers (III), (IV), and (V) was 55, 35, and 10%.

(b) *3-Chlorotetrafluoropyridine and aqueous potassium hydroxide.* A reaction between 3-chlorotetrafluoropyridine (1·0 g., 0·0054 mole) and potassium hydroxide (0·65 g., 0·012 mole) in water (10 ml.) was carried out as in (1b). A small amount of 3-chlorotetrafluoropyridine was recovered, leaving a mixture of 3-chlorotrifluorohydroxypyridines (0·62 g., 63%), identified by infrared and n.m.r. spectra. The fluorine-19 n.m.r. spectrum showed the composition of this mixture to be 3-chloro-2,5,6-trifluoro-4-hydroxypyridine (90%) and 3-chloro-2,4,5-trifluoro-6-hydroxypyridine (10%).

3. *3,5-Dichlorodifluorohydroxypyridines.*—(a) *3,5-Dichlorotrifluoropyridine and potassium hydroxide in t-butyl alcohol.* 3,5-Dichlorotrifluoropyridine (3·0 g., 0·015 mole), potassium hydroxide (1·68 g., 0·03 mole), and t-butyl alcohol (30 ml.) were treated as described in (1a). The product, after sublimation under reduced pressure, gave a mixture of 3,5-dichlorodifluoro-hydroxypyridines (2·5 g., 85%) (Found: C, 30·0; Cl, 35·9; F, 19·0. $C_5HCl_2F_2NO$ requires C, 30·0; Cl, 35·5; F, 19·0%), which on repeated fractional sublimation [(i) 80°/2—3 mm. and (ii) 120°/2—3 mm.] and recrystallisation from light petroleum (b. p. 40—60°)–chloroform afforded (i) *3,5-dichloro-2,6-difluoro-4-hydroxypyridine,* m. p. 101·5—102·5°, $\nu_{max.}$ 3175, 1709, 1608, 1582, 1488, 1440, 1412, 1309, 1182, 1143, 1079, 776, and 745 cm.$^{-1}$, and (ii) *3,5-dichloro-2,4-difluoro-6-hydroxy-pyridine,* m. p. 149—150°, $\nu_{max.}$ 3030, 1629, 1608, 1592, 1477, 1456, 1410, 1351, 1247, 1147, 1104, 1060, 1050, 811, 793, 746, and 685 cm.$^{-1}$. The fluorine-19 n.m.r. spectrum of the complete product showed three chemically shifted peaks at 73·317, 74·117, and 99·547 p.p.m., and from their relative intensities it is apparent that the peak at 74·117 p.p.m. can be assigned to one isomer and the other two peaks to a second isomer. The single peak must arise from the symmetrical 4-hydroxy-compound (VII), and the remaining peaks (which both show a coupling constant of 13·6 c./sec.) must arise from (VI). From the spectrum it was deduced that the isomer ratios were approximately 70% (VI) and 30% (VII).

(b) *3,5-Dichlorotrifluoropyridine and aqueous potassium hydroxide.* Reaction between 3,5-dichlorotrifluoropyridine (1·0 g., 0·005 mole) and potassium hydroxide (0·56 g., 0·01 mole) in water (10 ml.) was carried out as in (1b). A small amount of 3,5-dichlorotrifluoropyridine was recovered, leaving a mixture of 3,5-dichloro-2,6-difluoro-4-hydroxypyridine and 3,5-dichloro-2,4-difluoro-6-hydroxypyridine (0·85 g., 85%), identified by its infrared and n.m.r. spectra. The fluorine-19 n.m.r. spectrum showed the composition of this mixture to be 3,5-dichloro-2,6-difluoro-4-hydroxypyridine (90%) and 3,5-dichloro-2,4-difluoro-6-hydroxypyridine (10%).

(c) *Reaction between 3,5-dichlorotrifluoropyridine and sodium methoxide.* Dry methanol (20 ml.) containing sodium (0·5 g., 0·022 mole) was added dropwise to a stirred solution of 3,5-dichlorotrifluoropyridine (4·0 g., 0·020 mole) in dry methanol (5 ml.). The vessel was maintained at 10° throughout the addition and then for a further 10 min. When the contents of the vessel were then poured into cold water, oily droplets were precipitated and were extracted into methylene dichloride; the organic layer was separated, dried, and evaporated. A pale yellow liquid (3·9 g.) remained, which was shown by analytical scale g.l.c. to consist of a small amount of solvent and methanol (< 5%) and three other compounds (ratio of peak areas 1:15:4). The compound present in the smallest amount had a retention time coincident with that of starting material, and the other two were separated by preparative-scale g.l.c. (silicone elastomer on

Celite at 170°) and found to be: (i) 3,5-*dichloro*-2,6-*difluoromethoxypyridine* (Found: C, 33·9; Cl, 33·5; F, 17·9. $C_6H_3Cl_2F_2NO$ requires C, 33·6; Cl, 33·2; F, 17·8%), b. p. 214—215° (slight decomp.), $n_D^{20}$ 1·4987, $\nu_{max.}$ 3008, 2959, 2874, 1695, 1605, 1562, 1475, 1418, 1357, 1196, 1136, 1111, 1079, 1007, 937, 880, 787, 763, 746, 722, 693, 673, 615, and 564 cm.$^{-1}$. The fluorine-19 n.m.r. spectrum consists of a single peak at 71·92 p.p.m. from monofluorotrichloromethane as an internal reference; the chemical shift of the peak shows it to arise from fluorine atoms α to nitrogen; (ii) 3,5-*dichloro*-2-*fluoro*-4,6-*dimethoxypyridine* (Found: C, 37·0; Cl, 31·5; F, 8·7. $C_7H_6Cl_2FNO$ requires C, 37·2; Cl, 31·4; F, 8·4%), m. p. 67—68°, $\nu_{max.}$ 3008, 2959, 2874, 1613, 1558, 1477, 1412, 1401, 1385, 1269, 1196, 1135, 1109, 1075, 982, 926, 763, 719, 694, 671 cm.$^{-1}$.

3,5-*Dichloro*-2,6-*difluoro*-4-*hydroxypyridine from* 3,5-*dichloro*-2,6-*difluoro*-4-*methoxypyridine*. 3,5-Dichloro-2,6-difluoro-4-methoxypyridine (0·9 g., 0·0042 mole) prepared as above and purified by preparative g.l.c. was treated as in (1c) with aqueous hydriodic acid (7 ml., 54% w/w), and 3,5-dichloro-2,6-difluoro-4-hydroxypyridine (0·68 g., 80%), identified by m. p. (101—102°) and infrared spectrum, was obtained.

*Reaction of* 3-*chlorotetrafluoropyridine with aqueous ammonia*. 3-Chlorotetrafluoropyridine (1·30 g., 0·007 mole) and aqueous ammonia (*d* 0·88) (2 ml.) were heated to 80° for 1 hr. After being cooled to room temperature, the organic layer solidified. Water was added to the mixture, which was then extracted with ether. Distillation of the dry ethereal solution afforded white crystals (1·1 g., 85%). Sublimation under reduced pressure and recrystallisation from light petroleum (b. p. 80—100°) gave 4-*amino*-3-*chloro*-*trifluoropyridine*, m. p. 117—118° (Found: C, 32·7. $C_5H_2ClF_3N_2$ requires C, 32·9%); $\nu_{max.}$ 3490, 3333, 3210, 1634, 1508, 1466, 1397, 1332, 1235, 1104, 1067, 841, 733, 699, 666, 645, and 571 cm.$^{-1}$. The fluorine-19 n.m.r. spectrum of this compound shows three groups of chemically-shifted peaks in the ratio 1:1:1 at 77·963, 95·588, and 166·697 p.p.m. These values are consistent with the expected values for 4-amino-3-chloro-trifluoropyridine; moreover, the two low-field peaks were broader than the high-field peak, showing that these fluorine atoms are on carbon atoms adjacent to the nitrogen.

*Reaction of* 3,5-*dichlorotrifluoropyridine with aqueous ammonia*. 3,5-Dichlorotrifluoropyridine (1·2 g., 0·006 mole) and aqueous ammonia (*d* 0·88) (2 ml.) were heated to 80° for 15 min. On cooling, the organic layer became solid. Working up as above afforded 4-*amino*-3,5-*dichloro*-*difluoropyridine* (1·05 g., 89%), m. p. 112—113° (Found: C, 29·9. $C_5H_2Cl_2F_2N_2$ requires C, 30·1%): $\nu_{max.}$ 3460, 3333, 3200, 1626, 1610, 1567, 1493, 1449, 1399, 1387, 1325, 1136, 1078, 1029, 901, 759, 736, 650, and 600 cm.$^{-1}$.

The fluorine-19 n.m.r. spectrum consists of a single broad peak at 75·600 p.p.m., showing that both fluorine atoms are on carbon atoms adjacent to the nitrogen.

*Reaction between* 3-*chlorotetrafluoropyridine and hydrazine hydrate*. When 3-chlorotetrafluoropyridine (1·0 g., 0·005 mole) was slowly added to hydrazine hydrate (1·0 g., 0·02 mole) in dioxan (10 ml.) an exothermic reaction occurred. The mixture was stirred for 15 min. and poured into ice-cold water (10 ml.) and the solution was extracted with methylene dichloride. The organic layer was dried ($MgSO_4$) and the solvent removed by distillation to yield a pale yellow solid. Sublimation, twice, under reduced pressure afforded 3-*chlorotrifluoro*-4-*hydrazinopyridine* (0·75 g., 70%), m. p. 101—102° (Found: C, 30·40. $C_5H_3ClF_3N_2$ requires C, 30·4%); $\nu_{max.}$ 3361, 3226, 1629, 1608, 1515, 1462, 1429, 1397, 1299, 1175, 1098, 1064, 939, and 872 cm.$^{-1}$.

*Reaction between* 3,5-*dichlorotrifluoropyridine and hydrazine hydrate*. 3,5-Dichlorotrifluoropyridine (1·0 g., 0·005 mole) was slowly added to hydrazine hydrate (1·0 g., 0·02 mole) in dioxan (10 ml.). The mixture was kept at 10—15° throughout the addition and then stirred for a further 10 min. at room temperature. The product was worked up as described above and afforded 3,5-*dichlorodifluoro*-4-*hydrazinopyridine* (0·95 g., 90%) (Found: C, 28·0. $C_5H_3Cl_2F_2N_3$ requires C, 28·0%); $\nu_{max.}$ 3371, 3274, 3231, 1610, 1567, 1506, 1429, 1406, 1387, 1280, 1199, 1109, 1067, 948, 795, and 730 cm.$^{-1}$.

*Reduction of* 3-*chlorotrifluoro*-4-*hydrazinopyridine with aqueous hydriodic acid*. 3-Chlorotrifluoro-4-hydrazinopyridine (0·70 g., 0·0036 mole) was heated under reflux with aqueous hydriodic acid (6 ml.; 54—56% w/w) for 2 hr., after which the solution was treated with sodium pyrosulphite to remove the iodine. The solution was extracted with methylene dichloride, the organic layer was dried, and the solvent removed to yield a pale yellow solid (0·41 g., 60%). Sublimation (100°/3—5 mm.) and recrystallisation from light petroleum (b. p. 80—100°) gave 4-amino-3-chlorotrifluoropyridine, m. p. 116—117°, identified by comparison of its infrared spectrum with that of a sample prepared by the reaction between 3-chlorotetrafluoropyridine and aqueous ammonia.

*Reduction of 3,5-dichlorodifluoro-4-hydrazinopyridine with aqueous hydriodic acid.* In a reaction similar to that described above, 3,5-dichlorodifluoro-4-hydrazinopyridine yielded 4-amino-3,5-dichlorodifluoropyridine, identified by comparison of its infrared spectrum and melting point with those of a sample prepared by the reaction between 3,5-dichlorotrifluoropyridine and aqueous ammonia.

*Competition Reactions between Mixtures of Perhalogenopyridines and Ammonia.*—Ammonia gas (0·033 g., 0·0019 mole) was sealed under vacuum in a Carius tube with a mixture of pentafluoropyridine (0·473 g., 0·0028 mole) and 3-chlorotetrafluoropyridine (0·487 g., 0·0026 mole). The tube was allowed to warm to room temperature, by which time reaction appeared to be complete. After 90 min. the tube was opened and the contents were washed into a separating funnel with water and methylene dichloride. The organic layer was separated and solvent and unchanged halogenopyridines removed by distillation. The composition of the aminohalogenopyridines was found by analytical scale g.l.c. to be 4-aminotetrafluoropyridine (22 mole-%) and 4-amino-3-chlorotrifluoropyridine (78 mole-%). The g.l.c. apparatus was precalibrated with authentic compounds. The corresponding result for an equimolar mixture of starting material is 21 mole-% and 79 mole-%, respectively, indicating an order of reactivity towards ammonia of 1:3·7.

In a similar experiment with a mixture of 3-chlorotetrafluoropyridine and 3,5-dichlorotrifluoropyridine, it was found that the order of reactivity towards ammonia was in the ratio 1:3·3.

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Department of Chemistry, University Science Laboratories,
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