Peroxy-acid Oxidation of *NN*-Disubstituted Aminotetrafluoro-, Amino-3-chlorotrifluoro-, and Amino-3,5-dichlorodifluoro-pyridines

By **S. M. Roberts** and **H. Suschitzky,*** Chemistry Department, University of Salford, Salford M5 4WT

Peroxy-acid oxidation of *NN*-disubstituted 4-aminotetrafluoropyridines occurred with rearrangement of the expected intermediate *N*-oxide to give the *NNO*-trisubstituted hydroxylamines. The 2,4-bis-(*NN*-disubstituted amino)trifluoropyridines gave the 2-mono-*N*-oxide only. The oxidation of *NN*-dialkylamino-3-chlorotrifluoro- and -3,5-dichlorodifluoropyridines was also studied and the influence of the amino- and methoxy-groups and of the different halogens on the result is discussed. The observed behaviour is compared and contrasted with that of the analogous derivatives of pentachloropyridine, and the differences in the behaviours of the polyhalogenated pyridines are rationally explained.

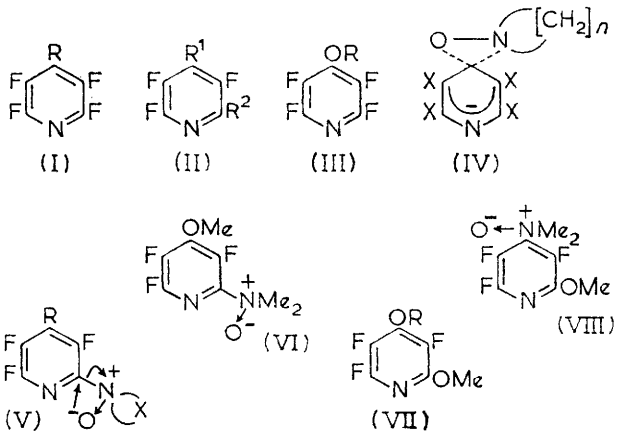
PENTAFLUOROPYRIDINE reacted with secondary amines at 0° to give solely the 4-substituted derivatives (I; R = $C_5H_{10}N$ or Me_2N), irrespective of the solvent, as previously reported.[1] When pentafluoropyridine was heated under reflux with excess of the appropriate amine in dioxan the 2,4-disubstituted derivatives (II; $R^1 = R^2 = C_5H_{10}N$ or Me_2N) were formed.

Oxidation of the tertiary amines (I; R = $C_5H_{10}N$ or Me_2N) with performic acid at room temperature gave the hydroxylamine derivatives (III; R as before); this result is similar to that reported for the *NN*-disubstituted 2-aminotetrachloropyridines but contrasts with the behaviour of the *NN*-disubstituted 4-aminotetrachloropyridines.[2] The difference is due to steric interference by the two chlorine atoms *ortho* to the amino-group with the formation of the *N*-oxide and the transition state (IV; X = Cl) preceding the rearrangement to the hydroxylamine.

[1] R. E. Banks, J. E. Burgess, W. M. Cheng, and R. N. Haszeldine, *J. Chem. Soc.*, 1965, 575.

[2] S. M. Roberts and H. Suschitzky, *J. Chem. Soc.* (*C*), 1968, 1537.

Oxidation of the disubstituted derivatives [*e.g.* (II; $R^1 = R^2 = C_5H_{10}N$)] with performic acid gave mono-*N*-oxides {*e.g.* (V; X = $[CH_2]_5$, R = $C_5H_{10}N$)}. Oxidation occurred exclusively at the 2-amino-group, as was shown for the two compounds containing both dimethylamino- and piperidino-groups (II; $R^1 = C_5H_{10}N$, $R^2 = Me_2N$ and $R^1 = Me_2N$, $R^2 = C_5H_{10}N$). The position of oxidation could be inferred from the ^1H n.m.r. spectra, which showed a pronounced downfield shift (*ca.* 2 τ units) of the signal for the methylene protons



α to the oxidized nitrogen atom. Also the signal of the α-methylene protons of the non-oxidized amino-group [*i.e.* R in (V)] was moved downfield by about 0·5 τ units. This smaller shift is presumably due to the ' drain ' of electrons from the non-oxidized nitrogen atom into the pyridine ring, by the inductive effect of the *N*-oxide group. The resultant decrease in the electropositive character of the α-carbon atom in the pyridine ring preserves the *N*-oxide by stopping its nucleophilic rearrangement into the hydroxylamine [*cf.* (V)].

Similarly when 2-dimethylaminotrifluoro-4-methoxypyridine (II; R^1 = OMe, $R^2 = NMe_2$) was oxidized with performic acid at room temperature, the *N*-oxide (VI) was obtained. In contrast, oxidation of the 2-methoxy-isomer (II; $R^1 = NMe_2$, R^2 = OMe) gave of the hydroxylamine (VII; R = Me_2N). The difference is due to a combination of several factors. First, the transition state for the rearrangement of the intermediate 4-*N*-oxide, (VIII) ⟶ (VII), involves a *p*-quinonoid form [*e.g.* (IV)], which is known to be thermodynamically more favourable [3] than an *o*-quinonoid transition state necessary for a similar rearrangement of the 2-*N*-oxide (VI). Second, in the *N*-oxide (VI) the significant resonance form (IX) implies an increase in electron density in the pyridine ring, which is sufficient to prevent the rearrangement. In addition, the large nucleophilic activation of the 4-carbon atom by the pyridine nitrogen atom facilitates the rearrangement of the transitory 4-*N*-oxide (VIII). The different reaction of the *NN*-disubstituted 4-amino-compound is yet another example supporting the generalization [4] that the ' heteroaromatic nitrogen ' is the predominant factor governing the nucleophilic substitution pattern of polyfluoro-*N*-heterocycles. The oxidation products from the analogous trichloro-compounds (X; R^1 = OMe or $C_5H_{10}N$, $R^2 = C_5H_{10}N$) are in each case the hydroxylamines (X; R^1 = OMe or $C_5H_{10}N$, $R^2 = O{\cdot}NC_5H_{10}$) and not the *N*-oxides (X; R^1 as before, $R^2 = N(O)C_5H_{10}$); a contribution analogous to the structure (IX) cannot be important in this case, because the 3- and 5-chlorine atoms interfere with the required coplanarity of the methoxy- or piperidino-group.

Oxidation of trifluoro-2-hydroxy-4-piperidinopyridine (II; $R^1 = C_5H_{10}N$, R^2 = OH) gave a water-soluble product which was not isolated. However the original amine was regenerated when sulphur dioxide was passed through an aqueous solution of the compound; this indicated the presence of the *N*-oxide (II; $R^1 = C_5H_{10}\overset{+}{N}\text{–}\bar{O}$, R^2 = OH).

When 3,5-dichlorotrifluoropyridine was treated with piperidine or morpholine in ethanol or dioxan at room temperature, the 2-substituted derivatives (XI; R^1 = F, $R^2 = C_5H_{10}N$ or morpholino) were obtained. This pyridine also reacted with pyrrolidine and dimethylamine in dioxan at room temperature to give the corresponding amino-compounds (XI; R^1 = F, $R^2 = C_4H_8N$ or Me_2N) but in ethanol a mixture of the 2- and the 4-substituted compounds (XI; R^1 and R^2 as before and $R^1 = C_4H_8N$ or Me_2N, R^2 = F) were formed in the ratio 65 : 35. Orientations of the compounds were assigned by ^{19}F n.m.r. (see Experimental section).

Treatment of 3,5-dichlorotrifluoropyridine with excess of amine in boiling ethanol gave disubstituted products. With piperidine only the 2,6-isomer was formed (XII; R = $C_5H_{10}N$), while with dimethylamine both the 2,6-isomer (XII; R = NMe_2) and the 2,4-isomer (XI; $R^1 = R^2 = Me_2N$) were obtained.

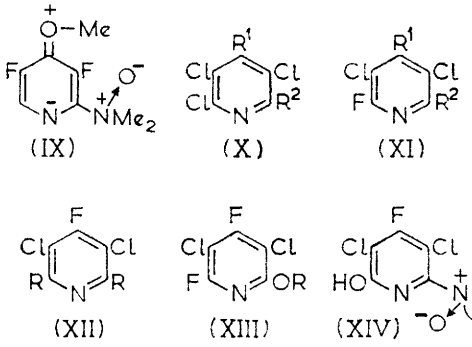
All the *NN*-disubstituted amino-derivatives of 3,5-dichlorotrifluoropyridine described behaved like their perchloro-analogues [2] towards peracid oxidation. The 2-substituted derivatives gave the hydroxylamines (XIII; R = $C_5H_{10}N$, NMe_2, or morpholino) in good yields on treatment with performic acid at room temperature, while the 4-substituted derivatives were unaffected. Use of stronger oxidation conditions [trifluoroacetic acid and hydrogen peroxide (30%)] on the 4-dimethylamino-compound (XI; $R^1 = Me_2N$, R^2 = F) caused demethylation to give the 4-methylamino-derivative (XI; R^1 = MeNH, R^2 = F). Formation of this dealkylated product is reliable evidence for an intermediate *N*-oxide which, however, rearranges by a Polonovski type reaction [5] with loss of one of the methyl groups. Performic acid oxidation of the 2,6-diamino-compound (XII; R = $C_5H_{10}N$) gave the *N*-oxide (XIV; X = $[CH_2]_5$), a result also observed for the trichloro-compound (XII; R = $C_5H_{10}N$, F = Cl), the reaction of which proceeds

[3] N. B. Chapman and D. Q. Russell-Hill, *J. Chem. Soc.*, 1956, 1563.

[4] R. D. Chambers, J. Hutchinson, and W. K. R. Musgrave, *J. Chem. Soc.* (*C*), 1966, 220; R. D. Chambers, J. A. H. MacBride, and W. K. R. Musgrave, *ibid.*, 1968, 2116.

[5] O. Meth-Cohn and H. Suschitzky, *J. Chem. Soc.*, 1963, 4666.

via a di-*N*-oxide with hydroxylamine rearrangement and fragmentation of one of the *N*-oxide groups.[2]



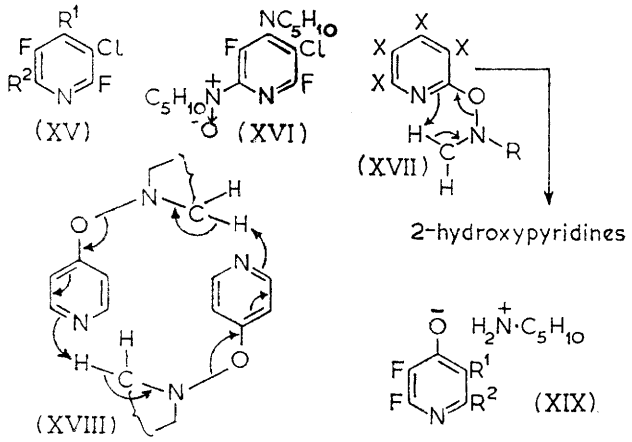
The study of 3-chlorotetrafluoropyridine was of special interest as its *NN*-disubstituted amino-*N*-oxides were expected to show a behaviour intermediate between that of the corresponding *N*-oxides of tetrachloro- and tetrafluoro-pyridine.

3-Chlorotetrafluoropyridine reacted with piperidine or dimethylamine in benzene, ethanol or dioxan at room temperature to give substitution in both the 4-position (XV; $R^1 = C_5H_{10}N$ or NMe_2, $R^2 = F$) and the 6-position (XV; $R^1 = F$, $R^2 = C_5H_{10}N$ or NMe_2). The isomer ratio was influenced by the solvent (see Experimental section): a greater proportion of the 6-isomer was formed in benzene or dioxan than in ethanol. However, in all cases the 4-substituted derivative was the major product. The 4,6-diamino-compounds (XV; $R^1 = R^2 = C_5H_{10}N$ or Me_2N) were produced in good yield by heating the pyridine under reflux with excess of the appropriate amine in dioxan. Orientation of the fluorine atoms was again determined by ^{19}F n.m.r. (see Experimental section).

Performic acid oxidation of the 6-piperidino-compounds (XV; $R^1 = F$, $R^2 = C_5H_{10}N$) gave the hydroxylamine (XV; $R^1 = F$, $R^2 = O{\cdot}NC_5H_{10}$). The 4-piperidino-compound (XV; $R^1 = C_5H_{10}N$, $R^2 = F$) was not affected by cold performic acid but reacted with trifluoroperacetic acid at room temperature. In this case degradation of the piperidine ring as in the corresponding tetrachloro-compound (X; $R^1 = C_5H_{10}N$, $R^2 = Cl$)[2] did not occur, but the hydroxylamine (XV; $R^1 = O{\cdot}NC_5H_{10}$, $R^2 = F$) was obtained in high yield. The oxidative behaviour of this compound is thus intermediate between those of its perfluoro- and perchloro-analogues.

The disubstituted derivative (XV; $R^1 = R^2 = C_5H_{10}N$) was oxidized by performic acid to give the *N*-oxide (XVI), which was readily deoxygenated by sulphur dioxide to regenerate the original amine. However, the *N*-oxide rearranged spontaneously in a few hours to the hydroxylamine (XV; $R^1 = C_5H_{10}N$, $R^2 = O{\cdot}NC_5H_{10}$). The intermediacy of the behaviour of the latter towards oxidation (between trifluoro- and trichloro-2,4-dipiperidinopyridine) is apparent. It can be rationalised by ascribing to the 4-substituent in (XV) a sufficient electron release, in spite of the steric influence of the 3-chlorine atom, to slow the nucleophilic *N*-oxide rearrangement [*cf.* (V)] to an observable rate at room temperature.

The hydroxylamines (XIII; $R = C_5H_{10}N$, C_4H_8N, Me_2N, or morpholino) and (XV; $R^1 = F$, $R^2 = O{\cdot}NC_5H_{10}$) were decomposed when heated in anhydrous dioxan for 2 hr. to give 3,5-dichloro-2,4-difluoro-6-hydroxypyridine[3] and 3-chloro-2,4,5-trifluoro-6-hydroxypyridine respectively. A concerted mechanism (XVII) involving an intramolecular 1,6-proton abstraction, proposed by us to account for the loss of the amino-group in the structurally similar perchloropyridylhydroxylamines[2] (X; $R^1 = Cl$, $R^2 = O{\cdot}NR_2$), also appears feasible in this case. However, we also found that the tetrafluoro-4-hydroxylamino-compounds (III; $R = C_5H_{10}N$ and Me_2N) underwent fragmentation to give tetrafluoro-4-hydroxypyridine (III; R = H) in boiling dioxan. A similar intramolecular path is obviously not feasible for this reaction and we suggest tentatively that two molecules are involved in the reaction of the 4-hydroxylamino-compounds, as shown (XVIII). This would also account for the fact that the tetrachloro-4-pyridyloxypiperidine (X; $R^1 = O{\cdot}NC_5H_{10}$, $R^2 = Cl$) does not decompose when heated in a boiling solvent. In this case, the approach and interaction of two molecules as shown (XVIII) is rendered impossible by the bulky *ortho*-chlorine atoms. This explanation also accounts for the very slow fragmentation of the hydroxylamine (XV; $R^1 = O{\cdot}NC_5H_{10}$, $R^2 = F$); the 3-chlorine atom sets up a small, but not unsurmountable barrier to the reaction.



Catalytic reduction of the hydroxylamines (III; $R = C_5H_{10}N$), (VII; $R = NC_5H_{10}$), and (XV; $R^2 = F$, $R^1 = O{\cdot}NC_5H_{10}$) gave the corresponding piperidinium salts (XIX; $R^1 = R^2 = F$; $R^1 = F$, $R^2 = OMe$; and $R^1 = Cl$, $R^2 = F$, respectively). Other hydroxylamines, for example (XIII; $R = C_5H_{10}N$, C_4H_8N, Me_2N, or morpholino) and (XV; $R^1 = C_5H_{10}N$, $R^2 = O{\cdot}NC_5H_{10}$) could be cleaved directly to the hydroxy-compounds, giving 3,5-dichloro-2,4-difluoro-6-hydroxypyridine (XI; $R^1 = F$, $R^2 = OH$) and 3-chloro-2,5-difluoro-6-hydroxy-4-piperidinopyridine (XV; $R^1 = C_5H_{10}N$, $R^2 = OH$), respectively.

EXPERIMENTAL

NN-Disubstituted 4-Aminotetrafluoropyridines.—These were prepared by the method described.[1] *4-Piperidinotetrafluoropyridine* had b.p. 120°/12 mm. (Found: C, 51·5; H, 4·55; N, 11·7. $C_{10}H_{10}F_4N_2$ requires C, 51·3; H, 4·3; N, 12·0%).

2(6),4-Disubstituted Trifluoropyridines.—(*a*) Pentafluoropyridine (2·0 g.) was heated under reflux in dioxan or ethanol with the appropriate amine (4 mol.) for 24 hr. Water was added to the cooled solution, which was then extracted with chloroform. The combined extracts were dried and evaporated. The 2,4-dimethylamino-derivative [1] (II; $R^1 = R^2 = NMe_2$) was obtained in 68% yield and *trifluoro-2,4-dipiperidinopyridine*, b.p. 170°/12 mm., in 64% yield (Found: C, 60·3; H, 7·1; N, 13·8. $C_{15}H_{20}F_3N_3$ requires C, 60·2; H, 6·7; N, 14·1).

(*b*) 4-Dimethylaminotetrafluoropyridine (2·0 g.) was heated under reflux with piperidine (3 mol.) in dioxan for 24 hr. Isolation as in (*a*) gave *4-dimethylaminotrifluoro-2-piperidinopyridine*, b.p. 120°/1·5 mm. (75%) (Found: C, 55·75; H, 6·35; N, 15·95. $C_{12}H_{16}F_3N_3$ requires C, 55·6; H, 6·1; N, 16·2%).

(*c*) Tetrafluoro-4-piperidinopyridine (2·0 g.) was heated under reflux with dimethylamine (26% solution in water) in dioxan for 24 hr. Work-up gave *2-dimethylaminotrifluoro-4-piperidinopyridine*, b.p. 150°/10 mm. (86%) (Found: C, 55·8; H, 6·2; N, 15·65. $C_{12}H_{16}F_3N_3$ requires C, 55·6; H, 6·1; N, 16·2%).

(*d*) Tetrafluoro-4-methoxypyridine [6] (2·0 g.) was heated under reflux with a 26% aqueous solution of dimethylamine (2·1 mol.) in dioxan (50 ml.) for 16 hr. The solution was cooled, added to water (300 ml.), and extracted with chloroform. The combined extracts were dried and evaporated to give 2-dimethylaminotrifluoro-4-methoxypyridine (61%; 1·4 g.), b.p. 110°/12 mm. (Found: C, 47·0; H, 4·8; N, 13·3. $C_8H_9F_3N_2O$ requires C, 46·6; H, 4·4; N, 13·6%).

(*e*) The appropriate *NN*-disubstituted 4-aminotetrafluoropyridine (2·5 g.) was heated under reflux with sodium (1 mol.) in dry methanol (50 ml.) for 16 hr. The solution was evaporated as much as possible, and the residue was taken up in chloroform–water. The aqueous layer was well washed with chloroform, and the combined chloroform extracts were dried and evaporated. *4-Dimethylaminotrifluoro-2-methoxypyridine* (1·6 g., 60%) had b.p. 112°/20 mm. (Found: C, 46·6; H, 4·8; N, 13·8. $C_8H_9F_3N_2O$ requires C, 46·6; H, 4·4; N, 13·6%). *Trifluoro-2-methoxy-4-piperidinopyridine* (2·0 g., 76%) had b.p. 114°/3·5 mm. (Found: C, 53·2; H, 4·9; N, 11·1. $C_{11}H_{13}F_3N_2O$ requires C, 53·7; H, 5·3; N, 11·4).

(*f*) 4-Dimethylaminotetrafluoropyridine (3·1 g.) was stirred with sodium hydroxide (4 g.) in boiling water (100 ml.) for 16 hr. The solution was cooled and made acid with 4N-hydrochloric acid, then extracted with chloroform. The combined extracts were dried and evaporated to give *4-dimethylaminotrifluoro-2-hydroxypyridine* (2·5 g., 81%), m.p. 164° (from benzene) (Found: C, 43·45; H, 3·6; N, 14·35. $C_7H_7F_3N_2O$ requires C, 43·75; H, 3·6; N, 14·6%).

2,(6)-Substituted 3,5-Dichlorodifluoropyridines.— To 3,5-dichlorotrifluoropyridine (4 g.) dissolved in dioxan (50 ml.) the appropriate amine in dioxan was added slowly with stirring. Stirring was continued for 3 hr., then the solution was diluted with water (500 ml.) and extracted with chloroform. The combined extracts were dried and evaporated to yield the products (Table 3).

4-Substituted 3,5-Dichlorodifluoropyridines.—To 3,5-dichlorotrifluoropyridine (4 g.) in ethanol (50 ml.) the appropriate secondary amine, in ethanol (20 ml.), was added with stirring. After 3 hr. the solution was diluted with water and extracted with chloroform. The combined extracts were dried and evaporated. The residue was chromatographed on a silica gel column in light petroleum (b.p. 60—80°). The 2-isomer was eluted first in both cases. Details of the 4-isomers are given in Table 3. The 2 : 4-isomer ratios were: dimethylamino- 65 : 35; pyrrolidino- 64 : 36, respectively.

2,6-Disubstituted and 2(6),4-Disubstituted 3,5-Dichlorofluoropyridines.—3,5-Dichlorotrifluoropyridine (2 g.) and the appropriate amine (4 mol.) were heated under reflux in ethanol for 48 hr. The cooled solution was diluted with water and then extracted with chloroform. The combined extracts were dried and evaporated and the residue was chromatographed on a silica gel column with light petroleum (b.p. 60—80°). The 2,6-isomer was eluted first. Details of the products are given in Table 3. The 2,6 : 2,4-dimethylamino-isomer ratio was 7 : 3. Only the 2,6-dipiperidino-isomer was obtained.

NN-Disubstituted 4- and 6-Amino-3-chlorotrifluoropyridines.—3-Chlorotetrafluoropyridine (4 g.) was dissolved

[6] R. D. Chambers, J. Hutchinson, and W. K. R. Musgrave, *J. Chem. Soc.*, 1964, 3736.

TABLE 1

Hydroxylamines from the performic acid oxidation of *NN*-disubstituted 4-amino-fluoropyridines

Hydroxylamine	Yield (%)	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
(III; R = $C_5H_{10}N$)	70	48·1	3·9	10·8	$C_{10}H_{10}F_4N_2O$	48·0	4·0	11·2
(III; R = Me_2N)	74	40·5	2·6	13·7	$C_7H_6F_4N_2O$	40·0	2·9	13·3
(VII; R = $C_5H_{10}N$)	88	50·9	4·9	10·65	$C_{11}H_{13}F_3N_2O_2$	50·4	4·9	10·7
(VII; R = Me_2N)	58	43·6	4·5	12·7	$C_8H_9F_3N_2O_2$	43·2	4·05	12·6

TABLE 2

N-Oxides (V) obtained by oxidation with performic acid of 2,4-bis-(*NN*-disubstituted amino)trifluoropyridines

N-Oxide (V) R	*N*-Oxide (V) X	Yield (%)	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
$C_5H_{10}N$	$[CH_2]_5$	65	51·0	6·5	12·0	$C_{15}H_{20}F_3N_3O$ ($2H_2O$)	51·3	6·8	12·0
Me_2N	Me_2	62	41·6	5·1	15·8	$C_9H_{12}F_3N_3O$ ($1·5H_2O$)	41·2	5·7	16·0
$C_5H_{10}N$	Me_2	72	47·6	6·1	14·4	$C_{12}H_{16}F_3N_3O$ ($1·5H_2O$)	47·7	6·3	13·9
Me_2N	$C_5H_{10}N$	67	51·0	6·3	14·3	$C_{12}H_{16}F_3N_3O$ ($0·5H_2O$)	50·7	6·0	14·8

in dioxan or ethanol (50 ml.). The appropriate secondary amine (2 mol.) in the same solvent was added slowly with stirring. The solution was then kept for 3 hr., poured into water (300 ml.), and extracted with chloroform. The combined extracts were dried and evaporated *in vacuo* and the residue was chromatographed on silica column in light petroleum (b.p. 60—80°). The 6-isomer was eluted first in both cases. Details of the individual isomers are listed in Table 5. The 6 : 4-isomer ratios were as follows: piperidino-37 : 63 (in dioxan) and 20 : 80 (in ethanol); dimethylamino-30 : 70 (in dioxan) and 10 : 90 (in ethanol).

Oxidation of NN-Disubstituted Aminohalogenopyridines.—(*a*) The *NN*-disubstituted 4-aminofluoropyridine (2·0 g.) was dissolved in chloroform (25 ml.), formic acid (25 ml.), and 30% hydrogen peroxide (5 ml.). The solution was stirred for 16 hr. at room temperature. The formic acid was neutralized with a concentrated solution of potassium carbonate, with cooling and stirring. The chloroform layer was separated and the aqueous layer was washed with chloroform. The combined chloroform extracts were dried and evaporated *in vacuo* to yield product (Table 1).

(*b*) 2-Dimethylaminotrifluoro-4-methoxypyridine was oxidised as already described. The *N*-oxide (VI) (95%) had m.p. 165° (from ethanol) (Found: C, 42·8; H, 3·7; N, 12·2. $C_8H_9F_3N_2O_2$ requires C, 43·2; H, 4·1; N, 12·6). When the *N*-oxide was dissolved in a mixture of benzene and 4N-sulphuric acid and gaseous sulphur dioxide was passed through the deoxygenated compound was obtained in high yield.

(*c*) Oxidation of 4-dimethylaminotrifluoro-2-hydroxypyridine, carried out as before gave no product on evaporation of the chloroform layer. The aqueous phase was acidified with conc. sulphuric acid to give a clear solution. Gaseous sulphur dioxide was passed through. The precipitate was identified as starting material (1·2 g., 60%).

(*d*) The 2,4-*NN*-disubstituted aminotrifluoropyridines usually gave a viscous oil containing the corresponding hydrated *N*-oxide (Table 2). Attempts to remove the water resulted in rapid and complete decomposition.

(*e*) 2(6)-*NN*-Disubstituted amino-3,5-dichlorodifluoropyridines were oxidised as already described. Details of the hydroxylamines obtained are given in Table 4.

(*f*) A solution of 3,5-dichloro-4-dimethylaminodifluoropyridine (1·5 g.) in chloroform (20 ml.) and trifluoroacetic acid (20 ml.) was treated with 30% hydrogen peroxide (4 ml.) and stirred for 16 hr. The acid was neutralized with a concentrated solution of potassium carbonate, the chloroform layer was separated, and the aqueous phase was extracted with chloroform. The combined chloroform fractions were dried and evaporated to give *3,5-dichloro-2,6-difluoro-4-methylaminopyridine* (64%, 0·9 g.), m.p. 103° (lit.,[7] 105—106°).

(*g*) From 3,5-dichloro-4-fluoro-2,6-dipiperidinopyridine, *N-(3,5-dichloro-4-fluoro-6-hydroxy-2-pyridyl)piperidine N-oxide*, m.p. 155°, was obtained (48%) (Found: C, 43·0; H, 3·9; N, 10·3. $C_{10}H_{11}FCl_2N_2O_2$ requires C, 42·7; H, 3·9; N, 10·0%).

Deoxygenation with sulphur dioxide as before gave *3,5-dichloro-4-fluoro-2-hydroxy-6-piperidinopyridine*, m.p. 102°, in high yield (Found: C, 44·9; H, 4·6; N, 10·1. $C_{10}H_{11}FCl_2N_2O$ requires C, 45·3; H, 4·15; N, 10·6%).

(*h*) Details of the hydroxylamines formed by oxidation from the *NN*-disubstituted 6-amino-3-chlorotrifluoropyridines are in Table 5.

[7] Dutch P. 611,766.

TABLE 3

2(6)- and 4-Substituted derivatives of 3,5-dichlorotrifluoropyridine

	Yield (%)	M.p. (B.p./mm.)	Found (%) C	H	N	Formula	Required (%) C	H	N
2(6)-Substituent									
Me_2N	44	80°/6	37·3	2·8	11·8	$C_7H_6Cl_2F_2N_2$	37·0	2·6	12·3
$C_5H_{10}N$	74	132/5	45·4	3·8	10·5	$C_{10}H_{10}Cl_2F_2N_2$	44·9	3·75	10·5
C_4H_8N	45	49	43·0	3·2	11·1	$C_9H_8Cl_2F_2N_2$	42·7	3·2	11·1
Morpholino	93	72	40·3	3·05	10·4	$C_9H_8Cl_2F_2N_2O$	40·15	3·0	10·4
4-Substituent									
Me_2N	24	44	37·4	2·9	11·9	$C_7H_6Cl_2F_2N_2$	37·0	2·6	12·3
C_4H_8N	25	141/6	42·6	3·5	11·0	$C_9H_8Cl_2F_2N_2$	42·7	3·2	11·1
2- and 6-Substituents									
Me_2N	60	67	43·0	4·95	16·7	$C_9H_{12}Cl_2F_2N_3$	42·9	4·8	16·7
$C_5H_{10}N$	52	82	54·2	6·35	12·8	$C_{15}H_{20}Cl_2F_2N_3$	54·2	6·0	12·65
2(6)- and 4-Substituents									
NMe_2	25	120/3	43·2	4·7	16·6	$C_9H_{12}Cl_2F_2N_3$	42·9	4·8	16·7

TABLE 4

Hydroxylamines (XI; R^1 = F) obtained by oxidation of *NN*-disubstituted 2-amino-3,5-dichlorodifluoropyridines

Hydroxylamine R^2	Yield (%)	M.p.	Found (%) C	H	N	Formula	Required (%) C	N	N
$O{\cdot}NC_5H_{10}$	54	52°	42·9	3·65	9·7	$C_{10}H_{10}Cl_2F_2N_2O$	42·4	3·5	9·9
$O{\cdot}N<[CH_2]_2>[CH_2]_2$	91	116 (decomp.)	38·1	2·8	9·6	$C_9H_8Cl_2F_2N_2O_2$	37·9	2·8	9·8
Me_2N	63	*							
$O{\cdot}NC_4H_8$	52	†							

* Liquid, decomp. 40°. † Decomposes at room temp.

(*i*) 3-Chloro-2,5,6-trifluoro-4-piperidinopyridine gave the corresponding hydroxylamine as an oil (see Table 5). Trifluoroperoxyacetic acid was the oxidising agent.

(*j*) Oxidation of 3-chloro-2,5-difluoro-4,6-dipiperidinopyridine (4 g.) gave a viscous oil which was deoxygenated with sulphur dioxide in almost quantitative yield. The oil slowly solidified. The solid was not affected by sulphur dioxide but was decomposed in boiling dioxan to 3-chloro-2,5-difluoro-6-hydroxy-4-piperidinopyridine (see later), suggesting that isomerization to the hydroxylamine (XV; $R^1 = C_5H_{10}N$, $R^2 = O{\cdot}NC_5H_{10}$) had occurred (Table 5).

Fragmentation of the Hydroxylamines in Anhydrous Dioxan.—(*a*) The polyfluorohydroxylamine (III; R = NMe_2 or $C_5H_{10}N$) (2 g.) was dissolved in dry dioxan (25 ml.). The solution was boiled for 2 hr. The dioxan was then removed *in vacuo* and the residue was taken up in chloroform. The chloroform solution was extracted with 4N-sodium hydroxide. The combined extracts were neutralized with conc. hydrochloric acid and the aqueous phase was extracted with chloroform. The combined chloroform extracts were dried and evaporated *in vacuo* to give tetrafluoro-4-hydroxypyridine (60%), m.p. 96° (lit.,[8] 95—97°).

(*b*) The hydroxylamine (III; $R = C_5H_{10}N$) (1·0 g.) was dissolved in ethanol (25 ml.) and palladium–charcoal (0·2 g.) was added. The solution was shaken for 16 hr. at room temperature under hydrogen. The catalyst was filtered off and the ethanol was removed *in vacuo*. The *piperidinium salt of tetrafluoro-4-hydroxypyridine* (XIX; $R^1 = R^2 = F$) obtained (80%) had m.p. 199° (from ethanol) (Found: C, 47·8; H, 4·8; N, 11·1. $C_{10}H_{12}F_4N_2O$ requires C, 47·6; H, 4·8; N, 11·0%).

(*c*) The hydroxylamine (II; $R^1 = O{\cdot}NC_5H_{10}$, R^2 = OMe) was decomposed as described in (*a*) to give *3,5,6-trifluoro-4-hydroxy-2-methoxypyridine* (50%), m.p. 53° [from light petroleum (b.p. 80—100°)] (Found: C, 40·0; H, 2·4; N, 7·9. $C_6H_4F_3NO_2$ requires C, 40·2; H, 2·2; N, 7·8%).

[8] R. D. Chambers, J. Hutchinson, and W. K. R. Musgrave, *J. Chem. Soc.*, 1964, 5634.

TABLE 5

4- (XV; $R^2 = F$) and 6- (XV; $R^1 = F$) Substituted derivatives of 3-chloropolyfluoropyridine (XV)

	Yield (%)	M.p. (B.p./mm.)	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
4-Substituent									
$C_5H_{10}N$	56	160°/30	47·6	4·4	11·7	$C_{10}H_{10}ClF_3N_2$	47·9	4·0	11·2
Me_2N	58	116/22	39·6	3·0	13·3	$C_7H_6ClF_3N_2$	39·9	2·85	13·3
Morpholino	60		45·4	3·9	11·0	$C_{10}H_{10}ClF_3N_2O$	45·1	3·8	10·5
6-Substituent									
$C_5H_{10}N$	17	140/14	47·4	3·6	10·7	$C_{10}H_{10}ClF_3N_2$	47·9	4·0	11·2
Me_2N	11	130/42	39·8	2·7	13·65	$C_7H_6ClF_3N_2$	39·9	2·85	13·3
Morpholino	48	60	45·6	3·9	10·3	$C_{10}H_{10}ClF_3N_2O$	45·1	3·8	10·5
6- and 4-Substituents									
$N[CH_2]_5$	55	160/1	56·8	6·1	13·3	$C_{15}H_{20}ClF_2N_3$	57·05	6·3	13·3
NMe_2	79	53	45·8	5·0	17·7	$C_9H_{12}ClF_2N_3$	45·85	5·1	17·6
$6\text{-}O{\cdot}NC_5H_{10}$ / $4\text{-}NC_5H_{10}$	85	64	54·3	6·0	12·7	$C_{15}H_{20}ClF_2N_3O$	54·3	6·0	12·7

TABLE 6

^{19}F Chemical shifts and coupling constants of polyfluoropyridines (p.p.m. from $CFCl_3$ as internal standard)

	Ring position of fluorines 2	3	4	5	6	Spin-coupling constants (c./sec.)
(XI; $R^1 = F$, $R^1 = C_5H_{10}N$)			98·3		71·4	$J_{4,6}$ 15·0
(XI; $R^1 = F$, $R^2 = Me_2N$)			98·2		71·5	$J_{4,6}$ 14·6
(XI; $R^1 = F$, $R^2 = O{\cdot}NC_5H_{10}$)			91·4		65·6	
(XI; $R^1 = Me_2N$, $R^2 = F$)	72·4				72·4	
(XI; $R^1 = C_5H_{10}N$, $R^2 = F$)	74·7			155·9	92·0	$J_{2,5}$ 22·6 $J_{2,6}$ 13·7 $J_{5,6}$ 20·8
(XV; $R^1 = F$, $R^2 = C_5H_{10}N$)	73·2			123·4	157·8	$J_{2,4}$ 11·4 $J_{2,5}$ 26·5 $J_{4,5}$ 17·4
(XV; $R^1 = Me_2N$, $R^2 = F$)	75·0			156·4	92·8	$J_{2,5}$ 22·2 $J_{2,6}$ 13·2 $J_{5,6}$ 21·2
(XV; $R^1 = F$, $R^2 = Me_2N$)	73·4		124·2	161·0		$J_{2,4}$ 11·0 $J_{2,5}$ 26·0 $J_{4,5}$ 16·8
(III; $R = C_5H_{10}N$)	85·6	142·9		142·9	85·6	
(II; $R^1 = Me_2N$, R^2 = MeO)		145·8		151·4	90·6	
(VII; $R = Me_2N$)		147·9		154·3	88·5	
(V; $R = C_5H_{10}N$, $X = [CH_2]_5$)		118·7		137·9	85·4	
(XIX; $R^1 = R^2 = F$) *	18·1	87·1		87·1	18·1	$J_{2,3}$ 18·1 $J_{2,5}$ 22·3 $J_{2,6}$ 14·4 $J_{3,5}$ 6·9

* P.p.m. from $CF_3{\cdot}CO_2H$ as internal standard.

(*d*) The hydroxylamine (II; R = O·NC_5H_{10}, R^2 = OMe) was reduced as described in (*b*) to give the *piperidinium salt of trifluoro-4-hydroxy-2-methoxypyridine* (65%), m.p. 184° (from benzene) (Found: C, 49·4; H, 5·8; N, 10·8. $C_{11}H_{15}F_3N_2O_2$ requires C, 50·0; H, 5·7; N, 10·6%).

(*e*) The hydroxylamines (XIII; R = $C_5H_{10}N$, C_4H_8N, morpholino, or Me_2N) were decomposed as in (*a*). 3,5-Dichloro-2,4-difluoro-6-hydroxypyridine was obtained; m.p. 148° (lit.,[7] 149—150°).

(*f*) In the decomposition of the hydroxylamine (XV; R^1 = O·NC_5H_{10}, R^2 = F) the reaction time was extended to 24 hr. A small amount of 3-chloro-trifluoro-4-hydroxypyridine (15%), m.p. 126—128° (lit.[9] 124°) was isolated from the sodium hydroxide extracts. Starting material (60%) was recovered.

(*g*) The hydroxylamine (XV; R^1 = O·NC_5H_{10}, R^2 = F) was reduced as in (*b*) to give the *piperidinium derivative* of 3-chlorotrifluoro-4-hydroxypyridine, m.p. 136° [from light petroleum (b.p. 80—100°)] (Found: C, 44·2; H, 4·1. $C_{10}H_{12}ClF_3N_2O$ requires C, 44·5; H, 4·5).

(*h*) The hydroxylamine (XV; R^1 = $C_5H_{10}N$, R^2 = O·NC_5H_{10}) decomposed readily in dioxan. After evaporation of the solvent, the residue was recrystallized to give *3-chloro-2,5-difluoro-6-hydroxy-4-piperidinopyridine*, m.p. 140° (Found: C, 48·5; H, 4·1; N, 11·3. $C_{10}H_{11}ClF_2N_2O$ C, 48·3; H, 4·4; N, 11·3%).

3-Chlorotrifluoro-4-piperidinopyridine (1 g.) was stirred with sodium hydroxide (1 g.) in boiling water (25 ml.) for 16 hr. The solution was acidified with conc. hydrochloric acid and extracted with chloroform. The combined extracts were dried and evaporated to give a compound (0·7 g.) identical with that just described.

We thank the S.R.C. for support (to S. M. R.), Dr. M. B. Green of Imperial Chemical Industries, Mond Division, for his interest and gifts of polyhalogenopyridines, and Dr. J. I. Hollies for measuring and interpreting ^{19}F n.m.r. spectra.

[8/1810 *Received, December 9th*, 1968]

[9] Dutch P. 6,611,714.