722. *Polyfluoro-heterocyclic Compounds. Part II.*[1] *Nucleophilic Substitution in Pentafluoropyridine.*

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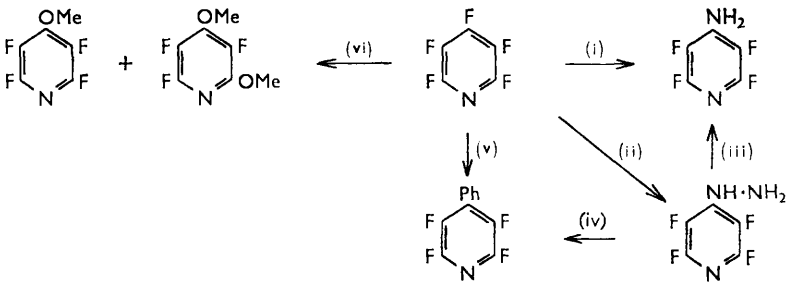
Reactions of pentafluoropyridine with ammonia, hydrazine, phenyl-lithium, and methoxide ion are described and the orientation of the products has been established by nuclear magnetic resonance measurements and by interconversions. Orientation of nucleophilic attack is governed by the five fluorine atoms and occurs primarily in the 4-position.

REACTION of pentachloropyridine with potassium fluoride in an autoclave at elevated temperatures, provided a convenient route to pentafluoropyridine [1] which had been prepared previously in low yield.[2,3] It has not been possible to detect any basic properties of this compound, *e.g.*, no hydrochloride was formed [2] and we have been unable to prepare a co-ordination compound with boron trifluoride in pentane. Beyond this, the chemistry of polyfluoropyridines has not been developed and we here report the reactions of pentafluoropyridine with nucleophilic reagents.



(i) aq. NH_3, (ii) Hydrazine hydrate, (iii) aq. HI, (iv) Bleaching powder in C_6H_6, (v) PhLi, (vi) MeOH (anhyd.) + Na.

Pentafluoropyridine reacted readily with aqueous ammonia giving aminotetrafluoropyridine, shown to be exclusively (>95%) the 4-amino-isomer, by its n.m.r. spectrum. Hydrazine hydrate and pentafluoropyridine in dioxan gave the tetrafluorohydrazinopyridine which on treatment with aqueous hydriodic acid gave 4-aminotetrafluoropyridine, identical with the sample obtained from the reaction described above. This confirms that hydrazine attacks the 4-position. Treatment of tetrafluoro-4-hydrazinopyridine with bleaching powder in benzene gave tetrafluoro-4-phenylpyridine, *i.e.*, analogous to the reaction of pentafluorophenylhydrazine.[4] However, tetrafluoro-4-phenylpyridine, prepared by reaction of pentafluoropyridine with phenyl-lithium showed four extra bands in the infrared (i.r.) spectrum and also melted over a range of 5°, at a lower temperature than the sample prepared as described above. This indicates that, in addition to attack at the 4-position, phenyl-lithium being a strongly nucleophilic reagent, also attacks other positions to a small extent (<5%).

Reaction between pentafluoropyridine and methoxide ion is so vigorous that very mild conditions must be used in order to obtain any of the monoether. The n.m.r. spectra of the ethers indicate initial attack at the 4-position, followed by attack at the 2-position.

The greater ease of nucleophilic displacement of fluoride ion from pentafluoropyridine than from hexafluorobenzene is quite striking. Thus, quantitative reaction of pentafluoropyridine with aqueous ammonia occurs at 80° for 2 hours, whereas a temperature

[1] Part I, Chambers, Hutchinson, and Musgrave, *J.*, 1964, 3573.
[2] Burdon, Gilman, Patrick, Stacey, and Tatlow, *Nature*, 1960, **186**, 231.
[3] Banks, Ginsberg, and Haszeldine, *Proc. Chem. Soc.*, 1960, 211.
[4] Birchall, Haszeldine, and Parkinson, *J.*, 1962, 4966.

of 167° is reported for the corresponding production of pentafluoroaniline from hexafluorobenzene.[5] Also, reaction of pentafluoropyridine with methoxide ion proceeds rapidly at 0° to give the monoether and at ambient temperature, quantitative conversion into the diether occurs during 15 minutes, whereas at least one hour at reflux appears to be necessary for the analogous preparation of pentafluoroanisole.[6,7]

Pyridine is considerably less reactive than benzene towards electrophilic substitution and even nucleophilic displacement of a hydrogen atom in position 2 in pyridine can be achieved by the Tschitschibabin reaction.[8] On this basis, an increased susceptibility towards nucleophilic attack with introduction of fluorine may have been expected but orientation to the 2-position in pentafluoropyridine would have been predicted. That orientation to the 4-position occurs indicates that pentafluoropyridine resembles pentafluorobenzene rather than pyridine, showing that the five fluorine atoms, and not the nitrogen, govern the orientation.

Although the analogy between pyridine and nitrobenzene has often been suggested, there is obviously no parallel between the orientation reactions of the corresponding perfluoro-compounds since substitution by ammonia and amines in pentafluoronitrobenzene occurs mainly at the *ortho*-position [9] (unlike other pentafluorobenzenes [10]) but the overall reactivities do seem to be similar. The function of the five fluorine atoms in governing the orientation of nucleophilic attack in pentafluoropyridine is difficult to rationalise; the obviously unique feature of the 4-position is that there is no *para*-fluorine which can deactivate that position by mesomeric electron release. Beyond this type of argument [9] no satisfactory explanation has yet been given to account for the orientation of nucleophilic attack in pentafluorobenzenes, where the same problem obtains.

Experimental

4-Aminotetrafluoropyridine.—Pentafluoropyridine (1·0 g., 0·0059 mole) and ammonia (2 ml.; 0·88 s.g.) were sealed in a Carius tube and heated to 80° for 2 hr. On cooling the tube to room temperature, the organic layer became solid. Water was added to the mixture which was then extracted with ether. Distillation of the dried ($MgSO_4$) ether layer afforded a white crystalline material (0·69 g., 70%). Sublimation under reduced pressure and recrystallisation from light petroleum (b. p. 80—100°) gave *4-aminotetrafluoropyridine*, m. p. 85—86° (Found: C, 36·6. $C_5H_2F_4N_2$ requires C, 36·1%); $\nu_{max.}$ 3509, 3356, 3215, 1667, 1664, 1538, 1484, 1407, 1337, 1282, 1171, 1107, 905, 729, 640, and 606 cm.$^{-1}$; $\lambda_{max.}$ 2043 and 2388 Å in cyclohexane.

Tetrafluoro-4-hydrazinopyridine.—On adding pentafluoropyridine (2·0 g., 0·0118 mole) to a stirred solution of hydrazine hydrate (1 g., 0·02 mole) in dioxan (10 ml.) an exothermic reaction occurred. The mixture was refluxed for 2 hr. after which it was poured into cold (0°) water (10 ml.). Precipitation of a heavy pale yellow oil occurred. The solution was extracted with methylene dichloride. The organic layer was then dried ($MgSO_4$) and the solvent removed to yield a yellow oil. Sublimation (100°/3—5 mm.), twice, afforded *tetrafluoro-4-hydrazinopyridine* (1·49 g., 70%), m. p. 56—57° (Found: C, 32·9. $C_5H_3F_4N_3$ requires C, 33·1%); $\nu_{max.}$ 3390, 3257, 1650, 1616, 1531, 1473, 1404, 1314, 1278, 1172, 1079, 961, 908, 746, and 720 cm.$^{-1}$.

Treatment of a solution of the hydrazine in methanol containing a drop of concentrated sulphuric acid with benzaldehyde gave *benzaldehyde 2,3,5,6-tetrafluoropyridylhydrazone*, m. p. 201·5—202·5° (from aqueous methanol) (Found: C, 53·5. $C_{12}H_7F_4N_3$ requires C, 53·5%).

Reaction between Tetrafluoro-4-hydrazinopyridine and Aqueous Hydriodic Acid.—The hydrazine (1·0 g., 0·0055 mole) was heated under reflux with aqueous hydriodic acid (8 ml.; 54 w/w) for 2 hr. after which the solution was treated with sodium metabisulphite. Steam distillation afforded crystalline material which was extracted into ether. The solution was dried ($MgSO_4$) and the solvent distilled off to yield a pale yellow solid. Recrystallisation from light petroleum (b. p. 80—100°) and sublimation under reduced pressure gave 4-aminotetrafluoropyridine (0·50 g., 54%), m. p. 85—86°, identified by comparison of its i.r. spectrum

[5] Brooke, Burdon, Stacey, and Tatlow, *J.*, 1960, 1768.
[6] Godsell, Stacey, and Tatlow, *Nature*, 1956, **178**, 199.
[7] Forbes, Richardson, Stacey, and Tatlow, *J.*, 1959, 2019.
[8] Tschitschibabin, *Ber.*, 1923, **56**, 1879.
[9] Brooke, Burdon, and Tatlow, *J.*, 1961, 802.
[10] Tatlow, *Endeavour*, 1963, **22**, 89.

with that of a sample prepared by the reaction between pentafluoropyridine and aqueous ammonia.

Reaction of Tetrafluoro-4-hydrazinopyridine with Bleaching Powder in Benzene.—The hydrazine (0·90 g., 0·005 mole) in dry benzene (5 ml.) was added to a stirred suspension of bleaching powder (3 g.) in benzene (10 ml.). On adding the hydrazine, an exothermic reaction occurred and the solution became yellow. The mixture was maintained at 60° for 1 hr. after which the solution was filtered. The benzene was distilled off to leave an orange solid (0·40 g., 35%). Recrystallisation from aqueous methanol and treatment with charcoal failed to remove the coloured impurity but two sublimations *in vacuo* (80°) gave pure *2,3,5,6-tetrafluoro-4-phenylpyridine* (Found: C, 58·1. $C_{11}H_5F_4N$ requires C, 58·2%), m. p. 106—107°; $\nu_{max.}$ 1639, 1456, 1431, 1420, 1408, 1316, 1289, 1255, 1147, 1119, 1076, 1004, 956, 926, 916, 872, 776, 743, 715, 691, 649, 628, and 608 cm.$^{-1}$

Phenylation of Pentafluoropyridine.—To pentafluoropyridine (2·1 g., 0·012 mole) in dry ether (5 ml.) was added phenyl-lithium (0·012 mole) in dry ether (15 ml.) at a rate sufficient to maintain a gentle reflux. The mixture was stirred for 1 hr., water was added, and the ether layer separated, dried ($MgSO_4$), filtered, and evaporated to leave a yellow liquid from which was sublimed (80°/2—4 mm.) a white crystalline material (0·70 g., 26%). Crystallisation from aqueous methanol, twice, and sublimation gave a material (Found: C, 57·8. Calc. for $C_{11}H_5F_4N$: C, 58·2%), m. p. 94—100°, whose i.r. spectrum was identical with that of tetrafluoro-4-phenylpyridine but for additional weak-peaks at 1244, 1092, 1011, and 856 cm.$^{-1}$. The proton and fluorine-19 n.m.r. spectra were identical with those of tetrafluoro-4-phenylpyridine.

Reaction between Pentafluoropyridine and Sodium Methoxide.—(i) Pentafluoropyridine (1 g., 0·0059 mole) was added slowly to dry methanol (6 ml.) in which had been dissolved sodium (0·3 g., 0·013 mole). An exothermic reaction occurred during the addition. The mixture was stirred for a further 15 min. and then poured into cold (0°) water. Oily droplets were precipitated which were extracted into methylene dichloride. The organic layer was separated, dried ($MgSO_4$), and concentrated to give a pale yellow oil (0·90 g.) which was shown by analytical-scale g.l.c. to consist of a small amount of solvent and methanol (~5%), and two other compounds (ratio of peak areas 1 : 9). The main product (*i.e.*, that with the longer retention time) was obtained pure by preparative-scale g.l.c. (silicone elastomer on Celite at 150°) and found to be *trifluoro-2,4-dimethoxypyridine* (Found: C, 43·6; F, 29·3. $C_7H_6F_3NO_2$ requires C, 43·7; F, 29·5%), b. p. 199—200°, n_D^{20} 1·4545; $\lambda_{max.}$ 2045 and 2692 Å, in cyclohexane; $\nu_{max.}$ 2994, 2963, 2903, 2845, 1645, 1587, 1515, 1490, 1441, 1393, 1200, 1149, 1111, 1029, 979, 943, 762, 739, and 692 cm.$^{-1}$

(ii) The reaction was repeated under milder conditions. During the addition of the pyridine to the sodium methoxide solution, the vessel was maintained at 0°. As soon as the addition was complete, the mixture was poured into cold (0°) water. The product (0·92 g.), obtained as before, was shown by analytical-scale g.l.c. to contain compounds (ratio of peak area 9 : 1) with retention times coincident with those of the compounds produced in the previous reaction. The main product was isolated by preparative-scale g.l.c. (silicone elastomer on Celite at 150°) and found to be *tetrafluoro-4-methoxypyridine* (Found: C, 40·0; F, 42·1. $C_6H_3F_4NO$ requires C, 39·8; F, 42·0%), b. p. 161°, n_D^{20} 1·4237; $\lambda_{max.}$ 2045, 2154, and 2573 Å, in cyclohexane; $\nu_{max.}$ 3019, 2967, 2899, 2845, 1639, 1595, 1513, 1477, 1437, 1193, 1138, 1109, 1096, 981, 928, 735, and 693 cm.$^{-1}$

The orientation of monosubstituted perfluoropyridines has been established by examination of the ^{19}F nuclear magnetic resonance spectra. In all cases a symmetrical AA′XX′ spectrum arises which can occur only if the system has two-fold symmetry, *i.e.*, the substituent is in the 4-position. Since the chemical shift between the A and X parts of the spectrum is in all cases large compared with the coupling constants, then the mid-point of each multiplet can be taken as the chemical shift of the fluorine atom.[11] The chemical shifts measured in this way are:

	δ (p.p.m.)	
	2–F	3–F
NH_2	95·72	165·94
Ph	92·83	145·86
OMe	92·29	161·05

[11] Corio, *Chem. Rev.*, 1960, **60**, 363.

The fluorine-19 n.m.r. spectrum of the dimethoxytrifluoropyridine shows three chemically shifted groups of peaks, only one of which shows the broadening effect expected from proximity to the nitrogen-14 nucleus. The compound has therefore only one 2-fluorine. The other two fluorine resonances are each doublets of quartets, arising from large F–F and small F–OMe coupling constants. The presence on each of these peaks of F–OMe coupling shows that both are *ortho* to a methoxy-group, and the similarity of their chemical shifts indicates that they are in the 3- and the 5-position. The compound is therefore trifluoro-2,4-dimethoxypyridine.

This assignment is confirmed by the proton n.m.r. spectrum, which shows that the 2-methoxy-group does not show spin-coupling with any fluorines, and that the 4-methoxy-group spin-couples equally with two fluorines, and hence has two *ortho*-fluorine neighbours.

The chemical shifts and coupling constants in this molecule are:

^{19}F chemical shifts [relative to CCl_3F (p.p.m.)]		^{19}F coupling constants (c.sec.$^{-1}$)	^{1}H chemical shifts (τ, relative to $SiMe_4$ = 10 p.p.m.)		H–F coupling constants (c.sec.$^{-1}$)
				τ	
3-F	168·73	$J_{35} = 0$			
5-F	161·73	$J_{56} = 25{\cdot}20 \pm 0{\cdot}10$	2-OMe	6·10	J (2-OMe–3-F) = 0
6-F	94·90	$J_{36} = 21{\cdot}55 \pm 0{\cdot}10$	4-OMe	5·78	J (4-OMe–3-F) = 2·5 ± 0·1

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