93. *Heterocyclic Polyfluoro-compounds. Part IV.*[1] *Nucleophilic Substitution in Pentafluoropyridine: The Preparation and Properties of Some 4-Substituted 2,3,5,6-Tetrafluoropyridines.*

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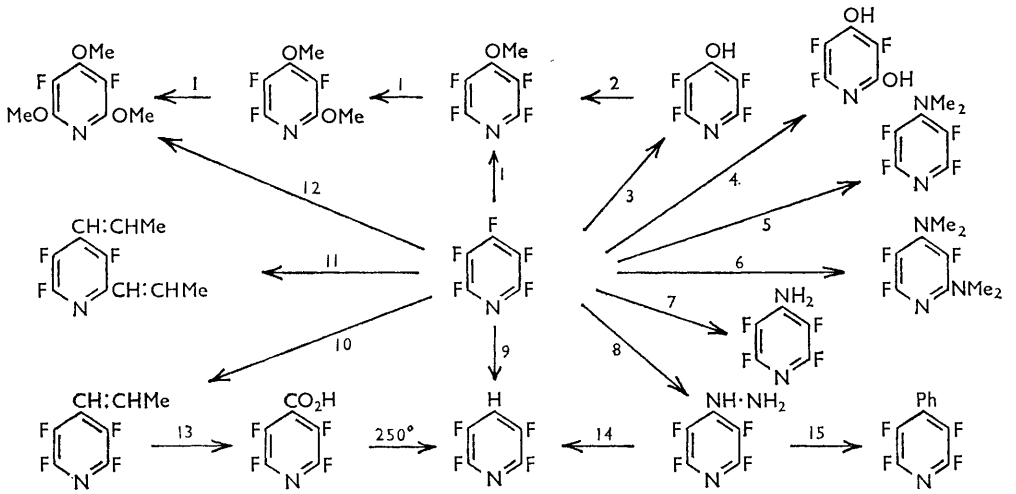
The preparation and some of the properties of fourteen new fluorinated pyridine derivatives are described. The 4-substituted 2,3,5,6-tetrafluoropyridines 4-X·C_5F_4N (where X = H, OH, OMe, NH_2, $NH{\cdot}NH_2$, NMe_2, and CH:CHMe) are obtained when pentafluoropyridine is treated with the appropriate nucleophilic reagents. 2,3,5,6-Tetrafluoropyridine is also obtained when 2,3,5,6-tetrafluoro-4-hydrazinopyridine is treated with aqueous copper sulphate solution, and when 2,3,5,6-tetrafluoropyridine-4-carboxylic acid, obtained by oxidation of 2,3,5,6-tetrafluoro-4-propenylpyridine, is thermally decarboxylated. Reaction of pentafluoropyridine with an excess of methanolic sodium methoxide yields 3,5,6-trifluoro-2,4-dimethoxy- or 3,5-difluoro-2,4,6-trimethoxy-pyridine. 3,5,6-Trifluoro-2,4-dipropenylpyridine and 2,4-bisdimethylamino-3,5,6-trifluoropyridine are obtained when pentafluoropyridine is treated with an excess of propenyl-lithium and dimethylamine respectively. Infrared spectroscopy reveals a characteristic ring vibration for these fluorinated pyridine derivatives near 1480 $cm.^{-1}$.

Pentafluoropyridine is a colourless, almost odourless liquid, b. p. 83·3° (cf. pyridine,[2] b. p. 115·3°; hexafluorobenzene,[3] b. p. 80·5°), prepared by defluorination of undecafluoropiperidine with hot iron [4] or nickel [5] or by reaction of pentachloropyridine with anhydrous potassium fluoride.[6]

[1] Part III, Banks, Cheng, and Haszeldine, *J.*, 1964, 2485.
[2] " Handbook of Chemistry and Physics," Chemical Rubber Publishing Co., Cleveland, 1957, 39th edn.
[3] Désirant, *Bull. Soc. chim. belges*, 1958, **67**, 676.
[4] Banks, Ginsberg, and Haszeldine, *J.*, 1961, 1740.
[5] Burdon, Gilman, Patrick, Stacey, and Tatlow, *Nature*, 1960, **186**, 231.
[6] Banks, Haszeldine, Latham, and Young, *Chem. and Ind.*, 1964, 835; *J*, 1965, 594.

The aromatic character of pentafluoropyridine is revealed by its spectroscopic properties,[4] and a detailed analysis of its infrared and Raman spectra supports the assumption that the ring is planar.[7] The infrared spectrum of pentafluoropyridine vapour in the range 650—5000 cm.$^{-1}$ shows strong bands at 980, 1075, and 1081 cm.$^{-1}$ (doublet), attributable to C–F stretching vibrations, and three strong ring vibrations at 1645, 1529, and 1497 cm.$^{-1}$; the absorption at 1497 cm.$^{-1}$ is the most intense band in the spectrum. The ultraviolet spectrum of pentafluoropyridine shows a *B*-band at $\lambda_{max.}$ 256 mμ (ε 1180 in hexane). Pyridine itself



1, NaOMe; 2, CH_2N_2; 3, aq. NaOH; 4, 40% NaOH; 5, Me_2NH; 6, excess of Me_2NH; 7, NH_3; 8, N_2H_4; 9, $LiAlH_4$; 10, MeCH:CHLi; 11, excess of MeCH:CHLi; 12, excess of NaOMe; 13, HNO_3; 14, aq. $CuSO_4$; 15, C_6H_6–$CaOCl_2$.

shows ring vibrations in the infrared [8] at 1485, 1570, and 1580 cm.$^{-1}$, and its ultraviolet spectrum in hexane is characterised by a *B*-band at $\lambda_{max.}$ 250 mμ (ε 2000).[9]

Pentafluoropyridine is miscible with many organic solvents, but is immiscible with, and unaffected by, cold water. Pentafluoropyridine appears to be non-basic: it does not form a hydrochloride when treated with hydrogen chloride in ether, and no end-point is observed when it is titrated potentiometrically against dilute acid in aqueous ethanol.[5] It is unaffected by hot concentrated hydrochloric acid, but reacts with hot aqueous sodium hydroxide solution to give 2,3,5,6-tetrafluoro-4-hydroxypyridine * in 58% yield; hot (80°) 40% aqueous sodium hydroxide solution converts pentafluoropyridine completely into ammonia, carbonate, and fluoride ions, and 3,5,6-trifluoro-2,4-dihydroxypyridine (20% yield) during 12 hr. These hydroxyfluoropyridines arise by nucleophilic displacement of fluorine from pentafluoropyridine by hydroxyl ion, a type of reaction that occurs readily and can be used to prepare the new pyridine derivatives shown in the annexed scheme. The mechanism of nucleophilic substitution in pentafluoropyridine, which occurs more readily than in hexafluorobenzene, will be discussed in a later Paper.[10]

The infrared spectra of all the compounds derived from pentafluoropyridine show a strong band near 1480 cm.$^{-1}$ that is assigned to the principal ring vibration, and strong C–F stretching bands in the 900—1000 cm.$^{-1}$ region.

* The structures of all the pyridine derivatives described here were determined by ^{19}F n.m.r. spectroscopy, but chemical proof of structure has been obtained and will be reported later.

[7] Long and Bailey, *Trans. Faraday Soc.*, 1963, **59**, 599.

[8] Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen and Co., London, 1958, 2nd edn., p. 279.

[9] Silverstein and Bassler, " Spectrometric Identification of Organic Compounds," John Wiley and Sons New York, 1963, p. 102.

[10] Banks, Cheng and Haszeldine, *J.*, to be published.

Principal ring vibration frequencies ($cm.^{-1}$) for polyfluoropyridines.

Pentafluoropyridine	Vap.	1497
2,3,5,6-Tetrafluoropyridine	Vap.	1497
2,3,5,6-Tetrafluoro-4-hydroxypyridine	Mull †	1481
2,3,5,6-Tetrafluoro-4-methoxypyridine	Liq. film	1481
4-Amino-2,3,5,6-tetrafluoropyridine	Mull †	1486
4-Dimethylamino-2,3,5,6-tetrafluoropyridine	Solid film	1479
2,3,5,6-Tetrafluoro-4-hydrazinopyridine	Solid film	1481
2,3,5,6-Tetrafluoro-4-propenylpyridine	Liq. film	1460
2,3,5,6-Tetrafluoropyridine-4-carboxylic acid	Mull †	1471
3,5,6-Trifluoro-2,4-dihydroxypyridine	Solid film	1495, 1529
3,5,6-Trifluoro-2,4-dimethoxypyridine	Liq. film	1437, 1481, 1488 (doublet)
2,4-Bisdimethylamino-3,5,6-trifluoropyridine	Mull †	1433, 1499
3,5,6-Trifluoro-2,4-dipropenylpyridine	Liq. film	1418, 1460
3,5-Difluoro-2,4,6-trimethoxypyridine	Solid film	1481
2,3,5,6-Tetrafluoro-4-phenylpyridine	Mull †	1439, 1468

† In Nujol or hexachlorobutadiene.

2,3,4,5-*Tetrafluoro-4-hydroxypyridine.*—This is a white hygroscopic solid that has a typical phenolic odour, liberates carbon dioxide from sodium bicarbonate, readily forms an anilinium salt, and combines smoothly with diazomethane to yield 2,3,5,6-tetrafluoro-4-methoxypyridine. Whereas 4-hydroxypyridine is a weak acid ($pK_a = 11{\cdot}09$ at 20° in H_2O) and in fact is a weaker acid than phenol ($pK_a = 9{\cdot}98$ at 20° in H_2O) owing to its tendency to exist mainly in the tautomeric amide form (pyrid-4-one),[11] 2,3,5,6-tetrafluoro-4-hydroxypyridine is a strong acid ($pK_a = 3{\cdot}21$ at 20° in H_2O), and is considerably more acidic than pentafluorophenol[12] ($pK_a = 5{\cdot}53$ at 25° in H_2O). From spectroscopy, it appears that less than 5%, if any, of 2,3,5,6-tetrafluoro-4-hydroxypyridine exists in the amide form, 2,3,5,6-tetrafluoropyrid-4-one; thus the difference in acid strength between 2,3,5,6-tetrafluoro-4-hydroxypyridine and pentafluorophenol is ascribed to the greater electron-withdrawing effect of the ring nitrogen in the former compared with the *para* fluorine substituent in the latter.

The ^1H n.m.r. spectrum of an aqueous solution of 2,3,5,6-tetrafluoro-4-hydroxypyridine[13] shows a single broad band associated with coalesced water-solute absorption, and gives no useful structural information. The ^{19}F n.m.r. absorption of the hydroxypyridine in aqueous solution is a typical AA'XX' spectrum,[13] as would be expected for either 2,3,5,6-tetrafluoro-4-hydroxypyridine or for 2,3,5,6-tetrafluoropyrid-4-one, or for a mixture of these tautomers undergoing rapid interconversion. However, the close similarity in chemical shift values and spin–spin coupling constants characteristic of the ^{19}F n.m.r. spectra of 2,3,5,6-tetrafluoro-4-hydroxypyridine and 2,3,5,6-tetrafluoro-4-methoxypyridine indicates that the former compound exists either in the hydroxy-form or as a rapidly interconverting tautomeric mixture with the hydroxy-form predominating.

The infrared spectrum of 2,3,5,6-tetrafluoro-4-hydroxypyridine (mull) shows a broad band centred on 3100 $cm.^{-1}$ that is attributed to intermolecular OH hydrogen bonding. A 1% solution of the hydroxy-compound in carbon tetrachloride shows a sharp strong " free " hydroxyl band at 3571 $cm.^{-1}$ and a much weaker broad bonded hydroxyl band at 3175 $cm.^{-1}$. No band that can be definitely assigned to a carbonyl group is present in the infrared spectrum: strong absorptions occur at 1653 for the mull and at 1667 and 1637 $cm.^{-1}$ for the carbon tetrachloride solution, but all of the fluorinated pyridine derivatives described here exhibit one or two bands in this region.

The ultraviolet spectrum of 2,3,5,6-tetrafluoro-4-hydroxypyridine shows $\lambda_{max.}$ at 255 mμ (ε 1790) in hexane, and at 243 mμ (ε 2270) with λ_{infl} at 264—270 mμ (ε 850—730) in ethanol. These values suggest that the compound exists in the hydroxy-form because they are similar to those for pentafluoropyridine and for 2,3,5,6-tetrafluoro-4-methoxypyridine [$\lambda_{max.}$ at 215 (ε 4920), 259 (ε 2120) in hexane, and at 218 (ε 5780) and 258 mμ

[11] Albert and Hampton, *J.*, 1954, 505.
[12] Birchall and Haszeldine, *J.*, 1959, 3653.
[13] Part V, Lee and Orrell, following Paper.

(ε 2020) in ethanol]. The ultraviolet absorption spectrum of pyrid-4-one is quite different from that of 4-hydroxypyridine.[14] The spectrum of the anion, obtained by dissolving 2,3,5,6-tetrafluoro-4-hydroxypyridine in 0·01N-aqueous sodium hydroxide, shows an intense band at $\lambda_{max.}$ 233 mμ (ε 11,450) with λ_{infl} at 268—279 mμ (ε 96—53).

Experimental

Infrared and ultraviolet spectra were measured with a Perkin-Elmer spectrophotometer model 21 (sodium chloride optics) and a Unicam S.P. 700 spectrophotometer, respectively. Perkin-Elmer Fraktometers (models 116 and 451) were used for gas–liquid chromatographic analysis.

Preparation of Pentafluoropyridine.—Pentafluoropyridine was prepared by defluorination of undecafluoropiperidine by the technique described previously;[4] a mild steel pyrolysis tube (115 cm. × 7·5 cm. i.d., heated length 90 cm.) packed tightly with steel wool (5 kg.) was used.

In a typical experiment, undecafluoropiperidine (25·5 g.), prepared in 7·5% yield by electrochemical fluorination of pyridine,[4] was pyrolysed over steel wool at 600°/<1 mm. (contact time *ca.* 1 sec.). The product (15·1 g.) was distilled through a 10 cm. × 8 mm. adiabatic column packed with 2·2 mm. Fenske glass rings to yield a mixture (12·4 g.) of perfluoro-2,3,4,5-tetrahydropyridine, perfluoro-(1-methylpyrrolidine), and perfluoro-(*N*-butylidenemethylamine), b. p. 35—45°, and pentafluoropyridine (2·1 g.) (Found: C, 35·4; N, 8·1%; *M*, 173. Calc. for C_5F_5N: C, 35·5; N, 8·3%; *M*, 169), b. p. 83·5°, with a g.l.c. (gas–liquid chromatography) purity of >99%. The mixture, b. p. 35—45°, of partially-defluorinated and isomerised products[15] (consisting mainly of perfluoro-2,3,4,5-tetrahydropyridine) was recycled through the pyrolysis tube to yield more pentafluoropyridine (1·6 g.; total yield 24%).

Reactions of Pentafluoropyridine.—(a) *With concentrated hydrochloric acid.* Pentafluoropyridine (0·45 g.) was shaken with concentrated hydrochloric acid (5 ml.) in a 15-ml. Pyrex ampoule at 20° for 3 days, then at 50° for 3 days, and finally at 70° for 7 days. The organic layer was separated, washed with water, dried (P_2O_5), and identified by infrared spectroscopy and gas–liquid chromatography as pentafluoropyridine (0·43 g.; 96% recovery).

(b) *With aqueous sodium hydroxide solution.* (i) Pentafluoropyridine (1·45 g., 8·58 mmoles), sodium hydroxide (0·72 g., 18·00 mmoles), and water (12 ml.) were heated under reflux for 2 hr. The homogeneous product was acidified with concentrated hydrochloric acid (3 ml.) and extracted with ether (3 × 25 ml.). The ethereal extract was dried ($MgSO_4$), then evaporated to give a white solid that was sublimed at 60°/<1 mm. to yield 2,3,5,6-*tetrafluoro*-4-*hydroxypyridine* (0·83 g., 58%) (Found: C, 36·3; H, 0·7; N, 8·1%; Equiv., 167. C_5HF_4NO requires C, 35·9; H, 0·6; N, 8·4%; Equiv., 167), m. p. 73—75°.

(ii) Pentafluoropyridine (1·00 g.) and 40% aqueous sodium hydroxide solution (5 ml.) were heated in a 20-ml. Pyrex ampoule at 80° for 12 hr. Ammonia was detected by its characteristic odour when the ampoule was opened. The solid product was washed out of the ampoule with water (50 ml.), and the resulting solution gave a positive test for F^-. The solution was acidified (concentrated hydrochloric acid, 6 ml.), filtered to remove silicic acid, and the filtrate was extracted with ether (4 × 25 ml.). Evaporation of the dry ($MgSO_4$) ethereal extract gave a white solid that was recrystallised from water to yield 3,5,6-*trifluoro*-2,4-*dihydroxypyridine* (0·20 g., 20%) (Found: C, 36·4; H, 1·2%. $C_5H_2F_3NO_2$ requires C, 36·4; H, 1·2%) as white needles, m. p. 188°.

(c) *With potassium hydroxide in t-butyl alcohol.* Pentafluoropyridine (1·94 g., 11·48 mmole), potassium hydroxide (1·57 g., 28·68 mmole), and t-butyl alcohol (30 ml.) were heated under reflux for 2·5 hr. The product was cooled to room temperature and treated with water (50 ml.). The alcohol was distilled off and the aqueous solution was acidified (5N-hydrochloric acid, 15 ml.) and extracted with ether (4 × 20 ml.). The ethereal extract was dried ($MgSO_4$), then evaporated to give a white solid that was sublimed at 60°/<1 mm. to yield 2,3,5,6-tetrafluoro-4-hydroxypyridine (1·22 g., 64%), m. p. 73—75°.

(d) *With sodium methoxide.* (i) A mixture of pentafluoropyridine (3·00 g., 17·7 mmoles) and 0·51N-sodium methoxide in anhydrous methanol (35 ml., 17·7 mmoles) was heated under reflux for 3 hr. The product was treated with water (50 ml.) and extracted with ether (4 × 30 ml.). The ethereal extract was dried ($MgSO_4$) and distilled to yield 2,3,5,6-*tetrafluoro*-4-*methoxypyridine* (1·80 g., 57%) (Found: C, 40·0; H, 1·6; N, 7·8%. $C_6H_3F_4NO$ requires C, 39·8; H, 1·7; N, 7·7%), b. p. 68°/30 mm., n_D^{20} 1·4167, d_4^{20} 1·493.

[14] Specker and Gawrosch, *Ber.*, 1942, **75**, *B*, 1338.
[15] Banks, Cheng, and Haszeldine, *J.*, 1962, 3407.

In a duplicate experiment where the reactants were shaken together at room temperature for 10 min., 2,3,5,6-tetrafluoro-4-methoxypyridine was obtained in 66% yield.

(ii) A mixture of pentafluoropyridine (1·90 g., 11·2 mmoles) and 1·54N-sodium methoxide in methanol (39·0 ml., 60·0 mmoles) was heated under reflux for 6 hr. The product was cooled to 20° and water (50 ml.) was added. A white solid precipitated and was filtered off, washed with water, dried (P_2O_5 *in vacuo*), and sublimed at 40°/<1 mm. to yield 3,5-*difluoro*-2,4,6-*trimethoxypyridine* (1·70 g., 74%) (Found: C, 46·9; H, 4·3; N, 7·1%. $C_8H_9F_3NO_3$ requires C, 46·8; H, 4·4; N, 6·8%), m. p. 50—54°, $\lambda_{max.}$ 279 mμ (ε 5750), λ_{infl} 226—233 mμ (ε 2230—1520) in hexane; $\lambda_{max.}$ 281 mμ (ε 5550), λ_{infl} 225—233 mμ (ε 2310—1530) in ethanol. The aqueous filtrate was titrated against N-hydrochloric acid and found to contain 26·4 mmoles of unchanged base.

(e) *With lithium aluminium hydride.* To a cold (0°), stirred solution of pentafluoropyridine (4·0 g., 23·7 mmoles) in ether (10 ml.) was added 0·32N-lithium aluminium hydride in ether (100 ml.) cooled to 0°. On completion of the addition (1 hr.), the reaction mixture was heated under reflux (4 hr.), then cooled (0°) and treated with undried ether (2 ml.) and 2N-sulphuric acid (10 ml.). The ethereal layer was distilled through a 20 cm. × 1 cm. i.d. adiabatic column packed with $\frac{1}{16}$ in. × $\frac{1}{16}$ in. nickel Dixon rings until only *ca.* 4 ml. of distilland remained; this was fractionated by trap-to-trap fractional condensation *in vacuo*, to yield a colourless liquid (3·2 g.) that was shown by gas–liquid chromatography (2 m. 30% w/w paraffin oil–Celite at 100°) to contain pentafluoropyridine (18%) and one other compound (82%). This other compound was isolated by large-scale gas–liquid chromatography (3 m. × 2·2 cm. 30% w/w Silicone oil–Celite at 110°) and shown by elemental analysis and infrared and ^{19}F n.m.r. spectroscopy to be 2,3,5,6-*tetrafluoropyridine* (Found: C, 40·0; H, 0·8; N, 9·3%; *M*, 152. C_5HF_4N requires C, 39·7; H, 0·7; N, 9·3%; *M*, 151), b. p. 102°. The yield of this tetrafluoropyridine, calculated from chromatographic data, was 74%.

(f) *With ammonia.* Heat was evolved and a white precipitate formed immediately when aqueous ammonia (s.g. 0·880; 1·0 g., 18·0 mmoles) was added to pentafluoropyridine (1·0 g., 5·9 mmoles) in anhydrous ethanol (3·0 ml.). The mixture was heated in a 10-ml. Pyrex ampoule at 110° for 8 hr. and then poured into water (10 ml.). The product was extracted with ether (3 × 10 ml.), and the extract was dried ($MgSO_4$) then evaporated to yield a solid (0·80 g., 81%) that was sublimed at 80°/<1 mm. to afford white crystals of 4-*amino*-2,3,5,6-*tetrafluoropyridine* (Found: C, 36·2; H, 1·4; N, 17·2%. $C_5H_2F_4N_2$ requires C, 36·2; H, 1·2; N, 16·9%), m. p. 83·5—84·0°.

(g) *With dimethylamine.* (i) An exothermic reaction occurred when a cold (0°) mixture of 25% w/w aqueous dimethylamine solution (1·8 g., 10 mmoles) and ethanol (2·5 g.) was added to a stirred solution of pentafluoropyridine (0·80 g., 4·73 mmoles) in ethanol (2·5 g.) at 0°. When the reaction mixture was cooled to 0°, 4-*dimethylamino*-2,3,5,6-*tetrafluoropyridine* (0·47 g., 51%) (Found: C, 43·3; H, 3·4; N, 14·4%. $C_7H_6F_4N_2$ requires C, 43·3; H, 3·1; N, 14·4%) precipitated as a white, crystalline solid, m. p. 23·5°, b. p. 85°/3 mm.

(ii) A mixture of pentafluoropyridine (1·0 g., 5·9 mmoles), 25% w/w aqueous dimethylamine solution (2·8 g., 15·5 mmoles), and ethanol (2·5 g.) was heated in a 10-ml. Pyrex ampoule at 100° for 20 hr. When the ampoule was cooled to 20° a white solid (1·0 g., 82%) precipitated; this was filtered and sublimed *in vacuo* to give 2,4-*bisdimethylamino*-3,5,6-*trifluoropyridine* (Found: C, 50·0; H, 5·7; N, 20·1%. $C_9H_{12}F_3N_3$ requires C, 49·3; H, 5·5; N, 19·2%), m. p. 35—38°.

(h) *With hydrazine.* Pentafluoropyridine (5·0 g., 29·6 mmoles), hydrazine hydrate (3·6 g., 72 mmoles), and ethanol (65 ml.) were mixed at 0°; a white precipitate of hydrazine hydrofluoride formed immediately. The mixture was stirred at 0° for 2 hr., then filtered to remove hydrazine hydrofluoride (1·5 g., 30 mmoles); the filtrate was evaporated, *in vacuo*, and the residue was sublimed at 70°/10^{-2} mm. to yield 2,3,5,6-*tetrafluoro*-4-*hydrazinopyridine* (4·0 g., 75%) (Found: C, 33·4; H, 1·8; N, 23·4%. $C_5H_3F_4N_3$ requires C, 33·2; H, 1·7; N, 23·2%) as a white solid, m. p. 56·5°, $\lambda_{max.}$ 238 mμ (ε 10,200), in hexane, $\lambda_{max.}$ 248 mμ (ε 13,400) in ethanol.

(i) *With propenyl-lithium.* Propenyl-lithium containing mainly (*ca.* 90%) the *cis* isomer was prepared as described previously.[16]

(*a*) A 100-ml. three-necked flask was fitted with a mercury-sealed stirrer, a dropping funnel, and a thermometer (−80° to 30°). The apparatus was flushed with dry nitrogen for 1 hr. and the flow of nitrogen was maintained throughout the experiment. A solution of pentafluoropyridine (3·33 g., 19·70 mmoles) in dry ether (10 ml.) was placed in the flask, which was then

[16] Birchall, Clarke, and Haszeldine, *J.*, 1962, 4977.

cooled to −20°. A solution of propenyl-lithium (0·87 g., 18·10 mmoles) in dry ether (19 ml.) was added from the dropping funnel during 1·5 hr. The reaction mixture was allowed to warm slowly to room temperature and poured into 0·5N-hydrochloric acid (50 ml.). The organic layer was separated, and the aqueous layer was extracted with ether (2 × 20 ml.). The ethereal extract and the organic layer were combined, dried ($MgSO_4$), and distilled to remove the ether, then fractionated in a small Vigreux still to yield a mixture of *cis*- and *trans*-2,3,5,6-*tetrafluoro*-4-*propenylpyridine* (2·50 g., 66%) (Found: C, 50·2; H, 2·3; N, 7·3%. $C_8H_5F_4N$ requires C, 50·3; H, 2·6; N, 7·3%), b. p. 54°/10 mm. G.l.c. analysis (2 m. 30% w/w Silicone MS 550–Celite at 143°) revealed that the *cis* : *trans* ratio was 6 : 1.

(*b*) The above experiment was repeated using a 1 : 2 molar ratio of pentafluoropyridine to propenyl-lithium. A solution of propenyl-lithium (2·76 g., 58·00 mmoles) in ether (190 ml.) was added to a solution of pentafluoropyridine (4·85 g., 28·70 mmoles) in dry ether (15 ml.) at −20° during 2·5 hr. The product was worked up as before to yield 3,5,6-*trifluoro*-2,4-*dipropenylpyridine* (3·60 g., 62%) (Found: C, 61·9; H, 4·7; N, 6·4%. $C_{11}H_{10}F_3N$ requires C, 62·0; H, 4·7; N, 6·6%), b. p. 91—92°/5 mm. G.l.c. analysis (1 m. 30% w/w Silicone MS 550–Celite at 180°) revealed the presence of four geometrical isomers (peak–area ratio 66 : 20 : 10 : 2).

Properties and Reactions of 2,3,5,6-*Tetrafluoro*-4-*hydroxypyridine*.—(a) *Acidity*. Tetrafluoro-4-hydroxypyridine turns damp blue litmus paper red, liberates carbon dioxide briskly from cold aqueous sodium bicarbonate solution, and darkens ferric chloride solution. The dissociation constant of tetrafluoro-4-hydroxypyridine was determined by potentiometric titration of a 0·005N-solution of the hydroxypyridine in carbonate-free distilled water against aqueous sodium hydroxide; the value for the " half-neutralisation " point at 20° gave $K_a = 7{\cdot}7 \times 10^{-4}$, whence $pK_a = 3{\cdot}21$.

(b) *Reaction with aniline*. Ether was added dropwise to a slurry of 2,3,5,6-tetrafluoro-4-hydroxypyridine (0·20 g., 1·20 mmoles) in n-hexane (4 ml.) until a homogeneous solution formed. This solution was then treated with an ethereal solution of aniline, and the resulting white precipitate was recrystallised from n-hexane to yield the *anilinium salt* of 2,3,5,6-tetrafluoro-4-hydroxypyridine (0·18 g., 58%) (Found: C, 51·0; H, 3·1; N, 10·7%. $C_{11}H_8F_4N_2O$ requires C, 50·8; H, 3·1; N, 10·8%), m. p. 132°.

(c) *Reaction with diazomethane*. A solution of 2,3,5,6-tetrafluoro-4-hydroxypyridine (0·20 g., 1·20 mmoles) in ether (2 ml.) was treated with a 5% excess of diazomethane in ether at 0°. The mixture was allowed to warm slowly to 20°, and ether was distilled off. The residual oil was distilled under reduced pressure in a micro Vigreux still, to yield 2,3,5,6-tetrafluoro-4-methoxypyridine (0·60 g., 67%) (Found: C, 40·0; H, 1·6; N, 7·8%. $C_6H_3F_4NO$ requires C, 39·8; H, 1·7; N, 7·7%), b. p. 68°/30 mm.

Preparation of 3,5,6-*Trifluoro*-2,4-*dimethoxypyridine*.—A mixture of 2,3,5,6-tetrafluoro-4-methoxypyridine (2·60 g., 14·4 mmoles) and 0·53N-sodium methoxide in methanol (28·0 ml., 14·8 mmoles) was heated under reflux for 4 hr. Water (60 ml.) was added to the product and the mixture was extracted with ether (4 × 30 ml.). Distillation of the ethereal extract (dried over $MgSO_4$) gave g.l.c. pure (2 m. 30% w/w didecyl phthalate–Celite at 168°) 3,5,6-*trifluoro*-2,4-*dimethoxypyridine* (1·90 g., 69%) (Found: C, 43·5; H, 3·0; N, 7·5%. $C_7H_6F_3NO_2$ requires C, 43·5; H, 3·1; N, 7·3%), b. p. 87—88°/15 mm., n_D^{20} 1·4532, d_4^{20} 1·4240, $\lambda_{max.}$ 271 mμ (ε 3860), λ_{infl} 204—216 mμ (ε 9460—4820) in hexane, $\lambda_{max.}$ 270 (ε 3790), λ_{infl} 204—214 mμ (ε 9600—5200) in ethanol.

Preparation of 3,5-*Difluoro*-2,4,6-*trimethoxypyridine*.—A mixture of 3,5,6-trifluoro-2,4-dimethoxypyridine (0·86 g., 4·46 mmoles) and 0·78N-sodium methoxide in methanol (6·0 ml., 4·68 mmoles) was heated under reflux for 6 hr. The product was cooled (20°) and treated with water (10 ml.), whereupon a white waxy solid separated. This solid was filtered off, washed with water, dried (P_2O_5 *in vacuo*), and sublimed at 40°/<1 mm. to yield 3,5-*difluoro*-2,4,6-*trimethoxypyridine* (0·76 g., 83%) (Found: C, 46·9; H, 4·2; N, 7·1%. $C_8H_9F_2NO_3$ requires C, 46·8; H, 4·4; N, 6·8%), m. p. 48—52°, $\lambda_{max.}$ 279 mμ (ε 5750), λ_{infl} 226—233 mμ (ε 2230—1515) in hexane, $\lambda_{max.}$ 281 mμ (ε 5550), λ_{infl} 225—233 mμ (ε 2310—1530) in ethanol.

Preparation of 2,3,5,6-*Tetrafluoropyridine*-4-*carboxylic Acid*.—2,3,5,6-Tetrafluoro-4-propenylpyridine (1·20 g.) and concentrated nitric acid (5 ml.) were heated in a 25-ml. Pyrex ampoule at 110° for 45 min. The product, a homogeneous dark green liquid, was poured into a mixture of crushed ice and water (*ca.* 100 g.) and the resulting colourless solution was extracted with ether (8 × 25 ml.). The ethereal extract was dried ($MgSO_4$) and then evaporated to give a pale yellow solid, which was sublimed at 70°/<1 mm. to yield 2,3,5,6-*tetrafluoropyridine*-4-*carboxylic acid*

(0·40 g., 33%) (Found: C, 36·9; H, 0·5; N, 7·1%. $C_6HF_4NO_2$ requires C, 36·9; H, 0·5; N, 7·2%), m. p. 98—100°.

A solution of 2,3,5,6-tetrafluoropyridine-4-carboxylic acid (0·10 g.) in water (3 ml.) was treated with dilute aqueous sodium hydroxide solution until the pH was 4, when an aqueous solution of *S*-benzylthiuronium chloride was added. The resulting white precipitate was recrystallised from water to give the S-*benzylthiuronium* derivative of 2,3,5,6-tetrafluoropyridine-4-carboxylic acid (0·12 g., 65%) (Found: C, 46·3; H, 3·1; N, 11·7%. $C_{14}H_{11}F_4N_3O_2S$ requires C, 46·5; H, 3·0; N, 11·6%), m. p. 148°.

Reaction of 2,3,5,6-tetrafluoro-4-propenylpyridine with acetonic potassium permanganate at −40°, at −20°, and at 0° failed to yield 2,3,5,6-tetrafluoropyridine-4-carboxylic acid. In each experiment no organic product could be isolated from the reaction mixture, which contained fluoride ion after treatment with water. In separate experiments, pentafluoropyridine was treated with acetonic potassium permanganate at −20° and at 0°, and was apparently completely destroyed.

Preparation of 2,3,5,6-*Tetrafluoropyridine.*—(a) *From pentafluoropyridine.* The reaction of pentafluoropyridine with lithium aluminium hydride to yield 2,3,5,6-tetrafluoropyridine is described earlier in this section.

(b) *From* 2,3,5,6-*tetrafluoropyridine-4-carboxylic acid.* 2,3,5,6-Tetrafluoropyridine-4-carboxylic acid (0·10 g., 0·51 mmole) was heated in an evacuated 15-ml. Pyrex ampoule at 250° for 1 hr. The volatile product was transferred to a vacuum system, leaving behind a black residue, and separated by fractional condensation *in vacuo* into carbon dioxide (0·02 g., 0·45 mmole) and 2,3,5,6-tetrafluoropyridine (0·06 g., 0·40 mmole; 78%) (Found: C, 40·0; H, 1·0; N, 9·1%; *M*, 154. Calc. for C_5HF_4N: C, 39·7; H, 0·7; N, 9·3%; *M*, 151), which was spectroscopically (infrared) identical with the compound obtained from the reaction of pentafluoropyridine with lithium aluminium hydride.

(c) *From* 2,3,5,6-*tetrafluoro-4-hydrazinopyridine.* Copper sulphate (19·0 g., 75 mmoles) in water (90 ml.) was added during 1·5 hr. to a stirred suspension of 2,3,5,6-tetrafluoro-4-hydrazinopyridine (4·00 g., 22·6 mmoles) in water (50 ml.) at 20°; reaction was instantaneous with liberation of nitrogen. After the addition was complete, the reaction mixture was boiled under reflux for 2 hr. and then steam-distilled to yield a yellow oil. This oil was dried (P_2O_5) and distilled in a micro Vigreux still to yield 2,3,5,6-tetrafluoropyridine (1·8 g., 54%), b. p. 102°, which was identified by g.l.c. analysis and by infrared and ^{19}F n.m.r. spectroscopy. A total of 400 ml. (80%) of nitrogen was evolved in the reaction.

Reaction of 2,3,5,6-*Tetrafluoro-4-hydrazinopyridine with Benzene.*—The hydrazine (4·6 g.) in sodium-dried benzene (100 ml.) was added during 3 hr. to a stirred suspension of bleaching powder (25 g.) in sodium-dried benzene (200 ml.) at 20°. Nitrogen (520 ml., 85%) was evolved. The product was filtered and the filtrate was evaporated at 25 mm. pressure, leaving a black crystalline residue (1·0 g.) that was sublimed at 40°/<1 mm. to yield 2,3,5,6-*tetrafluoro-4-phenylpyridine* (Found: C, 58·4; H, 1·9; N, 6·3%. $C_{11}H_5F_4N$ requires C, 58·2; H, 2·2; N, 6·2%; *M*, 227) as a white solid, m. p. 102—103°. Formation of this product presumably involves attack on benzene by 2,3,5,6-tetrafluoropyridyl radicals generated by oxidation of 2,3,5,6-tetrafluoro-4-hydrazinopyridine (cf. formation of pentafluorophenyl radicals *via* oxidation of pentafluorophenylhydrazine [17]).

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[17] Birchall, Haszeldine, and Parkinson, *J.*, 1962, 4966.