Heterocyclic Polyfluoro-compounds. Part X.[1] Nucleophilic Substitution in Tetrafluoropyrimidine

By R. E. Banks, D. S. Field, and R. N. Haszeldine, Chemistry Department, The University of Manchester Institute of Science and Technology, Manchester 1

Tetrafluoropyrimidine, prepared in high yield by reaction of tetrachloropyrimidine with anhydrous potassium fluoride at elevated temperatures, is highly susceptible to attack by nucleophiles; the ease of displacement of ring fluorines decreases in the order 4- and 6- > 2- ≫ 5-. Through use of appropriate nucleophilic reagents the following fluoro-pyrimidines have been prepared: 4-X·$C_4F_3N_2$ (X = OH), 4-Y·$C_4F_3N_2$, and 4,6-Y_2·$C_4F_2N_2$ (Y = NH_2, OMe, NHPh, NHMe, or NMe_2), and 2,4,6-Z_3·C_4FN_2 (Z = OMe). The structures of these compounds were established by nuclear magnetic resonance spectroscopy. Interpretation of the orientation of nucleophilic attack on tetrafluoropyrimidine and on pentafluoropyridine is provided.

As disclosed recently,[2,3] a mixture of tetrafluoro- and 5-chloro-2,4,6-trifluoro-pyrimidine can be obtained by heating an intimate mixture of tetrachloropyrimidine and an excess of anhydrous potassium fluoride; our best yield of the former product is 85%, from a fluorination carried out at 480° for 42 hr. This method is superior to that used previously [4] to obtain tetrafluoropyrimidine

$$5H\text{–}C_4Cl_3N_2 \xrightarrow{AgF} 5H\text{–}C_4F_3N_2 \xrightarrow{AgF_2} C_4F_4N_2$$

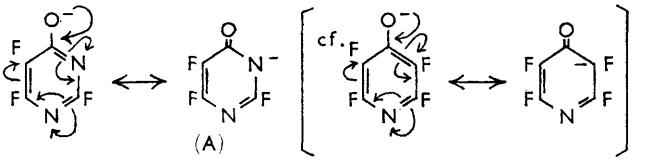
and is analogous to the only viable route to pentafluoropyridine.[5]

2,4,6-Trifluoropyrimidine can be prepared by heating 2,4,6-trichloropyrimidine with anhydrous potassium fluoride in the presence of antimony trioxide;[6] the yield is increased from 48 to 71% by raising the reaction temperature from 260 to 310°.

Tetrafluoropyrimidine is a lachrymatory liquid, b. p. 82—83°/750 mm. (cf. pentafluoropyridine,[7] b. p. 83·3°; hexafluorobenzene,[8] 80·5°), which [4] readily suffers nucleophilic displacement of fluorine from position 4 under mild conditions. Use of more drastic conditions causes displacement of fluorine from position 6 (not from position 2 as deduced previously [4]), and subsequently from position 2; the fluorine substituent in the 5-position resists displacement, and in this respect resembles the 3- and 5-fluorines in pentafluoropyridine.[9] The Scheme shows the reactions studied. The structures of all the compounds prepared were established by spectroscopic methods, principally nuclear magnetic resonance (see Experimental section); discussion of mass spectral data will form the basis of a separate Paper.[10]

2,5,6-Trifluoropyrimidin-4-ol, like 2,3,5,6-tetrafluoropyridin-4-ol,[9] appears to exist predominantly or even exclusively in the hydroxy-form. It is a stronger acid than the hydroxypyridine by *ca.* 1 pK_a unit; this may be attributed to the contribution of form (A) to the structure of the oxy-anion.

When an approximately equimolar mixture of tetrafluoropyrimidine and pentafluoropyridine is shaken with an excess of methanol and sodium carbonate at room



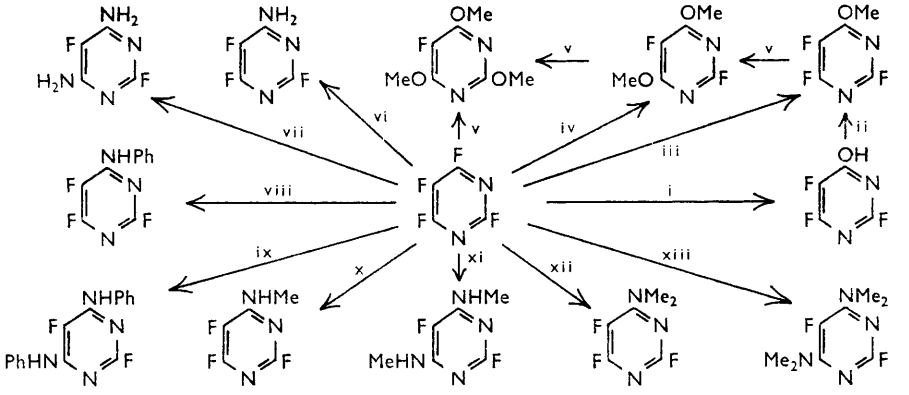
(A)

temperature the pyridine is recovered unchanged but the pyrimidine is converted into 2,4,5-trifluoro-6-methoxypyrimidine; similarly, when pentafluoropyridine and hexafluorobenzene are allowed to compete for a limited amount of methanolic sodium methoxide under reflux conditions only the pyridine is attacked, to yield 2,3,5,6-tetrafluoro-4-methoxypyridine. These results confirm the conclusion reached in more qualitative fashion from preparative experience that the order of susceptibility towards nucleophilic attack is tetrafluoropyrimidine > pentafluoropyridine > hexafluorobenzene.

The differences in the reactivities of tetrafluoropyrimidine, pentafluoropyridine, and hexafluorobenzene towards nucleophilic reagents, and the orientation of attack in the cases of the two heterocycles, seem best interpreted through consideration of the stabilities of the transition states involved, which can be discussed in terms of Wheland-type intermediates; this approach has been used to account for the orientation and reactivity relationships established for nucleophilic substitution in polyhalogeno-benzenes.[11] The intermediates [(I), (II), and (III)] arising from attack at the 2-, 4- (or 6-), and 5-positions in tetrafluoropyrimidine are resonance hybrids, each with three contributing forms [(a), (b), and (c)]. Forms in which the negative charge resides on the carbon of a CF group are destabilised by the I_π-repulsive effect of fluorine and presumably are

[1] Part IX, R. E. Banks and E. D. Burling, *J. Chem. Soc.*, 1965, 6077.
[2] Belg.P. 660,907/1965.
[3] R. D. Chambers, J. A. H. MacBride, and W. K. R. Musgrave, *Chem. and Ind.*, 1966, 1721.
[4] H. Schroeder, E. Kober, H. Ullrich, R. Rätz, H. Agahyan, and C. Grundman, *J. Org. Chem.*, 1962, **27**, 2580.
[5] R. E. Banks, R. N. Haszeldine, J. V. Latham, and I. M. Young, *J. Chem. Soc.*, 1965, 595.
[6] V. G. Nemets, B. A. Ivin, and V. I. Slesarev, *J. Gen. Chem.* (*U.S.S.R.*), 1965, **35**, 1433.
[7] R. E. Banks, A. E. Ginsberg, and R. N. Haszeldine, *J. Chem. Soc.*, 1961, 1740.
[8] Y. Désirant, *Bull. Soc. chim. belges*, 1958, **67**, 676.
[9] R. E. Banks, J. E. Burgess, W. M. Cheng, and R. N. Haszeldine, *J. Chem. Soc.*, 1965, 575.
[10] R. E. Banks, D. S. Field, and W. T. Flowers, in preparation.
[11] J. Burdon, *Tetrahedron*, 1965, **21**, 3373; J. Burdon, P. L. Coe, C. R. Marsh, and J. C. Tatlow, *ibid.*, 1966, **22**, 1183; J. Burdon, D. R. King, and J. C. Tatlow, *ibid.*, p. 2541.

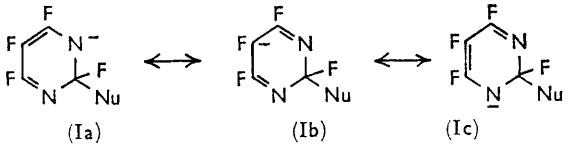
less stable than those in which a ring nitrogen carries the charge. On this basis, attack by a nucleophile at the 5-position is least preferred. The greater reactivity of the 4-position compared with that of the 2-position reflects the higher stability of hybrid (II) compared with (I), possibly owing [11,12] to the greater contributions made by the *para*-quinonoid forms [(Ib) and (IIb); the latter is the more stable since the negative charge resides on nitrogen] to the structures of intermediates (I) and (II) than those of the *ortho*-quinonoid forms [(Ia and c) and (IIa and c)].



Nucleophilic displacement of fluorine from tetrafluoropyrimidine

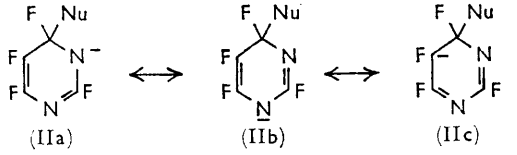
Reagents: i, H_2O in tetrahydrofuran, room temp.; ii, CH_2N_2 in ether, 20°; iii, MeOH–Na_2CO_3, room temp.; iv, MeOH–MeONa, 0°; v MeOH–MeONa, heat under reflux; vi, NH_3 aq., room temp.; vii, NH_3 aq., 60°; viii, $PhNH_2$–Na_2CO_3 in tetrahydrofuran, —15°; ix, $PhNH_2$ in tetrahydrofuran, heat under reflux; x, $MeNH_2$ aq., 0—20°; xi, $MeNH_2$ aq. in dimethylformamide, 60°; xii, Me_2NH aq., 0—20°; xiii, Me_2NH aq. in dimethylformamide, 60°.

2 – Substitution



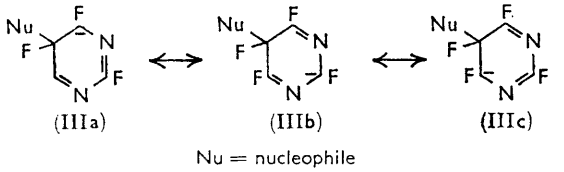
(Ia) (Ib) (Ic)

4 – Substitution



(IIa) (IIb) (IIc)

5 – Substitution



(IIIa) (IIIb) (IIIc)

Nu = nucleophile

The observed order of ease of displacement of fluorine from pentafluoropyridine by nucleophiles (4- > 2- or 6- ≫ 3- or 5-) can be interpreted in the same way; also the argument can be extended logically to account for preferential nucleophilic attack in the 6-position of the 4-substituted trifluoropyrimidines obtained in this work.

Accommodation of the negative charge of an attacking nucleophile by the ring nitrogen of pentafluoropyridine, and even more efficiently by the 1- and 3-nitrogens of tetrafluoropyrimidine, with consequent lowering of the activation energies necessary for fluorine displacement, thus accounts for the reactivity order tetrafluoropyrimidine > pentafluoropyridine > hexafluorobenzene.

As in the cases of tetrafluoropyrimidine and pentafluoropyridine, nucleophilic attack on tetrafluoropyridazine occurs with preferential displacement of the fluorine *para* to a ring nitrogen (*i.e.*, from position 4); [13] also, the ease of such attack is greater than in the cases of pentafluoropyridine or tetrafluoropyrazine [3] in which all four fluorines lie *ortho* to a ring nitrogen. These facts can also be interpreted as described, by consideration of the relative stabilities of Wheland-type intermediates used as models for transition states.

EXPERIMENTAL

Infrared and ultraviolet spectra were measured with a Perkin-Elmer spectrophotometer model 21 (sodium chloride optics) and a Unicam SP 700 spectrophotometer, respectively. The n.m.r. results were obtained with a Perkin-Elmer R10 spectrometer, and an A.E.I. MS/2H instrument was employed for mass spectrometry.

Tetrachloropyrimidine (Found: C, 22·3; Cl, 65·3; N, 12·7. Calc. for $C_4Cl_4N_2$: C, 22·0; Cl, 65·1; N, 12·8%), m. p. 66—67° (lit.,[14] 66—68°), was prepared on a 0·5 kg. scale by chlorination of barbituric acid with a mixture of phosphorus pentachloride and phosphoryl chloride.[14]

Preparation of Tetrafluoropyrimidine.—An intimate, finely-ground mixture of tetrachloropyrimidine (108·0 g., 0·495 mole) and anhydrous potassium fluoride (400·0 g., 6·90 moles) was contained in a seamless mild steel tube

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

[13] R. D. Chambers, J. A. H. MacBride, and W. K. R. Musgrave, *Chem. and Ind.*, 1966, 904.

[14] S. J. Childress and R. C. McKee, *J. Amer. Chem. Soc.*, 1950, **72**, 4271.

[18·0 × 2·5 (outside diameter) × 0·25 in.] closed with two 0·5 in. thick welded mild steel plates, one of which was fitted with a mild steel neck [4·0 × 1·0 (outside diameter) × 0·15 in.] sealed with an Ermeto coupling attached to a *ca.* 70 atm. bursting-disc assembly. The apparatus was heated at 410° for 22 hr. in an electric furnace coupled to an automatic control device. The tube was allowed to cool to room temperature, the bursting-disc assembly was replaced by a rubber tube leading to a vacuum system, and the volatile product was pumped into two cold (−196°) traps in series while the mild steel tube was heated to *ca.* 150° to assist transference. The product (64·6 g.) was distilled to give tetrafluoropyrimidine (43·0 g., 0·283 mole, 57%), b. p. 82—83°/750 mm., $\lambda_{max.}$ (hexane) 240 mμ (ε 2660) $\lambda_{max.}$ (vapour) 6·03w, 6·19s, 6·37m, 6·68s, 6·95s (fluorinated pyrimidine nucleus), 9·16m, 9·22m (doublet), 9·46m, 9·51m (doublet), 9·54msh (C–F stretch), 12·45mbr, 12·86m, 12·96m–s, and 13·08m μ, which did not give a good analysis (Found: C, 32·2; H, 0·3; N, 19·3. Calc. for $C_4F_4N_2$: C, 31·6; H, 0·0; N, 18·4%) although no impurity could be detected by g.l.c. (which would have revealed the presence of any 2,4,6-trifluoropyrimidine) or ^{19}F n.m.r. analysis, and 5-chloro-2,4,6-trifluoropyrimidine (20·6 g., 0·122 mole, 25%) (Found: C, 28·8; N, 16·6. Calc. for $C_4ClF_3N_2$: C, 28·5; N, 16·6%), b. p. 114·5°/750 mm., $\lambda_{max.}$ 245 mμ (ε 2780) in hexane, $\lambda_{max.}$ (liquid film) 6·10, 6·26, 6·41 (triplet), 6·90, 7·04, 7·08 (triplet) (fluorinated pyrimidine nucleus), 9·39, 9·63 (C–F stretch), 12·96 (ring vibration?), and 14·32 (C–Cl stretch) μ.

In two similar experiments (one carried out by Mr. R. S. Jacques), tetrachloropyrimidine (100 or 120 g.) and anhydrous potassium fluoride (400 or 312 g.), at 475° for 19 hr. or 480° for 42 hr., gave tetrafluoropyrimdine (51 g., 73%; or 71 g., 85%), b. p. 82—83°/754 mm., which gave only one peak on g.l.c.

The mild steel apparatus used in these experiments, and also for the preparation of pentafluoropyridine from pentachloropyridine and anhydrous potassium fluoride, has proved the most satisfactory of several types, including commercial autoclaves. The tube is corroded by the reaction mixture and should be discarded after about 4 experiments; the neck, which, during the heating process, protrudes from the furnace, can be salvaged and welded on to a new body. Use of a bursting disc is essential; on one occasion a tube sealed with an Ermeto coupling and a steel plug swelled and split longitudinally when the furnace controller failed and the temperature rose above 600°.

The mass spectrum of tetrafluoropyrimidine showed peaks with the *m/e* values (% relative intensities and assignments in parentheses): 152 (100; $C_4F_4N_2^+$), 133 (20; $C_4F_3N_2^+$), 121 (10; $C_3F_3N_2^+$), 107 (35; $C_3F_3N^+$), 88 (15; $C_3F_2N^+$), 83 (10; $C_3FN_2^+$), 81 (10; C_4FN^+), 76 (10; $C_2F_2N^+$), 69 (25; C_3FN^+), 62 (40; $C_2F_2^+$), 57 (10; C_2FN^+), 43 (10; C_2F^+), and 31 (70; CF^+). That of 5-chloro-2,4,6-trifluoropyrimidine showed the following major peaks: 170 (33; $C_4{}^{37}ClF_3N_2^+$), 168 (100; $C_4{}^{35}ClF_3N_2^+$), 149 (5; $C_4{}^{35}ClF_2N_2^+$), 133 (15; $C_4F_3N_2^+$), 125 (5; $C_3{}^{37}ClF_2N^+$), 123 (15; $C_3{}^{35}ClF_2N^+$), 88 (8; $C_3F_2N^+$), 80 ($C_2{}^{37}ClF^+$), 78 (25; $C_2{}^{35}ClF^+$), 69 (10; C_3FN^+), and 31 (25; CF^+).

Preparation of 2,4,6-Trifluoropyrimidine.—An intimate mixture of 2,4,6-trichloropyrimidine (44·0 g., 0·240 mole; from barbituric acid and phosphoryl chloride [15]), anhydrous potassium fluoride (200·0 g., 3·45 moles), and anhydrous antimony trioxide (5·0 g., 0·017 mole) was heated at 310° for 2 hr. in the mild steel tube. The volatile product was distilled to give 2,4,6-trifluoropyrimidine (23·0 g., 0·171 mole, 71%) (Found: C, 35·9; H, 1·0; N, 21·0. Calc. for $C_4HF_3N_2$: C, 35·8; H, 0·7; N, 20·9%), b. p. 98·5—99·5° (lit.,[4,6] 98 and 98—99°), $\lambda_{max.}$ (vapour) 6·26 (with broad shoulder 6·1—6·22), 7·06, 7·10 (doublet, fluorinated pyrimidine nucleus), 8·60, 8·63, 8·67 (triplet), 9·23, 9·29 (doublet), 9·83br (C–F stretch), 11·85, 11·95, and 12·06 (triplet) μ, $\lambda_{max.}$ (hexane) 230 mμ (ε 2290).

The mass spectrum of 2,4,6-trifluoropyrimidine showed peaks with *m/e* values: 134 (100; $C_4HF_3N_2^+$), 115 (15; $C_4HF_2N_2^+$), 107 (10; $C_3F_3N^+$), 89 (20; $C_3HF_2N^+$), 88 (5; $C_3F_2N^+$), 70 (15; C_3HFN^+), 69 (8; C_3FN^+), 62 (8; $C_2F_2^+$), 44 (35; C_2HF^+), and 31 (35; CF^+).

Reactions of Tetrafluoropyrimidine.—(a) *With water.* A mixture of tetrafluoropyrimidine (8·35 g., 54·9 mmoles), water (2 ml.), and tetrahydrofuran (20 ml.) was stirred at room temperature for 72 hr. Evaporation of the product under reduced pressure and sublimation of the residue gave 2,5,6-trifluoropyrimidin-4-ol (4·82 g., 32·1 mmoles, 58%), as needles, m. p. 125—126° [light petroleum (b. p. 100—120°)] (lit.,[4] 121°) (Found: C, 32·2; H, 0·9; F, 38·4; N, 18·6. Calc. for $C_4HF_3N_2O$: C, 32·0; H, 0·7; F, 38·0; N, 18·7%), $\lambda_{max.}$ (hexane) 246 mμ (ε 5250), $\lambda_{max.}$ ($CHCl_3$) 2·71, 2·76 (sharp; "free" O–H stretch), 2·8—4·5 (broad "bonded" OH absorption), 6·14, 6·64 (fluorinated pyrimidine nucleus), 9·04, and 9·57 (C–F stretch) μ. The base peak in the mass spectrum of the hydroxypyrimidine corresponded to $C_4F_3N_2O^+$; the parent ion had a relative intensity of 10%.

Trifluoropyrimidin-4-ol turns damp blue litmus paper red and liberates carbon dioxide briskly from aqueous sodium hydrogen carbonate; the dissociation constant of the hydroxy-compound in water at 21° was $1·2 \times 10^{-2}$ (by titration with standard alkali to the "half-neutralisation" point).

(b) *With ammonium hydroxide.* Aqueous ammonia (*d* 0·880; 20 ml.) was added slowly (30 min.) to stirred tetrafluoropyrimidine (7·98 g., 52·5 mmoles). An exothermic reaction occurred and a precipitate appeared. The product was treated with water (20 ml.) and the resulting mixture was extracted with ether. The ethereal extract was dried ($MgSO_4$) and evaporated, and the residue was subjected to vacuum sublimation, to give 4-amino-2,5,6-trifluoropyrimidine (4·23 g., 28·4 mmoles, 54%), as needles, m. p. 156—157° (from chloroform) (lit.,[4] 158°) (Found: C, 32·4; H, 1·6; N, 28·3. Calc. for $C_4H_2F_3N_3$: C, 32·2; H, 1·3; N, 28·2%), $\lambda_{max.}$ (ethanol) 222 and 260 mμ (ε 9100 and 7650), $\lambda_{min.}$ 240 mμ (ε 3520), $\lambda_{max.}$ (mull) 2·95, 3·02, 3·13, 5·98br, 6·27, 6·56, 6·88, 7·00, 7·14, 7·62, 8·08, 8·88, 9·05, 9·88, 12·58, 13·05, and 13·92 μ.

A solution of tetrafluoropyrimidine (4·36 g., 28·7 mmoles) in dioxan (5 ml.) was added slowly (30 min.) to a stirred mixture of aqueous ammonia (*d* 0·880; 10 ml.) and dioxan (10 ml.) at 60°; a precipitate formed immediately. After 3·5 hr. at 60°, the reaction mixture was treated with water (20 ml.), and the solid product was filtered off and sublimed *in vacuo* to give 4,6-*diamino*-2,5-*difluoropyrimidine* (3·22 g., 22·1 mmoles, 77%) (Found: C, 33·1; H, 2·3; N, 38·0. $C_4H_4F_2N_4$ requires C, 32·9; H, 2·7; N, 38·3%), m. p. 232—233° (from chloroform), $\lambda_{max.}$ (mull) 2·98, 3·04, 3·19, 6·02, 6·10br (doublet), 6·24, 6·59, 6·74, 7·22, 7·46, 8·17, 8·44, 9·47, 9·92, 12·87, and 13·18 μ.

(c) *With methanol.* Tetrafluoropyrimidine (4·8 g., 31·6 mmoles) was added to a stirred mixture of methanol

[15] J. Baddiley and A. Topham, *J. Chem. Soc.*, 1944, 678.

(10 ml.) and sodium carbonate (1·7 g.) at room temperature; an exothermic reaction occurred and carbon dioxide was evolved. After 30 min., the volatile product was removed *in vacuo* and distilled to yield 2,4,5-*trifluoro*-6-*methoxypyrimidine* (2·7 g., 16·5 mmoles, 52%) (Found: C, 36·3; H, 1·9; N, 16·9. $C_5H_3F_3N_2O$ requires C, 36·6; H, 1·8; N, 17·1%), b. p. 55—56°/20 mm., $\lambda_{max.}$ (hexane) 245 mμ (ε 5900), $\lambda_{max.}$ (liquid film) 3·36, 5·77, 5·86, 6·10, 6·12, 6·26, 6·62, 6·88, 7·11, 7·81, 8·06, 8·40, 9·00, 9·52, 10·58, 12·36, 12·90, and 13·79 μ.

2,4,5-Trifluoro-6-methoxypyrimidine was also obtained (43%) by treatment of 2,5,6-trifluoropyrimidin-4-ol with diazomethane in ether at 20°.

(d) *With sodium methoxide.* Tetrafluoropyrimidine (4·34 g., 28·6 mmoles) in tetrahydrofuran (5 ml.) was added during 5 min. to a cold (0°) mixture prepared from sodium (0·68 g., 29·6 mg.-atom), methanol (5 ml.), and tetrahydrofuran (10 ml.). The reaction mixture was stirred at 0° for 2 hr. then evaporated under reduced pressure. The residue was sublimed to give 2,5-*difluoro*-4,6-*dimethoxypyrimidine* (1·71 g., 9·7 mmoles, 34%), m. p. 106—108° (from aqueous ethanol), $\lambda_{max.}$ (hexane) 215 and 250 mμ (ε 2650 and 10,350) (Found: C, 40·7; H, 3·4; N, 15·8. $C_6H_6F_2N_2O_2$ requires C, 40·9; H, 3·4; N, 15·9%). The volatile product contained (g.l.c.) tetrafluoropyrimidine and 2,4,5-trifluoro-6-methoxypyrimidine.

2,5-Difluoro-4,6-dimethoxypyrimidine (0·85 g., 4·8 mmoles, 87%) was also isolated by standard procedures from a product obtained by heating under reflux (7 hr.) a mixture of 2,4,5-trifluoro-6-methoxypyrimidine (0·98 g., 5·5 mmoles), sodium methoxide (0·32 g., 5·9 mmoles), and methanol (10 ml.).

A mixture of tetrafluoropyrimidine (1·70 g., 11·2 mmoles), sodium methoxide (2·7 g., 5·0 mmoles), and methanol (15 ml.) was heated under reflux for 6 hr. The product was evaporated under reduced pressure, to leave a residue which was sublimed *in vacuo* to give 5-*fluoro*-2,4,6-*trimethoxypyrimidine* (1·13 g., 5·7 mmoles, 51%) (Found: C, 44·7; H, 5·0; F, 9·8; N, 15·0. $C_7H_9FN_2O_3$ requires C, 44·8; H, 4·8; F, 10·1; N, 14·9%), m. p. 98—99°, $\lambda_{max.}$ (hexane) 219 and 258 mμ (ε 5300 and 9700). An identical sample of this trimethoxy-compound was prepared (70%) by heating under reflux for 5 hr. a 1 : 2 molar mixture of 2,5-difluoro-4,6-dimethoxypyrimidine and sodium methoxide in methanol.

(e) *With aniline.* Aniline (0·88 g., 9·5 mmoles) in tetrahydrofuran (5 ml.) was added during 15 min. to a cold (−15°) stirred mixture of tetrafluoropyrimidine (1·35 g., 8·9 mmoles), sodium carbonate (2 g.), and tetrahydrofuran (5 ml.). After 3 hr., the volatile product was removed *in vacuo* and the residue was sublimed *in vacuo* to give 4-*anilino*-2,5,6-*trifluoropyrimidine* (1·32 g., 5·9 mmoles, 66%) (Found: C, 53·2; H, 2·6; N, 19·0. $C_{10}H_6F_3N_3$ requires C, 53·4; H, 2·7; N, 18·7%), m. p. 96—97° [from petroleum (b. p. 100—120°)], $\lambda_{max.}$ (ethanol) 286 mμ (ε 18,400), $\lambda_{max.}$ (mull) 2·92, 3·26, 6·08, 6·13, 6·24, 6·31, 6·51, 6·66, 6·71, 6·76, 6·91, 7·15, 7·75, 8·14, 8·27, 9·00, 9·13, 9·34, 9·52, 9·61, 11·03, 12·41, 13·27, 13·35, and 14·49 μ.

A mixture of aniline (7·0 g., 75·3 mmoles), tetrafluoropyrimidine (2·3 g., 15·1 mmoles), and tetrahydrofuran (5 ml.) was heated under reflux for 3 hr. The product was evaporated under reduced pressure and the residue was sublimed to remove anilinium fluoride; the residue gave 4,6-*dianilino*-2,5-*difluoropyrimidine* (0·65 g., 2·2 mmoles, 15%) (Found: C, 64·3; H, 4·0; N, 18·8. $C_{16}H_{12}F_2N_4$ requires C, 64·4; H, 4·0; N, 18·8%) as fine white needles, m. p. 192—193° [from benzene (charcoal)], $\lambda_{max.}$ (mull) 2·91, 3·00, 3·07, 3·16, 3·26, 5·09, 5·15, 6·09, 6·24, 6·29, 6·55, 6·67, 6·88, 7·27, 7·43, 7·60, 8·18, 8·54, 9·05, 9·20, 9·32, 9·47, 10·18, 10·44, 11·18, 11·79, 13·25, 14·32, and 14·56 μ.

(f) *With methylamine.* A 30% w/v solution of methylamine in water (5 ml.) was added during 10 min. to stirred, cold (0°) tetrafluoropyrimidine (3·32 g.). The mixture was warmed to room temperature and, after 30 min., treated with water (10 ml.). The precipitate of 2,5,6-*trifluoro*-4-*methylaminopyrimidine* (2·97 g., 83%) (Found: C, 37·1; H, 2·3; N, 26·0. $C_5H_4F_3N_3$ requires C, 36·8; H, 2·5; N, 25·8%) was isolated and dried, m. p. 122—123°, $\lambda_{max.}$ (ethanol) 232 and 262 mμ (ε 10,500 and 8040), $\lambda_{min.}$ 247 mμ (ε 6510), $\lambda_{max.}$ (mull) 2·98, 3·06sh, 3·23, 3·35, 3·48, 3·58, 3·82, 6·06, 6·20, 6·50, 6·85, 7·01, 7·19, 7·60, 8·23, 8·74, 9·76, 10·22, 12·42, 13·14, 13·78, 13·86, and 14·98 μ.

A 30% w/v solution (16 ml.) of methylamine (0·16 mole) in water was added during 15 min. to a stirred solution of tetrafluoropyrimidine (4·88 g., 32·1 mmoles) in dimethylformamide (10 ml.); a precipitate appeared. The mixture was stirred and kept at 60° for 3 hr. A brown oil formed which solidified when the mixture was cooled to 20°. After treatment with water (10 ml.), the product was filtered to give 2,5-*difluoro*-4,6-*bis*(*methylamino*)*pyrimidine* (2·77 g., 16·0 mmoles, 50%) (Found: C, 41·4; H, 4·9; N, 32·1. $C_6H_8F_2N_4$ requires C, 41·4; H, 4·6; N, 32·2%), m. p. 180—182° (from chloroform), $\lambda_{max.}$ (ethanol) 214 and 271 mμ (ε 31,500 and 19,400), $\lambda_{min.}$ 240 mμ (ε 1505), $\lambda_{max.}$ (mull) 2·93, 2·96sh, 3·29, 3·36, 3·41, 6·11, 6·55, 7·14, 7·27, 7·45, 8·46, 8·81, 9·22, 9·86, 12·53, and 13·14 μ.

(g) *With dimethylamine.* Dimethylamine (67·0 mmoles) in water (10 ml.; 30% w/v solution) was added during 15 min. to stirred, cold (0°) tetrafluoropyrimidine (4·54 g., 29·9 mmoles); a precipitate formed immediately. The mixture was warmed to 20°, stirred for 1 hr., and filtered, to give 4-*dimethylamino*-2,5,6-*trifluoropyrimidine* (2·76 g., 15·6 mmoles, 52%) (Found: C, 40·7; H, 3·5; N, 23·7. $C_6H_6F_3N_3$ requires C, 40·7; H, 3·4; N, 23·7%), m. p. 45—47° [from petroleum (b. p. 100—120°)], $\lambda_{max.}$ (ethanol) 240 and 272 mμ (ε 10,400 and 9850), $\lambda_{min.}$ 255 mμ (ε 7000), $\lambda_{max.}$ (mull) 3·36, 3·42, 3·51, 6·12, 6·27, 6·53, 6·84, 7·01, 7·18, 7·72, 8·09, 9·35, 9·64, 12·68, 13·12, and 14·14 μ.

Dimethylamine (0·12 mole) in water (18 ml.; 30% w/v solution) and tetrafluoropyrimidine (3·81 g., 25·1 mmoles) in dimethylformamide (10 ml.), were mixed at 0° and heated at 60° for 3 hr. The product was treated with water (10 ml.) and filtered to give 4,6-bis(dimethylamino)-2,5-difluoropyrimidine (3·00 g., 14·9 mmoles, 59%) (Found: C, 47·6; H, 6·5; N, 27·8. Calc. for $C_8H_{12}F_2N_4$: C, 47·5; H, 6·0; N, 27·7%), m. p. 93—94° [from petroleum (b. p. 100—120°)] (lit.,[4] 96—97°), $\lambda_{max.}$ (ethanol) 227 and 287 mμ (ε 26,400 and 21,600), $\lambda_{min.}$ 259 mμ (ε 2000), $\lambda_{max.}$ (mull) 3·38, 3·45sh, 3·55sh, 5·71, 6·15, 6·22, 6·5—7·5, 8·08, 9·42, 9·67, 12·81, and 13·28 μ.

Competition Reactions.—(a) *Tetrafluoropyrimidine* vs. *pentafluoropyridine.* A mixture of tetrafluoropyrimidine (0·65 g., 4·3 mmoles) and pentafluoropyridine (0·83 g., 4·9 mmoles) was shaken with methanol (4 ml.) containing sodium carbonate (0·24 g., 2·3 mmoles) at 20° for 3 hr. The volatile product, removed from the reaction vessel *in vacuo*, contained (g.l.c.) methanol, pentafluoropyridine (4·7 mmoles, 94% recovery), and 2,4,5-trifluoro-6-methoxypyrimidine (3·5 mmoles, 81%) but no tetrafluoropyrimidine or 2,3,5,6-tetrafluoro-4-methoxypyridine.

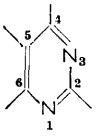
(b) *Pentafluoropyridine* vs. *hexafluorobenzene* (carried out by W. M. Cheng). A mixture of pentafluoropyridine (4·30 g., 25·4 mmoles) and hexafluorobenzene (4·80 g., 25·8 mmoles) was heated under reflux for 5 hr. with 0·6N-sodium methoxide in methanol (28·0 ml., 16·8 mmoles). The product was treated with water (150 ml.), and the resulting mixture was extracted with ether (5 × 20 ml.). The extract was dried ($MgSO_4$) and distilled to yield a mixture (7·70 g.) containing (g.l.c. and infrared spectroscopy) pentafluoropyridine (12% by wt.), hexafluorobenzene (48%), and 2,3,5,6-tetrafluoro-4-methoxypyridine (40%). No pentafluoromethoxybenzene was detected in the mixture, which was analysed under conditions which gave a difference of almost 6 min. in the retention times of this compound and tetrafluoromethoxypyridine.

Nuclear Magnetic Resonance Spectra.—Spectra were measured at 60·00 (^1H) or 56·46 (^{19}F) Mc./sec., 14,092 gauss and 35°. Trifluoroacetic acid was used as external reference for ^{19}F nuclei, and no attempt was made to correct for bulk diamagnetic susceptibility differences.

^{19}F Chemical shift values (positive values are to high field of $CF_3{\cdot}CO_2H$) and some spin–spin coupling constants for the polyfluoropyrimidines examined are given in the Table. The spectrum of tetrafluoropyrimidine shows three absorption band systems of relative intensities 1 : 2 : 1 at −30·6, −3·8, and +99·0 p.p.m. The system at −3·8 p.p.m. is assigned to the 4- and 6-fluorines and shows the broadness of components expected from the proximity of a quadrupolar ^{14}N nucleus at positions 1 and 3; the low-field absorption at −30·6 p.p.m. is assigned to the 2-fluorine since the proximity of two nitrogens is expected to reduce the shielding (cf. pentafluoropyridine [16]) and the expected broadness of components is observed. Owing to the broadening of components, which also occurs with the absorptions assigned to the 2-, 4-, and 6-fluorines of the substituted fluoropyrimidines examined, the coupling constant of smallest magnitude, $J_{2,4}$, was not measurable for tetrafluoropyrimidine and most of its derivatives.

For the substituted fluoropyrimidines, the chemical shifts of the 2-, 6- (or 4-), and 5-fluorines lie within the ranges −35·2 to −24·8, −24·0 to +14·6, and +69·9 to 111·2 p.p.m., respectively; the F–F coupling constants show little variation: $|J_{2,5}|$ = 24·8—28·2 c./sec., and $|J_{4,5}|$ and $|J_{5,6}|$ = 16·4—17·9 c./sec. The fluorine chemical shifts are dependent upon the nature and position of the substituent(s), and will be discussed in a later Paper [18] in which the spectral data listed in the Table and data obtained for other fluoro-pyrimidines will be presented in detail.

N.m.r. data for fluoropyrimidines



	Ring ^{19}F chemical shifts (p.p.m.)				Moduli of spin–spin coupling constants (c./sec.) Ring F–F			
	2	4	5	6	$\|J_{2,5}\|$	$\|J_{5,6}\|$	$\|J_{2,6}\|$	Others
$C_4F_4N_2$	−30·6	−3·8	99·0	−3·8	26·0	17·9	?	
5-H·$C_4F_3N_2$	−35·2	−24·0	—	−24·0			?	$\|J_{2F,5H}\| = 1·1$; $\|J_{4F,5H}\| = 1·8$
2-H·$C_4F_3N_2$ [a]		2·0	93·4	2·0		?		
4-H·$C_4F_3N_2$ [a]	−28·0		83·0	−1·5	?	?	?	
4-HO·$C_4F_3N_2$ [b]	−25·4		103·0	7·8	24·8	16·4	4·6	
4-MeO·$C_4F_3N_2$ [c]	−29·6		101·8	5·6	25·9	16·9	?	$\|J_{5F,CH}\| \leqslant 0·3$
4-H_2N·$C_4F_3N_2$ [b]	−27·6		103·2	11·2	25·7	17·5	?	
4-MeNH·$C_4F_3N_2$ [b]	−28·4		105·6	14·6	26·5	17·5	?	$\|J_{5F,NH}\| = 1·7$; $\|J_{NH,CH}\| = 4·8$
4-Me_2N·$C_4F_3N_2$ [c]	−30·0		98·4	9·8	26·1	17·5	?	$\|J_{5F,CH}\| = 2·2$
4-PhNH·$C_4F_3N_2$ [b]	−29·8		101·2	10·0	26·6	16·9	2·8	$\|J_{5F,NH}\| = 2·8$
5-Cl·$C_4F_3N_2$	−33·8	−21·0	—	−21·0			?	
4,6-H_2·$C_4F_2N_2$ [a]	−24·8		69·9		?			
4,6-$(MeO)_2$·$C_4F_2N_2$ [c]	−29·8		102·6		26·7			$\|J_{5F,CH}\| \leqslant 0·3$
4,6-$(H_2N)_2$·$C_4F_2N_2$ [d]	−24·8		107·2		27·1			
4,6-$(MeNH)_2$·$C_4F_2N_2$ [b]	−26·6		110·2		27·4			$\|J_{5F,NH}\| = 1·7$
4,6-$(Me_2N)_2$·$C_4F_2N_2$ [c]	−28·0		92·2		27·0			$\|J_{5F,CH}\| = 3·0$
4,6-$(PhNH)_2$·$C_4F_2N_2$ [b]	−28·6		100·8		28·2			
2,4,6-$(MeO)_3$·C_4FN_2 [d]			111·2					$\|J_{5F,CH}\| \leqslant 0·3$

[a] Obtained by treatment of tetrafluoropyrimidine with lithium aluminium hydride.[17] [b] In acetone. [c] In chloroform. [d] In dimethylformamide.

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[16] J. Lee and K. G. Orrell, *J. Chem. Soc.*, 1965, 582.
[17] R. E. Banks, D. S. Field, and R. N. Haszeldine, work in progress.
[18] M. G. Barlow and I. M. Young, in preparation.