Heterocyclic Polyfluoro-compounds. Part XX.[1] Nucleophilic Substitution in Perfluoro-(4-phenylpyridine)

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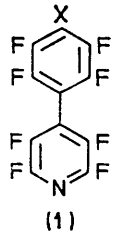
Reaction of perfluoro-(4-phenylpyridine) (1) with sodium methoxide in methanol gives 3,5,6-trifluoro-2-methoxy-4-pentafluorophenylpyridine and a small amount of 2,3,5,6-tetrafluoro-4-(4-methoxytetrafluorophenyl)pyridine, 3,5,6-trifluoro-2-methoxy-4-(4-methoxytetrafluorophenyl)pyridine, and 3,5-difluoro-2,6-dimethoxy-4-(4-methoxytetrafluorophenyl)pyridine; (ii) with aqueous ammonia gives 2-amino-3,5,6-trifluoro-4-pentafluorophenylpyridine, 2-amino-3,5,6-trifluoro-4-(4-aminotetrafluorophenyl)pyridine, and 2,6-diamino-3,5-difluoro-4-(4-aminotetrafluorophenyl)pyridine; and (iii) with potassium hydroxide in t-butyl alcohol gives 3,5,6-trifluoro-2-hydroxy-4-pentafluorophenylpyridine and 3,5,6-trifluoro-2-hydroxy-4-(4-hydroxytetrafluorophenyl)pyridine. ^{19}F N.m.r. spectral data for these products are presented.

PERFLUORO-(4-PHENYLPYRIDINE) is reported [2] to afford only products (1a, b) derived from substitution of fluorine in the pentafluorophenyl ring when attacked by the anions $[(\pi\text{-}C_5H_5)Fe(CO)_2]^-$ and $[Re(CO)_5]^-$, but yields were low (17 and 25%, respectively) and much starting material was not accounted for.



(1)

a; X = $Fe(CO)_2(\pi\text{-}C_5H_5)$
b; X = $Re(CO)_5$
c; X = OMe

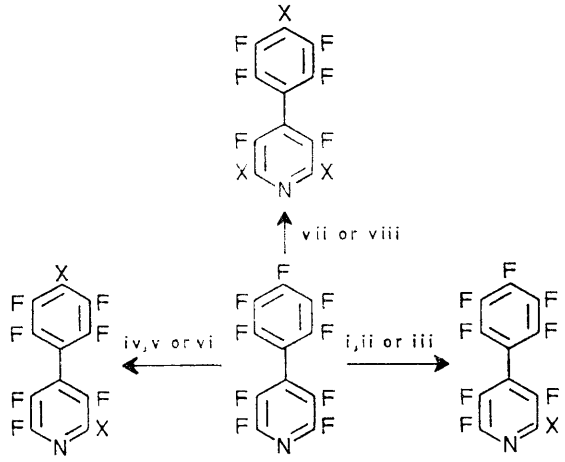
We find that initial anionic attack by sodium methoxide in methanol, concentrated aqueous ammonia, or potassium hydroxide in t-butyl alcohol occurs predominantly or exclusively at the 2-position in the tetrafluoropyridyl ring. Further attack on the monosubstituted compounds thus formed occurs first at the 4-position in the pentafluorophenyl ring and then, in the cases of the first two reagents, at the 6-position in the pyridyl ring (see Scheme); an attempt to force a third hydroxy-function into perfluoro-(4-phenylpyridine) failed, in keeping with the deactivating influence of an $-O^-$ substituent on fluoroaromatic systems.[3] Both the crude and the pure product from each reaction shown in the Scheme were analysed by ^{19}F n.m.r. spectroscopy, and in only the case of mono-substitution by methoxide was any evidence found for the formation of an isomer other than the final pure product. Thus, the crude product isolated following treatment of perfluoro-(4-phenylpyridine) with one molar equivalent of sodium methoxide comprised 3,5,6-trifluoro-2-methoxy-4-pentafluorophenylpyridine contaminated with *ca.* 10 mole % of each of perfluoro-(4-phenylpyridine), 3,5-difluoro-2-methoxy-(4-methoxytetrafluorophenyl)pyridine, and a

[1] Part XIX, R. E. Banks, D. S. Field, and R. N. Haszeldine, *J. Chem. Soc.* (*C*), 1970, 1280.

[2] M. Green, A. Taunton-Rigby, and F. G. A. Stone, *J. Chem. Soc.* (*A*), 1968, 2762.

[3] K. C. Ho and J. Miller, *Austral. J. Chem.*, 1966, **19**, 423.

component that gave rise to ^{19}F n.m.r. absorption systems at 14·2 and 81·2 p.p.m. (to high field of trifluoroacetic acid) assigned to the 2,6- and 3′,5′-fluorine nuclei, respectively, of the 4′-methoxy-derivative, tetrafluoro-4-(4-methoxytetrafluorophenyl)pyridine (1c).



Reagents: i, One-molar proportion NaOMe in MeOH, 0—23 °C, (2; X = OMe) (88%); ii, NH_3 aq. (*d* 0·880), 94 °C (4; X = NH_2) (91%); iii, KOH in Bu^tOH, reflux (3; X = OH) (85%); iv, two-molar proportion NaOMe in MeOH, 23—50 °C (5; X = OMe) (59%); v, NH_3 aq. (*d* 0·880), 116 °C (7; X = NH_2) [44% + 55% of (4)]; vi, excess of KOH in Bu^tOH, reflux (6; X = OH) (60%); vii, three-molar proportion NaOMe, reflux (8; X = OMe) (55%); viii, NH_3 aq. (*d* 0·880), 165 °C (9; X = NH_2) (61%).

(Band systems were expected, on the basis of the effect of introducing a 4′-methoxy-substituent, to occur at *ca.* 14, 64 (two), and 81 p.p.m.; presumably the missing bands were obscured by those caused by the other components. The observed bands had the expected band envelopes, but the spectral intensity was insufficient for extraction of coupling constants.)

As revealed by ^{19}F n.m.r. (see below) and u.v. spectroscopic data for perfluoro-(4-phenylpyridine) [$\lambda_{max.}$(hexane) 204 (*E*-band) (ε 10,100), 232 (*K*-band) (ε 11,500), 275 (*B*-band) (ε 5500)],[4] the two rings are highly non-coplanar. As regards orientation of nucleophilic attack, therefore, the system would be expected to behave like an equimolar mixture of a 2,3,5,6-tetrafluoropyridine carrying a 4-substituent with electron-withdrawing capacity lying between that of chlorine and bromine [5] and a pentafluorophenyl derivative C_6F_5Y, where Y is a substituent of higher electronegativity than pentafluorophenyl.[6] Hence, it is not unreasonable that initial nucleophilic substitution should occur predominantly or even exclusively in the pyridine nucleus, which is highly activated by the ring nitrogen towards anionic attack.[1,7]

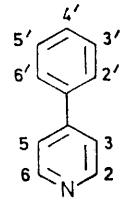
[4] *Cf.* D. E. Fenton, *Chem. and Ind.*, 1969, 695.
[5] A. G. Massey, E. W. Randall, and D. Shaw, *Chem. and Ind.*, 1963, 1244; J. M. Holmes, R. D. Peacock, and J. C. Tatlow, *J. Chem. Soc.* (*A*), 1966, 150.
[6] *Cf.* the relative acid strengths of tetrafluoro-4-hydroxypyridine and pentafluorophenol, R. E. Banks, J. E. Burgess, W. M. Cheng, and R. N. Haszeldine, *J. Chem. Soc.*, 1965, 575.
[7] R. E. Banks, D. S. Field, and R. N. Haszeldine, *J. Chem. Soc.* (*C*), 1967, 1822.

The orientation of nucleophilic attack on a 2-substituted tetrafluoro-4-pentafluorophenylpyridine will obviously be affected by the electronic influence of the 2-substituent, and the results shown in the Scheme can be ascribed to the known [3] deactivating influences of the groups MeO, NH_2, and O^- (which increase markedly in that order). Regarding the introduction of a third substituent, both rings in one of the disubstituted compounds are deactivated to a similar extent and hence substitution would be predicted to occur in the pyridine nucleus under the activating influence of the ring nitrogen.

N.m.r. Spectra.—The ^{19}F n.m.r. spectroscopic data of the polyfluoro-(4-phenylpyridines) are shown in Tables 1 and 2. Chemical shift assignments were made by

TABLE 1

^{19}F Chemical shifts (in p.p.m.) of polyfluoro-(4-phenylpyridines).*



Substituents	Ring position 2,6	3	5	2′,6′	3′,5′	4′
(1)	13·8	63·4	63·4	61·6	85·5	73·9
(2) 2-Methoxy	16·7	63·2	74·4	61·9	85·7	74·8
(3) 2-Hydroxy	16·5	63·7	74·6	62·0	85·7	75·0
(4) 2-Amino	16·7	64·6	81·3	62·2	86·2	75·7
(5) 2,4′-Dimethoxy	17·0	63·3	74·5	64·0	81·6	
(6) 2,4′-Dihydroxy	16·4	63·2	73·8	64·4	85·0	
(7) 2,4′-Diamino	17·3	64·1	80·2	65·7	85·6	
(8) 2,6,4′-Trimethoxy		73·4	73·4	64·0	81·4	
(9) 2,6,4′-Triamino		78·5	78·5	66·6	86·8	

* To high field of external $CF_3{\cdot}CO_2H$, as 20—25% solutions in acetone.

analogy with previous studies of polyfluoro-pyridines [8] and -benzenes [9–11] and the effect expected from the replacement of fluorine by another substituent. The n.m.r. spectrum of perfluoro-(4-phenylpyridine) was analysed as independent AA′XX′- (for pyridine ring-fluorines) and AA′PXX′-systems (for the phenyl ring-fluorines), in which the components of the absorption systems of the 3,5- and 2′,6′-fluorine nuclei were further split into 1 : 2 : 1 triplets. Furthermore, in the 2-substituted derivatives, the 2′,6′-fluorine nuclei were chemically equivalent and approximately equally coupled to the non-equivalent 3,5-fluorines. These results suggest that, on a time-averaged basis, the two rings are mutually perpendicular.

The chemical shifts of the phenyl ring-fluorines are

[8] J. Lee and K. G. Orrell, *J. Chem. Soc.*, 1965, 582.
[9] R. J. Abraham, D. B. Macdonald, and E. S. Pepper, *J. Amer. Chem. Soc.*, 1968, **90**, 147.
[10] R. Fields, J. Lee, and D. J. Mowthorpe, *J. Chem. Soc.* (*B*), 1968, 308.
[11] M. G. Hogben and W. A. G. Graham, *J. Amer. Chem. Soc.*, 1969, **91**, 283.

TABLE 2

Moduli of ^{19}F spin–spin coupling constants (Hz)

Compd. No. [a]	$\|J_{2,3}\|$	$\|J_{2,5}\|$	$\|J_{2,6}\|$	$\|J_{3,5}\|$	$\|J_{3,6}\|$	$\|J_{5,6}\|$	$\|J_{3,2'}\|$ $\|J_{3,6'}\|$	$\|J_{5,2'}\|$ $\|J_{5,6'}\|$	$\|J_{2',3'}\|$ $\|J_{5',6'}\|$	$\|J_{2',4'}\|$ $\|J_{4',6'}\|$	$\|J_{2',6'}\|$ $\|J_{3',6'}\|$	$\|J_{2',6'}\|$	$\|J_{3'5'}\|$	$\|J_{3',4'}\|$	Others [b]
(1)	20·4	29·0	14·4	1·3	29·0	20·4	9·9	9·9	21·2	3·9	8·0	6·1	0·4	19·9	
(2)				4·9	30·2	21·7	8·9	8·6	21·4	3·3	7·8	5·5	0·3	20·1	
(3)				5·8	30·2	22·7	9·1	8·8	21·2	3·2	7·7	5·4	<0·5	20·4	
(4)				8·4	30·9	24·3	8·5	8·3	22·0	3·1	8·2	5·3	0·8	20·1	
(5)				4·4	30·0	21·9	9·2	8·8	20·6		8·2	4·7	2·1		$\|J_{3',4'}\|=J_{4',5'}\|$
(6)				4·7	29·5	22·9	9·7	9·4	21·6		8·9	5·7	4·9		=1·8
(7)				6·4	30·4	24·6	9·7	9·3	20·7		8·2	4·1	8·6		$\|J_{3',4'}\|=J_{4',5'}\|$
(8)				?			8·2	8·2	20·7		8·5	4·8	2·1		=1·4
(9) [c]				?			7·8	7·8	?		?	?	?		

[a] See Table 1 for key to compounds. [b] When distinguished from zero. [c] Spectral intensity inadequate for extraction of further coupling constants.

rather similar to those reported for perfluorobiphenyl,[10] and replacement of a 2-fluorine in the pyridine ring by a substituent results in a small shift to high-field of the 4'-fluorine absorption; this presumably reflects a reduction in the electronic demand of the pyridine nucleus.

Coupling constant data are shown in Table 2. The inter-ring coupling constant moduli fall within a narrow range (7·8—9·9 Hz). The *ortho*- and *para*-fluorine–fluorine coupling constants were assigned by analogy with previous studies ($|^3J_{FF}| > |^5J_{FF}|$ for polyfluorobenzenes[10,11] and $|^3J_{FF}| < |^5J_{FF}|$ for polyfluoropyridines).[8] For the phenyl-ring, the *meta*-fluorine–fluorine coupling constants, $J_{2',6'}$ and $J_{3',5'}$, were assigned on the basis of previously suggested substituent contributions,[9] when the values for $J_{2',6'}$ are probably negative and the larger values at least of $J_{3',5'}$ are positive.

EXPERIMENTAL

^{19}F N.m.r. spectra were measured with a Perkin-Elmer R10 instrument operated at 56·46 MHz.

Perfluoro-(4-phenylpyridine) (Found: C, 41·7; N, 4·3. Calc. for $C_{11}F_9N$: C, 41·6; N, 4·4%), m.p. 98—99 °C (lit.,[12] 98·5—99·5 °C), was isolated (73% yield) by sublimation (70—74 °C at *ca.* 0·3 mmHg) of the yellow-brown solid obtained by reaction of pentafluoropyridine with pentafluorophenylmagnesium bromide.[12]

Reactions of Perfluoro-(4-phenylpyridine).—(a) *With sodium methoxide.* (i) 1 : 1 Molar ratio. Sodium methoxide (0·23 g, 4·29 mmol) in methanol (3 ml) was added slowly (1 h) to a cold (0 °C) solution of perfluoro-(4-phenylpyridine) (1·36 g, 4·3 mmol) in methanol (50 ml). The reaction mixture was warmed to 23 °C, stirred at this temperature for 3 h, and then treated with water (50 ml). The crude product, isolated in conventional fashion by ether extraction and shown by ^{19}F n.m.r. spectroscopy to contain small amounts of perfluoro-(4-phenylpyridine), tetrafluoro-4-(4-methoxytetrafluorophenyl)pyridine and trifluoro-2-methoxy-4-(4-methoxytetrafluorophenyl)pyridine, was sublimed (70 °C at *ca.* 0·4 mmHg) to give 3,5,6-*trifluoro*-2-*methoxy*-4-*pentafluorophenylpyridine* (1·24 g, 3·77 mmol; 88%) (Found: C, 43·8; H, 1·0; N, 4·6. $C_{12}H_3F_8NO$ requires C, 43·8; H, 0·9; N, 4·3%), m.p. 81—82 °C.

(ii) 1 : 2 Molar ratio. Sodium methoxide (0·448 g, 8·96 mmol) in methanol (3 ml) was added (30 min) to a solution of perfluoro-(4-phenylpyridine) (1·42 g, 4·48 mmol) in methanol (30 ml) at room temperature. The reaction mixture was warmed to 50 °C, maintained at this temperature for 4 h and then treated with water (50 ml). Work-up of the product *via* ether extraction gave a yellow oil that slowly solidified; sublimation (60 °C at *ca.* 0·4 mmHg) of the resulting solid gave 3,5,6-*trifluoro*-2-*methoxy*-4-(4-*methoxytetrafluorophenyl*)*pyridine* (0·9 g, 2·64 mmol; 59%) (Found: C, 45·8; H, 1·8; N, 4·2. $C_{13}H_6F_7NO_2$ requires 45·8; H, 1·8; N, 4·1%), m.p. 64—65 °C.

(iii) 1 : 3 Molar ratio. A solution of perfluoro-(4-phenylpyridine) (1·36 g, 4·29 mmol) and sodium methoxide (0·69 g, 12·9 mmol) in methanol (60 ml) was heated under reflux for 7 h. The product was treated with water (100 ml) and the mixture was extracted with ether (2 × 50 ml). The extract was washed with water (2 × 15 ml), dried ($MgSO_4$) and evaporated. Sublimation of the white residue (1·43 g) at 60 °C and 0·4 mmHg gave 3,5,6-trifluoro-2-methoxy-4-(4-methoxytetrafluorophenyl)pyridine (0·49 g, 1·44 mmol; 33·5%), m.p. 64—65 °C, with a correct i.r. spectrum, and a residue that was recrystallised from light petroleum (b.p. 40—60 °C) to yield 3,5-*difluoro*-2,6-*dimethoxy*-4-(4-*methoxytetrafluorophenyl*)*pyridine* (0·84 g, 2·4 mmol, 55%) (Found: C, 47·7; H, 2·8; N, 4·2. $C_{14}H_9F_6NO_3$ requires C, 47·6; H, 2·6; N, 4·0%), m.p. 64—65 °C.

(b) *With ammonia.* Perfluoro-(4-phenylpyridine) (1·31 g) was heated with aqueous ammonia (4 ml, *d* 0·880) at 94 °C for 3·5 h in a small Pyrex ampoule. The solid product was isolated by filtration, washed with water (30 ml), and sublimed at 90 °C and 0·4 mmHg to give 2-*amino*-3,5,6-*trifluoro*-4-*pentafluorophenylpyridine* (1·18 g, 91%) (Found: C, 42·2; H, 0·8; N, 8·9. $C_{11}H_2F_8N_2$ requires C, 42·1; H, 0·7; N, 8·9%), m.p. 101—102 °C.

The solid organic product obtained in a similar manner from perfluoro-(4-phenylpyridine) (1·0 g) and aqueous ammonia (6 ml; *d* 0·880) at 116 °C (3 h) was fractionally sublimed to yield (at 70° and 0·3 mmHg) 2-amino-3,5,6-trifluoro-4-pentafluorophenylpyridine (0·55 g, 55%) and (at 110 °C and 0·4 mmHg) 2-*amino*-3,5,6-*trifluoro*-4-(4-*aminotetrafluorophenyl*)*pyridine* (0·43 g, 44%) (Found: C, 42·2; H, 1·0; N, 13·4. $C_{11}H_4F_7N_3$ requires C, 42·5; H, 1·3; N, 13·5%), m.p. 194 °C.

The solid product similarly obtained from perfluoro-4-phenylpyridine (1·36 g) and aqueous ammonia (12 ml; *d* 0·880) at 165 °C (23 h) was sublimed at 182 °C and *ca.* 0·3 mmHg to yield a white solid from which 2,6-*diamino*-3,5-*difluoro*-4-(4-*aminotetrafluorophenyl*)*pyridine* (0·81 g, 61%) (Found: C, 42·7; H, 2·1; N, 18·0. $C_{11}H_6F_6N_4$ requires C, 42·9; H, 2·0; N, 18·2%), m.p. 260—261 °C, was extracted with light petroleum (b.p. 100—120 °C).

(c) *With potassium hydroxide.* A mixture of perfluoro-(4-phenylpyridine) (1·36 g, 4·29 mmol), potassium hydroxide

[12] R. D. Chambers, J. Hutchinson, and W. K. R. Musgrave, *J. Chem. Soc.*, 1965, 5040.

(0·6 g, 11 mmol), and t-butyl alcohol (20 ml) was heated under reflux for 2 h. The product was mixed with water (15 ml) and distilled to remove t-butyl alcohol. The aqueous product was acidified with 4N-sulphuric acid (10 ml) and extracted with ether (2 × 100 ml). The extract was dried ($MgSO_4$) and evaporated, and the residue was fractionally sublimed to give (at 70 °C and *ca.* 0·4 mmHg) perfluoro-(4-phenylpyridine) (0·26 g, 0·82 mmol; 19% recovery) and (at 110 °C and *ca.* 0·4 mmHg) 3,5,6-*trifluoro*-2-*hydroxy*-4-*pentafluorophenylpyridine* (0·66 g, 2·95 mmol; 85% based on 4-C_6F_5·C_5F_4N consumed) (Found: C, 41·9; H, 0·3; N, 4·8. $C_{11}HF_8NO$ requires C, 41·9; H, 0·3; N, 4·4%), m.p. 155—156 °C.

The product obtained by heating under reflux for 6 h a mixture of perfluoro-(4-phenylpyridine) (1·36 g, 4·29 mmol), potassium hydroxide (1·2 g, 21 mmol), and t-butyl alcohol (40 ml) was worked up as described above. The yellow residue (1·23 g) obtained by evaporation of the ether extract was dissolved in warm benzene (20 ml) and the solution was filtered to remove a small amount of insoluble brown material. Light petroleum (b.p. 60—80 °C; 50 ml.) was added to the filtrate until no more solid precipitated; the mixture was then heated until the precipitate redissolved and the solution thus obtained was left at room temperature to provide crystals of 2-*hydroxy*-3,5,6-*trifluoro*-4-(4-*hydroxytetrafluorophenyl*)*pyridine* (0·81 g, 2·59 mmol; 60%) (Found: C, 42·4; H, 0·8; N, 4·5. $C_{11}H_2F_7NO_2$ requires C, 42·2; H, 0·6; H, 4·5%), m.p. 198—199 °C.

An attempt to prepare 2,4-dihydroxy-3,5-difluoro-4-(4-hydroxytetrafluorophenyl)pyridine from perfluoro-(4-phenylpyridine) (1·36 g; 4·29 mmol) and an excess of potassium hydroxide (1·8 g, 32 mmol) in t-butyl alcohol (60 ml) under reflux (11·5 h) gave only 2-hydroxy-3,5,6-trifluoro-4-(4-hydroxytetrafluorophenyl)pyridine (0·52 g, 1·66 mmol; 39%), m.p. 198—199 °C, with correct i.r. and ^{19}F n m.r. spectroscopic properties.

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