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HETEROCYCLIC POLYFLUORO-COMPOUNDS. PART XXVII[1]. NUCLEOPHILIC SUBSTITUTION IN PERFLUORO-(4-PHENYLPYRIMIDINE)

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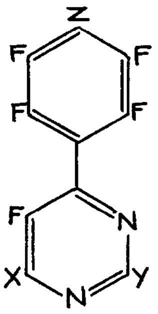
SUMMARY

Treatment of tetrafluoropyrimidine with pentafluorophenylmagnesium bromide provides perfluoro-(4-phenylpyrimidine) (1) and perfluoro-(4,6-diphenylpyrimidine)(2). Attack on the former product by appropriate nucleophiles yields compounds **(3)-(5) and thence** (6)-(10). ^{19}F N.m.r. data for all these new pyrimidine derivatives are discussed.



Y = Z = F:
(1) X = F
(2) X = C_6F_5
(3) X = OMe
(4) X = NH_2
(5) X = $Fe(CO)_2(\pi\text{-}C_5H_5)$

Z = F:
(6) X = Y = OMe
(7) X = Y = NH_2

Y = F:
(8) X = Z = $Fe(CO)_2(\pi\text{-}C_5H_5)$

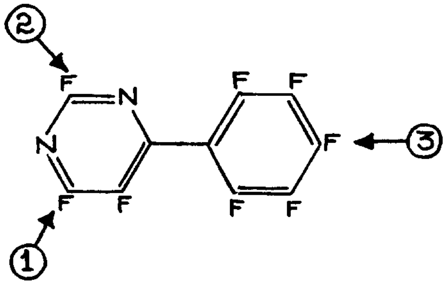
(9) X = Y = Z = OMe
(10) X = Y = Z = NH_2

INTRODUCTION

To extend earlier studies on the 'hybrid' polynuclear system perfluoro-(4-phenylpyridine) [2] and on polyfluoropyrimidines [3-5], we have prepared perfluoro-(4-phenylpyrimidine) via treatment of tetrafluoropyrimidine with pentafluorophenylmagnesium bromide and investigated its reactions with some nucleophiles. As expected [3], the Grignard reagent attacks tetrafluoropyrimidine under mild conditions (-40 to 20 °C) and some di-substitution occurs, giving perfluoro-(4,6-diphenylpyrimidine).

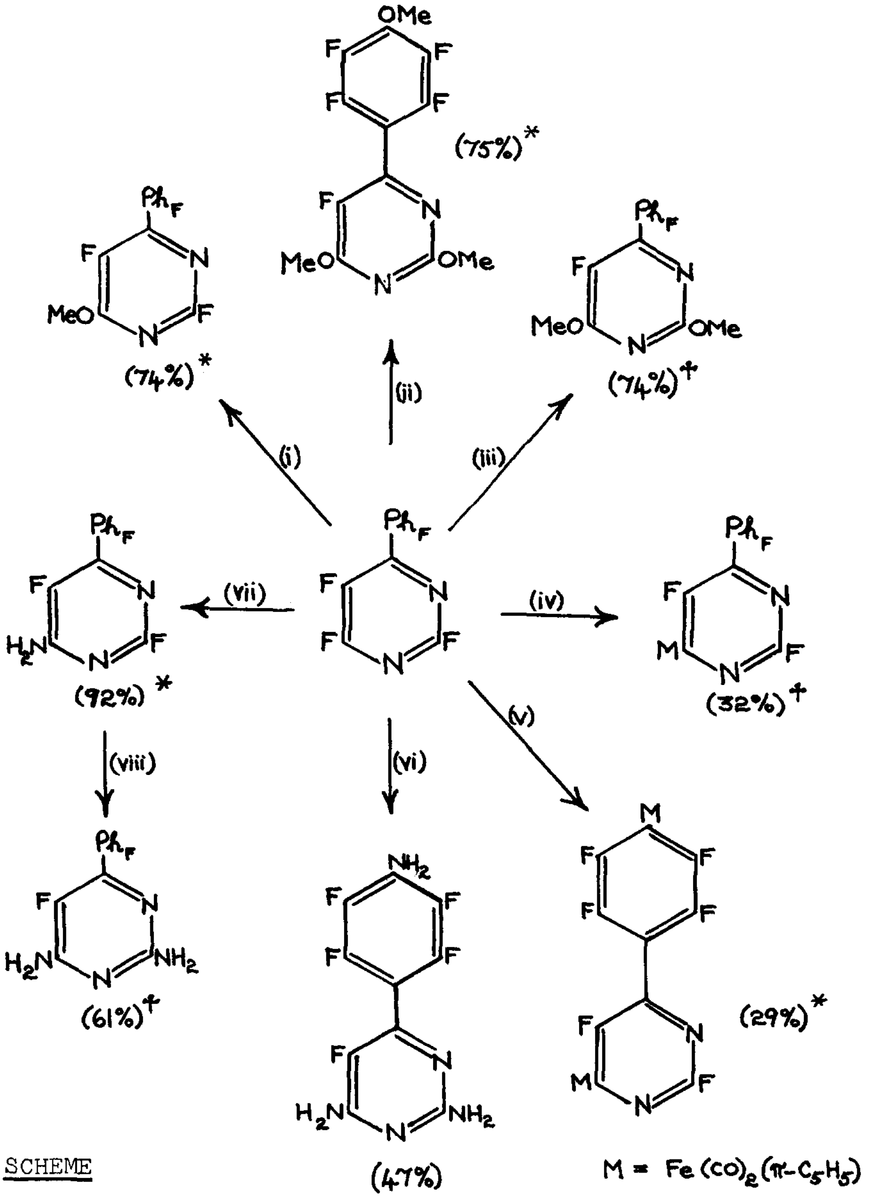
RESULTS

The outcome (see the Scheme) of reactions involving perfluoro-(4-phenylpyrimidine) and the nucleophilic reagents MeOH-Na_2CO_3, MeONa-MeOH, and NH_3 aq. shows that the predominant, or even exclusive, order in which the fluorines are displaced is:



In the case of the anion $[(\pi\text{-}C_5H_5)Fe(CO)_2]^-$, however, the second displacement occurs in the homocyclic portion of the substrate; no tri-substitution was observed under the conditions employed.

As revealed by ^{19}F n.m.r. (see below) and u.v. spectroscopic data for perfluoro-(4-phenylpyrimidine) [$\lambda_{max.}$ (hexane) 237·5 (K-band) (ε 7500), 263 (B-band) (ε 11000)] [6], the two rings are markedly non-coplanar; when under attack by a nucleophile, therefore, the system would be predicted to behave like an equimolar mixture of a 2,5,6-trifluoropyrimidine carrying



<u>SCHEME</u>

* No other product was detected in the crude reaction product by ^{19}F n.m.r. spectroscopy. The yields quoted throughout the Scheme are for isolated products.

† Major product, the minor one being the corresponding di- or tri-substituted product shown in the Scheme.

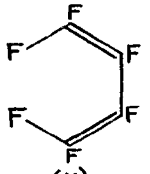
Reagents: (i) MeOH-Na_2CO_3, -10 to 20 °C ; (ii) *ca*. three-molar proportion of NaOMe in MeOH, 0 to 20 °C ; (iii) *ca*. two-molar proportion of NaOMe in MeOH, -35 to 0 °C ; (iv) $Na[(\pi\text{-}C_5H_5)Fe(CO)_2]$ in THF, -35 to 20 °C ; (v) xs. $Na[(\pi\text{-}C_5H_5)Fe(CO)_2]$ in THF, 20 °C ; (vi) xs. NH_3 aq. (*d* 0.880), 100 °C ; (vii) NH_3 aq. (*d* 0.880), 70 °C ; (viii) NH_3 aq. (*d* 0.880), 60 °C .

an electronegative 4-substituent capable of exerting a greater -I effect than bromine [7], and a pentafluorophenyl derivative C_6F_5R , where R is a substituent of higher electronegativity than tetrafluoro-4-pyridyl [8]. On this basis, the orientation of monosubstitution of fluorine by all the nucleophiles employed, and of di- and tri-substitution by ammonia or methoxide ion, is fully consistent with previous work in this area [2,3,9]; that attack leading to disubstitution by the anion $[(\pi\text{-}C_5H_5)Fe(CO)_2]^-$ seems to occur in only the *para*-position of the homocyclic component of the system conforms with the claim [10] that interaction of perfluoro-(4-phenylpyridine) with this and the related anion $[Re(CO)_5]^-$ provides only products derived from expulsion of the 4-fluorine of the pentafluorophenyl group.

N.m.r. Spectra.- ^{19}F N.m.r. parameters for the polyfluoro-(6-phenylpyrimidines) prepared in this study are listed in Tables 1 and 2, chemical shift assignments (Table 1) being made through consideration of published data for polyfluorinated pyrimidines [3] and benzenes [11-13]. The spectral components arising from the pentafluorophenyl substituents approximated to AA'XX' or AA'PXX' systems, in which the absorptions caused by the 2', 6'-fluorine nuclei were split into doublets by the 5-fluorine nucleus.

The chemical shifts of the fluorine nuclei of the pentafluorophenyl groups compare well with those for the corresponding fluorines in perfluorobiphenyl [12] and, in particular, polyfluoro-(4-phenylpyridines) [2]. In general, replacement of fluorines in the pyrimidine segment of perfluoro-(4-phenylpyrimidine) results in a small shift to high field of the 4′-F absorption; this parallels the situation for the analogous pyridine series $2\text{-}XC_5F_3N.C_6F_5$ (4′-F chemical shifts to high field of $CF_3.CO_2H$: X = F, 73.9 ; NH_2, 75.7 ; OMe, 74.8 ; OH, 75.0 [2]) and presumably reflects a decrease in the electron demand of the heterocyclic moiety.

The inter-ring coupling constant moduli (see Table 2) fall within the range 7.9 - 15.0 Hz, compared with 7.8 - 9.9 Hz for polyfluoro-(4-phenylpyridines) [2], with a tendency in both systems for increasing replacement of fluorine to favour a constant of smaller magnitude. The chemical equivalence of the 2′- and 6′-fluorine nuclei in both the pyrimidine and pyridine series suggests that on the average the planes of the two rings in each system are mutually perpendicular. In practice, the preferred dihedral angle may not be 90°, but the barrier to oscillation about this mean position must be small. The results of theoretical calculations [14] indicate that the five-bond F-F coupling constant in perfluorobutadiene (11) is dominated by the Fermi contact term for dihedral angles in the range 0° [i.e., s-cis-(11)] to 120°, and calculated values for angles of 60, 90, and 120° are 11.7, 15.4, and 20.6 Hz, respectively; these are close to the values of the averaged five-bond coupling constants [$J_{5,6'}$ (= $J_{5,2'}$)] for the polyfluoro-(6-phenylpyrimidines) (12) and the related pyridines (13)[12]. On the basis that the averaged coupling constant should slowly rise in value with increasing deviation from 90° of the dihedral angle between the ring planes in systems (12) or (13), the somewhat larger values observed for the pyrimidines [e.g., $J_{3,2'}$ (= $J_{3,6'}$) for perfluoro-(4-phenylpyridine) is 9.9 Hz] are ascribed to the smaller steric demand of a ring nitrogen compared with a CF group.



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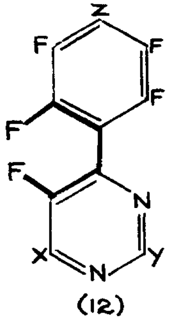

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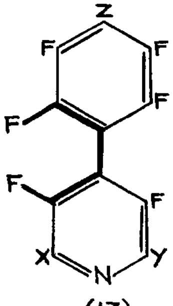

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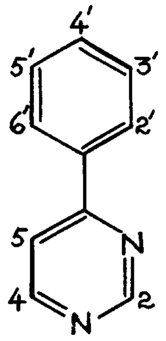
TABLE 1

^{19}F Chemical shifts (in p.p.m.) of polyfluoro-(6-phenylpyrimidines)*



		Ring Fluorine Positions					
	Substituents (other than F)	2	4	5	2',6'	3',5'	4'
(1)	—	29.8	3.1	-75.9	-64.0	-85.6	-73.5
(2)	4-pentafluorophenyl	27.2	-	-56.0	-63.6	-85.4	-73.2
(3)	4-Methoxy	30.5	-	-75.1	-61.8	-83.6	-72.8
(4)	4-Amino	26.8	-	-78.0	-63.8	-85.9	-75.9
(5)	4-Dicarbonylcyclopentadienyliron	23.8	-	-35.8	-64.0	-86.1	-76.1

(6)	2,4-Dimethoxy	-	-	-81.9	-62.0	-84.1	-74.2
(7)	2,4-Diamino	-	-	-89.9	-64.3	-86.5	-77.8
(8)	4,4′-Bis(dicarbonylcyclopentadienyliron)	23.5	-	-36.0	-67.2	-30.1	-
(9)	2,4,4′-Trimethoxy	-	-	-81.9	-63.8	-80.1	-
(10)	2,4,4′-Triamino	-	-	-89.4	-67.9	-86.2	-

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* Positive values are to low field of external $CF_3.CO_2H$, Compounds were examined as <u>ca</u>. 20% solutions in acetone, except for (1) (neat liq.), (3) (50% in $CDCl_3$), (6) (50% in CCl_4), (8) (20% in HMPA), and (9) (20% in CCl_4).

TABLE 2

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

Compd. No. $^{\underline{b}}$	$\lvert \underline{J}_{2,4}\rvert$	$\lvert \underline{J}_{2,5}\rvert$	$\lvert \underline{J}_{4,5}\rvert$	$\lvert \underline{J}_{5,2'}\rvert$ $\lvert \underline{J}_{5,6'}\rvert$	$\lvert \underline{J}_{2',3'}\rvert$ $\lvert \underline{J}_{5',6'}\rvert$	$\lvert \underline{J}_{2',4'}\rvert$ $\lvert \underline{J}_{4',6'}\rvert$	$\lvert \underline{J}_{2',5'}\rvert$ $\lvert \underline{J}_{3',6'}\rvert$	$\lvert \underline{J}_{2',6'}\rvert$	$\lvert \underline{J}_{3',5'}\rvert$	$\lvert \underline{J}_{3',4'}\rvert$	Others $^{\underline{c}}$
(1)	2.4	28.0	20.3	13.0	20.4	4.2	8.2	5.8	<1	19.0	
(2)	-	28.6	-	15.0	22.4	3.6	8.3	5.8	<1	19.8	
(3)	-	27.4	-	11.7	21.8	3.5	8.2	4.5	0.5	19.7	
(4)	-	27.6	-	10.9	21.5	3.2	7.9	4.4	1.2	19.9	
(5)	-	30.1	-	11.8	20.9	2.7	7.7	3.7	0.8	20.3	
(6)	-	-	-	10.7	21.3	2.6	8.1	4.3	0.8	20.6	
(7)	-	-	-	7.9	21.7	2.1	8.1	3.4	0.8	20.5	
(8)$^{\underline{d}}$	-	30.6	-	11.5	?	-	?	?	?	-	
(9)	-	-	-	11.4	21.3	-	9.1	4.1	0.9	-	$\lvert J_{3'4'(H)}\rvert = 1.6$
(10)	-	-	-	9.3	21.2	-	8.6	2.3	8.1	-	

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[a] Estimated to be accurate to ± 0.5 Hz, or better. [b] See Table 1 for key to compounds.

[c] When distinguished from zero. [d] Spectral intensity insufficient for extraction of further coupling constants.

The *meta* F-F coupling constants $J_{2',6'}$ and $J_{3',5'}$ (C_6F_5 group) for the polyfluoro-(6-phenylpyrimidines) were assigned on the basis of substituent contributions suggested previously [11]. Slight asymmetry within the AA'XX' systems indicated that $J_{2',6'}$ and $J_{3',5'}$ are of the same sign (probably negative) in compounds (3),(4),(6), and (7), and of opposite sign ($J_{3',5'}$ probably positive) in (9) and (10). The coupling constant $J_{2',4'}$ is probably positive [11 , 13]. Replacement of pyrimidine ring fluorine by amino or methoxy substituents causes $J_{2',4'}$ to decrease and $J_{2',6'}$ to increase; this corresponds to a contribution from a group having less electron-demand.

EXPERIMENTAL

^{19}F N.m.r. spectra were measured with a Perkin-Elmer R10 instrument operating at 56.46 MHz.

Preparation of Perfluoro-(4-phenylpyrimidine)

Pentafluorophenylmagnesium bromide [from 15.0 g (60.8 mmol) of bromopentafluorobenzene and 2.1 g of magnesium] in ether (20 cm^3) was added slowly (3 h) to a cold (-45 to -50 °C) stirred solution of tetrafluoropyrimidine (9.3 g, 61 mmol) in dry ether (15 cm^3). The mixture was stirred at *ca.* -40 °C for 1.5 h and then at 20 °C for 2 days. (A nitrogen atmosphere was maintained in the reaction vessel throughout). The product was treated with 2M-sulphuric acid (75 cm^3) then worked up by standard techniques (ether extraction, *etc.*) to yield perfluoro-(4-phenylpyrimidine) (nc) (7.35 g, 24.5 mmol, 40%)(Found: C, 40.2 ; N, 9.0. $C_{10}F_8N_2$ requires C, 40.0 ; N, 9.3%), b.p. 66-67 °C at *ca.* 1 mmHg, and perfluoro-(4,6-diphenylpyrimidine)(nc) (2.57 g, 5.7 mmol, 9%)(Found: C, 42.7 ; F, 50.3 ; N, 6.1. $C_{16}F_{12}N_2$ requires C, 42.8 ; F, 50.9 ; N, 6.25%), m.p. 110-112 °C, b.p. 132 °C at *ca.* 1 mmHg, $\lambda_{max.}$ (hexane) 212 (ε 9000), 238 (ε 9400), and 265 (ε 17000) nm.

Reactions of Perfluoro-(4-phenylpyrimidine)

(a) With methanol

Dry methanol (5 cm^3) was added slowly (2 h) to a cold (*ca.* - 10 °C) stirred mixture of perfluoro-(4-phenylpyrimidine) (1.10 g, 3.67 mmol), ether (10 cm^3), and anhydrous sodium carbonate (0·21 g). The reaction mixture was allowed to warm to 20 °C then poured into water (100 cm^3). Conventional work-up (ether extraction, etc.) provided 2,5-difluoro-4-methoxy-6-(pentafluorophenyl)-pyrimidine (nc) (0.85 g, 2·73 mmol, 74%) (Found: C, 42.2 ; H, 1·0 ; F, 43·2 ; N, 9·2. $C_{11}H_3F_7N_2O$ requires C, 42.4 ; H, 1·0 ; F, 42·6 ; N, 9·0%), m.p. 40-41 °C.

(b) With sodium methoxide

Sodium methoxide (0·49 g, 9·1 mmol) in methanol (10 cm^3) was added slowly (3 h) to a cold (*ca.* -25 °C) stirred solution of perfluoro-(4-phenylpyrimidine) (1·32 g, 4·40 mmol) in methanol (10 cm^3). The mixture was warmed to 0 °C, stirred at this temperature for 2 h, and then allowed to warm to room temperature before being treated with water (100 cm^3). Ether extraction followed by distillation gave 5-fluoro-2,4-dimethoxy-6-(pentafluorophenyl)pyrimidine (nc)(1.05 g, 3.24 mmol, 74%)(Found: C, 44.7 ; H, 2.1 ; F, 34.8 ; N, 8.5. $C_{12}H_6F_6N_2O_2$ requires C, 44·4 ; H, 1·85 ; F, 35·2 ; N, 8·6%), b.p. 113-114 °C at 1 mmHg. Sublimation of the residue gave 5-fluoro-2,4-dimethoxy-6-(4-methoxytetrafluorophenyl)pyrimidine (nc)(0·15 g, 0·45 mmol, 10%) (Found: C, 46·7 ; H, 3·0 ; F, 28·3 ; N, 8.0. $C_{13}H_9F_5N_2O_3$ requires C, 46·4 ; H, 2·7 ; F, 28·3 ; N, 8.3%), m.p. 84-85 °C. Similar treatment of perfluoro-(4-phenylpyrimidine) (0·32 g, 1·07 mmol) with sodium methoxide (0·21 g, 3·8 mmol) in methanol (5 cm^3) at 0 °C gave only 5-fluoro-2,4-dimethoxy-6-(4-methoxytetrafluorophenyl)pyrimidine (0·27 g, 0·80 mmol, 75%).

(c) With ammonia

A mixture of aqueous ammonia (0.2 cm^3, *d* 0.880) in acetone (4 cm^3) was added dropwise during 2 h to a cold (0 $^{\circ}$C) stirred solution of perfluoro-(4-phenylpyrimidine) (0·91 g, 3·0 mmol) in acetone (10 cm^3). The reaction mixture was stirred at 0 $^{\circ}$C (2 h) then at 20 $^{\circ}$C for 1 h, and finally poured into water (100 cm^3). The solid that precipitated was isolated by filtration, washed with water (30 cm^3), and sublimed at 100 $^{\circ}$C *in vacuo* to yield 4-amino-2,5-difluoro-6-(pentafluorophenyl)pyrimidine (nc)(0·52 g, 1·75 mmol, 58%)(Found: C, 40·5 ; H, 0.8 ; F, 44.1 ; N, 14.3 . $C_{10}H_2F_7N_3$ requires C, 40·4 ; H, 0.7 ; F, 44.8 ; N, 14.1%), m.p. 174 -175 $^{\circ}$C. When the above reaction was repeated at 70 $^{\circ}$C (6 h), the yield of 4-amino-2,5-difluoro-6-(pentafluorophenyl)-pyrimidine rose to 92%.

When a mixture of perfluoro-(4-phenylpyrimidine) (0.85 g, 2.83 mmol) and aqueous ammonia (4.5 cm^3, *d* 0.880) was heated at 100 $^{\circ}$C for 40 h in a Pyrex ampoule (80 cm^3) in the absence of air, the product contained only a trace of 4-amino-2,5-difluoro-6-(pentafluorophenyl)pyrimidine (detected by t.l.c.); the major products were isolated by column chromatography [1 m x 1 cm silica gel (60-120 mesh), eluted with 80 : 20 v/v ether-chloroform] and found to be 2,4-diamino-5-fluoro-6-(pentafluorophenyl)pyrimidine (nc) (0.12 g, 0.41 mmol, 14%)(Found: C, 41·1 ; H, 1.7 ; N, 19·2 . $C_{10}H_4F_6N_4$ requires C, 40 8 ; H, 1.4 ; N, 19.0%), m.p. 135-136 $^{\circ}$C, and 2,4-diamino-5-fluoro-6-(4-aminotetrafluorophenyl)pyrimidine (0.39 g, 1.34 mmol, 47%)(Found: C,41.5; H, 2.2 ; F, 32.9 ; N, 24.4 . $C_{10}H_6F_5N_5$ requires C, 41.2 ; H, 2.1 ; F, 32·6 ; N, 24.1%), m.p. 207-208 $^{\circ}$C .

(d) With the anion $[(\pi\text{-}C_5H_5)Fe(CO)_2]^-$

A solution of $Na[(\pi\text{-}C_5H_5)Fe(CO)_2]$, prepared from the dimer $[(\pi\text{-}C_5H_5)Fe(CO)_2]_2$ (0.83 g, 2.34 mmol), in tetrahydrofuran (50 cm^2) was added slowly (2 h) to a cold (*ca.* -35 $^{\circ}$C) solution of perfluoro-(4-phenylpyrimidine) (1.0 g, 3.3 mmol) in THF (40 cm^3) under nitrogen. The mixture was stirred at room temperature overnight, filtered, then stirred with 'Florisil' (2 g, 100-200 mesh) whilst being evaporated at water pump pressure. The residue, adsorbed on the 'Florisil', was subjected to column chromatography (60 cm x 2 cm 'Florisil'); elution with 1:1 (v/v) benzene-light petroleum (b.p. 40-60 °C) provided orange-brown crystals of 2,5-difluoro-4-(dicarbonylcyclopentadienyliron)-6-(pentafluorophenyl)pyrimidine (nc), mp. 126 °C(0.49 g, 1.07 mmol, 32 (Found: C, 44.7 ; H, 1.2 ; F, 28.6 ; N, 6.0 . $C_{17}H_5F_7FeN_2O_2$ requires C, 44.5 ; H, 1.1 ; F, 29.0 ; N, 6.1%), and subsequent elution with 1:1 (v/v) benzene-dichloromethane gave 2,5-difluoro-4-(dicarbonylcyclopentadienyliron)-6-[4-(dicarbonylcyclopentadienyliron)tetrafluorophenyl]-pyrimidine (nc) (0.13 g, 0.21 mmol, 6%) (Found: C, 46.8 ; H, 1.9 ; F, 18.5 ; N, 4.7 . $C_{24}H_{10}F_6Fe_2N_2O_4$ requires C, 46.75 ; H, 1.6 ; F, 18.5 ; N, 4.5%), an orange-brown solid, m.p. > 250 °C.

When a solution of $Na[(\pi\text{-}C_5H_5)Fe(CO)_2]$, prepared from 4.05 g (11.4 mmol) of the dimer $[(\pi\text{-}C_5H_5)Fe(CO)_2]_2$, in tetrahydrofuran (75 cm^3) was added (1.5 h) to perfluoro-(4-phenylpyrimidine) (2.43 g, 8.10 mmol) in the same solvent (50 cm^3) at 20 °C, the product [isolated by chromatography, as above, and finally purified by recrystallisation from 1:1 (v/v) dichloromethane-hexane] was 2,5-difluoro-4-(dicarbonylcyclopentadienyliron) 6-[4-(dicarbonylcyclopentadienyliron)tetrafluorophenyl]pyrimidine (1.45 g, 2.35 mmol, 29%). No evidence for the presence of a product of tri-substitution was found by analysis of the total crude reaction product by t.l.c. or ^{19}F n.m.r. spectroscopy.

Reaction of 4-Amino-2,5-difluoro-6-(pentafluorophenyl)pyrimidine with Ammonia

Chromatographic (1 m x 1 cm silica gel, eluted with ether) separation of the product obtained by heating 4-amino-2,5-difluoro-6-(pentafluorophenyl)pyrimidine (0.75 g, 2.53 mmol) with aqueous ammonia (2 cm^2, d 0.880) in a Pyrex ampoule (80 cm^3) at 60 °C for 4 days in the absence of air provided starting material (0.12 g, 0.40 mmol, 16% recovery), 2,4-diamino-5-fluoro-6-(pentafluorophenyl)pyrimidine (0.38 g, 1.30 mmol, 61% based on starting material consumed), and 2,4-diamino-5-fluoro-6-(4-aminotetrafluorophenyl)-pyrimidine (0.12 g, 0.41 mmol, 19%).

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