Remarkable Orientational Effects in the Displacement of the Fluorine from Heptafluoro-isoquinoline and -quinoline towards Sulfur Nucleophiles. Further Reactions with Oxygen Nucleophiles

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Heptafluoroisoquinoline **1** and heptafluoroquinoline **2** have been treated with a variety of sulfur and oxygen nucleophiles and some reactivities have been measured relative to treatment with ethoxide. The significant feature is that the major sites of attack by the sulfur and the oxygen nucleophiles are significantly different: attack occurs at the 6-position by sulfur and the 1-position by oxygen nucleophiles in the isoquinoline derivative **1** irrespective of the relative reactivities; and at the 4-position by sulfur and at both the 2- and 4-positions by oxygen nucleophiles in the quinoline derivative **2**. The results have been rationalised on the basis of the relative hardness/softness of the nucleophiles and the known activating influences of the fluorine atoms at sites remote from the reaction centre.

Nucleophilic substitution of fluorine in heptafluoroisoquinoline **1** and heptafluoroquinoline **2** by a variety of nucleophiles, *e.g.* sodium methoxide, ammonia, hydrazine and lithium aluminium hydride, was first described in 1966.[1] The isoquinoline **1** was reported to give only 1-substituted products, while disubstituted products arose from the further replacement of the 6-fluorine. Heptafluoroquinoline **2** gave a mixture of the 2- and 4-ethers in the ratio of 77:23 with sodium methoxide and mixtures of 2- and 4-isomers resulting from treatment with ammonia and hydrazine.

In this paper we describe the reactions of **1** and **2** with a variety of sulfur nucleophiles: hydrosulfide, methanethiolate, propane-2-thiolate, 2-methylpropane-2-thiolate, benzenethiolate and various *p*-substituted benzenethiolates, which give remarkably different patterns of substitution to those found in the earlier work. We have also examined the reactions of **1** and **2** with two oxygen nucleophiles, phenoxide and *p*-nitrophenoxide, and re-examined the reaction of **1** with sodium methoxide and compared it with sodium ethoxide. The precise isomer ratio for monosubstitution of **2** with ammonia is reported.

Results

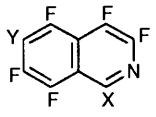
The isoquinoline **1** was treated with sodium hydrosulfide in a mixture of ethylene glycol (EG) and *N*,*N*-dimethylformamide (DMF) at *ca.* 0 °C to give *exclusively* the 6-substituted product **3** (by ^{19}F NMR) in essentially quantitative yield. The structure of **3** was determined by ^{19}F NMR spectroscopy utilising knowledge about the parent heterocycle **1**: the chemical shifts of the fluorines (in particular, the low field absorptions at δ −62.1 and −96.7 due to the 1-F and 3-F respectively), and the large coupling constants $J_{1\text{-F},4\text{-F}}$ 33, $J_{1\text{-F},8\text{-F}}$ 61 and $J_{4\text{-F},5\text{-F}}$ 48 Hz (see the Experimental section). Thus, the absorption in the isoquinolinethiol compound, at δ −62.9 (coupling constants 59.2 and 33.1 Hz) identified the 1-F which in turn revealed the 8-F (δ −143.3; *J* 59.7 Hz) and the 4-F (δ −155.8; *J* 51.9 and 33.4 Hz). The larger coupling constant on 4-F showed that the absorption at δ −117.75 (*J* 51.9 Hz) was the 5-F, and the 3-F resonated at δ −97.3. The distinction between the positions 6 and 7 for the SH group was deduced by examining the chemical shifts of the two fluorines *ortho* to the SH and comparing them with the corresponding fluorines in the parent compound **1** (the substituent chemical shift, SCS) with the knowledge that 2-SH in 1,3,4,5,6,7,8-heptafluoronaphthalene-2-thiol deshields both the 1-F and 3-F absorptions by 29 and 21.2 ppm respectively in 1,2,3,4,5,6,7,8-octafluoronaphthalene.[2] The SH in **3** is clearly at position 6 since the 5-F peri is deshielded 28.1 ppm [−117.7 − (−145.8) ppm] and the 7-F is deshielded by 21.1 ppm [−132.0 − (−153.1) ppm]. If the SH group had been at position 7, the 6-F absorption would have been deshielded 13.4 ppm [−132.0 − (−145.4) ppm] and the 8-F shielded by 3.6 ppm [−139.7 − (−143.3 ppm)]. When the reaction of the isoquinoline **1** and sodium hydrosulfide was carried out in methanol both the 6- **3** and 1- **4** thiols were formed in the ratio 92:8 respectively, the minor isomer being identified by the absence of a 1-F absorption at *ca.* δ −62.

The isoquinoline **1** was also treated at < −90 °C in ethanol with thiolates of increasing steric complexity (sodium salts of methanethiol, propane-2-thiol and 2-methylpropane-2-thiol) and with 4-substituted benzenethiolates having substituents of increasing electron demand [*N*,*N*-dimethylamino, methoxy, hydro (*i.e.* the parent benzenethiolate) and nitro], all of which were prepared from sodium ethoxide in ethanol and the corresponding thiol. Monosubstituted isomers (the 6- and/or 1-compounds) and sometimes 1,6-disubstituted compounds were formed in these reactions, the proportions of which were determined by ^{19}F NMR and are shown in Table 1. Most of the products were separated by column chromatography and their structures determined by ^{19}F NMR spectroscopy. The 1-isomers were identified by the absence of a low field absorption at *ca.* δ −62 while the structures of the 6-isomers and 1,6-disubstituted products were deduced using arguments similar to the ones used for identifying the isoquinoline-6-thiol **3**. In some cases where the 1-substituted isomer was present in such a low proportion as to be unisolable, the 1,6-disubstituted derivative was prepared and, using SCS data, the expected shifts from the fluorines in the 1-isomer were calculated which enabled the 1-isomer in the product to be identified with certainty. The treatment of the 2-methylpropane-2-thiolate with **1** was originally performed without a large excess of thiol present, but the crude reaction product was complicated by the formation of ethoxy-substituted compounds. Thus, the 1- **11** and 6- **12** *tert*-butylthio isomers and the 1,6- **13** di(*tert*-butylthio) compound were accompanied by the 1-ethoxy-6-*tert*-butylthio **14** and 1-ethoxy **25** compounds in the ratio 14:72:3:3:8 respectively. No detectable ethoxy-substituted products accompanied the reactions with methanethiolate, propane-2-thiolate or the arenethiolates. The 1-ethoxyisoquinoline **25** was identified by its

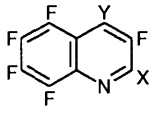
Table 1 Reactions of heptafluoroisoquinoline **1** with nucleophiles

Nucleophile	Solvent	Product ratio[a] 1-Isomer (%)	6-Isomer (%)	1,6-Disubstituted product (%)
HS^-	DMF–EG		100 (**3**)	
HS^-	MeOH	8 (**4**)	92 (**3**)	
MeS^-	EtOH	22 (**5**)	73 (**6**)	5 (**7**)
Pr^iS^-	EtOH	24 (**8**)	71 (**9**)	5 (**10**)
Bu^tS^-	EtOH	16 (**11**)	79 (**12**)	5 (**13**)[b]
PhS^-	EtOH		99 (**15**)	1 (**16**)
$4\text{-}Me_2NC_6H_4S^-$	EtOH	2 (**18**)	97.5 (**19**)	0.5 (**20**)
$4\text{-}MeOC_6H_4S^-$	EtOH	2 (**21**)	97.5 (**22**)	0.5 (**23**)
$4\text{-}NO_2C_6H_4S^-$	EtOH		100 (**24**)	
EtO^-	EtOH	94 (**25**)	6 (**26**)	
MeO^-	MeOH	93 (**28**)	7 (**29**)	
PhO^-	EtOH	93 (**30**)	7 (**31**)	
$4\text{-}NO_2C_6H_4O^-$	EtOH	100 (**32**)		

[a] Calculated on the basis of starting material converted (compound numbers in parentheses). [b] With a ten-fold excess of Bu^tSH present.



1 X = Y = F
3 X = F, Y = SH
4 X = SH, Y = F
5 X = MeS, Y = F
6 X = F, Y = MeS
7 X = Y = MeS
8 X = Pr^iS, Y = F
9 X = F, Y = Pr^iS
10 X = Y = Pr^iS
11 X = Bu^tS, Y = F
12 X = F, Y = Bu^tS
13 X = Y = Bu^tS
14 X = OEt, Y = Bu^tS
15 X = F, Y = PhS
16 X = Y = PhS
17 X = OEt, Y = PhS
18 X = 4-Me_2N-C_6H_4S, Y = F
19 X = F, Y = 4-Me_2N-C_6H_4S
20 X = Y = 4-Me_2N-C_6H_4S
21 X = 4-MeO-C_6H_4S, Y = F
22 X = F, Y = 4-MeO-C_6H_4S
23 X = Y = 4-MeO-C_6H_4S
24 X = F, Y = 4-NO_2-C_6H_4S
25 X = OEt, Y = F
26 X = F, Y = OEt
27 X = Y = OEt
28 X = OMe, Y = F
29 X = F, Y = OMe
30 X = PhO, Y = F
31 X = F, Y = PhO
32 X = NO_2-C_6H_4O, Y = F



2 X = Y = F
33 X = F, Y = SH
34 X = MeS, Y = F
35 X = F, Y = MeS
36 X = Y = MeS
37 X = Pr^iS, Y = F
38 X = F, Y = Pr^iS
39 X = Y = Pr^iS
40 X = Bu^tS, Y = F
41 X = F, Y = Bu^tS
42 X = Y = Bu^tS
43 X = OEt, Y = Bu^tS
44 X = F, Y = PhS
45 X = Y = PhS
46 X = OEt, Y = PhS
47 X = OEt, Y = F
48 X = F, Y = OEt
49 X = PhO, Y = F
50 X = F, Y = PhO
51 X = 4-NO_2-C_6H_4O, Y = F
52 X = F, Y = 4-NO_2-C_6H_4O
53 X = NH_2, Y = F
54 X = F, Y = NH_2

independent synthesis from **1** and sodium ethoxide in ethanol which gave two monosubstituted products: the 1- **25** and the 6- **26** isomers in the ratio 94:6 respectively. The 6-isomer was identified by ^{19}F NMR spectroscopy but not isolated, and the mixture of isomers and more ethoxide gave the 1,6-diethoxy compound **27**. The reaction of **1** and sodium methoxide in methanol originally reported in 1966 was repeated and the 6-isomer was formally identified; the 1-**28** and 6- **29** isomers were present in the ratio 97:3 respectively.

Two other oxygen nucleophiles have also been treated with the isoquinoline **1**, sodium phenoxide and sodium 4-nitrophenoxide, to enable a more comprehensive comparison to be made with some of the sulfur analogues. All the results are summarised in Table 1.

The quinoline **2** was treated with sodium hydrosulfide under conditions similar to those used for **1** to give only the 4-thiol **33**, the structure of which was deduced by ^{19}F NMR spectroscopy: the absence of a large peri coupling constant; the presence of a doublet at δ −78.1 due to 2-F ($J_{2\text{-}F,3\text{-}F}$ 31 Hz) and a doublet at δ −136.1 due to 3-F (J 31 Hz and an SCS of +24.6 ppm). Interestingly, in the ^1H NMR spectrum, the hydrogen of the SH group coupled with the 3-F ($J_{3\text{-}F,H}$ 9 Hz) and the 5-F ($J_{5\text{-}F,H}$ 27 Hz).

The quinoline **2** was also treated at < −80 °C in ethanol with the sodium salts of methanethiol, propane-2-thiol, 2-methylpropane-2-thiol and benzenethiol. With the exception of the reaction with sodium hydrosulfide and sodium benzenethiolate, 2- and 4-monosubstituted products and 2,4-disubstituted products were formed. Once again, a considerable excess 2-methylpropane-2-thiol was required to suppress the formation of an ethoxy-substituted product, the 2-ethoxy-4-*tert*-butylthio compound **43**, which was otherwise formed by the incomplete reaction of the sodium ethoxide with the thiol. The quinoline **2** was also treated with three oxygen nucleophiles with substituents having increasing electron demand: ethoxide, phenoxide and 4-nitrophenoxide. The previously described reaction with aqueous ammonia in acetone has also been reinvestigated. The data for all these reactions are given in Table 2.

Discussion

The present position with regard to the orientation of fluorine displacement in heptafluoro-isoquinoline **1** and -quinoline **2** swings remarkably from one extreme to the other, depending on the nucleophile (see Tables 1 and 2). The isoquinoline **1** reacts with sodium methoxide in methanol to give the 1- and 6-derivatives in the ratio of 97:3 respectively, but with sodium hydrosulfide and sodium benzenethiolate, only the 6-substituted product is formed. With the quinoline **2**, sodium ethoxide in ethanol gives 2- and 4-derivatives in the ratio of 79:21 respectively, whereas with sodium hydrosulfide and sodium benzenethiolate, only the 4-substituted product is formed. We have checked that the reaction with the isoquinoline **1** is not proceeding *via* an electron-transfer process by carrying out a reaction with benzenethiolate in the dark with *m*-dinitrobenzene present as a radical-trapping agent: there was no change in the

Table 2 Reactions of heptafluoroquinoline **2** with nucleophiles

Nucleophile	Solvent	Product ratio[a] 2-Isomer (%)	4-Isomer (%)	2,4-Disubstituted product (%)
HS^-	DMF–EG		>95 (**33**)	
MeS^-	EtOH	4 (**34**)	95 (**35**)	1 (**36**)
Pr^iS^-	EtOH	5 (**37**)	91 (**38**)	4 (**39**)
Bu^tS^-	EtOH	5 (**40**)	93 (**41**)	2 (**42**)[b]
PhS^-	EtOH		>97 (**44**)	
EtO^-	EtOH	76 (**47**)	24 (**48**)	
PhO^-	EtOH	37 (**49**)	63 (**50**)	
$4\text{-}NO_2C_6H_4O^-$	EtOH	16 (**51**)	84 (**52**)	
NH_3	Acetone	43 (**53**)	57 (**54**)	

[a] Calculated on the basis of starting material converted (compound numbers in parentheses). [b] With a ten-fold excess of Bu^tSH present.

Table 3 Relative reactivities of **1** and **2** towards nucleophiles

	$4\text{-}Me_2N\text{–}C_6H_4S^-$	$4\text{-}MeO\text{–}C_6H_4S^-$	Pr^iS^-	PhS^-	EtO^-	$4\text{-}NO_2\text{–}C_6H_4S^-$
Reaction with **1**						
At position 6	12 000	3000	400	300	1	0.25
At position 1			10		1	
Reaction with **2**						
At position 4				1000	1	

orientation pattern. The only precedent for a significant change in the 'normal' pattern of substitution in polyfluoroheterocyclic compounds is the heterogeneous reaction of some sodium oximates with pentafluoropyridine in benzene or diethyl ether which give significant proportions of the 2-substituted compounds.[3] Specific interaction between the ring nitrogen and sodium cation were invoked to explain these observations.

The relative reactivities of some thiolates and ethoxide towards displacement of fluorine in the isoquinoline **1** and quinoline **2** in ethanol have been estimated by competition reactions whereby equimolar amounts of mixtures of nucleophiles were treated with a very small amount of the heterocycle—conditions which ensure that the ratios of products formed are directly proportional to the ratio of the second order rate constants for each reaction. The reactions carried out at −85 to −90 °C were quenched with trifluoroacetic acid at low temperatures (−60 to −70 °C) to minimise the formation of disubstituted products, and the crude reaction products were examined by ^{19}F NMR spectroscopy. The results are summarised in Table 3.

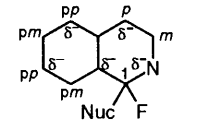
Finally the relative reactivities of the isoquinoline **1** and the quinoline **2** towards ethoxide have been measured. Equimolar amounts of **1** and **2** with a very low molecular proportion of ethoxide gave a product containing 12% **25** from the isoquinoline **1** and 68% **47** and 20% **48** from the quinoline **2**, *i.e.* the quinoline is more reactive than the isoquinoline by a factor of *ca.* 7. The equivalent factor towards benzenethiolate was *ca.* 30.

The major question raised by the results described in this paper is why do we observe such a dramatic change in orientation of nucleophilic attack from oxygen to sulfur nucleophiles? Table 3 shows that there is a very wide range in reactivity of the nucleophiles and this range of reactivity is an obvious potential cause of change. However, it is equally clear from the tables that no relationship between orientation and overall reactivity exists. Another alternative would be the intervention of single-electron transfer processes, which would be more likely with sulfur, but the addition of inhibitors and performance of the reactions completely in the dark leaves this possibility unlikely. Consequently, the most reasonable cause of the difference is the hardness/softness of the nucleophile.

Hard nucleophiles are more influenced by polar effects and preference for the harder 2-position, *i.e.* adjacent to nitrogen, in perfluoroquinoline and the 1-position in perfluoroisoquinoline, is evident for the oxygen-centred nucleophiles (Tables 1 and 2). Thus, we are left to account for the preference of sulfur-centred nucleophiles for the 6-position in perfluoroisoquinoline and the 4-position perfluoroquinoline.

It has previously been established[4] for highly fluorinated benzenoid and pyridine systems that nucleophilic displacement of fluorine is activated by fluorine atoms that are situated *ortho*- or *meta*- to the C–F reaction site, whereas fluorine that is *para*- to the reaction site is slightly deactivating. Furthermore, these findings have been extended to include bi- and poly-cyclic systems, by considering fluorine atom substituents in adjacent rings and adjacent to centres of developing high charge density as pseudo-*meta* (*i.e.* activating) or attached directly to these centres as pseudo-*para* (*i.e.* slightly deactivating).[5] Using this approach, we can compare the effect of fluorine substituents on the relative reactivities of various sites, in the quinoline and isoquinoline systems (see Schemes 1 and 2). Sites of nucleophilic attack that are not able to localise charge on nitrogen are discounted.

Therefore, in the isoquinoline system, **A**–**D**, Scheme 1, it is clear that 6-attack **C** maximises the activating effects of fluorine substituents and it seems reasonable to conclude, therefore, that these fluorine effects control the orientation of nucleophilic attack by sulfur-centred nucleophiles, on perfluoroisoquinoline. However, the alkanethiols and hydrosulfide nucleophiles also gave significant proportions of products arising from 1-substitution (Table 1), whereas even the 4-dimethylamino- and 4-methoxy-benzenethiolates gave barely detectable amounts of 1-substitution products. The alkanethiolate anions will be the

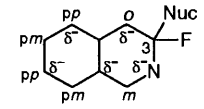


A

1*m* + 2p*m*, activating F-atoms

1*p* + 2p*p*, deactivating

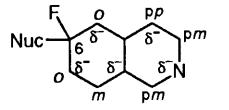
o = *ortho*, *m* = *meta*, p*p* = pseudo-*para*, p*m* = pseudo-*meta*



B

1*o*, 1*m* + 2p*m* } activating F-atoms

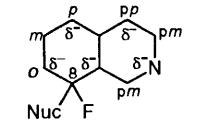
2p*p*, deactivating



C

2*o*, 1*m* + 2p*m* } activating F-atoms

1p*p*, deactivating

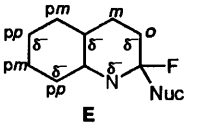


D

1*o*, 1*m* + 2p*m* } activating F-atoms

1*p* + 1p*p*, deactivating

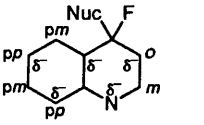
Scheme 1 Nucleophilic attack on perfluoroisoquinoline



E

1*o*, 1*m* + 2p*m* } activating F-atoms

2p*p*, deactivating



F

1*o*, 1*m* + 2p*m* } activating F-atoms

2p*p*, deactivating

Scheme 2 Nucleophilic attack on perfluoroquinoline

harder nucleophiles of this thiol series and therefore we see some influence of hardness, even with thiols. Considering **E** and **F**, Scheme 2, for attack on the perfluoroquinoline system, the activating influences of the fluorine substituents do not indicate any clear preference between 2- and 4-attack and this implies, therefore, that any difference between 4- and 2-substitution arises from effects of nitrogen discriminating between these two positions, since nitrogen is obviously the major activating influence in these systems.[6] With sulfur nucleophiles, attack at position 4- is clearly favoured (Table 2) and this must reflect a lower localisation energy for **F**, than **E**.

Therefore, the problem is directed towards explaining why, with oxygen nucleophiles, there is a greater tendency towards attacking the position adjacent to nitrogen, *i.e.* the 1-position in perfluoroisoquinoline and the 2-position in perfluoroquinoline. Oxygen is a 'harder' nucleophile than sulfur and it may be argued that coulombic influences become greater[7] with the harder nucleophile, and therefore attack occurs at the 'harder' centres, *i.e.* adjacent to nitrogen. This conclusion has some support from the results contained in Table 2 where, as we proceed from EtO^-, PhO^-, $4\text{-}NO_2C_6H_4O^-$, then the 'hardness' of the nucleophile diminishes and, correspondingly, we have a change in preference from 2-attack in perfluoroquinoline, by the harder EtO^-, to 4-attack by the softer $4\text{-}NO_2C_6H_4O^-$. In the perfluoroisoquinoline system, however, there is little discernible change in preference with these nucleophiles and we conclude, therefore, that orientation of attack is more finely balanced in the quinoline system.

Thus, although the orientating effects of fluorine substituents in polyfluoroaromatic systems are reasonably clear, it is now more obvious that the nature of the nucleophile itself can have more substantial effects on the preferred orientation of attack, than had been realised, hitherto.

Experimental

NMR spectra were obtained with a Bruker AC250 spectrometer [^1H (250 MHz) and ^{19}F (235 MHz)]. Chemical shifts are downfield from internal $SiMe_4$ or upfield from internal $CFCl_3$. *J*-Values are given in Hz. Previously the ^{19}F NMR spectra of 1,3,4,5,6,7,8-heptafluoroisoquinoline **1** and 2,3,4,5,6,7,8-heptafluoroisoquinoline **2** had been measured in [$^2H_6$]acetone; these have now been remeasured in $CDCl_3$: δ_F for **1** −62.1 (1-F), −96.7 (3-F), −155.7 (4-F), −145.8 (5-F), −145.4 (6-F), −153.1 (7-F) and −139.7 (8-F); $J_{1\text{-}F,8\text{-}F}$ 61; $J_{1\text{-}F,4\text{-}F}$ 33 and $J_{4\text{-}F,5\text{-}F}$ 48; δ_F for **2** −72.4 (2-F), −160.8 (3-F), −124.1 (4-F), −146.1 (5-F), −154.3 (6-F), −150.5 (7-F) and −148.3 (8-F); $J_{2\text{-}F,3\text{-}F}$ 26, $J_{3\text{-}F,4\text{-}F}$ 26 and $J_{4\text{-}F,5\text{-}F}$ 46.

Mass spectroscopy data were obtained with a VG 7070E instrument. Molecular ions M^+ are quoted for electron ionisation.

Reactions of 1,3,4,5,6,7,8-*Heptafluoroisoquinoline* **1**.—(A) *With sulfur nucleophiles.* (i) *With sodium hydrosulfide.* The isoquinoline **1** (1.362 g, 5.34 mmol) in a mixture of anhydrous *N*,*N*-dimethylformamide (DMF) (5 cm^3) and ethylene glycol (EG) (2.5 cm^3) was treated at −5 to 2 °C with sodium hydrosulfide (0.612 g, 10.9 mmol) in a mixture of DMF (5 cm^3) and EG (2.5 cm^3) over 10 min. The internal temperature was raised to 26 °C and after 30 min the mixture was acidified (2 mol dm^{-3} H_2SO_4), extracted with diethyl ether, the extracts dried ($MgSO_4$) and the solvent evaporated. The crude residue (1.46 g), shown by ^{19}F NMR spectroscopy ($CDCl_3$) to contain only one compound, was sublimed at < 55 °C/0.05 mmHg and the sublimate (1.27 g) recrystallised from light petroleum (b.p. 30–40 °C) to give 1,3,4,5,7,8-*hexafluoroisoquinoline*-6-*thiol* **3**, m.p. 74.0–74.5 °C (Found: C, 40.2; H, 0.3; N, 4.91. C_9HF_6NS requires C, 40.16; H, 0.37; N, 5.20%); $\delta_F(CDCl_3)$ −62.9 (ddd, 1-F), −97.3 (br s, 3-F), −117.75 (dd, 5-F), −132.0 (d, 7-F), −143.3 (dt, 8-F) and −155.8 (ddd, 4-F); $J_{1\text{-}F,4\text{-}F}$ 33.2, $J_{1\text{-}F,8\text{-}F}$ 59.4, $J_{3\text{-}F,4\text{-}F}$ 15.3, $J_{4\text{-}F,5\text{-}F}$ 51.9, $J_{5\text{-}F,8\text{-}F}$ 18.9 and $J_{7\text{-}F,8\text{-}F}$ 18.6; ν_{max}/cm^{-1} 2600 (SH).

The treatment of the isoquinoline **1** (0.249 g, 0.98 mmol) with sodium hydrosulfide (0.117 g, 2.09 mmol) in methanol (10 cm^3) at −33 to −43 °C gave two major products: the 6-thiol **3** (92 parts) and the 1-thiol **4** (8 parts). The minor component **4** was recognised in the product by ^{19}F NMR spectroscopy; $\delta_F(CDCl_3)$ −95.5 (3-F), −137.1 (8-F), −145.1 (5-F), −147.6 (6-F), −154.8 (7-F) and −158.3 (4-F); $J_{4\text{-}F,5\text{-}F}$, 51; the spectrum was identical with that of the material obtained by the dealkylation of 3,4,5,6,7,8-hexafluoro-1-(*tert*-butylthio)isoquinoline **11** with trifluoroacetic acid.

(ii) *With Sodium Methanethiolate.*—The solution made by passing methanethiol gas through sodium ethoxide solution (0.369 mol dm^{-3}; 2.4 cm^3, 0.89 mmol) was added to a suspension of the isoquinoline **1** (0.248 g, 0.97 mmol) in anhydrous ethanol (40 cm^3) at −85 to −90 °C, over 2 min. The mixture was allowed to warm up to room temperature, acidified (2 mol dm^{-3} H_2SO_4) and extracted with diethyl ether. The ether extracts were dried ($MgSO_4$), the solvent evaporated and the crude product (0.226 g) was shown by ^{19}F NMR spectroscopy to contain unchanged starting material **1** (12%) and the three products (88%): the 1-methylthio **5**, the 6-methylthio **6** and the 1,6-di(methylthio) **7** compounds present in the ratio 22:73:5 respectively. The mixture was separated by flash chromatography on silica using carbon tetrachloride as eluent to give an enrichment of the two faster moving components, while crystallisation of the mixture of the two slowest eluting

components (one of which was the unchanged isoquinoline **1**) gave 1,3,4,5,7,8-*hexafluoro*-6-(*methylthio*)*isoquinoline* **6**, m.p. 47.5–48.0 °C [from light petroleum (b.p. 60–80 °C)] (Found: C, 42.5; H, 1.1; N, 4.8%; M^+, 283. $C_{10}H_3F_6NS$ requires C, 42.41; H, 1.07; N, 4.95%; *M*, 283); $\delta_F(CDCl_3)$ −63.1 (ddd, 1-F), −97.5 (s, 3-F), −114.7 (dd, 5-F), −130.3 (d, 7-F), −143.8 (dt, 8-F) and −154.9 (ddd, 4-F); $J_{1-F,4-F}$ 35; $J_{1-F,8-F}$ 57, $J_{4-F,5-F}$ 54 and $J_{5-F,8-F}$ 19.3; $\delta_H(CDCl_3)$ 2.72 (t, CH_3, *J* 1.1). Flash chromatography of the enriched faster moving components, on silica using light petroleum (b.p. 60–80 °C) as eluent gave as faster moving component 3,4,5,6,7,8-*hexafluoro*-1-(*methylthio*)*isoquinoline* **5**, m.p. 65.0–65.5 °C [from light petroleum (b.p. 60–80 °C)] (Found: C, 42.1; H, 1.1; N, 4.8%; M^+, 283. $C_{10}H_3F_6NS$ requires C, 42.41; H, 1.07; N, 4.95%; *M*, 283); $\delta_F(CDCl_3)$ −96.6 (d, 3-F), −134.4 (t, 8-F), −145.7 (dt, 5-F), −149.0 (t, 6-F), −155.7 (t, 7-F) and −161.4 (dd, 4-F); $J_{3-F,4-F}$ 18 and $J_{4-F,5-F}$ 51; $\delta_H(CDCl_3)$ 2.64 (s, CH_3). A larger amount of the minor slower eluting compound prepared from the 6-sulfide **6** by further treatment with sodium methanethiolate, was 3,4,5,7,8-*pentafluoro*-1,6-*di*(*methylthio*)*isoquinoline* **7**, m.p. 106.0–106.5 °C [from light petroleum (b.p. 60–80 °C)] (Found: C, 42.4; H, 2.1; N, 4.1%; M^+, 311. $C_{11}H_6F_5NS_2$ requires C, 42.44; H, 1.94; N, 4.05%; *M*, 311); $\delta_F(CDCl_3)$ −97.7 (d, 3-F), −114.0 (dd, 5-F), −132.9 (d, 7-F), −138.5 (t, 8-F) and −160.7 (dd, 4-F); $J_{3-F,4-F}$ 19, $J_{4-F,5-F}$ 61 and $J_{5-F,8-F}$ 19; $\delta_H(CDCl_3)$ 2.62 (s, 1-SCH_3) and 2.66 (d, 6-SCH_3).

(iii) *With Sodium Propane-2-thiolate.*—The thiolate was prepared by the treatment of sodium ethoxide in ethanol with 1 equivalent of propane-2-thiol and was treated with the isoquinoline **1** as in (ii). The product consisted of unchanged starting material **1** (26%) and three other products (74%); the 1-(isopropylthio) **8**, the 6-(isopropylthio) **9**, and the 1,6-di(isopropylthio) **10** compounds, present in the ratio 24:71:5 respectively. The mixture was chromatographed on silica using light petroleum (b.p. 40–60 °C); the fastest eluting component was 3,4,5,6,7,8-*hexafluoro*-1-(*isopropylthio*)*isoquinoline* **8**, m.p. 54.5–54.7 °C [from light petroleum (b.p. 40–60 °C)] (Found: C, 46.5; H, 2.1; N, 4.5%; M^+, 311. $C_{12}H_7F_6NS$ requires C, 46.31; H, 2.27; N, 4.50%; *M*, 311); $\delta_F(CDCl_3)$ −96.4 (d, 3-F), −134.1 (t, 8-F), −145.85 (dtd, 5-F), −149.2 (t, 6-F), −156.0 (t, 7-F) and −161.3 (dd, 4-F); $J_{3-F,4-F}$ 20.2 and $J_{4-F,5-F}$ 53.8; $\delta_H(CDCl_3)$ 1.46 [d, $(CH_3)_2$ and 4.09 (heptet, CH). The slowest moving component was 1,3,4,5,7,8-*hexafluoro*-6-(*isopropylthio*)*isoquinoline* **9**, m.p. 51.5–52.5 °C [from light petroleum (b.p. 40–60 °C)] (Found: C, 46.6; H, 2.1; N, 4.5%; M^+, 311. $C_{12}H_7F_6NS$ requires C, 46.31; H, 2.27; N, 4.50%; *M*, 311); $\delta_F(CDCl_3)$ −63.1 (ddd, 1-F), −97.7 (narrow m, 3-F), −112.1 (dd, 5-F), −128.7 (d, 7-F), −143.7 (dtd, 8-F) and −154.4 (dddd, 4-F); $J_{1-F,4-F}$ 33.3, $J_{1-F,8-F}$ 59.6, $J_{4-F,3-F}$ 15.4, $J_{4-F,5-F}$ 56.4, $J_{5-F,8-F}$ 19.5 and $J_{7-F,8-F}$ 19.7; $\delta_H(CDCl_3)$ 1.37 [d $(CH_3)_2$] and 3.85 (heptet, CH). The minor component of the product was obtained by treating a mixture of **8** and **9** with sodium propane-2-thiolate as before to give 3,4,5,7,8-*pentafluoro*-1,6-*di*(*isopropylthio*)*isoquinoline* **10**, an oil vapourising at 123 °C/0.05 mmHg (Found: C, 48.8; H, 3.6; N, 3.65%; M^+, 367. $C_{15}H_{14}F_5NS_2$ requires C, 49.04; H, 3.84; N, 3.81%; *M*, 367); $\delta_F(CDCl_3)$ −97.5 (d, 3-F), −111.6 (dd, 5-F), −131.5 (d, 7-F), −137.9 (t, 8-F) and −160.2 (dd, 4-F); $J_{3-F,4-F}$ 20.2, $J_{4-F,5-F}$ 61.8, $J_{5-F,8-F}$ 18 and $J_{7-F,8-F}$ 20; $\delta_H(CDCl_3)$ 1.37 [d, $(CH_3)_2$], 1.45 [d, $(CH_3)_2$] 3.76 (heptet, CH) and 4.04 (heptet, CH).

(iv) *With Sodium 2-Methylpropane-2-thiolate.*—The thiolate was prepared by the reaction of sodium ethoxide in ethanol with 2-methylpropane-2-thiol (1.05 equiv.), and was treated with the isoquinoline **1** as in (ii). The product consisted of unchanged starting material **1** (12%) and five other products (88%): the 1-(*tert*-butylthio) **11**, the 6-(*tert*-butylthio) **12**, the 1,6-di(*tert*-butylthio) **13**, the 1-ethoxy **25** and the 1-ethoxy-6-(*tert*-butylthio) **14** compounds present in the ratio 14:72:3.5:7:3.5. Chromatographic separation of the products was carried out as in (ii) to give: 1,3,4,5,7,8-*hexafluoro*-6-(*tert-butylthio*)*isoquinoline* **12**, m.p. 127.0–127.5 °C [from light petroleum (b.p. 60–80 °C)] (Found: C, 47.7; H, 2.85; N, 4.2%; M^+, 325. $C_{13}H_9F_6NS$ requires C, 48.00; H, 2.79; N, 4.31%; *M*, 325); $\delta_F(CDCl_3)$ − 62.5 (ddd, 1-F), −97.3 (3-5), −106.6 (dd, 5-F), −124.5 (d, 7-F), −142.9 (dt, 8-F) and −153.0 (ddd, 4-F); $J_{1-F,4-F}$ 33, $J_{1-F,8-F}$ 60, $J_{4-F,5-F}$ 59 and $J_{5-F,8-F}$ 20; $\delta_H(CDCl_3)$ 1.42 [s, $(CH_3)_3C$] and 3,4,5,6,7,8-*hexafluoro*-1-(tert-*butylthio*)*isoquinoline* **11**, m.p. 71.5–72.0 °C [from light petroleum (b.p. 60–80 °C)] (Found: C, 48.3; H, 2.8; N, 4.1%; M^+, 325. $C_{13}H_9F_6NS$ requires C, 48.00; H, 2.79; N, 4.31%; *M*, 325); $\delta_F(CDCl_3)$ −96.7 (d, 3-F), −132.3 (t, 8-F), −145.9 (dt, 5-F), −149.5 (t, 6-F), −156.0 (ddd, 7-F) and −161.3 (dd, 4-F); $J_{3-F,4-F}$ 21.5 and $J_{4-F,5-F}$ 54.4; $\delta_H(CDCl_3)$ 1.68 [s, $(CH_3)_2C$]. Two minor components found in the reaction were made in equimolar proportions from the 6-(*tert*-butylthio)isoquinoline **12** with sodium 2-methylpropane-2-thiolate in ethanol as before and separated by flash chromatography on silica using CCl_4 as eluent: 3,4,5,7,8-*pentafluoro*-1,6-*di*(tert-*butylthio*)*isoquinoline* **13**, an oil (Found: C, 51.8; H, 4.4; N, 3.2%; M^+, 395. $C_{17}H_{18}F_5NS_2$ requires C, 51.63; H, 4.59; N, 3.54%; *M*, 395); $\delta_F(CDCl_3)$ −97.7 (d, 3-F), −106.9 (dd, 5-F), −127.8 (d, 7-F), −135.5 (t, 8-F) and −159.1 (dd, 4-F); $J_{3-F,4-F}$ 20.5, $J_{4-F,5-F}$ 65 and $J_{5-F,8-F}$ 20; $\delta_H(CDCl_3)$ 1.39 [s, 6-$(CH_3)_3C$] and 1.69 [s, 1-$(CH_3)_3C$] and 1-*ethoxy*-3,4,5,7,8-*pentafluoro*-6-(tert-*butylthio*)*isoquinoline* **14**, m.p. 99.5–100.0 °C [from light petroleum (b.p. 60–80 °C)] (Found: C, 51.3; H, 3.8; N, 3.8%; M^+, 351. $C_{15}H_{14}F_5NOS$ requires C, 51.28; H, 4.02; N, 3.99%; *M*, 351); $\delta_F(CDCl_3)$ −99.5 (d, 3-F), −109.0 (dd, 5-F), −128.3 (d, 7-F), −140.1 (t, 8-F) and −163.8 (dd, 4-F); $J_{3-F,4-F}$ 18, $J_{4-F,5-F}$ 60.6 and $J_{5-F,8-F}$ 20.9; $\delta_H(CDCl_3)$ 1.39 [s, $(CH_3)_3C$], 1.50 (t, CH_3) and 4.54 (q, CH_2). The synthesis of the other minor component of the reaction, 1-ethoxy-3,4,5,6,7,8-pentafluoroisoquinoline **25** is described below.

A reaction similar to the one described above, carried out with a ten-fold excess of 2-methylpropane-2-thiol present, gave a product which contained unchanged starting material **1** (2%) and only three other products (98%): the 1-(*tert*-butylthio) compound **11**, the 6-(*tert*-butylthio) compound **12** and the 1,6-di(*tert*-butylthio) compound **13** present in the ratio 16:79:5 respectively.

(v) *With Sodium Benzenethiolate.*—The thiolate was prepared by the treatment of sodium ethoxide in ethanol with benzenethiol (1.1 equiv.) and then treated with the isoquinoline **1** as in (ii). The product consisted of unchanged starting material **1** (3%) and two other components (97%): the 6-phenylthio **15** and the 1,6-di(phenylthio) **16** compounds present in the ratio 99:1 respectively. Recrystallisation gave 1,3,4,5,7,8-*hexafluoro*-6-(*phenylthio*)*isoquinoline* **15**, m.p. 120.5–121.0 °C [from light petroleum (b.p. 60–80 °C)] (Found: C, 52.3; H, 1.4; N, 4.0%; M^+, 345. $C_{15}H_5F_6NS$ requires C, 52.18; H, 1.46; N, 4.06%; *M*, 345); $\delta_F(CDCl_3)$ −62.7 (ddd, 1-F), −97.2 (s, 3-F), −111.3 (dd, 5-F), −127.9 (d, 7-F), −142.6 (dt, 8-F) and −153.9 (ddd, 4-F); $J_{1-F,4-F}$ 34, $J_{1-F,8-F}$ 60.2, $J_{4-F,5-F}$ 55 and $J_{5-F,8-F}$ 19.5; $\delta_H(CDCl_3)$ 7.36 (m, ArH), 7.48 (m, ArH). The minor component, 3,4,5,7,8-*pentafluoro*-1,6-*di*(*phenylthio*)*isoquinoline* **16**, was prepared in a separate experiment from **1** and two equiv. of sodium benzenethiolate: m.p. 141.5–142.0 °C [from light petroleum (b.p. 100–120 °C)] (Found: C, 58.3; H, 2.3; N, 3.15%; M^+, 435. $C_{21}H_{10}F_5NS_2$ requires C, 57.93; H, 2.31; N, 3.22%; *M*, 435); $\delta_F(CDCl_3)$ −95.9 (3-F, d), −110.7 (5-F, dd), −130.3 (7-F, d), −136.6 (8-F, t) and −157.8 (4-F, d); $J_{4-F,5-F}$ 61; $\delta_H(CDCl_3)$ 7.58, 7.48 and 7.34 (all m, ArH).

A mixture of the isoquinoline **1** and *m*-dinitrobenzene (1.5

equiv.) in ethanol at < −80 °C was treated in the dark with sodium benzenethiolate (0.8 equiv.). The temperature was raised to −30 °C, the mixture than cooled to −50 °C and quenched with trifluoroacetic acid and worked up as before. The product consisted of unchanged starting material **1** (45%) and the 6-phenylthio compound **15**.

(vi) *With Sodium* 4-N,N-*Dimethylaminobenzenethiolate.*—The experiment carried out as in (v) gave a product which contained unchanged starting material **1** (0.5%) and three products (99.5%): the 1-substituted **18**, the 6-substituted **19**, and the 1,6-disubstituted **20** compounds, present in the ratio 0.5:97.5:2 respectively. The major product was 6-(4-N,N-*dimethylaminophenylthio*)-1,3,4,5,7,8-*hexafluoroisoquinoline* **19**, m.p. 155.0–155.5 °C [from light petroleum (b.p. 100–120 °C)] (Found: C, 52.3; H, 2.5; N, 7.0%; M^+, 388. $C_{17}H_{10}F_6N_2S$ requires C, 52.58; H, 2.60; N, 7.21%; *M*, 388); $\delta_F(CDCl_3)$ −63.1 (ddd, 1-F), −98.0 (s, 3-F), −113.6 (dd, 5-F), −129.2 (d, 7-F), −143.5 (dt, 8-F) and −154.5 (dt, 4-F); $J_{1-F,4-F}$ 33, $J_{1-F,8-F}$ 59.5 and $J_{4-F,5-F}$ 55.5; $\delta_H(CDCl_3)$ 7.47 (d, ArH), 6.62 (d, ArH) and 2.97 (s, CH_3). The minor component 1-(4-*N*,*N*-dimethylaminophenylthio)isoquinoline **18** had $\delta_F(CDCl_3)$ −94.7 (3-F), −132.8 (8-F), −144.8 (5-F), −149.2 (6-F), −156.0 (7-F) and −160.5 (4-F). The disubstituted product was made by the treatment of **19** with more nucleophile: 1,6-*di*(4-N,N-*dimethylaminophenylthio*)-3,4,5,7,8-*pentafluoroisoquinoline* **20**, m.p. 195.5–196.0 °C [from light petroleum (b.p. 100–120 °C)] (Found: C, 57.6; H, 3.9; N, 7.8%; M^+, 522. $C_{25}H_{20}F_5N_3S_2$ requires C, 57.57; H, 3.86; N, 8.06%; *M*, 522); $\delta_F(CDCl_3)$ −96.3 (d, 3-F), −113.1 (dd, 5-F), −131.8 (d, 7-F), −136.7 (t, 8-F) and −159.3 (dd, 4-F); $J_{4-F,5-F}$ 61; $\delta_H(CDCl_3)$ 7.46 (d, ArH), 7.36 (d, ArH), 6.74 (d, ArH), 6.62 (d, ArH), 3.02 (s, CH_3) and 2.97 (s, CH_3).

(vii) *With Sodium* 4-*Methoxybenzenethiolate.*—The experiment carried out as in (v) gave a product which contained only the 1-substituted **21**, the 6-substituted **22** and the 1,6-disubstituted **23** compounds present in the ratio 0.5:97.5:2 respectively. The major component of the product was obtained by sublimation (140 °C/0.1 mmHg) and recrystallisation: 1,3,4,5,7,8-*hexafluoro*-6-(4-*methoxyphenylthio*)*isoquinoline* **22**, m.p. 90.5–91.0 °C [from light petroleum (b.p. 60–80 °C)] (Found: C, 51.3; H, 1.85; N, 3.65%; M^+, 375. $C_{16}H_7F_6NOS$ requires C, 51.21; H, 1.88; N, 3.73%; *M*, 375); $\delta_F(CDCl_3)$ −62.9 (ddd, 1-F), −97.5 (s, 3-F), −112.6 (ddd, 5-F), −128.8 (d, 7-F), −143.1 (dt, 8-F) and −154.2 (ddd, 4-F); $J_{1-F,4-F}$ 33, $J_{1-F,8-F}$ 59.5 and $J_{4-F,5-F}$ 56; $\delta_H(CDCl_3)$ 7.44 (d, ArH), 6.79 (d, ArH) and 3.74 (s, CH_3). The minor component 1-(4-methoxyphenylthio)isoquinoline **21** had $\delta_F(CDCl_3)$ −95.6 (d, 3-F), −133.8 (t, 8-F), −146.0 (dt, 5-F), −149.2 (br t, 6-F), −155.8 (t, 7-F) and −160.0 (dd, 4-F). The disubstituted compound was obtained by the treatment of **22** with more nucleophile: 3,4,5,7,8-*pentafluoro*-1,6-*di*(4-*methoxyphenylthio*)*isoquinoline* **23**, m.p. 144.5–145.0 °C [from light petroleum (b.p. 100–120 °C)] (Found: C, 56.1; H, 2.8; N, 2.7%; M^+, 495. $C_{23}H_{14}F_5NO_2S_2$ requires C, 55.75; H, 2.85; N, 2.83%; *M*, 495); $\delta_F(CDCl_3)$ −96.2 (d, 3-F), −112.1 (dd, 5-F), −131.3 (d, 7-F), −136.8 (t, 8-F) and −158.4 (dd, 4-F); $J_{4-F,5-F}$ 61; $\delta_H(CDCl_3)$ 7.51 (d, ArH), 7.46 (d, ArH), 7.00 (d, ArH), 6.87 (d, ArH), 3.88 (s, CH_3) and 3.82 (s, CH_3).

(viii) *With Sodium* 4-*Nitrobenzenethiolate.*—The experiment carried out as in (v) gave a product which contained unchanged starting material **1** (11%) and only one product (89%): 1,3,4,5,7,8-*hexafluoro*-6-(4-*nitrophenylthio*)*isoquinoline* **24**, m.p. 112.0–112.5 °C [from light petroleum (b.p. 60–80 °C)] (Found: C, 46.15; H, 1.03; N, 7.05%; M^+, 390. $C_{15}H_4F_6N_2O_2S$ requires C, 46.16; H, 1.03; N, 7.18%; *M*, 390); $\delta_F(CDCl_3)$ −61.7 (ddd, 1-F), −95.7 (s, 3-F), −109.1 (dd, 5-F), −127.6 (d, 7-F), −141.1 (dt, 8-F) and −153.0 (ddd, 4-F); $J_{1-F,8-F}$ 60.3, $J_{1-F,4-F}$ 34 and $J_{4-F,5-F}$ 55.5; $\delta_H(CDCl_3)$ 8.19 (d, ArH), 7.46 (d, ArH).

(B) *With Oxygen Nucleophiles.*—(i) *With sodium methoxide.* Sodium methoxide (0.40 mmol) in methanol (5 cm^3) was added to a suspension of the isoquinoline **1** (0.47 mmol) in methanol (30 cm^3) at −82 to −84 °C over 2 min, the mixture warmed to room temperature, acidified (2 mol dm^{-3} H_2SO_4) and the product extracted into diethyl ether. The extracts were dried ($MgSO_4$), filtered and the solvent evaporated. The crude residue (0.140 g) was shown by ^{19}F NMR to contain residual starting material **1** (26%) and two products (74%): the 1-methoxy **28** and the 6-methoxy **29** compounds, present in the ratio 97:3 respectively.

(ii) *With Sodium Ethoxide.*—The experiment carried out as in (i) gave a product which was shown by ^{19}F NMR to contain residual starting material **1** (17%) and two products (83%): 1-ethoxy **25** and the 6-ethoxy **26** compounds, present in the ratio 94:6 respectively. Recrystallisation of the crude product gave 1-*ethoxy*-3,4,5,6,7,8-*hexafluoroisoquinoline* **25**, m.p. 52.0–52.5 °C [from light petroleum (b.p. 60–80 °C)] (Found: C, 47.1; H, 1.8; N, 4.8%; M^+, 281. $C_{11}H_5F_6NO$ requires C, 46.99; H, 1.79; N, 4.98%; *M*, 281); $\delta_F(CDCl_3)$ −98.2 (d, 3-F), −136.8 (d, 8-F), −147.6 (dt, 5-F), −148.9 (t, 6-F), −156.9 (t, 7-F) and −165.8 (dd, 4-F); $J_{4-F,5-F}$ 49 and $J_{5-F,8-F}$ 17.8; $\delta_H(CDCl_3)$ 4.45 (q, CH_2) and 1.43 (t, CH_3). The minor component, the 6-ethoxyisoquinoline **26** had $\delta_F(CDCl_3)$ −63.9 (ddd, 1-F), −98.8 (3-F), −141.8 (dd, 5-F), −142.9 (dt, 8-F), −148.1 (7-F) and −156.3 (4-F). The ^{19}F NMR of the product from the treatment of the isoquinoline **1** with a slight excess of sodium ethoxide showed the presence of only the 1-ethoxy compound **25** and the 1,6-diethoxyisoquinoline **27**—*i.e.* the 6-isomer had reacted further preferentially. A separate experiment with **25** and sodium ethoxide gave a yellow oil 1,6-*diethoxy*-3,4,5,7,8-*pentafluoroisoquinoline* **27** (Found: C, 51.3; H, 3.45; N, 4.5%; M^+, 307. $C_{13}H_{10}F_5NO_2$ requires C, 50.82; H, 3.28; N, 4.56%; *M*, 307); $\delta_F(CDCl_3)$ −100.4 (d, 3-F), −139.8 (t, 8-F), −142.7 (dd, 5-F), −151.9 (d, 7-F) and −166.5 (dd, 4-F); $J_{4-F,5-F}$ 54.8 and $J_{3-F,4-F}$ 18; $\delta_H(CDCl_3)$ 1.47 (t, CH_3) and 4.47 (overlapping q, CH_2).

(iii) *With Sodium Phenoxide.*—The phenoxide was prepared by the reaction of sodium ethoxide in ethanol with phenol (10 equiv.) and was treated with the isoquinoline as in (i). The excess of phenol was removed from the crude product by chromatography on silica using carbon tetrachloride as eluent to give a mixture of unchanged starting material **1** (25%) and four other products (75%): a pair of phenoxy isomers (8 parts), the 1-phenoxy **30** and the 6-phenoxy **31** compounds present in the ratio 93:7 respectively; and the pair of ethoxy isomers (2 parts), the 1-ethoxy **25** and the 6-ethoxy **26** compounds, present in the ratio 92:8 respectively. Exhaustive sublimation of the product at 45 °C/0.1 mmHg and crystallisation of the residue gave 3,4,5,6,7,8-*hexafluoro*-1-*phenoxyisoquinoline* **30**, m.p. 126.5–127.0 °C [from light petroleum (b.p. 60–80 °C)] (Found: C, 55.1; H, 1.45; N, 4.0%; M^+, 329. $C_{15}H_5F_6NO$ requires C, 54.73; H, 1.53; N, 4.25%; *M*, 329); $\delta_F(CDCl_3)$ −96.8 (d, 3-F), −136.4 (t, 8-F), −147.0 (dt, 5-F), −147.7 (t, 6-F), −155.6 (t, 7-F) and −162.2 (dd, 4-F); $J_{4-F,5-F}$ 49 and $J_{5-F,8-F}$ 17; $\delta_H(CDCl_3)$ 7.39 (m, ArH), 7.20 (m, ArH). The presence of the 6-phenoxy isomer **31** was inferred from two separate absorptions in the ^{19}F NMR of the crude reaction product: $\delta_F(CDCl_3)$ −62.9 (ddd, 1-F) and −141.0 (dt, 8-F).

(iv) *With Sodium* 4-*Nitrophenoxide.*—The experiment carried out as in (iii) gave a product which contained residual starting material **1** (99%) and the product (1%) 1-(4-nitrophenoxy)-

isoquinoline **32** only. The experiment was repeated at reflux temperature for 2 h and gave unchanged starting material **1** (13%) and only two other detectable products (87%): the 1-(4-nitrophenoxy) **32** and the 1-ethoxy **25** compounds, present in the ratio 93:7, respectively. Exhaustive sublimation of the crude product at 50 °C/0.1 mmHg and chromatography of the residue on silica using CCl_4–$CHCl_3$ 1:3 v/v as eluent to remove excess 4-nitrophenol gave 3,4,5,6,7,8-*hexafluoro*-1-(4-*nitrophenoxy*)-*isoquinoline* **32**, m.p. 145.0–145.5 °C [from light petroleum (b.p. 60–80 °C)] (Found: C, 48.0; H, 0.9; N, 7.35%; M^+, 374. $C_{15}H_4F_6N_2O_3$ requires C, 48.15; H, 1.08; N, 7.49%; *M*, 374); $\delta_F(CDCl_3)$ −96.9 (d, 3-F), −136.7 (t, 8-F), −146.0, −146.2 (overlapping multiplets 5-F, 6-F), −154.0 (t, 7-F) and −159.6 (dd, 4-F); $J_{4-F,5-F}$ 49 and $J_{5-F,8-F}$ 18; $\delta_H(CDCl_3)$ 8.36 (d, ArH), 7.42 (d, ArH).

Reactions of 2,3,4,5,6,7,8-*Heptafluoroquinoline* **2**.—(A) *With sulfur nucleophiles.* (i) *With sodium hydrosulfide.* The quinoline **2** (0.261 g, 1.02 mmol) in a mixture of anhydrous DMF (5 cm^3) and EG (2.5 cm^3) was treated at −6 to −4 °C over 2 min with sodium hydrosulfide (0.0977 g, 1.74 mmol) in a mixture of DMF (5 cm^3) and EG (2.5 cm^3). The mixture was maintained at −2 °C for 30 min and then rapidly worked up by diluting with pre-cooled diethyl ether (−10 °C) and iced water and acidifying with pre-cooled acid (2 mol dm^{-3} H_2SO_4 at 0 °C). The cold organic extract was dried ($MgSO_4$), the solvent evaporated under reduced pressure and the crude residue (0.284 g) sublimed at 60 °C/0.5 mmHg to give the sublimate (0.195 g, 71%) the ^{19}F NMR spectrum of which showed it was the 4-thiol accompanied by two minor components (neither of which gave an absorption slightly upfield of δ −124.1 where the 4-F would be expected in the 2-thiol from SCS calculations) present in the ratio 95:5 respectively. Recrystallisation of the sublimate gave 2,3,5,6,7,8-*hexafluoroquinoline*-4-*thiol* **33**, m.p. 106.5–107.0 °C [from light petroleum (b.p. 60–80 °C)] (Found: C, 40.1; H, 0.3; N, 5.1%; M^+, 269. C_9HF_6NS requires C, 40.16; H, 0.37; N, 5.20%; *M*, 269); $\delta_F(CDCl_3)$ −78.1 (d, 2-F), −136.1 (dt, 3-F), −143.3 (m, 5-F), −148.1 (td), −152.3 (td) and −156.2 (td) (all unassigned); $\delta_H(CDCl_3)$ 4.66 (dd, S–H); $J_{H,3-F}$ 9.3 and $H_{H,5-F}$ 27.3.

(ii) *With Sodium Methanethiolate.*—The solution made by passing an excess of methanethiol gas through sodium ethoxide solution (0.369 mol dm^{-3}; 2.4 cm^3, 0.88 mmol) was added to a suspension of the quinoline **2** (0.250 g, 0.98 mmol) in anhydrous ethanol (40 cm^3) at −85 to −90 °C over 2 min. The product was acidified (2 mol dm^{-3} H_2SO_4), extracted with diethyl ether, dried ($MgSO_4$), the solvent evaporated and the residue (0.264 g) shown by ^{19}F NMR spectroscopy to contain residual starting material **2** (2.5%) and three main components (97.5%): the 2-methylthio **34**, the 4-methylthio **35** and the 2,4-di(methylthio) **36** compounds, present in the ratio 4:95:1 respectively. Four fractions were collected from flash chromatography of the product on silica using carbon tetrachloride. The fourth fraction contained 2,3,5,6,7,8-*hexafluoro*-4-(*methylthio*)*quinoline* **35**, m.p. 61.5–62.0 °C [from light petroleum (b.p. 40–60 °C)] (Found: C, 42.3; H, 0.9; N, 4.9%; M^+, 283. $C_{10}H_3F_6NS$ requires C, 42.41; H, 1.07; N, 4.95%; *M*, 283); $\delta_F(CDCl_3)$ −78.8 (d, 2-F), −135.1 (d, 3-F); −138.5 (t), −148.4, −153.2 and −156.2 (all t, unassigned); $J_{2-F,3-F}$ 29; $\delta_H(CDCl_3)$ 2.80 (d, CH_3); $J_{CH,F}$ 5; the first fraction contained two components which were separated by re-chromatography on silica using light petroleum (b.p. 40–60 °C) to give firstly 3,4,5,6,7,8-*hexafluoro*-2-(*methylthio*)*quinoline* **34**, m.p. 54–56 °C (from methanol) (Found: C, 42.4; H, 1.0; N, 4.9%; M^+, 283. $C_{10}H_3F_6NS$ requires C, 42.41; H, 1.07; N, 4.95%; *M*, 283); $\delta_F(CDCl_3)$ −136.7 (dd, 4-F), −147.1 (m, 5-F), −148.4 (nm, 3-F) and −150.8. −153.8, −157.6 (all t, unassigned); $J_{3-F,4-F}$ 14 and $J_{4-F,5-F}$ 44; $\delta_H(CDCl_3)$ 2.73 (s, CH_3); the slower eluting component was 3,5,6,7,8-*pentafluoro*-2,4-*di*(*methylthio*)*quinoline* **36**, m.p. 93.5–95.0 °C [from light petroleum (b.p. 40–60 °C)] (Found: C, 42.35; H, 1.8; N, 4.4%; M^+, 311. $C_{11}H_6F_5NS_2$ requires C, 42.44; H, 1.94; N, 4.50%; M^+, 311); $\delta_F(CDCl_3)$ −117.9 (s, 3-F), −140.7 (m, 5-F); −151.1, −156.2 and −158.9 (all t, unassigned); $\delta_H(CDCl_3)$, 2.68 (s, CH_3) and 2.69 (d, CH_3).

(iii) *With Sodium Propane-2-thiolate.*—The thiolate was prepared by the reaction of sodium ethoxide in ethanol with propane-2-thiol (1.15 equiv.) and was treated with the quinoline **2** as in (ii). The product consisted of unchanged starting material **2** (9%) and three other products (91%): the 2-isopropylthio **37**, the 4-(isopropylthio) **38** and the 2,4-di(isopropylthio) **39** compounds, present in the ratio 5:91:4 respectively. Chromatographic separation of the product was carried out as in (ii) to give: 2,3,5,6,7,8-*hexafluoro*-4-(*isopropylthio*)*quinone* **38**, m.p. 79.5–80 °C (Found: 46.2; H, 2.2; N, 4.4%; M^+, 311. $C_{12}H_7F_6NS$ requires C, 46.31; H, 2.27; N, 4.50%; *M*, 311); $\delta_F(CDCl_3)$ −78.5 (dt, 2-F), −131.2 (dt, 3-F), −139.2 (m, 5-F); −148.5, −153.3 and −155.8 (all t, unassigned); $J_{2-F,3-F}$ 29.8; $\delta_H(CDCl_3)$ 1.36 [d, $(CH_3)_2$] and 3.95 (heptet, CH); 3,4,5,6,7,8-*hexafluoro*-2-(*isopropylthio*)*quinoline* **37**, m.p. 53.0–53.8 °C [from light petroleum (b.p. 40–60 °C)] (Found: C, 46.2; H, 2.1; N, 4.3%; M^+, 311. $C_{12}H_7F_6NS$ requires C, 46.31; H, 2.27; N, 4.50%; *M*, 311); $\delta_F(CDCl_3)$ −136.3 (dd, 4-F), −147.3 (overlapping multiplets, 3-F, 5-F); −151.1, −153.9 and −157.8 (all t, unassigned); $J_{3-F,4-F}$ 16 and $J_{4-F,5-F}$ 45; $\delta_H(CDCl_3)$ 1.50 [d, $(CH_3)_2$] and 4.28 (heptet, CH); and 3,5,6,7,8-*pentafluoro*-2,4-*di*(*isopropylthio*)*quinoline* **39**, m.p. 69.5–70 °C [from light petroleum (b.p. 40–60 °C)] (Found: C, 48.8; H, 3.6; N, 3.7%; M^+, 367. $C_{15}H_{14}F_5NS_2$ requires C, 49.04; H 3.84; N, 3.81%; *M*, 367); $\delta_F(CDCl_3)$ −113.4 (s, 3-F), −141.7 (m, 5-F); −151.5 (ddd), −156.4 (td) and −158.9 (t) all unassigned; $\delta_H(CDCl_3)$ 1.30 [d, $(CH_3)_2$], 1.50 [d, $(CH_3)_2$], 3.75 (heptet, 4-CH) and 4.23 (heptet, 2-CH).

(iv) *With Sodium* 2-*Methylpropane*-2-*thiolate.*—The thiolate was prepared by the treatment of sodium ethoxide in ethanol with 2-methylpropane-2-thiol (1.13 equiv.), and was treated with the quinoline **2** as in (ii). The product consisted of unchanged starting material **2** (10%) and four other products (90%): the 2-(*tert*-butylthio) **40**, the 4-(*tert*-butylthio) **41**, the 2,4-di(*tert*-butylthio) **42** and the 2-ethoxy-4-(*tert*-butylthio) **43** compounds, present in the ratio 2.5:96:1:0.5 respectively. The major component in the product was obtained by crystallisation: 2,3,5,6,7,8-*hexafluoro*-4-(tert-*butylthio*)*quinoline* **41**, m.p. 115.0–115.5 °C [from light petroleum (b.p. 60–80 °C)] (Found: C, 47.9; H, 2.4; N, 4.0%; M^+, 325. $C_{13}H_9F_6NS$ requires C, 48.00; H, 2.79; N, 4.31%; *M*, 325); $\delta_F(CDCl_3)$ −76.4 (d, 2-F), −122.1 (d, 3-F), 140.6 (dd, 5-F); −148.3 (t), −152.9 (s) and −154.3 (t), (all unassigned); $J_{2-F,3-F}$ 33; $\delta_H(CDCl_3)$ 1.40 [s, $(CH_3)_3C$]. The mother liquors were chromatographed twice as in (ii) to give: 3,4,5,6,7,8-*hexafluoro*-2-(tert-*butylthio*)*quinoline* **40**, m.p. 48.5–49.0 °C [from light petroleum (b.p. 60–80 °C)] (Found: C, 47.9; H, 2.7; N, 4.1%; M^+, 325. $C_{13}H_9F_6NS$ requires C, 48.00; H, 2.79; N, 4.31%; *M*, 325); $\delta_F(CDCl_3)$ −136.3 (dd, 4-F), −146.2 (d, 3-F), −147.2 (t, 5-F); −150.9 (t), −154.2 (t) and −157.8 (dt) (all unassigned); $J_{3-F,4-F}$ 16 and $J_{4-F,5-F}$ 44; $\delta_H(CDCl_3)$ 1.74 [s, $(CH_3)_3C$]. Treatment of **41** with sodium 2-methylpropane-2-thiolate gave the two minor components in the product **42** and **43**, in the proportion 59:41 respectively. Flash chromatography of the product on silica with carbon tetrachloride as eluent gave as faster moving component: 3,5,6,7,8-*pentafluoro*-2,4-*di*(tert-*butylthio*)*quinoline* **42**, m.p. 104.5–105.0 °C [from light petroleum (b.p. 60–80 °C)] (Found: 51.9; H, 4.75; N, 3.5%; M^+, 395. $C_{17}H_{18}F_5NS_2$ requires C, 51.63; H, 4.59; N, 3.54%; *M*, 395); $\delta_F(CDCl_3)$ −106.2 (s, 3-F), −141.9 (m, 5-F); −151.3, −156.4 and −157.8 (all t, all unassigned); $\delta_H(CDCl_3)$ 1.75 [s,

2-$(CH_3)_3C$] and 1.37 [s, 4-$(CH_3)_3C$]; the slower moving component was 3,5,6,7,8-*pentafluoro*-2-*ethoxy*-4-(tert-*butylthio*) *quinoline* **43**, m.p. 106.0–106.5 °C [from light petroleum (b.p. 60–80 °C)] (Found: C, 51.5; H, 4.1; N, 3.8%; M^+, 351. $C_{15}H_{14}F_5NOS$ requires C, 51.28; H, 4.02; N, 3.99%; *M*, 351); $\delta_F(CDCl_3)$ −120.1 (s, 3-F), −142.3 (m, 5-F), −142.3 (m, 5-F); −151.6 (t), −156.4 (dt) and −159.8 (dt) (all unassigned); $\delta_H(CDCl_3)$ 1.38 [s, 4-$(CH_3)_3Cl$], 1.53 (t, CH_3) and 4.82 (q, CH_2). A similar reaction carried out with a tenfold excess of 2-methylpropane-2-thiol present, gave a product which contained unchanged starting material **2** (14%) and only three other products (86%): the 2-(*tert*-butylthio) **40**, the 4-(*tert*-butylthio) **41** and the 2,4-di(*tert*-butylthio) **42** compounds present in the ratio 5:93:2 respectively.

(v) *With Sodium Benzenethiolate.*—The thiolate was prepared by the treatment of sodium ethoxide in ethanol with benzenethiol (1.4 equiv.) and treated with the quinoline **2** as in (ii). The product consisted of unconverted starting material **2** (2%) and one other component (98%) which was isolated by recrystallisation: 2,3,5,6,7,8-*hexafluoro*-4-(*phenylthio*)*quinoline* **44**, m.p. 121.5–122.0 °C [from light petroleum (b.p. 60–80 °C)] (Found: C, 51.9; H, 1.4; N, 3.85%; M^+, 345. $C_{15}H_5F_6NS$ requires C, 52.18; H, 1.46; N, 4.06%; *M*, 345); $\delta_F(CDCl_3)$ −77.2 (d, 2-F), −127.5 (d, 3-F), −139.7 (d, 5-F); −148.1, −152.7 and −154.9 (all t, unassigned); $J_{2-F,3-F}$ 28; $\delta_H(CDCl_3)$ 7.35 (m, ArH) and 7.45 (m, ArH).

(B) *With Oxygen Nucleophiles.*—(i) *With sodium ethoxide.* Sodium ethoxide (0.35 mmol) in (1 cm^3) was added to a solution of the quinoline **2** (0.0964 g, 0.38 mmol) in ethanol (30 cm^3) at −70 to −85 °C over 2 min, the mixture was warmed to room temperature, acidified (2 mol dm^{-3} H_2SO_4) and the product extracted into diethyl ether. The extracts were dried ($MgSO_4$), filtered and the solvent evaporated. The crude residue (0.099 g) was shown by ^{19}F NMR spectroscopy to contain residual starting material **2** (5%) and two products (95%): the 2-ethoxy **47** and the 4-ethoxy **48** compounds, present in the ratio 76:24 respectively. In a separate experiment, the two products were separated by chromatography on silica with CCl_4 as eluent to give as fastest component 4-*ethoxy*-2,3,5,6,7,8-*hexafluoroquinoline* **48**, m.p. 35.5–36.0 °C [from light petrolrum (b.p. 60–80 °C)] (Found: C, 47.1; H, 1.8; N, 4.9%; M^+, 281. $C_{11}H_5F_6NO$ requires C, 46.99; H, 1.79; N, 4.98%; *M*, 281); $\delta_F(CDCl_3)$ −76.3 (d, 2-F), −143.9 (t, 5-F); −150.1 (t), −153.2 (t), −157.7 (t) (all unassigned) and −160.6 (d, 3-F); $J_{2-F,3-F}$ 27.5; $\delta_H(CDCl_3)$ 1.53 (t, CH_3) and 4.66 (q, CH_2). The slower moving component was the 2-*ethoxy*-3,4,5,6,7,8-*hexafluoroquinoline* **47**, m.p. 41.5–42.0 °C [from light petroleum (b.p. 60–80 °C)] (Found: C, 46.75; H, 1.8; N, 4.75%; M^+, 281. $C_{11}H_5F_6NO$ requires C, 46.99; H, 1.79; N, 4.98%; *M*, 281); $\delta_F(CDCl_3)$ −133.0 (dd, 4-F), −147.8 (dt, 5-F); −151.2 (t), −154.3 (t), −159.8 (t) (all unassigned) and 161.0 (br s, 3-F); $J_{4-F,5-F}$ 45.8; $\delta_H(CDCl_3)$ 1.51 (t, CH_3) and 4.65 (q, CH_2).

(ii) *With Sodium Phenoxide.*—The phenoxide was prepared by the treatment of sodium ethoxide in ethanol with phenol (5 equiv.) and was treated with the quinoline **2** as in (i). The product consisted of unchanged starting material **2** (16%) and four products (84%): a pair of phenoxy isomers (93 parts), the 2-phenoxy **49** and the 4-phenoxy **50** compounds present in the ratio 37:63 respectively; and the pair of ethoxy isomers (7 parts), the 2-ethoxy **47** and the 4-ethoxy **48** compounds, present in the ratio 75:25 respectively. Sublimation of the product (40 °C/0.1 mmHg) removed as sublimate excess phenol along with **2**, **47** and **48**. Column chromatography of the residue on silica using CCl_4 as eluent gave as faster moving component 3,4,5,6,7,8-*hexafluoro*-2-*phenoxyquinoline* **49**, m.p. 76.5–77.0 °C [from light petroleum (b.p. 60–80 °C)] (Found: C, 55.0; H, 1.4; N, 4.1%; M^+, 329. $C_{15}H_5F_6NO$ requires C, 54.73; H, 1.53; N, 4.25%; *M*, 329); $\delta_F(CDCl_3)$ −130.5 (dd, 4-F), −147.6 (dt, 5-F); −149.8 (t), −153.4 (t), −158.1 (t) (all unassigned) and −159.7 (br s, 3-F); $J_{4-F,5-F}$ 45.5; $\delta_H(CDCl_3)$ 7.45 (m, ArH), 7.32 (m, ArH). The slower moving component was 2,3,5,6,7,8-*hexafluoro*-4-*phenoxyquinoline* **40**, m.p. 109.5–110.0 °C [from light petroleum (b.p. 60–80 °C)] (Found: C, 54.7; H, 1.3; N, 4.0%; M^+, 329. $C_{15}H_5F_6NO$ requires C, 54.73; H, 1.53; N, 4.25%; *M*, 329); $\delta_F(CDCl_3)$ −74.5 (d, 2-F), −145.5 (t, 5-F), −148.8 (t), −151.8 (overlapping m, one 3-F and one unassigned) and −155.4 (td, unassigned); $\delta_H(CDCl_3)$ 7.38 (m, ArH), 7.20 (m, ArH) and 7.00 (m, ArH).

(iii) *With Sodium* 4-*Nitrophenoxide.*—The experiment carried out as in (*ii*) gave a product which contained unchanged starting material **2** (61%) and four products (39%): a pair of 4-nitrophenoxy isomers (95 parts), the 2-(4-nitrophenoxy) **51** and the 4-(4-nitrophenoxy) **52** compounds, present in the ratio 16:84 respectively; and the pair of ethoxy isomers (5 parts), the 2-ethoxy **47** and the 4-ethoxy **48** compounds, present in the ratio 80:20 respectively. The excess 4-nitrophenol was removed from the product by chromatography on silica using CCl_4 as eluent, and re-chromatography using light petroleum (b.p. 60–80 °C) as eluent removed **2**, **47** and **48**. The two remaining compounds were washed off the column with chloroform and distilled at 120 °C/0.1 mmHg to give an inseparable mixture of 3,4,5,6,7,8-*hexafluoro*-2-(4-*nitrophenoxy*)*quinoline* **51** and 2,3,5,6,7,8-*hexafluoro*-4-(4-*nitrophenoxy*)*quinoline* **52** present in the ratio 17:83 respectively (Found: C, 48.0; H, 0.9; N, 7.1; M^+, 374. $C_{15}H_4F_6N_2O_3$ requires C, 48.15; H, 1.08; N, 7.49%; *M*, 374). The 2-(4-nitrophenoxy)quinoline **51**; $\delta_F(CDCl_3)$ −128.5 (dd, 4-F), −146.8 (dt, 5-F); −149.4 (t), −152.1 (t), −156.5 (t) (all unassigned) and −159.3 (br s, 3-F); $J_{4-F,5-F}$ 45.5; $\delta_H(CDCl_3)$ 8.36 (d, ArH) and 7.56 (d, ArH). The 4-(4-nitrophenoxy)-quinoline **52**; $\delta_F(CDCl_3)$ −73.1 (d, 2-F), −146.3 (br t, 5-F), −147.4 (br t, unassigned), −150.3 (overlapping t, one 3-F and one unassigned) and −153.6 (t, unassigned); $J_{2-F,3-F}$ 25; $\delta_H(CDCl_3)$ 8.29 (d, ArH) and 7.09 (d, ArH).

(C) *With Ammonia.*—The reaction described previously was repeated. The crude product was shown by ^{19}F NMR spectroscopy to contain the 4-amino **54** and the 2-amino **53** compounds in the ratio 57:43 respectively.

Semi-quantitative Kinetics.—General procedure. Competition reactions by two or three nucleophiles for the substrate (1,3,4,5,6,7,8-*heptafluoroisoquinoline* **1** or 2,3,4,5,6,7,8-heptafluoroquinoline **2**) were carried out. The molar concentrations of the nucleophiles in each experiment were identical and were *ca.* 25-fold larger than the fluoro-heterocycle—conditions which ensure that the ratios of the products formed are directly proportional to the ratio of the second order rate constants for each reaction. The nucleophiles in ethanol were added to the substrate in ethanol at −85 to −95 °C over 5 min, and the reaction then stopped by addition of trifluoroacetic acid to the mixture at −85 °C. The mixture was then diluted with dichloromethane, washed with water, the extracts dried ($MgSO_4$) and the solvent evaporated. The crude residue was examined by ^{19}F NMR spectroscopy, and the relative proportions of each component measured.

Treatment of the isoquinoline **1** with benzenethiol and trifluoroacetic acid at room temperature for 1 h and work-up from water gave only unchanged starting material **1**. Previously it had been shown that treatment of the quinoline **2** in concentrated sulfuric acid with methanol at 0 °C gave selective substitution of the fluorine at position 2.

Reactions with the Isoquinoline **1**.—(i) *Benzenethiolate* vs.

ethoxide. The product consisted of unchanged starting material **1** (18%) and three products (82%): the 6-(phenylthio)-isoquinoline **15**, a new compound, the 1-ethoxy-6-(phenylthio)isoquinoline **17**, and the 1-ethoxyisoquinoline **25**, present in the ratio 95:1.5:3.5 respectively. Since the isoquinoline **1** reacts with sodium ethoxide to give the 1-ethoxy **25** and the 6-ethoxy **26** in the ratio 94:6 respectively, the *maximum* amount of **26** which could be present in the product from the composition reaction here (assuming it does not react further with benzenethiolate) is 6/94 × 3.5%. Since **17** could arise from the further substitution of either **15** or **25**, the relative reactivity of PhS^- : EtO^- at the 6-position is either at least 400:1 or 300:1 respectively; the lower value is recorded in Table 3.

The new compound was prepared from the 1-ethoxyisoquinoline **25** and benzenethiolate: *1-ethoxy-3,4,5,7,8-pentafluoro-6-(phenylthio)isoquinoline* **17**, m.p. 144.5–145.0 °C [from light petroleum (b.p. 60–80 °C)] (Found: C, 55.1; H, 2.9; N, 3.7%; M^+, 371. $C_{17}H_{10}F_5NOS$ requires C, 54.99; H, 2.71; N, 3.77%; *M*, 371); $\delta_F(CDCl_3)$ −99.2 (d, 3-F), −112.9 (dd, 5-F), −131.4 (d, 7-F), −139.7 (t, 8-F) and −164.4 (dd, 4-F); $J_{4\text{-}F,5\text{-}F}$ 57.8 and $J_{5\text{-}F,8\text{-}F}$ 19; $\delta_H(CDCl_3)$ 1.47 (t, CH_3), 4.51 (q, CH_2), 7.29 (m, ArH) and 7.42 (m, ArH).

(ii) *Propane-2-thiolate* vs. *ethoxide*. The product consisted of starting material **1** (67%) and four products (33%): the 1-(isopropylthio)isoquinoline **8**, the 6-(isopropylthio)isoquinoline **9**, the 1,6-di(isopropylthio)isoquinoline **10** and the 1-ethoxyisoquinoline **25**, present in the ratio 20:78: < 0.5:2 respectively. At the 6-position therefore, the relative reactivity Pr^iS^- : EtO^- is 600:1, and at the 1 position, 10:1.

(iii) *Benzenethiolate* vs. *propane-2-thiolate* vs. *ethoxide*. The product from the reaction consisted of starting material **1** (45%) and five products (55%): the 6-(phenylthio)isoquinoline **15**, the 1-(isopropylthio)isoquinoline **8**, the 6-(isopropylthio)isoquinoline **9**, the 1,6-(isopropylthio)isoquinoline **10** and the 1-ethoxyisoquinoline **25**, present in the ratio 36:12:47:2:2 respectively. At the 6-position therefore, the relative reactivity Pr^iS^- : PhS^- : EtO^- is 400:300:1, and at the 1-position Pr^iS^- : EtO^- is 7:1.

(iv) *4-Methoxybenzenethiolate* vs. *benzenethiolate*. The product from the reaction consisted of starting material **1** (8%) and two products (92%): the 6-(4-methoxyphenylthio)isoquinoline **22** and the 6-(phenylthio)isoquinoline **15**, present in the ratio 91:9 respectively. At the 6-position therefore, the relative reactivity 4-MeO–$C_6H_4S^-$: PhS^- is 10:1.

(v) *4-N,N-Dimethylaminobenzenethiolate* vs. *4-methoxybenzenethiolate*. Prior to solvent extraction of the reaction products, the aqueous phase was adjusted to pH 6.0. Only two compounds were present in the product: the 6-(4-*N*,*N*-dimethylaminophenylthio)isoquinoline **19** and the 6-(4-methoxyphenylthio)isoquinoline **22** is the ratio 78:22 respectively. At the 6-position therefore, the relative reactivity 4-Me_2N–$C_6H_4S^-$: MeO–$C_6H_4S^-$ is 4:1.

(vi) *Ethoxide* vs. *4-nitrobenzenethiolate*. In this reaction the temperature was allowed to rise to −35 °C before quenching with acid at −80 °C. The product from the reaction consisted of starting material **1** (1%) and three products (99%): the 1-ethoxyisoquinoline **25**, the 6-ethoxyisoquinoline **26** and the 6-(4-nitrophenylthio)isoquinoline **24** present in the ratio 95:4:1 respectively. At the 6-position therefore, the relative reactivity EtO^- : 4-NO_2–$C_6H_4S^-$ is 1:0.25.

Reactions with the Quinoline **2**.—*Benzenethiolate* vs. *ethoxide*. The product (free from unchanged starting material **2**) consisted of three main components: the 4-(phenylthio)quinoline **44**, a new compound, the 2,4-di(phenylthio)quinoline **45** and another new compound, the 2-ethoxy-4-(phenylthio)quinoline **46** present in the ratio 92:4.5:3.5 respectively. Closer examination of the spectrum from a prolonged ^{19}F NMR scan (*ca.* 30 000 scans) showed the 2-ethoxyquinoline **47** to be present in 1 part per 300 parts 4-(phenylthio)quinoline **44**. Since the quinoline **2** reacts with sodium ethoxide to give the 2-ethoxy **47** and the 4-ethoxy **48** compounds in the ratio 76:24 respectively, the relative reactivity at the 4-position PhS^- : EtO^- is 1000:1.

Treatment of the 4-(phenylthio)quinoline **44** with benzenethiolate gave *3,5,6,7,8-pentafluoro-2,4-di(phenylthio)quinoline* **45**, m.p. 113.0–113.5 °C [from light petroleum (b.p. 60–80 °C)] (Found: C, 58.3; H, 2.35; N, 3.1%; M^+, 435. $C_{21}H_{10}F_5NS_2$ requires C, 57.93; H, 2.31; N, 3.22%; *M*, 435); $\delta_F(CDCl_3)$ −111.5 (s, 3-F), −142.0 (d, 5-F); −149.9, −155.4 and −156.9 (all t, unassigned); $\delta_H(CDCl_3)$ 7.31 (m, ArH), 7.46 (m, ArH) and 7.48 (m, ArH). Treatment of the 4-(phenylthio)quinoline **44** with ethoxide gave *2-ethoxy-3,5,6,7,8-pentafluoro-4-(phenylthio)quinoline* **46**, m.p. 95.5–96.0 °C [from light petroleum (b.p. 60–80 °C)] (Found: C, 54.7; H, 2.6; N, 3.7%; M^+, 371. $C_{17}H_{10}F_5NOS$ requires C, 54.99; H, 2.71; N, 3.77%; *M*, 371); $\delta_F(CDCl_3)$ −124.2 (s, 3-F), −142.7 (d, 5-H); −151.3, −155.9 and −159.9 (all t, unassigned); $\delta_H(CDCl_3)$ 1.49 (t, CH_3), 4.61 (q, CH_2), 7.31 (m, ArH) and 7.33 (m, ArH).

Relative Reactivities of the Isoquinoline **1** *and the Quinoline* **2**.—(i) *Towards ethoxide*. A solution of equivalent amounts of the heterocycles in ethanol was treated as in the previous experiments with 1/25th equivalent of sodium ethoxide. The product consisted of the starting materials **1** and **2** (98%) and three products (2%): the 1-ethoxyisoquinoline **25**, the 2-ethoxyquinoline **47** and the 4-ethoxyquinoline **48** present in the ratio 12:68:20. Therefore, the relative reactivity towards ethoxide of the two heterocycles, the quinoline **2**, the isoquinoline **1** is 7:1.

(ii) *Towards benzenethiolate*. A solution of the two heterocycles was treated as in (i) with 1/12th equivalent of sodium benzenethiolate. The only detectable product was the 4-(phenylthio)quinoline **44**. The addition of a second 1/12th equivalent of sodium benzenethiolate under the same conditions enabled two products to be detected: the 4-phenylthio)quinoline **44** and the 6-(phenylthio)isoquinoline **15**, present in the ratio 27:1 respectively—which is the measure of the reactivity of the quinoline **2**:isoquinoline **1** towards benzenethiolate.

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