Partially Fluorinated Heterocyclic Compounds. Part 18.[1] Formation of Fischer Indole Products from Acetophenone 1,3,4,5,6,7,8-Heptafluoro-2-naphthylhydrazone and Acetophenone Pentafluorophenylhydrazone. The Surprising Loss of *o*-Fluorine †

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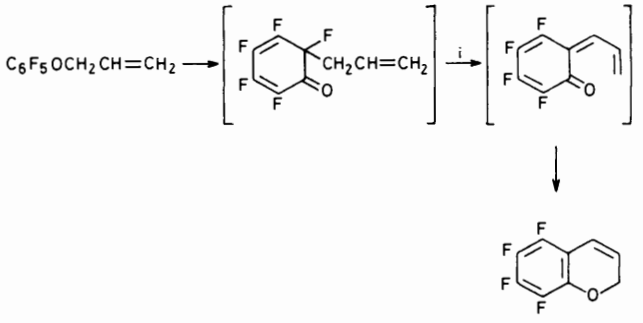
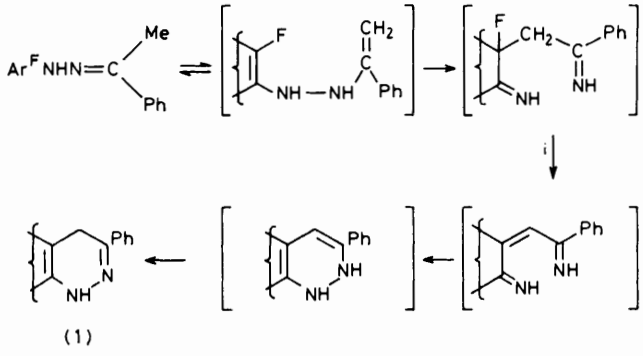
Acetophenone 1,3,4,5,6,7,8-heptafluoro-2-naphthylhydrazone (2) and acetophenone pentafluorophenylhydrazone (3) react in tetralin at reflux temperature to give among the products 4,5,6,7,8,9-hexafluoro-2-phenylbenz[*e*]indole (6) and 4,5,6,7-tetrafluoro-2-phenylindole (9) respectively; these are typical Fischer indole products, yet are formed by displacement of *o*-fluorine rather than *o*-hydrogen. The 2-naphthylamine (5) and 1,1',2,2',3,3',4,4'-octahydro-1,1'-bisnaphthyl (4) are also formed from (2), while ammonia, pentafluoro-*N*-(α-methylbenzylidene)aniline (8), 2,3,5,6-tetrafluoro-4-(1,2,3,4-tetrahydro-1-naphthyl)aniline (10) and the bisnaphthyl (4) are also formed from (3). Imine precursors are *not* the source of the cyclised compounds (6) and (9).

In earlier papers in this series, syntheses of partially fluorinated fused-ring heterocycles have been described which involve thermolyses of polyfluoroaryl prop-2-enyl sulphides [2] and prop-2-ynyl ethers.[3] These reactions proceed *via* Claisen-rearrangement intermediates, though the mechanism of the loss of the *o*-fluorine is uncertain in each case. In the previous paper,[1] the deliberate dehydrofluorination of the rearrangement product from polyfluoroarylprop-2-enyl ethers with potassium fluoride in a dipolar aprotic solvent, followed by electrocyclisation of the resulting *o*-quinomethanide-type material, was shown to give 2*H*-1-benzopyran derivatives. The procedure is illustrated in Scheme 1 with the pentafluorophenyl compound in dimethylformamide. This paper records the first attempted extension of the last-named reaction to prepare heterocycles containing two heteroatoms (nitrogen) with the use of acetophenone polyfluoroarylhydrazone compounds, since the key step in the Fischer indole synthesis from hydrocarbon arylhydrazones is now regarded as involving a [3,3]-sigmatropic shift of the tautomeric enehydrazine.[4] With fluorine substituents *ortho* to the hydrazone group, it was envisaged that the cyclic hydrazone (1) would be formed in the presence of KF (Scheme 2). The Fischer indole synthesis using phenylhydrazones is usually carried out in the presence of Lewis-acid catalysts (*e.g.* $ZnCl_2$, to facilitate formation of the enehydrazine tautomer), though reactions have been carried out successfully in high boiling solvents alone.[5] This paper reports the results of studies of uncatalysed thermolyses in refluxing tetralin of acetophenone 1,3,4,5,6,7,8-heptafluoro-2-naphthylhydrazone (2) and acetophenone pentafluorophenylhydrazone (3),[6] readily available from the reaction of acetophenone with 1,3,4,5,6,7,8-heptafluoro-2-naphthylhydrazine [7] and with pentafluorophenylhydrazine,[8] respectively. No potassium fluoride was present in the reaction mixtures since preliminary experiments had shown that this material apparently had no effect on the course of the reactions.

The naphthylhydrazone (2), heated under reflux in dry tetralin for 24 h, gave a complex mixture of products which was partially separated by a combination of column chromatography, thick layer chromatography, and sublimation. The products isolated were: (i) an impure sample of 1,1',2,2',3,3',4,4'-octahydro-1,1'-bisnaphthyl (4) (6%), identified by i.r. spectroscopy; (ii) 1,3,4,5,6,7,8-heptafluoro-2-naphthylamine [9] (5) (21%), identified by i.r., ^{19}F n.m.r., and mass spectroscopy; and (iii) 2-phenyl-4,5,6,7,8,9-hexafluorobenz[*e*]indole (6) (37%), identified by the parent ion (M^+ 351) in its mass spectrum, by the characteristic i.r. frequency at 3 460 cm^{-1} (NH), and by its ^1H and ^{19}F n.m.r. spectra. In particular, there was one proton at δ_H 7.0 (at position 3), and six fluorines, and only one pair had a large peri-coupling ($J_{7,8}$ 60 Hz), therefore excluding the other possible isomer (7). The results are summarised in Scheme 3.



Scheme 1. *Reagents:* i, KF (−HF)



Scheme 2. *Reagents:* i, KF (−HF)

The complexity of the product from the naphthylhydrazone (2) coupled with the relative insolubility of some of the

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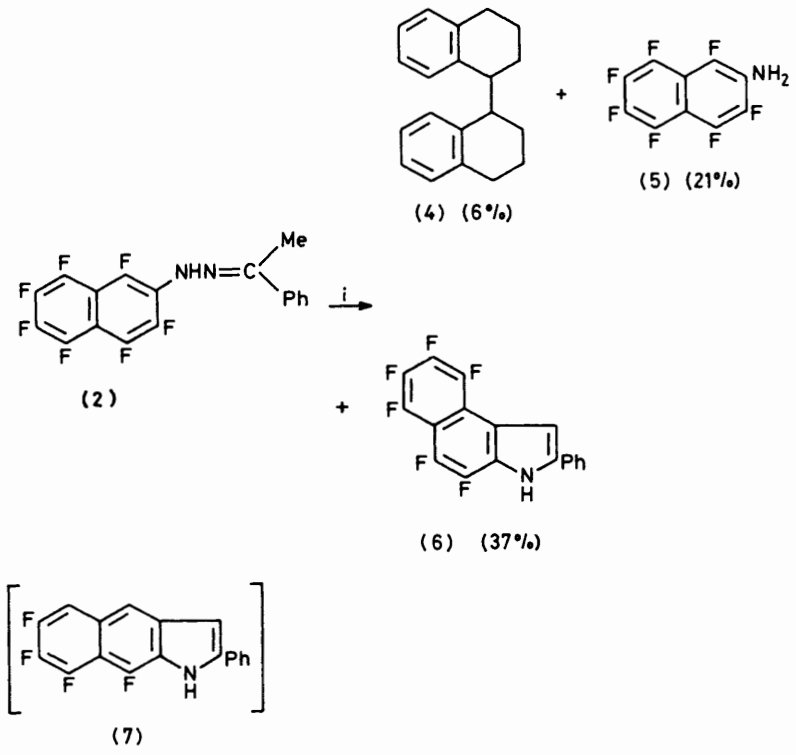
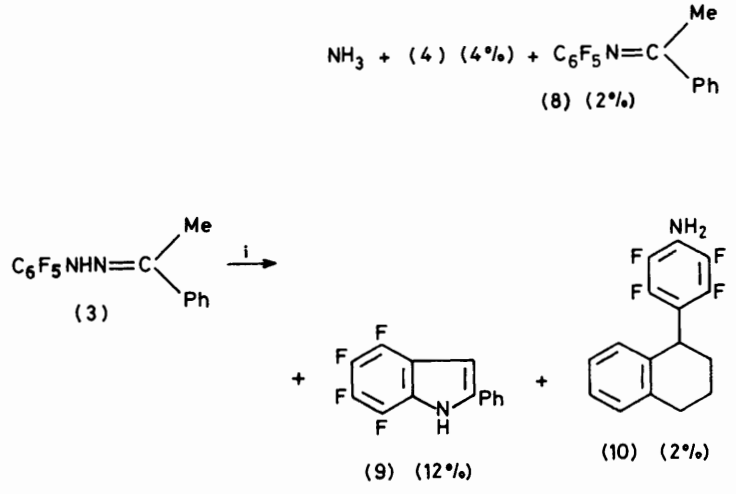


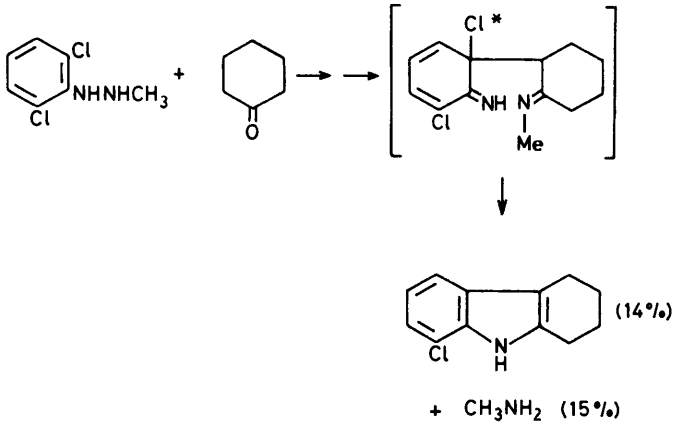
Scheme 3. *Reagents:* i, tetralin, reflux



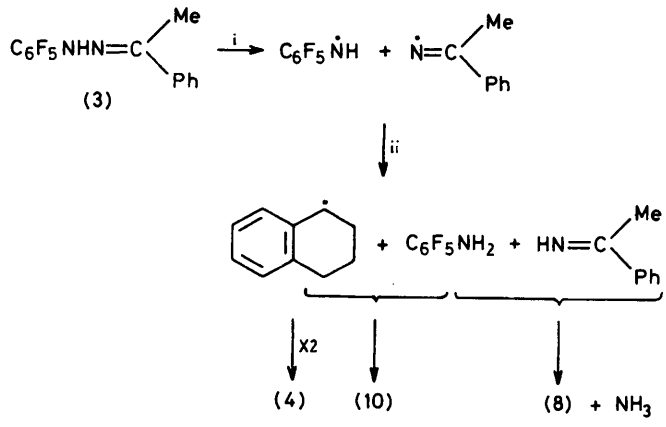
Scheme 4. *Reagents:* i, tetralin, reflux

unidentified materials dictated the examination of a lower molecular-weight starting material in the expectation that products might be isolated which, by analogy, would give some indication of the mode of formation of compound (6). Consequently, acetophenone pentafluorophenylhydrazone (3) was heated under reflux in tetralin for 24 h. During this period, ammonia, detected by its smell and by its action on moist red litmus, was evolved. A complex mixture of products was again formed, but only the more volatile components (those subliming up to 130 °C/0.05 mmHg) were separated, using a combination of column chromatography, thick layer chromatography, and fractional crystallisation. Four products were isolated: (i) 1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-bisnaphthyl (4) (4%); (ii) pentafluoro-*N*-(α-methylbenzylidene)aniline (8) (2%), identified by spectroscopic methods and by synthesis (30%) from pentafluoroaniline [8] and acetophenone; (iii) 4,5,6,7-tetrafluoro-2-phenylindole (9) (12%), a known compound; [10] and (iv) 2,3,5,6-tetrafluoro-4-(1,2,3,4-tetrahydro-1-naphthyl)aniline (10) (2%), which was identified by i.r. spectroscopy (absorptions at 3 380 and 3 475 cm^{-1} due to NH_2) and by readily interpretable ^1H and ^{19}F n.m.r. spectra. Scheme 4 summarises these results.

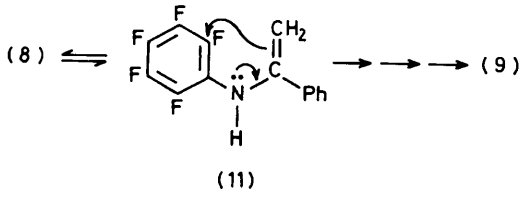
Russian workers had previously reported a conventional Fischer indole synthesis of (9) in 15% yield using acetophenone 2,3,4,5-tetrafluorophenylhydrazone and zinc chloride at 215 °C.[10] This procedure ultimately requires a simple 1,2,3,4-tetrafluorobenzenoid compound as the starting material, which is not readily available, followed by a multistage reaction sequence to give the corresponding hydrazine derivative. The work described in this present paper reports the remark-



Scheme 5. *Reagents:* i, C_6H_6, $-H_2O$



Scheme 7. *Reagents:* i, heat; ii, tetralin



(11)

Scheme 6

able formation of the Fischer indole product (9) in 12% yield from the readily accessible hydrazone (3), and an even more efficient preparation of (6) in 37% yield from the naphthylhydrazone (2); both substrates undergo the displacement of an *o*-fluorine in the process, in contrast to the displacement of an *o*-hydrogen (as H^+) in the conventional Fischer indole synthesis. Indeed, it is the mechanism of the displacement of the *o*-fluorine in compounds (2) and (3) which is the most fascinating aspect of the reactions described. Overall, the stoicheiometry of both cyclisation reactions [(2) ⟶ (6) and (3) ⟶ (9)] requires the overall loss of 'NH_2F'.

In searching for an explanation for the cyclisation reaction, it is noteworthy that there are two related precedents. The first involves the loss of an *o*-chlorine (Cl*) during the Fischer indole reaction, shown in Scheme 5,[11] in a reduction process by some (unidentified) readily oxidizable species in the reaction mixture. The second is the conversion of acetophenone pentachlorophenylhydrazone into 4,5,6,7-tetrachloro-2-phenylindole using polyphosphoric acid, a reaction which failed to give the corresponding tetrafluoroindole (9) when compound (3) was used.[6] While an analogous reduction process cannot be ruled out for the loss of fluorine in the two cases described in this paper, a more reasonable possibility was suggested in view of the isolation of compound (8). In principle, tautomerism of (8) to (11) followed by nucleophilic displacement of fluorine as fluoride ion and loss of a proton could give the indole (9) (Scheme 6). Previously, the adduct of pentafluoroaniline and diethyl acetylenedicarboxylate, a substrate closely related to (11), had been converted into the corresponding indole by reaction with sodium hydride in tetrahydrofuran under reflux, albeit in very low yield (<3%);[12] other enamines have also been used with considerable success in the formation of 4,5,6,7-tetrafluoroindole derivatives with hexafluorobenzene.[13] When the imine derivative (8) was heated in refluxing tetralin with added anhydrous zinc chloride (to catalyse the tautomerism) for 24 h, *no* indole derivative (9) could be detected in the reaction product; only starting material (83%) was recovered.

In view of the more efficient conversion of the naphthylhydrazone compound (2) into the Fischer indole product (6) (37%), the attempted cyclisation of heptafluoro-*N*-(α-methylbenzylidene)-2-naphthylamine (12) was considered a more stringent test of the possible cyclisation reaction. Compound (12), synthesised in low yield (17%) from the 2-naphthylamine (5) and acetophenone, was heated in refluxing tetralin with added zinc chloride and anhydrous potassium fluoride (to catalyse the tautomerism), for 24 h. However, the cyclised material (6) was not formed and the starting material (88%) was recovered. Consequently the formation of the cyclised products (6) and (9) from the corresponding hydrazones does *not* proceed through nucleophilic displacement of fluorine *via* imine intermediates and further work is required to define the process.

Finally, the formation of the other products from the thermolysis of the phenylhydrazone (3) can be rationalised in terms of an initial homolytic fission of the N–N bond (Scheme 7), a process which has been invoked previously in a related reaction.[14] An analogous scheme can be written for the naphthylhydrazone (2).

Experimental

^1H (60 MHz) and ^{19}F N.m.r. (56.4 MHz) were obtained with a Varian EM360L spectrometer. Chemical shifts δ_F are upfield from internal $CFCl_3$; δ_H are downfield from internal tetramethylsilane.

Acetophenone 1,3,4,5,6,7,8-*Heptafluoro*-2-*naphthylhydrazone* (2).—1,3,4,5,6,7,8-Heptafluoro-2-naphthylhydrazine[7] (22.67 g), acetophenone (10.76 g), and ethanol (130 ml) were heated together under reflux for 1 h, during which time a pink-white solid was precipitated. The mixture was filtered and the solid washed with further ethanol followed by light petroleum (b.p. 40—60 °C). Recrystallisation of the solid (18.8 g, 61%) from toluene gave the pure *naphthylhydrazone* (2), m.p. 181—182 °C (Found: C, 55.9; H, 2.3; N, 7.1%; M^+, 386. $C_{18}H_9F_7N_2$ requires C, 56.0; H, 2.3; N, 7.2%; *M*, 386).

Acetophenone Pentafluorophenylhydrazone (3).—This compound (98%) was prepared from pentafluorophenylhydrazine[8] by the method used in the previous experiment, m.p. 147—149 °C (lit.,[6] 149—150 °C).

Reaction of Acetophenone 1,3,4,5,6,7,8-*Heptafluoro*-2-*naphthylhydrazone* (2) *in Tetralin*.—The naphthylhydrazone (2) (2.137 g) was heated under reflux with dry tetralin for 24 h.

The solvent was distilled under reduced pressure at 65 °C/0.05 mmHg and the tarry residue (2.85 g), shown to be a complex mixture by analytical t.l.c., was partially separated by chromatography on silica (2 ft 6 in × 1 in) using $CHCl_3$–CCl_4 (50 : 50 v/v) as eluant. The fastest moving components were collected as one fraction which was further separated by thick layer chromatography with the same solvent to give an impure sample of 1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-bisnaphthyl (4) (0.089 g, 6%), identified by ^1H n.m.r. spectroscopy (see later). The next fraction was a mixture of two components which was separated by sublimation at 50—95 °/0.05 mmHg into a sublimate, identified as 1,3,4,5,6,7,8-heptafluoro-2-naphthylamine (5) [8] (0.314 g, 21%) by its ^{19}F n.m.r. and i.r. spectrum and by its molecular weight (M^+ 269), and a non-sublimable residue, 4,5,6,7,8,9-*hexafluoro*-2-*phenylbenz*[e]*indole* (6) (0.718 g, 37%), m.p. 207.5—208.5 °C [from toluene–light petroleum (b.p. 100—120 °C)] (Found: C, 61.5; H, 1.8; N, 3.8%; M^+, 351. $C_{18}H_7F_6N$ requires C, 61.5; H, 2.0; N, 4.0%; *M*, 351); δ_F[$(CD_3)_2CO$] 145.6 (t), 148.0 (doublet of m, peri-F, $J_{7,8}$ 60 Hz), 155.6 (m), 157.3 (dd; peri-F), 160.8 (triplet of m), and 162.8 p.p.m. (t), with intensities in the ratio 1 : 1 : 1 : 1 : 1 : 1; δ_H 7.0 (1 H, 3 H), 7.4 and 7.75 (3 and 2 H, respectively, Ph), and 11.35 (NH); $\nu_{max.}$ 3 460 cm^{-1} (NH).

Reaction of Acetophenone Pentafluorophenylhydrazone (3) *in Tetralin.*—The phenylhydrazone (3) (5.881 g) was heated under reflux with dry tetralin (60 ml) for 24 h. The solvent was distilled under reduced pressure (0.05 mmHg) using an external water-bath at 55 °C. The black residue was sublimed at 0.05 mmHg from room temperature to 130 °C and the sublimate (3.088 g) was partially separated by chromatography on silica (2 ft 6 in × 1 in), using CCl_4 as eluant. Three fractions were collected. The fastest moving components were further separated by thick layer chromatography on silica using light petroleum (b.p. 60—80 °C) and afforded 1,1′2,2′,3,3′,4,4′-octahydro-1,1′-bisnaphthyl (4) (0.195 g, 4%) as an oil [Found: C, 91.5; H, 8.5%; M^+ (C.I. with isobutane) 262. $C_{20}H_{22}$ requires C, 91.5; H, 8.5%; *M*, 262]; δ_H ($CDCl_3$) 1.8 (2- and 3-H) and 2.8 (4-H), intensities in the ratio *ca.* 2 : 1.

The second fraction contained *pentafluoro*-N-(α-*methylbenzylidene*)*aniline* (8) (0.117 g, 2%) (from light petroleum, b.p. 60—80 °C), m.p. 104.5—105 °C (Found: C, 59.2; H, 3.0; N, 4.8%; M^+ 285. $C_{14}H_8F_5N$ requires C, 59.0; H, 2.8; N, 4.9%; *M*, 285); δ_F ($CDCl_3$) 152.7 (m) and 164.0 p.p.m. (m), intensities in the ratio 2 : 3; δ_H ($CDCl_3$) 2.38 (s, Me), and 7.5 and 8.0 (m, 3 and 2 H, Ph).

The third fraction (0.719 g) contained three components, readily discernible by ^{19}F n.m.r. spectroscopy. Crystallisation from CCl_4 conveniently afforded 4,5,6,7-tetrafluoro-2-phenylindole (9), m.p. 134.5—135.5 °C (lit.,[10] 129.5—133 °C) (Found: C, 63.7; H, 2.5; N, 5.3%; M^+, 265. $C_{14}H_7F_4N$ requires C, 63.4; H, 2.7; N, 5.3%; *M*, 265); δ_F ($CDCl_3$) 151.7 (t), 160.9 (t), 168.0 (t), 171.2 p.p.m. (t), intensities in the ratio 1 : 1 : 1 : 1; δ_H ($CDCl_3$) 6.95 (1 H, 3-H), 7.35 and 7.85 (2 × m, 3 and 2 H, Ph), and 11.22 p.p.m. (NH); $\nu_{max.}$ 3 480 cm^{-1} (NH).

The mother liquors from the crystallisation of (9) were partially separated by chromatography on silica (7 ft × 1 in), using CCl_4 as eluant. The first component coming from the column was the indole derivative (9), but later fractions contained in addition increasing proportions of another compound. This mixture was crystallised from light petroleum (b.p. 40—60 °C) with external cooling, and ' foreign ' crystals were removed from the main body of crystals by mechanical separation under a microscope. Finally, recrystallisation of the main sample from light petroleum (b.p. 40—60 °C) gave 2,3,5,6-*tetrafluoro*-4-(1,2,3,4-*tetrahydro*-1-*naphthyl*)*aniline* (10), m.p. 97—98 °C (Found: C, 64.9; H, 4.5; N, 4.5%; M^+, 295. $C_{16}H_{13}F_4N$ requires C, 65.1; H, 4.4; N, 4.7%; *M*, 295) δ_F ($CDCl_3$) 146.4 (m) and 162.8 p.p.m. (m), intensities in the ratio 2 : 2; δ_H ($CDCl_3$) 2.0 (br, 4 H, 2 × β-H), 2.85 (br, 2 H, 2 × α-H), 3.65 (br, NH_2), 4.4 (br t, α-H), and 6.95 (m, C_6H_4); $\nu_{max.}$ 3 380 and 3 475 cm^{-1} (NH_2).

The slowest moving component on the 7-ft column was unchanged phenylhydrazone (3). A preliminary analysis of the ^{19}F n.m.r. spectrum of the third fraction (0.719 g) containing the three components had shown that they were unchanged phenylhydrazone (3) (0.003 g), the indole derivative (9) (0.617 g, 12%), and the 4-substituted aniline derivative (10) (0.099 g, 2%).

Preparation of Schiff's Bases of Acetophenone.—(i) *From pentafluoroaniline.* The reaction was carried out in refluxing tetralin during 24 h using anhydrous zinc chloride as a catalyst, and gave the imine (8) (30%).

(ii) *From* 1,3,4,5,6,7,8-*heptafluoro*-2-*naphthylamine.* The reaction was carried out using the method used in (i) and gave *heptafluoro*-N-(α-*methylbenzylidene*)-2-*naphthylamine* (12) (17%), m.p. 142—143.5 °C (from toluene) (Found: C, 58.4; H, 2.0; N, 3.8%; M^+, 371. $C_{18}H_8F_7N$ requires C, 58.2; H, 2.2; N, 3.8%; *M*, 371).

Attempted Cyclisations of Schiff's Bases.—(i) The *N*-pentafluorophenylimine (8) (0.624 g), anhydrous $ZnCl_2$ (0.86 g), and dry tetralin (20 ml) were heated together under reflux for 24 h. The mixture was diluted with water, extracted with ether, the extracts dried ($MgSO_4$) and the solvent evaporated. Removal of tetralin by distillation under reduced pressure (0.05 mmHg) with external heating at 50 °C, and examination of the tarry product by ^{19}F n.m.r., failed to reveal any of the indole derivative (9). Sublimation of the product at 90 °C/0.05 mmHg gave unchanged imine (8) (0.517 g, 83%), identified by ^{19}F n.m.r. spectroscopy.

(ii) The *N*-naphthylimine (12) (0.148 g), anhydrous KF (0.218 g), anhydrous $ZnCl_2$, and dry tetralin (10 ml) were heated together under reflux for 24 h. The mixture was worked up as in (i) and was examined by t.l.c. on silica using CCl_3–$CHCl_3$ (50 : 50 v/v). No pyrrole derivative (6) was detected. The mixture was separated by thick layer chromatography (silica; solvent as for the analytical experiment) and gave unchanged starting material (12) (0.131 g, 88%), identified by i.r. spectroscopy. No pyrrole derivatives were detected by i.r. in other minor fractions obtained from the separations.

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