Reactions Involving Fluoride Ion. Part IX.[1] Syntheses Involving Octafluoroisobutene

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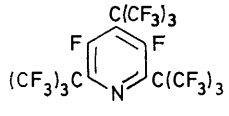
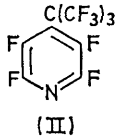
Octafluoroisobutene reacts with pentafluoropyridine in the presence of fluoride ion, at 80°, to give perfluoro-2,4,6-tri-t-butylpyridine whereas, at 20°, perfluoro-4-t-butylpyridine is formed. Reaction of octafluoroisobutene with tetrafluoropyridazine, at 80°, gives perfluoro-3,6-di-t-butylpyridazine exclusively, although at lower temperatures perfluoro-4-t-butyl or -3,5-t-butyl derivatives are obtained. The variation in the orientation of products formed with the olefin used in polyfluoroalkylations with tetrafluoropyridazine is discussed. *Perfluoro-t-butylpyridines* show no indication of restricted rotation even at low temperatures and this illustrates how increased crowding can *lower* a rotational barrier.

We have been concerned recently with establishing some of the factors controlling the orientation of substitution in polyfluoroalkylation, *i.e.* the fluoride-ion induced reaction of a fluoro-olefin with an activated polyfluoroaromatic compound. Originally, it was observed that, with hexafluoropropene and either pentafluoropyridine,[2] or tetrafluoropyridazine,[3] a mixture of products arising from both kinetic and thermodynamic control is formed, and other workers have made similar observations.[4] More recently, however, we have shown that, with tetrafluoroethylene, the products arise exclusively from kinetic control[5] and we now report the other extreme, where the products more readily arise from thermodynamic control in reactions involving octafluoroisobutene.

At 80°, reaction occurred rapidly between octafluoroisobutene (*N.B. extremely toxic*) and pentafluoropyridine in tetrahydrothiophen dioxide, with caesium fluoride as initiator, to give exclusively perfluoro-2,4,6-tri-t-butylpyridine (I) in 85% yield. At lower temperatures, *e.g.* 30°, the product contained mainly perfluoro-4-t-butylpyridine (II), together with a small amount of a perfluorodi-t-butylpyridine which was not characterised.



(I)



(II)

The 2,4,6-isomer (I) was the only perfluorotrialkylpyridine isolated; none of the corresponding 2,4,5-isomer was detected. This is in contrast to the corresponding reaction of tetrafluoroethylene which gives perfluoro-2,4,5-triethylpyridine as the exclusive trisubstitution product,[5] although a mixture of perfluoro-2,4,5- and -2,4,6-tri-isopropylpyridines is obtained when hexafluoropropene is used, the proportion depending on the reaction temperature.[2]

Surprisingly, the sole product from reaction between octafluoroisobutene and tetrafluoropyridazine at 80° was perfluoro-3,6-di-t-butylpyridazine (VIIIc) (75% yield). At 20°, with a deficiency of octafluoroisobutene, perfluoro-4-t-butylpyridazine (IIIc) was the only product (80%), while at 40° with an excess of octafluoroisobutene a mixture of *ca.* equal proportions of the disubstituted derivatives, perfluoro-3,5-di-t-butylpyridazine (VIc) and the corresponding 3,6-isomer (VIIIc), was isolated. It is clear that the disubstituted product (VIc) is an intermediate in the formation of the isomeric compound (VIIIc) because, on heating with caesium fluoride in tetrahydrothiophen dioxide to 110°, compound (VIc) was converted into its isomer (VIIIc). These reactions contrast even more markedly with those[5] using tetrafluoroethylene and hexafluoropropene than do the reactions involving pentafluoropyridine described above. Perfluoro-4,5-diethylpyridazine (IVa) was the only disubstituted product from the reaction of tetrafluoropyridazine with tetrafluoroethylene, while a mixture of perfluoro-4,5-di-isopropylpyridazine (IVb) and the 3,5-isomer (VIb) was obtained from hexafluoropropene.

Taken together the results indicate that, for polyfluoroalkylations using octafluoroisobutene, there is a preference for producing the least crowded isomer. In reactions of pentafluoropyridine, attack by $(CF_3)_3C^-$ probably occurs directly at the 6-position in forming the 2,4,6-isomer (I) from the intermediate 2,4-derivative. This is probable since, unlike the analogous reactions with $(CF_3)_2CF^-$,[2] neither the perfluoro-2,4,5-tri-t-butylpyridine nor the corresponding perfluoro-2,5-di-t-butylpyridine was detected. However, initial attack by $(CF_3)_3C^-$ occurs at the 4-position in tetrafluoropyridazine, giving monosubstituted product (IIIc), but a rearrangement must take place to give the disubstituted product (VIIIc), which is the product of thermodynamic control. Because of the diversity of the products formed, it is useful to summarise and compare the results of polyfluoroalkylation of tetrafluoropyridazine by tetrafluoroethylene, hexafluoropropene, and octafluoroisobutene. The substitution pattern is critically dependent on the olefin used and the various compounds which we have now isolated and characterised are shown in the Scheme. There is more than one mechanistic pathway available

[1] Part VIII, R. D. Chambers, M. Y. Gribble, and E. Marper, preceding paper.

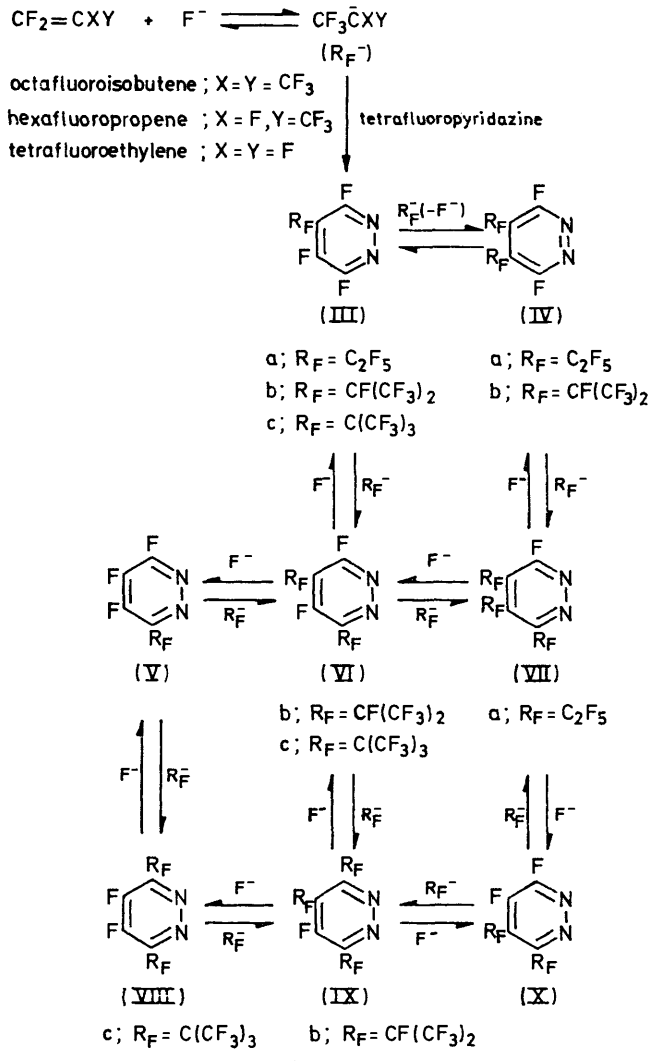
[2] R. D. Chambers, R. P. Corbally, J. A. Jackson, and W. K. R. Musgrave *Chem. Comm.*, 1969, 127; R. D. Chambers, R. P. Corbally, and W. K. R. Musgrave, *J.C.S. Perkin I*, 1972, 1281.

[3] R. D. Chambers, Yu. A. Cheburkov, J. A. H. MacBride, and W. K. R. Musgrave, *J. Chem. Soc.* (*C*), 1971, 532.

[4] C. J. Drayton, W. T. Flowers, and R. N. Haszeldine, *Chem. Comm.*, 1970, 662; *J. Chem. Soc.* (*C*), 1971, 2750.

[5] (*a*) R. D. Chambers, R. P. Corbally, M. Y. Gribble, and W. K. R. Musgrave, *Chem. Comm.*, 1971, 1345; (*b*) R. D. Chambers and M. Y. Gribble, *J.C.S. Perkin I*, 1973, 1405.

for the formation of some of these compounds and the alternatives are outlined.



SCHEME

Compounds indicated are those which have been isolated

The 4- and 5-positions in tetrafluoropyridazine are the most susceptible to nucleophilic attack and, consistent with this, the anion $CF_3CF_2^-$ gives the substituted products (IIIa), (IVa), and (VIIa); no products of rearrangement are observed. A more complicated situation occurs, however, with the anion $(CF_3)_2CF^-$ where the perfluoroisopropylpyridazines (IIIb), (IVb), (VIb), and (IXb) are obtained. The 4,5-isomer (IVb) can be converted into the 3,5-isomer (VIb), together with some of the products (IXb) and (IIIb), by heating with fluoride ion, and the rearrangement could occur by either of two routes: (IV) ⟶ (VII) ⟶ (VI),[4] or (IV) ⟶ (III) ⟶ (VI). We now believe that the first of these alternatives occurs more readily with $(CF_3)_2CF^-$ because, with either tetrahydrothiophen dioxide or 2,5,8,11,14-pentaoxapentadecane as solvent, the trisubstituted derivative (IXb) can be produced in direct polyfluoroalkylations of tetrafluoropyridazine at temperatures significantly below that at which appreciable rearrangement of the 4,5-disubstituted compound (IVb) to products (VIb), (IIIb), and (IXb) occurs in the presence of caesium fluoride in these solvents. This suggests that the activation energy for attack of $(CF_3)_2CF^-$ on compound (IVb) is lower than for attack of fluoride ion on this compound.

Nevertheless, at higher temperatures a perfluoroisopropyl group is displaced from compound (IVb) by fluoride ion;[3] if the reaction is carried out in the presence of tetrafluoropyridazine then only the 4-substituted product (IIIb) is obtained. This is a useful synthetic process since it is difficult to obtain the monosubstituted derivative (IIIb) directly. Displacement of a perfluoroisopropyl group from the 3-position exclusively occurs in a similar reaction of the trisubstituted derivative (IXb) to give product (VIb). In reactions with $(CF_3)_3C^-$, formation of the 3,5-isomer (VIc) probably occurs by direct substitution in the 3-position of the monosubstituted product (IIIc), rather than *via* products (IV) and (VII) [where $R_F = C(CF_3)_3$], since no 4,5-isomer was detected. Furthermore it is highly unlikely that a derivative corresponding to compound (VII), with three adjacent perfluoro-t-butyl groups, would be formed because of the steric requirements of these groups. A more ambiguous situation obtains, however, in the formation of the 3,6-isomer (VIIIc). Displacement of the 5-substituent in the 3,5-isomer (VIc) by fluoride ion occurs at 80°, with transfer to tetrafluoropyridazine, to give perfluoro-3- and -4-t-butylpyridazine (V) and (IIIc). This indicates that compound (V) could be an intermediate in the formation of the 3,6-isomer (VIIIc) but the detection of a trace of a compound which is probably the trisubstituted product [IX; $R_F = C(CF_3)_3$] suggests that processes involving both compounds (V) and (IX) are possible.

The variation in the observed products indicated in the Scheme is consistent with the ease of formation as well as the steric requirements increasing in the series $CF_3{\cdot}CF_2^- < (CF_3)_2CF^- < (CF_3)_3C^-$ and these results provide a striking example of the interplay of kinetic and thermodynamic control of reaction products in nucleophilic aromatic substitution.

^{19}F *N.m.r. Spectra.*—The ^{19}F n.m.r. spectrum of perfluoro-2,4,6-tri-t-butylpyridine (I) established its structure by showing a resonance attributable to two equivalent ring fluorine atoms with appropriate chemical shift.[6]

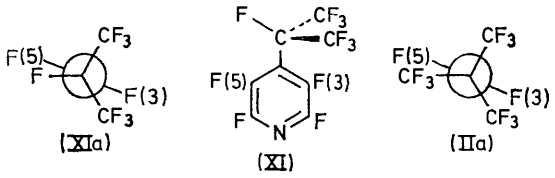
Chemical shift data for ring fluorine atoms in perfluoro-t-butylpyridazines are given in the Table; the changes in chemical shift on substitution for compounds (IIIc) and (VIc) parallel those observed previously[3] for the corresponding perfluoroisopropyl derivatives (IIIb) and (VIb). The structures of compounds (Vc) and (VIIIc) then follow directly from the change in chemical shift on substitution.

The chemistry of perfluoro-3,6-di-t-butylpyridazine (VIIIc) is also consistent with the assigned structure.

[6] R. D. Chambers, J. A. Jackson, W. K. R. Musgrave, L. H. Sutcliffe, and G. J. T. Tiddy, *Tetrahedron*, 1970, **26**, 71.

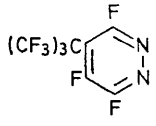
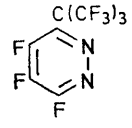
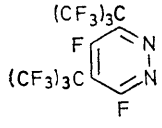
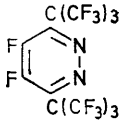
Although tetrafluoropyridazine [7] and perfluoro-4,5-di-isopropylpyridazine [3] (IVb) are soluble in concentrated sulphuric acid and are both susceptible to acid-induced displacement of the 3- and 6-fluorine atoms, the derivative (VIIIc) is insoluble in concentrated sulphuric acid. Conversely, compound (VIIIc) is very susceptible to nucleophilic attack; potassium hydroxide in t-butyl alcohol gave a high molecular weight polymer which contained perfluoro-t-butyl groups and is almost certainly a polyether. The polymer was unchanged after being heated to 350° in air.

3- and 5- ring fluorine atoms. If a similar barrier obtained for perfluoro-t-butylpyridines, then non-equivalent



trifluoromethyl groups would be observed. However, the spectrum of perfluoro-4-t-butylpyridine (II) showed,

^{19}F N.m.r. data for perfluoro-t-butylpyridazines

Compound		Chemical shifts (p.p.m.) [a] (Change in chemical shift on substitution [p.p.m.]) 3-F	4-F	5-F	6-F	Reference compound
		93·9	147·6			
	(IIIc)	62·9 (−31)		107·3 (−40·3)	97·0 (+3·1)	Tetrafluoropyridazine
	(Vc)		126·2 (−21·4)	153·9 (+6·3)	92·2 (−1·7)	Tetrafluoropyridazine
	(VIc)		87·8 (−19·5)		*ca.* 63 [b] (*ca.* 0)	(IIIc)
	(VIIIc)		129·2 (+3·0)	129·2 (−24·7)		(Vc)

[a] Relative to $CFCl_3$. [b] Contained in an absorption band 1·4 p.p.m. wide.

The trifluoromethyl resonances of perfluoro-t-butylpyridines are of considerable interest because of the restricted rotation which has been observed through the spectra of perfluoro-isopropyl- and -s-butylpyridines.[6,8] At low temperatures, the 4-perfluoroisopropyl group in compound (XI) exists in essentially a fixed conformation (XIa) arising from a barrier to rotation caused by interaction between the trifluoromethyl groups and the

for the trifluoromethyl resonance, a sharp triplet, arising from equal coupling with 3- and 5- ring fluorine atoms, down to −60°.

This is a good illustration of how a rotational barrier may be decreased by raising the energy of the minimum energy conformation. In comparing compounds (IIa) and (XIa) we have additional interactions arising from the extra trifluoromethyl group in (IIa). Our observa-

[7] R. D. Chambers, J. A. H. MacBride, and W. K. R. Musgrave, *J. Chem. Soc.* (*C*), 1968, 2989.

[8] R. D. Chambers, L. H. Sutcliffe, and G. J. T. Tiddy, *Trans. Faraday Soc.*, 1970, **66**, 1025.

tions agree with the conclusions of other workers [9] who have also illustrated that *increasing* the crowding can sometimes lead to *decreased* barriers to rotation.

EXPERIMENTAL

^{19}F N.m.r. spectra were measured using a Varian A56/60D spectrometer (CCl_3F as external reference).

Reactions of Octafluoroisobutene.—(a) *With pentafluoropyridine.* It is important to stress that octafluoroisobutene is an EXTREMELY HAZARDOUS COMPOUND [10] because of its acute toxicity. During the manipulation of this compound, or any systems in which it was likely to be produced, STRINGENT SAFETY PRECAUTIONS WERE EMPLOYED WHICH INCLUDED THE WEARING OF BREATHING APPARATUS. (i) At 80°. Reactions were carried out at near atmospheric pressure, in a simple apparatus which has been described previously.[5,6] Caesium fluoride (3·0 g, 20·0 mmol), tetrahydrothiophen dioxide (35 ml), and pentafluoropyridine (3·0 g, 17·8 mmol) were contained in a flask equipped with a magnetic stirrer and a condenser which was attached to a football bladder; the flask had previously been baked and purged with dry nitrogen. The flask was cooled in liquid air and evacuated; then the apparatus was sealed and gradually heated to 80°. Octafluoroisobutene was admitted from a pre-weighed cyclinder until a small positive pressure was indicated by the bladder. A vacuum quickly developed when the mixture was stirred vigorously, and further quantities of octafluoroisobutene were gradually admitted. After *ca.* 30 min the rate of olefin uptake decreased, even with a small positive pressure, and stirring was continued for a further 6·5 h. A vacuum developed slowly owing to dimerisation of the olefin.[11] The total weight of octafluoroisobutene (15·0 g, 75 mmol) consumed in the reaction was deduced by re-weighing the cylinder. Distillation of the reaction mixture under vacuum, up to *ca.* 90°, gave a liquid (4·0 g) and a solid which was contaminated with tetrahydrothiophen dioxide. Analysis of the liquid by g.l.c. showed that it contained dimers of octafluoroisobutene and another component corresponding to the solid. The original solid was washed with boiling water to remove tetrahydrothiophen dioxide, filtered, and recrystallised from ethyl acetate to give crystals (10·0 g, 85%), m.p. 161—162°, of *perfluoro-2,4,6-tri-t-butylpyridine* (I) (Found: C, 26·4; F, 71·9%; M^+, 769. $C_{17}H_{29}N$ requires C, 26·5; F, 71·7%; *M*, 769); δ_F 60·7 [4-$(CF_3)_3C$] and 61·8 [2,6-$(CF_3)_3C$] (total 27F) and 87·3 p.p.m. (2F, 3,5-F).

(ii) At 30°. In a similar experiment, a mixture of caesium fluoride (*ca.* 1 g), tetrahydrothiophen dioxide (30 ml), pentafluoropyridine (2·0 g, 11·8 mmol), and octafluoroisobutene (*ca.* 5 g, 25 mmol) was stirred at 30° for 4 h. A liquid (2·2 g) was removed under vacuum and shown by g.l.c. to be mainly one component (*ca.* 90%), which was separated by preparative scale g.l.c. (silicone elastomer; 100°) to give *perfluoro-4-t-butylpyridine* (II) (Found: F, 55·6%; M^+, 369. $C_9F_{13}N$ requires F, 66·39%; *M*, 369); δ_F 62·9 [9F, t, *J* 25 Hz, 4-$(CF_3)_3C$], 89·6 (2F, 2,6-F), and 129·9 p.p.m. (2F, 3,5-F). The minor component could not be obtained uncontaminated by the major product (II), but the mass and n.m.r. spectral data indicated that it was perfluoro-2,4-di-t-butylpyridine (Found: M^+, 569. $C_{13}F_{21}N$ requires *M*, 569); δ_F 62·3 [dd, *J* 24 and 27 Hz, 4-$(CF_3)_3C$], 63·5 [d, *J* 23 Hz, 2-$(CF_3)_3C$], and 83·5br [dd, *J* 23 and 30 Hz, 6-F]; the resonances arising from the remaining ring fluorine atoms were apparently too broad to be observed on the small sample available.

(b) *With tetrafluoropyridazine.* (i) At 80°. The procedure was similar to that described above. A mixture of caesium fluoride (3·0 g, 20 mmol), tetrahydrothiophen dioxide (35 ml), and tetrafluoropyridazine (3·0 g, 19·7 mmol) was stirred with perfluoroisobutene (12·0 g, 60·0 mmol) for 10 h at 80°. Removal of volatile products under vacuum, at temperatures up to 90°, gave a liquid (1·4 g). Analysis by g.l.c. indicated the presence of oligomers of the olefin, together with a major component which was identical with the product isolated from the residue (see below). When excess of water was added to the residue, crystals remained which were recrystallised from acetone to give *perfluoro-3,6-di-t-butylpyridazine* (VIIIc), m.p. 135—136° (7·5 g, total yield 75%) (Found: C, 26·3; F, 69·3%; M^+, 552. $C_{12}F_{20}N_2$ requires C, 26·1; F, 68·8%; *M*, 552); δ_F 62·4 [18F, 3,6-$(CF_3)_2C$] and 129·2 p.p.m. (2F, 4,5-F).

(ii) At 40°. A mixture of caesium fluoride (2·0 g, 13·1 mmol), tetrahydrothiophen dioxide (20 ml), and tetrafluoropyridazine (4·0 g, 26·3 mmol) was stirred with octafluoroisobutene (11·0 g, 55 mmol) for 1 day. Transfer of products under vacuum gave a mixture (8·1 g) of perfluoro-t-butylpyridazines, shown by g.l.c. and mass spectrometry to contain perfluoro-mono-, -3,5-di-, -3,6-di-, and -tri-t-butylpyridazines. Crystallisation from ether gave a solid (3·0 g) which was shown (see Discussion section) to be *perfluoro-3,5-di-t-butylpyridazine*, m.p. 50° (Found: C, 26·1; F, 68·5%; M^+, 552. $C_{12}F_{20}N_2$ requires C, 26·1; F, 68·85%; *M*, 552); δ_F 87·8 (1F, 4-F), and 62·9, [19F, m, 3- and 5-$(CF_3)_3C$ and 6-F]. Removal of volatile material from the residue from the crystallisation gave perfluoro-3,6-di-t-butylpyridazine (VIIIc) (3·1 g).

(iii) At 20°. A mixture of caesium fluoride (3·0 g, 19·7 mmol), tetrahydrothiophen dioxide (30 ml), and tetrafluoropyridazine (18·6 g, 122 mmol) was stirred with octafluoroisobutene (19·5 g, 97·5 mmol) for 4 h at 20°. Transfer under vacuum gave a liquid (28·5 g) together with a solid (2·8 g). The liquid was shown by g.l.c. to contain small amounts of tetrafluoropyridazine, oligomers of the olefin, traces of unidentified material, and the main component which was separated by preparative scale g.l.c. to give *perfluoro-4-t-butylpyridazine* (IIIc), m.p. 36—38° (Found: C, 27·1; F, 65·0%; M^+, 352. $C_8F_{12}N_2$ requires C, 27·3; F, 64·8%; *M*, 352). The solid was shown also to be mainly the product (IIIc) (total yield 80%).

Reaction of Perfluoro-3,5-di-t-butylpyridazine (VIc) *with Fluoride Ion.*—A mixture of the pyridazine (VIc) (0·4 g, 0·73 mmol), caesium fluoride (1·0 g, 6·6 mmol), and tetrahydrothiophen dioxide (6 ml), contained in a Carius tube under vacuum, was heated for 15 h at 110°. The product was distilled out of the tube under vacuum and shown to be perfluoro-3,6-di-t-butylpyridazine (0·2 g, 50%).

Reaction of a Mixture of Perfluoro-3,5-di-t-butylpyridazine (VIc) *and Tetrafluoropyridazine with Fluoride Ion.*—A mixture of perfluoro-3,5-di-t-butylpyridazine (VIc) (0·5 g, 0·082 mmol), tetrafluoropyridazine (0·6 g, 0·39 mmol), caesium fluoride (0·5 g, 3·28 mmol), and tetrahydrothiophen dioxide was stirred for 4 h at 80°, under dry nitrogen.

[9] J. E. Anderson, R. W. Franck, and W. L. Mandella, *J. Amer. Chem. Soc.*, 1972, **94**, 4608.

[10] See data and references given in ' Organic Fluorine Chemistry,' W. A. Sheppard and C. M. Sharts, Benjamin, New York, 1969, p. 452.

[11] D. P. Graham and W. B. McCormack, *J. Org. Chem.*, 1966, **31**, 958.

Volatile material (1·0 g) was removed by transfer under vacuum and shown to contain tetrafluoropyridazine, which was largely removed by distillation; a trace of a perfluoro-di-t-butylpyridazine; and *ca.* equal amounts of perfluoro-4-t-butylpyridazine (IIIc) and perfluoro-3-t-butylpyridazine (Vc). These isomers were not separated but the ^{19}F n.m.r. spectrum of the mixture clearly indicated the presence of the 3-substituted isomer; in addition to the resonances recorded in the Table, there was a peak at δ_F 62·4 p.p.m. [9F, d, J 19·5 Hz, $(CF_3)_3C$].

Reaction of a Mixture of Perfluoro-4,5-di-isopropylpyridazine (IVb) *and Tetrafluoropyridazine with Fluoride Ion.*—A mixture of perfluoro-4,5-di-isopropylpyridazine (IVb) (IVb) (15·8 g, 34·9 mmol), tetrafluoropyridazine (6·4 g, 42·1 mmol), and caesium fluoride (5 g, 32·9 mmol), in tetrahydrothiophen dioxide (95 ml), was stirred at 120° for 18 h. The volatile product (16·9 g) was shown by g.l.c. to contain perfluoro-4-isopropylpyridazine (IIIb) [3] (81%) and perfluoro-3,5-di-isopropylpyridazine (VIb) [3] (19%). Portions were separated and the compounds identified spectroscopically.

Reaction of a Mixture of Perfluoro-3,4,6-tri-isopropylpyridazine (IXb) *and Tetrafluoropyridazine with Fluoride Ion.*—A mixture of perfluoro-3,4,6-tri-isopropylpyridazine (IXb) (3·1 g, 5·15 mmol), tetrafluoropyridazine (1·15 g, 7·57 mmol), and caesium fluoride (3·0 g, 19·8 mmol), in 2,5,8,11,14-pentaoxapentadecane (20 ml), was stirred vigorously for 2 days at 120°. A volatile product (2·5 g) was isolated by transfer under vacuum and shown by g.l.c. to contain perfluoro-3,4,6-tri-isopropylpyridazine (5·8%), perfluoro-3,5-di-isopropylpyridazine (VIb) [3] (77·4%), and perfluoro-4-isopropylpyridazine (IIIb) [3] (16·8%). These components were separated and identified spectroscopically.

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