

Reactions involving Fluoride Ion. Part V.¹ Synthesis of Perfluoroisopropylquinolines

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Fluoride-ion-induced reaction of hexafluoropropene with perfluoroquinoline gives a mixture of perfluoroisopropylquinolines. Substitution occurs preferentially in the 2- and 4-positions, and is followed by attack at the 6-position. Rearrangement of perfluoro-2,4-di-isopropylquinoline occurs on heating with fluoride ion, giving the 2,6-isomer as well as other products. Unusually large 'through-space' coupling constants, between a 4-perfluoroisopropyl group and a 5-fluorine atom, are observed in the ¹⁹F n.m.r. spectra of these systems. Also, the fluorine n.m.r. spectra are temperature dependent and this phenomenon is discussed in terms of preferential population of particular conformations.

We previously described fluoride-ion-initiated reactions of hexafluoropropene with perfluorinated derivatives of pyridine,² pyridazine,³ and pyrazine; some similar work was discussed more recently by other workers.⁴ Part of the interest in these processes stems from the fact that they amount to the nucleophilic equivalent of Friedel-Crafts chemistry and, as such, help to extend the mechanistic framework of organic chemistry. The pyridine and pyridazine systems presented some unusual orientation problems, because of the reversibility of some polyfluoroalkylation reactions, and it was found that kinetic or thermodynamic control of products can occur,¹ depending on the system and the conditions of reaction. We now describe some polyfluoroalkylation reactions of perfluoroquinoline; the particular interest of this system lies in the effect of the *peri*-5-fluorine atom on the reactivity of the 4-position.

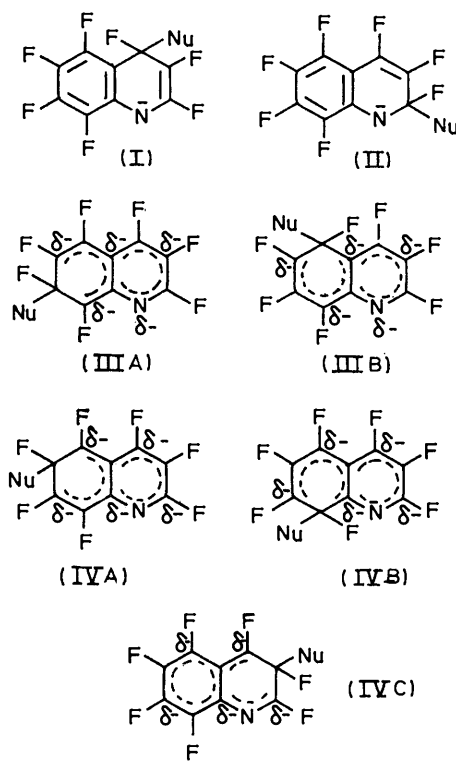
The gross features of orientation of nucleophilic attack in polyfluoroaromatic nitrogen heterocyclic compounds can be accounted for,⁵ in a qualitative fashion, by considering intermediates as models for transition states, and assuming that negative charge at the position *para* to the position of entry of the nucleophile is greater than at *ortho*-positions.⁵ It is also assumed that negative charge is best accommodated on a nitrogen atom where possible. On this basis it can be appreciated that attack at the 4- and 2-positions in perfluoroquinoline is preferred,⁶ *via* intermediates (I) and (II). Attack in the benzenoid ring is more likely to take place at the 7- (IIIA) and 5- (IIIB) rather than the 6- (IVA) and 8- (IVB) positions because, again, the negative charge can be localised on the ring nitrogen atom. Substitution in the 3-position (IVC) is similar to that in the 6- and 8-positions. Thus, the expected order of reactivity would be $4 \geq 2 \geq 7,5 > 3,6,8$. On polysubstitution, the order of reactivity of the vacant positions might well be changed by the electron-withdrawal and steric effects associated with the 2- and 4-perfluoroalkyl groups. These would stabilise the intermediates formed by substitution in the 6- and 8-positions whilst hindering, sterically, substitution in the 5- and 3-positions.

¹ Part IV, R. D. Chambers, R. P. Corbally, and W. K. R. Musgrave, preceding paper.

² R. D. Chambers, J. A. Jackson, W. K. R. Musgrave, and R. A. Storey, *J. Chem. Soc. (C)*, 1968, 2221.

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

We have found that reactions of perfluoroquinoline with perfluoroisopropyl anions, generated from hexafluoropropene with fluoride ion, easily lead to poly-substitution, and the complex mixture of products is



Nu = nucleophile

difficult to separate. A variety of column packings were investigated for application of preparative-scale g.l.c., but even the most useful columns, di-*n*-decyl phthalate and polyethylene glycol *o*-phthalate, gave only moderate resolution. In order to keep the mixture of products as simple as possible, reactions at room temperature were carried out; under these conditions some olefin was unchanged. The results of experi-

⁴ C. J. Drayton, W. T. Flowers, and R. N. Haszeldine, *Chem. Comm.*, 1970, 662.

⁵ For a summary and references, see R. D. Chambers, J. A. H. MacBride, and W. K. R. Musgrave, *J. Chem. Soc. (C)*, 1968, 2116.

⁶ R. D. Chambers, M. Hole, W. K. R. Musgrave, R. A. Storey, and B. Iddon, *J. Chem. Soc. (C)*, 1966, 2331.

ments in which either triglyme (2,5,8,11-tetraoxadodecane) or tetraglyme (2,5,8,11,14-pentaoxapentadecane) was used as solvent are recorded in Table 1.

TABLE I
Fluoride-ion-induced reactions of hexafluoropropene with perfluoroquinoline

Reagents				
Perfluoroquinoline (g)	8.3	7.8	7.2	7.3
C ₃ F ₆ (g)	18	18	7.5	8.0
CsF (g)	5.9	6.2	6.3	6.3
Solvent (ml)	45 ^a	45 ^a	50 ^b	50 ^b
Conditions				
Temp. (°C)	18	18	19	19
Time (h)	18	18	70	70
Products (% yield) ^c				
(C ₃ F ₆) _n (n = 1-3)	← Traces →			
Perfluoro-2,4,6-tri-isopropyl-quinoline (IX)	27	32	6	7
Perfluoro-2,4-di-isopropyl-quinoline (VIII)	47	44	25	25
Perfluoro-2- and -4-isopropyl-quinolines (VI) and (VII)	5 ^d	4 ^d	12 ^e	11 ^e
Perfluoroquinoline (V)	20	18	53	52

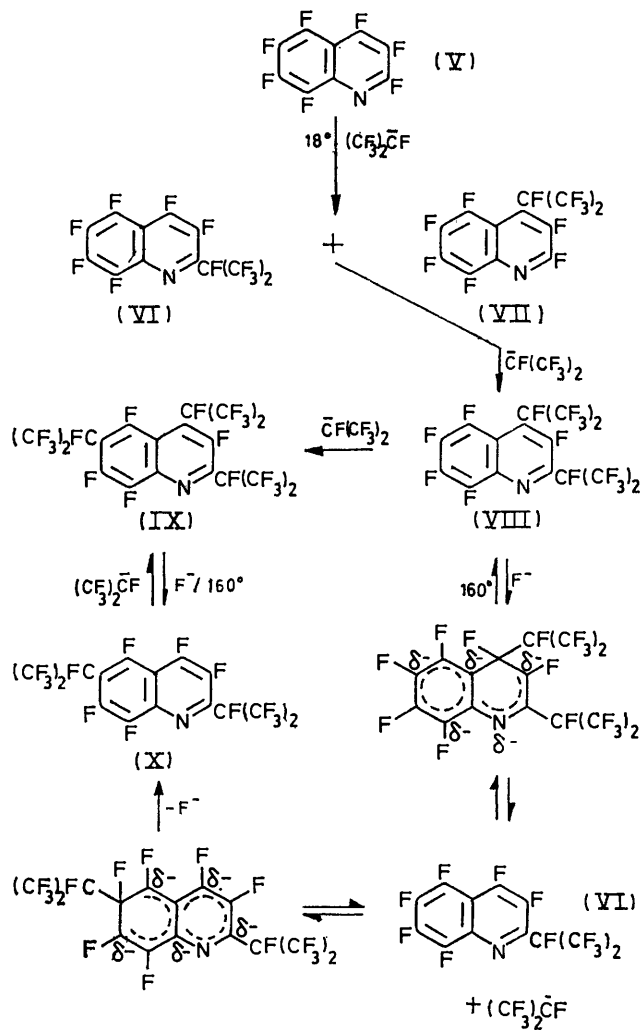
^a Triglyme. ^b Tetraglyme. ^c Residual olefin vented. ^d Approx. equal weights of (VI) and (VII). ^e Predominantly (VII).

With triglyme, a small amount of the 2- (VI) and 4- (VII) perfluoroisopropyl derivatives were obtained, together with the 2,4-di- (VIII) and 2,4,6-tri- (IX) substituted compounds. The main product was, however, the disubstituted compound (VIII) and this was accompanied by a small amount of an isomeric compound, the structure of which is not known. The tetraglyme system was useful because, when a lower proportion of olefin was used, the product contained mainly a single monoisopropyl derivative (VII) and the disubstituted derivative (VIII). The structures were established on the basis of their fluorine-19 n.m.r. spectra as described later.

It seems clear that in the carbocyclic ring, under the mild conditions used, the 6-position is greatly preferred for attack by the perfluoroisopropyl anion, once substitution has occurred in the 2- and 4-positions. Formation of the 2,4,6-trisubstituted compound (IX) indicates a reversal of the expected order of reactivities of the 6- and 7-positions in perfluoroquinoline, induced by the 2- and 4-(CF₃)₂CF groups. These groups stabilise intermediates of the type (IVA) and therefore activate the 6-position to attack. (*N.B.* The action of methoxide ion on perfluoroquinoline at room temperature produces the 2,4-dimethoxy-derivative but no trimethoxy-compound. At higher temperatures the 2,4,7-trimethoxy-derivative is obtained.⁷)

The complexity of mixtures obtained at higher temperatures (see Scheme) suggested that a fluoride-ion-induced rearrangement of (VIII) might occur, similar to the rearrangement of perfluoro-2,4,5-tri-isopropylpyridine to the corresponding 2,4,6-isomer.¹ This was confirmed by heating a sample of (VIII) with caesium fluoride at 160°, the temperature used for rearrangement of perfluoro-2,4,5-tri-isopropylpyridine. Re-

arrangement occurs to give mainly the 2,6-isomer (X) and the 2-isopropyl compound (VI) together with perfluoroquinoline (V) and the 2,4,6-tri-isopropyl-compound (IX) as by-products; this constitutes strong



SCHEME

evidence that the rearrangement is an intermolecular process, analogous to the rearrangement of perfluoro-2,4,5-tri-isopropylpyridine. The intermolecular nature of the latter reaction has been demonstrated by crossover experiments.¹

The main processes occurring at room temperature and at 160° are represented in the Scheme. Attack at the 2- and 4-positions takes place readily and the 2,4-disubstituted compound (VIII) is much more reactive towards fluoride ion than perfluoro-2,4-di-isopropylpyridine, which does not lose a (CF₃)₂CF group at 160°.

These results clearly present yet another example of the delicate balance between kinetic and thermodynamic control of reaction products⁸ which exists

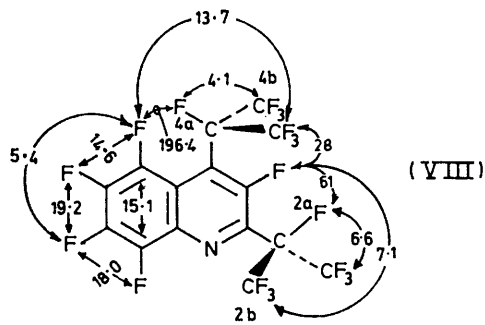
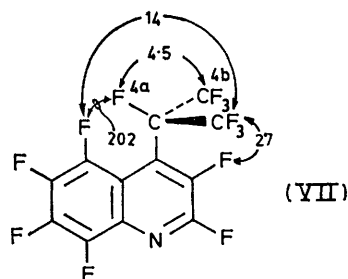
⁷ S. L. Bell, unpublished results.

⁸ R. D. Chambers, R. P. Corbally, M. Y. Gribble, and W. K. R. Musgrave, *Chem. Comm.*, 1971, 1345.

in polyfluoroalkylation reactions with hexafluoroisopropyl anions. It is apparently the crowding between the 4-heptafluoroisopropyl group and the *peri*-5-fluorine atom which leads to the thermodynamic instability of (VIII) with respect to (X). This crowding is reflected by the unusually large coupling constants in the ^{19}F n.m.r. spectra between the 4-(CF_3)₂CF group and the *peri*-5-F (see later).

Preliminary experiments on mixtures of perfluoroisopropylquinoline compounds at 160° for 14 h in the presence of caesium fluoride have indicated that the 4-heptafluoroisopropyl groups in (IX) and (VII) are also displaced giving other, as yet unidentified, products.

N.m.r. Spectra.—A complete analysis of the ^{19}F n.m.r. spectra of perfluoro-2,4-di-isopropylquinoline (VIII) has been carried out.⁹ The important coupling constants, *i.e.* those which are useful in the derivation of structures of other quinoline derivatives described here, are shown. Also illustrated, for comparison, are some derived values for perfluoro-4-isopropylquinoline (VII).



Coupling constants (Hz)

Derivation of Structure.—The important feature in the spectrum of (VIII) is the abnormally large coupling between 4a-F and 5-F. This is a particularly useful diagnostic feature for assigning the position of a 4-(CF_3)₂CF group, from which then follows the assignment of the 5-F resonance. A 2-(CF_3)₂CF group is characterised by the relative simplicity of the pattern of the 2b-F resonance, *i.e.* an overlapping doublet of doublets ($J_{2b,2a}$ and $J_{2b,3}$), whereas a 2-F, being adjacent to the nitrogen atom, is responsible for the lowest-field ring fluorine resonance in the spectrum. If both 4-F and 5-F are present, a prominent *peri*-coupling is evident. Furthermore, a (CF_3)₂CF group in the 6-position is diagnosed from coupling with the 5-F, and coupling between this 6-(CF_3)₂CF group and the 7-F then iden-

tifies the resonance arising from the 7-F. Assignment of the 8-F can be confirmed by the values of the coupling constants with the 7- and 5-fluorine atoms and by its chemical shift which, with the exception of perfluoro-2,4-di-isopropylquinoline (VIII), appears as the ring

TABLE 2

^{19}F Chemical shifts for perfluoroquinoline and perfluoroisopropylquinolines^a

F-	(V) ^b	(VI) ^c	(VII) ^c	(VIII) ^c	(IX) ^d	(X) ^e
2	75.48		78.91			
2a ^f		186.5		184.9	184.7	186.1
2b ^f		76.96		75.88	75.34	76.30
3	163.6	151.2	123.4	110.5	109.4	147.0
4	127.4	130.2				125.0
4a			170.3	165.9	169.2	
4b			75.48	74.94	74.09	
5	148.7	149.6	131.7	131.0	92.00	112.1
6	151.4	149.6	148.7	147.5		
6a					178.2	179.9
6b					76.50	77.43
7	154.4	154.0	154.1	153.7	132.6	132.4
8	158.1	154.0	154.1	145.3	145.9	150.2

^a Shifts are in p.p.m. upfield of external CFCl_3 and were measured at 40°. ^b 50% Solution in acetone. ^c Neat liquid. ^d 50% Solution in ether. ^e a-Fluorine is (CF_3)₂CF. ^f b-Fluorines are (CF_3)₂CF.

TABLE 3

J_{FF} Values for perfluoroisopropylquinolines^a

J	(VI) ^b	(VII) ^b	(VIII) ^c	(IX) ^d	(X) ^e
2,3		28			
2a,3	55		61.0	63	56
2b,2a	6.2		6.6	6	6
2b,3	6		7.1	7.5	5.5
4,3	f				14
4,5	48				65
4a,5		202	196.4	195	
4b,3		27	28.0	29	
4b,4a		4.5	4.1	3.5	
4b,5		13.5	13.7	16.5	
6a,5				f	48
6a,7				102	48
6b,5				20	14
6b,6a				4	5
6b,7				11	14

^a Values are in Hz obtained at 40° and the first named fluorine is that which gave J_{FF} more accurately. ^b Neat liquid. ^c Accurate to ± 0.2 Hz for 50% solution in CFCl_3 at 22°. ^d 50% Solution in ether. ^e 50% Solution in acetone. ^f Value not measured.

TABLE 4

J_{FF} Values (Hz) for perfluoroquinoline^a

J	J	J	J	J	J
2,3	27.6	3.5	7.0	4.8	4.55
2,4	26.5	3.6	4.05	5.6	14.95
2,5	3.1	3.7	8.15	5.7	1.9
2,6	6.1	3.8	2.5	5.8	17.9
2,7	1.5	4.5	48.0	6.7	17.1
2,8	8.3	4.6	1.5	6.8	2.45
3,4	14.5	4.7	3.4	7.8	19.15

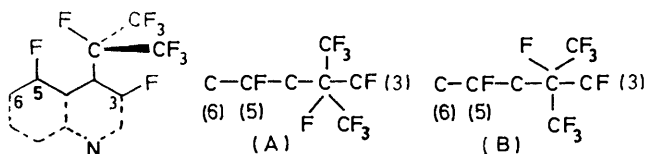
50% Solution in acetone at 40°; accurate to ± 0.1 Hz.

resonance at highest field. This leaves only the resonance of a 3-F, which is characteristically broad, since it couples with most of the available ring fluorine atoms.⁹ The complete chemical shift and coupling constant data are given in Tables 2 and 3. Table 4

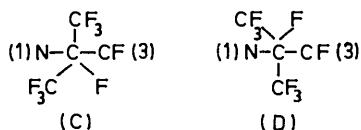
⁹ R. D. Chambers, L. H. Sutcliffe, and G. J. T. Tiddy, *Trans. Faraday Soc.*, 1970, **66**, 1025.

shows the coupling constant data for perfluoroquinoline, which has now been analysed completely.

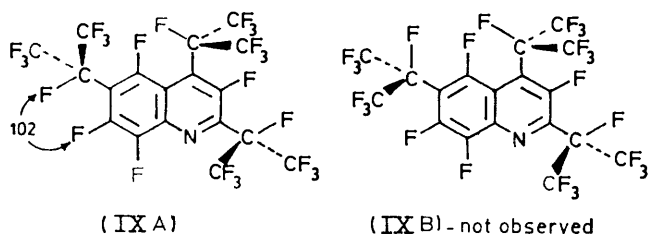
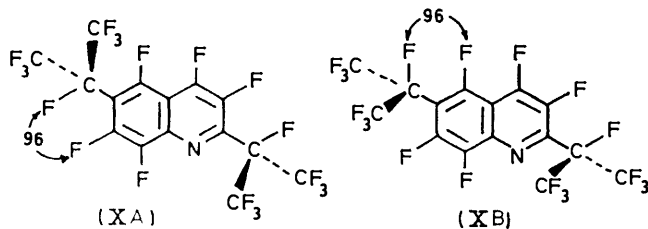
Rotational Isomerism.—The remarkably high values of $J_{4a,5}$ for the compounds (VII), (VIII), and (IX) point to the fact that the 4a-F and 5-F come close together in space; indeed these high values provide strong evidence for a 'through-space' contribution to coupling constants⁹ (as opposed to coupling through five bonds in these cases). Observed spectra arising from a 4-(CF₃)₂CF group are most logically accounted for by assuming that they arise from a time-average of conformations (A) and (B). In this way it can be



appreciated why (i) the spectrum of (VIII) is temperature invariant down to -80° , (ii) there is a significant coupling between 4b-F and 5-F and, (iii) there is only one 4b resonance. This implies that the barrier for eclipsing the 4b-CF₃ group and the 3-F is large and, of course, that the corresponding barrier for the 4b-CF₃ and the *peri*-5-F is even larger. A significant 4b-CF₃/3-F barrier has already been observed in perfluoroisopropylpyridines.^{9,10} For similar reasons, the preferred conformations of a 2-(CF₃)₂CF group are (C) and (D), time-averaged, as in (VIII).



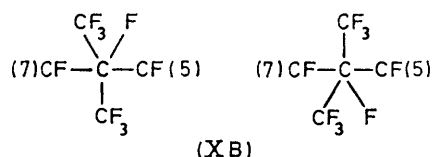
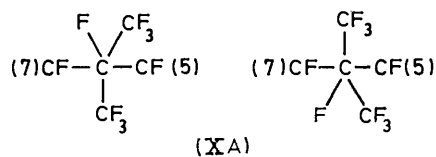
The situation becomes more delicately poised in the case of a 6-(CF₃)₂CF group because, for the di-isopropyl



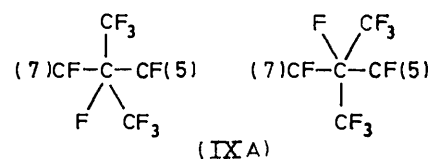
derivative (X) at 0° , both conformations averaging to an equal mixture of (XA) and (XB) are frozen out.

Only a single conformer averaging to (IXA) is observed for the tri-isopropyl derivative at 40° but at 80° the 6-(CF₃)₂CF group does show signs of rotation. In contrast, however, the 6-(CF₃)₂CF group in (X) appears to rotate freely at 80° . These conclusions were drawn from the fact that the 6a-F in (IXA) shows a large coupling (102 Hz) that was also shown by the 7-F. At 0° , the spectrum of (X) again shows a large coupling (96 Hz) for the 6a-F and the 7-F (XA), but the latter spectrum also contained a broad peak, apparently arising from coupling with the six 6b-fluorine atoms (XB), and these two sets of absorptions were approximately of equal intensity.

Therefore, the energy difference between (XA) and (XB) is small and at 0° these average conformers are both frozen out.



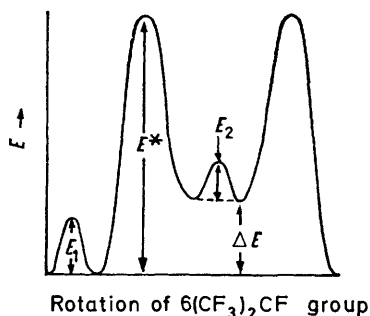
In comparing (IX) and (X), the variable temperature results show that the introduction of the 4-(CF₃)₂CF group into (X) produces not only a considerable change in the barrier to rotation of the 6-(CF₃)₂CF group but also a significant change in the relative stability of conformers (IXA) and (IXB), in comparison with (XA) and (XB), *i.e.* (IXA) is obtained exclusively up to 80° .



The relative stability of conformers is therefore influenced markedly by substituents which are not immediately adjacent to the perfluoroisopropyl group. This was observed previously for some perfluoroisopropylpyridines¹⁰ but the effect is more marked in (IX). It is important to distinguish this effect, *i.e.* the influence of substituents on the relative potential energies of conformers at energy minima (ΔE ; see Figure), from the effects on energy barriers to rotation (E_1 and E_2), *i.e.* the difference between conformers at energy minima and maxima. The small barriers, E_1 and E_2 , indicate the averaging of the two CF₃ groups as shown, *e.g.* for (IXA) above, while the large barrier E^* represents the

¹⁰ R. D. Chambers, J. A. Jackson, W. K. R. Musgrave, L. H. Sutcliffe, and G. J. T. Tiddy, *Tetrahedron*, 1970, **26**, 71.

interconversion of *e.g.* (IXA) and (IXB). It can be appreciated that the presence of a 4-(CF₃)₂CF group might increase *E** for rotation of a 6-(CF₃)₂CF group where two large barriers probably involve interaction



with the 5-F, but we cannot advance any explanation for the difference in stability (ΔE) between (IXA) and (IXB). Further work is proceeding with a view to measuring *E** in some cases.

EXPERIMENTAL

Polyfluoroalkylation of Perfluoroquinoline.—Details of quantities and yields are given in Table 1.

General procedure. A stainless steel autoclave (100 ml capacity), containing perfluoroquinoline,¹¹ hexafluoropropene, caesium fluoride, and solvent, was rotated in an oil-bath at room temperature. The product was poured into water containing sodium chloride and the aqueous solution was extracted with ether (3 × 40 ml). The extract was washed with water and dried (Na₂SO₄), the ether was removed, and then the residue was analysed quantitatively by g.l.c. (gas-density balance detector).

The products of reactions with triglyme as solvent were combined and fractionated (column of glass helices) and fractions A, b.p. 100–110° at 9 mmHg, and B, b.p. 50–70° at 0.1 mmHg, were separated by preparative-scale g.l.c. (di-n-decyl phthalate; 125°).

Fraction A gave *perfluoro-2,4-di-isopropylquinoline* (VIII) as a pale yellow oil or low-melting crystals (Found: C, 32.3; F, 64.6; N, 2.8%; *M*, 555). C₁₅H₁₉N requires C, 32.5; F, 65.0; N, 2.5%; *M*, 555), λ_{max} (cyclohexane) 217 and 246 nm (log ϵ 3.94 and 4.61), λ_{max} (film) 6.0, 6.25w, 6.57, 6.73, 7.04, 7.3, 7.65–8.1s, 8.35w, 8.5, 8.68, 9.57s, 9.95w, 10.16, 10.28, 10.67w, 12.34, 13.05w, 13.43, 13.53w, 13.8, 14.15s, 14.7, 15.0w, 15.1w, 15.35w, 17.9w, 18.45, 18.8, 19.0w, 19.36w, 19.75w, and 19.95w μm .

Fraction B gave *perfluoro-2,4,6-tri-isopropylquinoline* (IX) as a pale yellow viscous oil, b.p. >260° at 760 mmHg (Found: C, 30.8; F, 67.2; N, 2.35%; *M*, 705). C₁₈F₂₅N requires C, 30.65; F, 67.35; N, 2.0%; *M*, 705), λ_{max} (cyclohexane) 250 nm (log ϵ 4.57), λ_{max} (film) 6.05, 6.23w, 6.75, 7.07, 7.3w, 7.7–8.1s, 8.5s, 8.65w, 8.75w, 8.9, 9.3, 9.6, 9.95, 10.15–10.3s, 10.53, 11.78w, 12.05, 12.5w, 12.93w,

13.15, 13.3, 13.6w, 14.0–14.15, 14.75, 15.0w, 15.1, 15.3, 18.45, 19.05w, 19.4w, 19.75w, and 19.95w μm .

The products of reaction with tetraglyme as solvent were combined and fractionated (column of glass helices) and the fraction of b.p. 106–120° at 15 mmHg was separated by preparative-scale g.l.c. (polyethylene glycol *o*-phthalate 20% w/w on AW-Celite 80–100; 150°). *Perfluoro-4-isopropylquinoline* (VII) was obtained as a pale yellow oil, b.p. 228° at 754 mmHg (Siwoloboff) (Found: C, 35.8; F, 61.5; N, 3.8%; *M*, 405). C₁₂F₁₃N requires C, 35.6; F, 61.95; N, 3.45%; *M*, 405), λ_{max} (cyclohexane) 216 and 242 nm (log ϵ 3.89 and 4.38), λ_{max} (film) 6.0, 6.58, 6.85s, 7.33, 7.68s, 7.9–8.1s, 8.45, 8.7, 8.9w, 9.25, 9.68, 10.0, 10.3s, 11.7s, 12.05w, 12.4, 12.8w, 13.0, 13.55, 13.78, 13.95, 14.23, 15.3w, 15.7w, 16.4w, 17.15, 17.85, and 18.4 μm .

Rearrangement of Perfluoro-2,4-di-isopropylquinoline (VIII).—A stainless steel autoclave (100 ml capacity) containing perfluoro-2,4-di-isopropylquinoline (2.4 g), caesium fluoride (6.0 g), and tetrahydrothiophen dioxide (40 ml) was rotated in an oil-bath at 160° for 14 h. The product was poured into water containing sodium chloride and the aqueous solution was extracted with ether (3 × 40 ml). The extract was washed with water and dried (Na₂SO₄), the ether was removed, and then the residue was analysed quantitatively by g.l.c. (gas-density balance detector). The product consisted of perfluoro-2,4,6-tri-isopropylquinoline (IX) (0.1 g, 3%), perfluoro-2,4-di-isopropylquinoline (VIII) (0.07 g, 3%), perfluoro-2,6-di-isopropylquinoline (X) (0.57 g, 24%), perfluoro-2-isopropylquinoline (VI) (0.23 g, 13%), and perfluoroquinoline (V) (0.06 g, 6%). This was combined with similar products from further reactions and fractionated (column of glass helices). Fractions A, b.p. 90–130° at 11 mmHg, and B, b.p. 90–150° at 0.5 mmHg, were separated by preparative-scale g.l.c. (polyethylene glycol *o*-phthalate; 150°).

Fraction A gave *perfluoro-2-isopropylquinoline* (VI) as a pale yellow oil, b.p. 220° at 763 mmHg (Siwoloboff) (Found: C, 35.9; F, 60.7; N, 3.8%; *M*, 405). C₁₂F₁₃N requires C, 35.6; F, 60.95; N, 3.45%; *M*, 405), λ_{max} (cyclohexane) 232 nm (log ϵ 4.53), λ_{max} (film) 5.98, 6.07, 6.67s, 6.92s, 7.2w, 7.3w, 7.63s, 7.80s, 8.03s, 8.23s, 8.5, 8.77, 9.1w, 9.45s, 9.93, 10.17s, 11.28, 12.4, 12.94, 13.43, 13.63, 14.13, 14.78, 15.5, 16.3, 18.35, and 19.5w μm .

Fraction B gave *perfluoro-2,6-di-isopropylquinoline* (X) as a pale yellow oil (Found: C, 32.6; F, 65.5; N, 2.7%; *M*, 555). C₁₅F₁₉N requires C, 32.5; F, 65.0; N, 2.5%; *M*, 555), λ_{max} (cyclohexane) 232 and 279 nm (log ϵ 4.54 and 4.13), λ_{max} (film) 6.02, 6.12, 6.3w, 6.73, 7.0s, 7.3, 7.7s, 8.05s, 8.45s, 8.7, 8.9, 9.05w, 9.2w, 9.6w, 9.82w, 9.98w, 10.2s, 10.9s, 12.0w, 12.25w, 12.65w, 13.13, 13.38, 13.7, 14.15, 14.5, 14.9w, 15.45w, 16.1w, 16.8w, and 18.45br μm .

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¹¹ R. D. Chambers, M. Hole, B. Iddon, W. K. R. Musgrave, and R. A. Storey, *J. Chem. Soc. (C)*, 1966, 2328.