Competitive Cyclization in the Reaction of Hexafluoropropene with 2-Aminobenzamide

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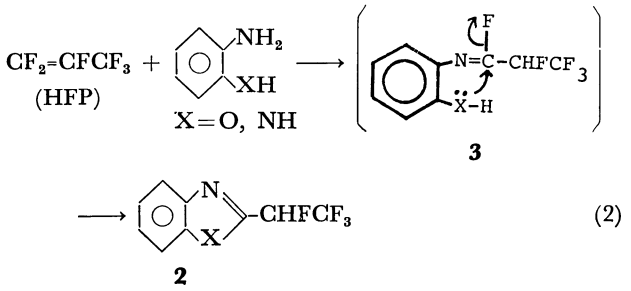
The reaction of hexafluoropropene (HFP) with 2-aminobenzamide afforded 2-(1,2,2,2-tetrafluoroethyl)-4(3*H*)-quinazolinone (**4**) and *N*-(2-cyanophenyl)-2,3,3,3-tetrafluoropropionamide (**5**) in *ca.*1 : 1 ratio, which is essentially independent of the reaction temperatures ranging from room temperature to 100 °C. The formation of the two products is explained in terms of the competitive cyclization of the imidoyl fluoride intermediate, the N-6 and O-6 ring closures ultimately yielding **4** and **5**, respectively. In contrast to the HFP reaction, 2-(trifluoromethyl)pentafluoropropene (OFIB) and 2-aminobenzamide gave only the O-6 cyclized product, *N*-(2-cyanophenyl)-2-trifluoromethyl-3,3,3-trifluoropropionamide. The difference in reactivity between HFP and OFIB is discussed.

It is well-known that amines undergo nucleophilic addition to perfluoroolefins affording acetamidine derivatives *via* reactive imidoyl fluoride intermediates (**1**)[1,2] (Eq. 1).

$$RNH_2 + CF_2{=}CFR_f \longrightarrow [R{-}N{=}CF{-}CHFR_f] \xrightarrow{RNH_2} \underset{\mathbf{1}}{R{-}N{=}C{-}CHFR_f} \quad (1)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad NHR$$

R_f=F, CF_3, *etc.*

The reaction of hexafluoropropene (HFP) with 2-substituted anilines afforded the heterocyclic compounds (**2**) in good yields[3] (Eq. 2). The formation of the heterocyclic products has been explained by the X-5[4] ring closure of the imidoyl fluoride (**3**).



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The reaction of perfluoroolefins with 2-aminobenzamide is of particular interest since the carbamoyl group is expected to act as "an ambident internal nucleophile"[5] affording the N-6 and/or O-6 cyclized products. Thus we have studied the reactions of HFP and 2-(trifluoromethyl)pentafluoropropene (OFIB, octafluoroisobutylene) with 2-aminobenzamide. This paper deals with the reaction mechanisms involving the competitive cyclization of the imidoyl fluoride intermediates.

Results and Discussion

Product Determinations. The reactions of HFP with 2-aminobenzamide were carried out in *N*,*N*-dimethylformamide (DMF) under various conditions in pressure vessels. As an example, a mixture of HFP and the benzamide in DMF was stirred overnight at room temperature and then at 60 °C for 6 h. Removal of DMF *in vacuo* gave a solid residue. Its ^{19}F NMR spectrum indicates that the residue consists of two compounds in nearly 1 : 1 ratio. The two compounds were then successfully separated by utilizing the great difference in solubility in hot water. On the basis of the spectral data, the water-soluble and insoluble parts were assigned to 2-(1,2,2,2-tetrafluoroethyl)-4(3*H*)-quinazolinone (**4**) and *N*-(2-cyanophenyl)-2,3,3,3-tetrafluoropropionamide (**5**), respectively. The formation of **4** was easily anticipated but that of **5** was somewhat surprising, and it is suggested that a dehydration process permitting the conversion of the carbamoyl to the cyano group was involved in the reaction.

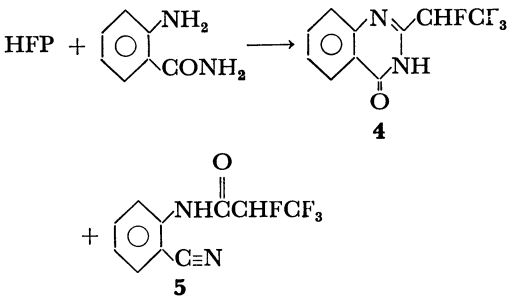

Table 1 gives the results of the reactions carried out under various conditions. The product ratio is seen to be independent of the reaction conditions.

TABLE 1. REACTIONS OF HFP WITH 2-AMINOBENZAMIDE

Run	Temp (°C)	Time (h)	Total yield (%)	Product ratio[a] **4** : **5**
1	50	10	41	1.0 : 1.06
2	60	6	63	1.0 : 1.02
3	70	5	33	1.0 : 1.19
4[b]	70	7	7.5	1.0 : 1.13
5	80	8	84	1.0 : 1.14
6	100	6	77	1.0 : 1.05
7	R. T.	5 day	28	1.0 : 1.37

a) Determined by ^{19}F NMR analysis of the reaction mixtures. The values are essentially the same as those obtained from weights of each compound separated from the reaction mixtures. b) The reaction was carried out in an open system in which which HFP was bubbled to a solution of the benzamide in DMF.

The structure proofs for **4** and **5** are as follows. Both mass spectral and elemental analytical data for **4** and **5** gave the same formula $C_{10}H_6F_4N_2O$.

For the quinazolinone **4**, the IR spectrum shows bands at 2900—3005 (NH), 1680 (C=O), and 1615 cm^{-1} (C=N). Both ^{19}F and ^1H NMR spectra un-

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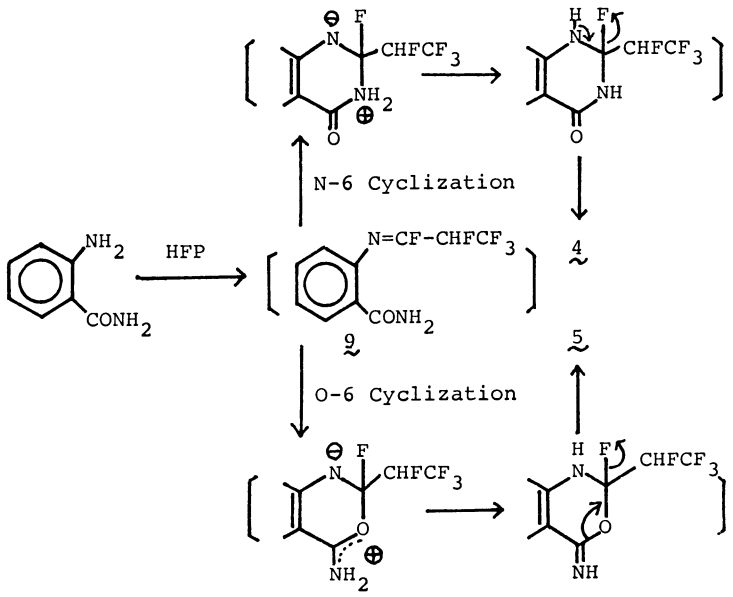


Scheme 1.

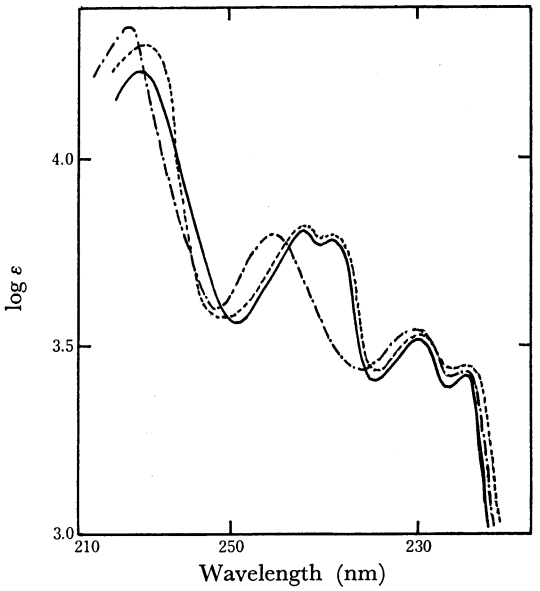
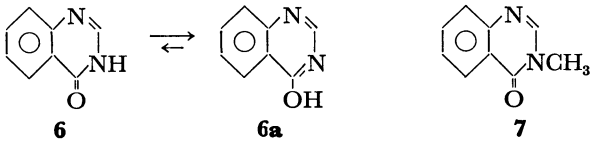
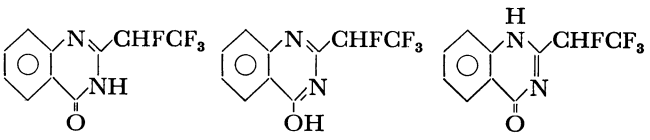


Fig. 1. UV spectra of the quinazolinone **4** and reference compounds in 95% ethanol.
—— **4**; —·—·— **6**; ---- **7**.

equivocally indicate the presence of the grouping of $-CHF-CF_3$ (see Experimental). Comparison of its UV spectrum with reported spectra[6] for 4(3*H*)-quinazolinone (**6**) and 3-methyl-4(3*H*)-quinazolinone (**7**) (Fig. 1) supports the quinazolinone structure for **4**. It has been established that the parent compound **6** exists mainly in the hydroxy tautomeric form (**6a**).[6,7] Although the three tautomeric forms, **4a**, **4b**, and **4c**, are possible for the product **4**, the spectrum of **4** is more similar to that of **7** than that of **6**, suggesting that **4** exists mainly in the tautomeric form **4a**.

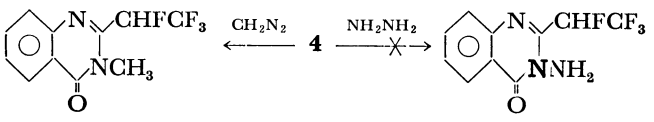


6 **6a** **7**



4a **4b** **4c**

Quinazolinone **4** fluoresces a light green color and is soluble in concentrated aqueous sodium carbonate solutions to give a salt stable even in the boiling solutions. On acidification **4** was recovered unchanged. Methylation of **4** with diazomethane in a mixture of ethanol and ether afforded a single product assigned to the 3-methylquinazolinone **8** based on the following spectral data. The IR spectrum of **8** showed bands at 1600 (C=O) and 1605 cm^{-1} (C=N), no absorption due to the NH being observed. The ^1H NMR spectrum showed not only a slightly split singlet at 3.4 ppm for the $N-CH_3$ protons but also the presence of the grouping of $-CHF-CF_3$. The finding supports the tautomeric structure **4a** for **4**. Although **6** (mainly **6a**) reacts with hydrazine hydrate giving 3-amino-4(3*H*)-quinazolinone *via* a ring-opening,[8] no similar reaction of **4** takes place under the same conditions.



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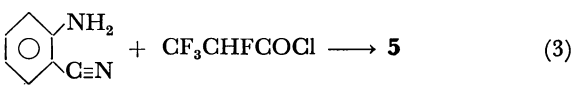
On the other hand, the structure of another product **5** was elucidated as follows. The IR spectrum of **5** showed bands at 3226 (NH), 2230 (C≡N), and 1684 cm^{-1} (C=O). Both the ^{19}F and ^1H NMR spectra indicated the presence of the grouping of $-CHF-CF_3$. The structure was confirmed by an independent synthesis of an authentic sample (Eq. 3). The authentic sample thus obtained was identical with **5**.

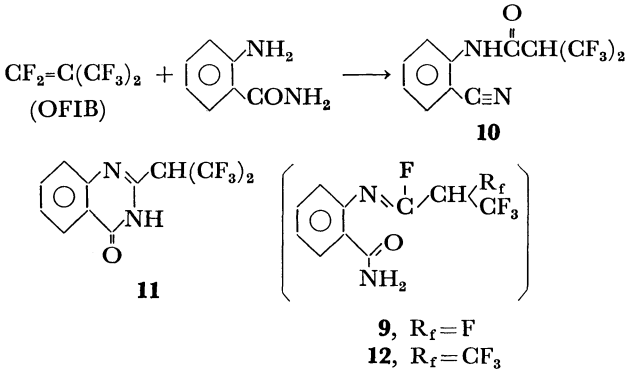


(3)

Reaction Mechanisms The formation of **4** and **5** can be explained in terms of the competitive N-6 *vs.* O-6 cyclization of the imidoyl fluoride intermediate (**9**) formed *via* addition of the amino group to HFP followed by elimination of HF (Scheme 1).

Imidoyl fluoride **9** thus formed undergoes the N-6 cyclization *via* the attack of the carbamoyl nitrogen at the imidoyl carbon atom followed by proton transfer and elimination of HF to give the quinazolinone **4**. Alternatively **8** undergoes the O-6 cyclization by the attack of the carbamoyl oxygen followed by elimination of HF accompanied by the cleavage of the carbon-oxygen bond, finally yielding the cyanoanilide **5**. The O-6 ring closure is of mechanistic and synthetic interest since it can be considered as an intramolecular dehydration reacion accomplishing the conversion of the amido into cyano groups.

Reaction of OFIB with 2-Aminobenzamide. The reaction of OFIB with 2-aminobenzamide was studied. The benzamide was allowed to react with OFIB in DMF at 60 °C for 4 h to afford only *N*-(2-cyanophenyl)-2-trifluoromethyl-3,3,3-trifluoropropioamide (**10**) in 82 % yield; no quinazolinone **11** was found in the resulting mixture. The IR spectrum of **10** showed a strong band at 2240 cm^{-1} due to the cyano group, and the ^{19}F NMR spectrum exhibited a doublet at −15 ppm for $CH(CF_3)_2$



It should be noted that the OFIB reaction proceeds more rapidly than the HFP reaction. Such a difference between HFP and OFIB can be interpreted by assuming the difference in the electrophilicity of the imidoyl carbon atoms in **9** and **12**; the carbon atom in **12** is more electron-deficient and might combine only with the more highly electron-donating carbamoyl oxygen rather than the carbamoyl nitrogen leading to the exclusive O-6 cyclization process.

Experimental

All melting points are uncorrected. IR and UV spectra were recorded on Hitachi 215 and EPS-3T spectrometers, respectively. ^{19}F NMR spectra were taken with a Hitachi R-24F spectrometer using trifluoroacetic acid (TFA) as an external standard, the chemical shifts being given in δ ppm upfield from TFA. ^1H NMR spectra were measured with a Hitachi R-24 and a Varian EM 360 spectrometer using tetramethylsilane (TMS) as an internal standard, the chemical shifts being given in δ ppm downfield from TMS. Mass spectra (MS) were recorded on a JEOL JMS-D100 spectrometer.

Reactions of HFP with 2-Aminobenzamide. A typical procedure is as follows. HFP (3 ml, 25 mmol) was transferred from the bomb to a trap tube cooled in a dry ice-acetone bath, and then put into a cooled pressure vessel equipped with a magnetic stirrer in which 2-aminobenzamide (2.0 g, 12 mmol) and 30 ml of DMF were placed. The vessel was then closed and brought to room temperature (internal pressure, 3.1 kg/cm^2). The mixture was stirred overnight at room temperature and then heated at 60 °C for 6 h. The vessel was carefully opened after being cooled and the resulting mixture was transferred to a distillation apparatus. The solvent was completely distilled under reduced pressure and the residual solid was cooled and collected to give a solid mixture (2.26 g, 63%). The solid mixture was separated by recrystallization from hot water (10 ml). The water-insoluble solid was filtered and recrystallized from methanol to give colorless plates of **4**; mp 210—212 °C; IR (KBr), 2900—3005 (NH), 1680 (C=O), and 1605 cm^{-1} (C=N); ^{19}F NMR (DMSO), δ −2.0 (d of d, J_{vic-HF}=10.8 and J_{vic-FF}=10.8 Hz, CHF-CF_3) and +126 (d of q, J_{vic-FF}=10.8 and J_{gem-HF}=36.2 Hz, CHF-CF_3); ^1H NMR ($CDCl_3$), δ 6.4 (d of q, CHF-CF_3) and 7.5—8.3 (m, 4H, aromatic protons); UV (ethanol) (Fig. 1), λ_{max} (log ε), 313.5 (3.47), 301 (3.57), 277.5 (3.80), 269 (3.81), and 227 nm (4.23); MS, *m/e* 246 (M^+, 100%).

Found: C, 48.41; H, 2.37; N, 11.37%. Calcd for $C_{10}H_6F_4N_2O$: C, 48.79; H, 2.46; N, 11.38%.

The filtrate was cooled in an ice box to give colorless needles of **5**; mp and mixed mp 95—96 °C; IR (KBr), 3226 (NH), 2230 (C≡N), and 1680 cm^{-1} (C=O); ^{19}F NMR (DMSO), δ −4.0 (d of d, J_{vic-HF}=9.9 and J_{vic-FF}=9.9 Hz, CHF-CF_3) and +125 (d of q, J_{gem-HF}=36.2 Hz, CHF-CF_3); ^1H NMR ($CDCl_3$), δ 3.3 (br s, 1H, NH), 6.08 (d of q, 1H, CHF-CF_3) and 7.2—8.0 (m, 4H, aromatic protons); MS, *m/e* 246 (M^+, 100%).

Found: C, 49.02; H, 2.66; N, 11.47%. Calcd for $C_{10}H_6F_4N_2O$: C, 48.79; H, 2.46; N, 11.38%.

Yields and product ratios are given in Table 1.

Preparation of an Authentic Sample of 5. 2,3,3,3-Tetrafluoropropionyl chloride (bp 48—49 °C) was prepared from phosphorus pentachloride and the tetrafluoropropionic acid[9] (7.3 g). The acid chloride (10 mmol) was added dropwise to a solution of 2-cyanoaniline (10 mmol) in 10 ml of benzene and the mixture was then refluxed for 15 min and allowed to stand overnight at room temperature. Crystals formed were filtered and recrystallized from hot water giving colorless needles; mp 95—96 °C.

Reaction of 4 with Diazomethane. Quinazolinone **4** (0.3 g) was dissolved in a mixture of ethanol (20 ml) and ether (20 ml) and diazomethane generated from Diazad (7 g) and potassium hydroxide (1.3 g) was bubbled into the mixture with stirring. The resulting mixture was stirred overnight at room temperature and the solvent was evaporated to give colorless plates (0.55 g, 84%) of the crude **8** (recrystallized from hexane); mp 132—133 °C; IR (KBr), 1660 cm^{-1} (C=O); ^1H NMR ($CDCl_3$), δ 3.4 (slightly split s, 3H, NCH_3), 5.9 (d of q, 1H, CHFCF_3) and 7.3—8.4 (m, 4H, aromatic protons).

Found: C, 50.70; H, 3.10; N, 10.49%. Calcd for $C_{11}H_8F_4N_2O$: C, 50.78; H, 3.09; N, 10.76%.

Reaction of OFIB with 2-Aminobenzamide. The reaction was carried out in the same way for the HFP reaction. A mixture of OFIB (2.5 ml) and 2-aminobenzamide (1.0 g) in DMF (7.5 ml) was stirred at room temperature for 2 h and then heated at 60 °C for 4 h with stirring. The resulting mixture was cooled and the vessel was opened carefully. The solvent was distilled *in vacuo* to give a solid residue (1.78 g, 82%). Recrystallization from benzene afforded colorless

needles; mp 185—186 °C; IR(KBr), 3270 (NH), 2240 (C≡N), and 1670 cm^{-1} (C=O); ^{19}F NMR (DMSO), δ −15 (d, $CH(CF_3)_2$).

Found: C, 44.89; H, 2.18; N, 9.50%. Calcd for $C_{11}H_6F_6N_2O$: C, 44.61; H, 2.04; N, 9.46%.

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