ortho-Disubstituted *F*-Benzenes. III. Preparation of (*F*-Benzo)heterocyclic Compounds from *F*-Benzoic Acid and *F*-Phenol, and the Reactions of Some Intermediary *F*-Benzoyl- and *F*-Phenoxy Compounds

Yoshinari INUKAI,† Yoshitsugu OONO, Takaaki SONODA, and Hiroshi KOBAYASHI*
Research Institute of Industrial Science, Kyushu University 86, Hakozaki, Higashi-ku, Fukuoka 812
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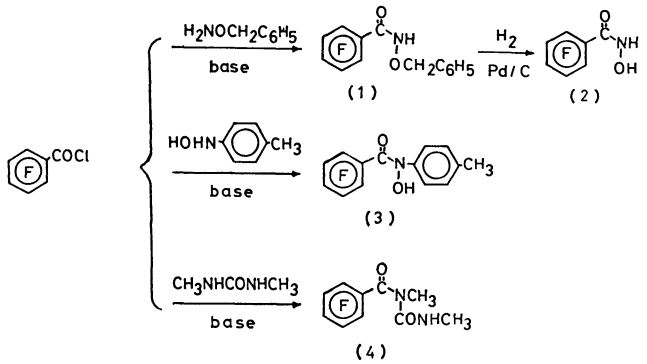
With the intention of achieving the selective *ortho*-substitution of *F*-benzoic acid and *F*-phenol *via* intramolecular nucleophilic cyclization, preparation of some requisite precursory *F*-benzoyl- and *F*-phenoxy compounds and their nucleophilic cyclization reactions were examined. 1,2-(*F*-Benz)isoxazol-3(2*H*)-one, 2-(*p*-tolyl)-1,2-(*F*-benz)isoxazol-3(2*H*)-one, 1,3-dimethyl(*F*-benzo)pyrimidine-2,4(1*H*,3*H*)-dione, and 1,4-(*F*-Benz)oxazin-3(2*H*)-one were obtained from the respective precursory *F*-benzohydroxamic acid, *N*-(*p*-tolyl)-*N*-hydroxy-*F*-benzamide, *N*,*N*′-dimethyl-*N*-(*F*-benzoyl)urea, and 2-(*F*-phenoxy)acetohydrazide. Attempted cyclizations of 2-(*F*-phenoxy)acetohydroxamic acid and (*F*-phenoxy)acetic acid were accompanied by simultaneous ring-opening and resulted in the formation of the identical product: (2-hydroxy-*F*-phenoxy)acetic acid. Transamidation of ethyl *F*-benzoate with hydroxylamine failed to give *F*-benzohydroxamic acid, which was then obtained by the catalytic debenzylation of *N*-benzyloxy-*F*-benzamide.

In the continuation of studies on the preparation of (*F*-benzo)heterocyclic compounds[1] from simple and readily accessible monofunctional *F*-benzenes by intramolecular cyclization,[2,3] syntheses and cyclization of some precursory compounds were investigated by use of *F*-benzoic acid and *F*-phenol as the starting substances.

Results and Discussion

Preparation of the Requisite Precursors. From F-*Benzoic Acid*: The precursory *F*-benzoyl compounds were fabricated by *F*-benzoylation of the amino compound carrying a cyclizing agent by use of *F*-benzoyl chloride, as shown in Scheme 1.

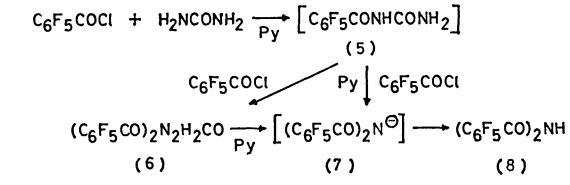


Scheme 1.

The oxygen in a *N*-hydroxycarbamoyl group is known to be one of the most effective nucleophiles, and is regarded as an effective cyclizing agent readily associable with an *F*-benzoyl group. Attempts to prepare *F*-benzohydroxamic acid (**2**)[4] from ethyl *F*-benzoate and hydroxylamine resulted in failure.[5] In the present case, *F*-benzohydroxamic acid (**2**) could be attained by the reductive debenzylation of *N*-benzyloxy-*F*-benzamide (**1**), which was derived from *F*-benzoyl chloride by the reaction with *O*-benzylhydroxylamine in the presence of base.

On the other hand, *N*-(*p*-tolyl)hydroxylamine reacted with *F*-benzoyl chloride to give *N*-(*p*-tolyl)-*N*-hydroxy-*F*-benzamide (**3**) in a usual manner.[6] Here, the *p*-tolyl group was introduced onto the amide nitrogen in such a way as to be favorable to the subsequent intramolecular cyclization due to its steric bulkiness.

The nitrogen of urea was also regarded as a nucleophile capable of replacing the fluorine atom on an *F*-phenyl nucleus. Then, we examined whether an *F*-benzoyl group could be combined with a urea molecule at the nitrogen only on one side. The reaction of *F*-benzoyl chloride with urea in the presence of pyridine, however, afforded none of the expected *N*-(*F*-benzoyl)urea (**5**). From the reaction mixture, di-(*F*-benzoyl)amine (**8**) was isolated and the mass spectrum of the crude product indicated the formation of a compound whose molecular weight corresponded to di(*F*-benzoyl)urea (**6**) as a minor by-product. Occurrence of the dibenzoylamine (**8**) indicates that, as shown in Scheme 2, the intermediary *F*-benzoyl derivatives, (**5**) and/or (**6**), cleaved in some way at the α–β bond relative to the *F*-benzoyl group prior to the intramolecular cyclization, to liberate di(*F*-benzoyl)amide anion (**7**) in the presence of pyridine.



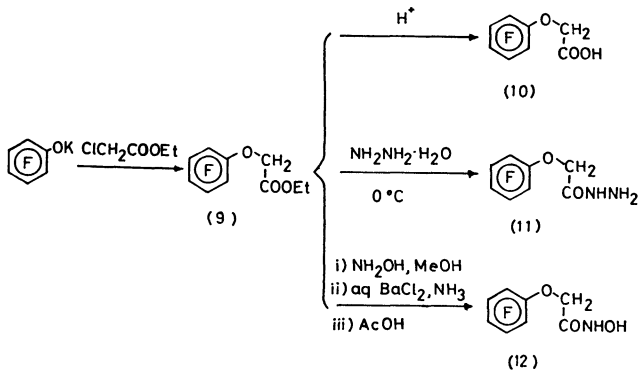
Scheme 2.

On the other hand, the reaction with *N*,*N*′-dimethylurea gave *N*,*N*′-dimethyl-*N*-(*F*-benzoyl)urea (**4**), in which no protic hydrogen was present at the α-amide nitrogen and the second *F*-benzoylation at the same site could not occur. Thus, the α–β bond cleavage seems to be suppressed. The electron-donation due to the methyl group on the nitrogen atom might also contribute to this stabilization.

† Present address: Government Industrial Research Institute in Kyushu, Shukumachi, Tosu, Saga 841.

From F-*Phenol*: For this purpose, we used ethyl (*F*-phenoxy)acetate (**9**), which was prepared by the reaction of potassium *F*-phenolate with ethyl chloroacetate.[7]

The carboxylic acid (**10**) from the ester (**9**), and its acyl derivatives, (**11**) and (**12**), were examined as the potential precursors for the subsequent intramolecular cyclization; they were prepared as shown in Scheme 3.



Scheme 3.

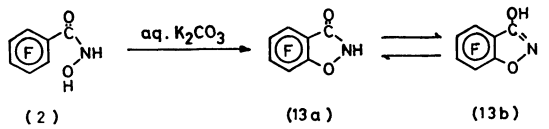
The ester function of the (*F*-phenoxy)acetate (**9**) was converted to a hydrazide to yield 2-(*F*-phenoxy)-acetohydrazide (**11**) by the reaction with hydrazine hydrate at 0 °C. Although the reactions were usually performed by heating under reflux,[8] the present ester (**9**) was treated under much milder conditions lest it should result in the formation of hydrazinium *F*-phenoxide.[9]

An oxygen nucleophile was fabricated at the terminal position of the side chain in the form of 2-(*F*-phenoxy)-acetohydroxamic acid (**12**), which was prepared in a usual manner.[5] Under a prolonged reaction time, the yield of the acetohydroxamic acid (**12**) decreased, while the more amount of *F*-phenol was generated as a by-product. The C–O bond fission to liberate *F*-phenol seems due to the higher stability of *F*-phenoxide, as often encountered in the reaction of *F*-phenoxy compounds in the presence of base.[10]

(*F*-Phenoxy)acetic acid (**10**) was regarded as another precursor carrying an oxygen nucleophile at the terminal position. The acetic acid (**10**) was obtained by the hydrolysis of the ester (**9**) in a good yield.[11]

Intramolecular Nucleophilic Cyclization. From F-*Benzoyl Compounds*: (*F*-Benzo)heterocyclic compounds were prepared by the base-catalyzed cyclization of the precursory *F*-benzoyl compounds (**2**, **3**, and **4**).

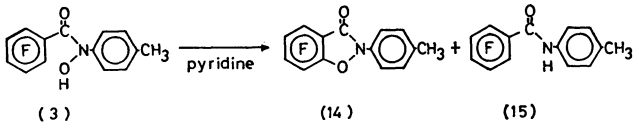
F-Benzohydroxamic acid (**2**) was refluxed with alkali in an aqueous solvent. The reaction proceeded to give 1,2-(*F*-benz)isoxazol-3(2*H*)-one (**13a**), *F*-aniline, and *F*-benzoic acid. The ^{1}H-NMR spectrum of the (*F*-benz)isoxazoline (**13**) indicated that it was a mixture of tautomers, (**13a**) and (**13b**). The ^{1}H-NMR signal in acetone-d_6 showed a broad peak centered at δ=6.2 at 35 °C, while at −58 °C the peak is separated into two peaks centered at δ=5.5 and 8.5, which correspond to the hydrogens of hydroxyl group in **13b** and amino group in **13a**. *F*-Aniline was the product which resulted from Lossen rearrangement[12]



Scheme 4.

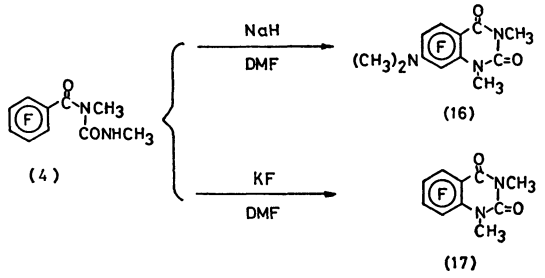
of *F*-benzohydroxamic acid (**2**), and *F*-benzoic acid could be generated by hydrolysis of the same compound (**2**). In order to prevent the hydrolysis, *F*-benzohydroxamic acid (**2**) was treated with base in anhydrous solvents such as DMF, DMSO, and pyridine. The reactions, however, were unsuccessful, resulting in a trace amount of the heterocyclic compound (**13**).

The reaction of *N*-(*p*-tolyl)-*N*-hydroxy-*F*-benzamide (**3**) showed somewhat peculiar behavior in basic media. In anhydrous pyridine, 2-(*p*-tolyl)-1,2-(*F*-benz)isoxazol-3(2*H*)-one (**14**) was isolated together with *N*-(*p*-tolyl)-*F*-benzamide (**15**) as a major product. When treated with base in an aqueous solvent of DMF, the sole product was the benzamide (**15**). The formation of the benzamide (**15**) suggested that the *N*-hydroxy-*F*-benzamide (**3**) favored the cleavage of N–O bond rather than the intramolecular cyclization in basic media. This N–O bond cleavage was presumably related with the electron-withdrawing effect of *F*-phenyl group. No further details of the mechanism were examined.



Scheme 5.

The *F*-benzoylurea (**4**) was intramolecularly cyclized to give 1,3-dimethyl-7-dimethylamino(*F*-benzo)pyrimidine-2,4(1*H*,3*H*)dione (**16**) in the presence of sodium hydride in anhydrous DMF. ^{19}F-NMR spectrum of the product shows three signals of equal intensity; their splitting patterns indicate that the product is of a 1,2,4-trisubstituted *F*-benzene structure. The assignment of the fluorine atom at 8-position of the product (**16**) is due to its multiplet peak, owing to the coupling between the adjacent *N*-methyl hydrogens and other fluorines.[13] The long-range coupling (J=9 Hz) of *N*-methyl hydrogens with the fluorine at the 8-position was also observed in the ^{1}H-NMR spectrum of the product (**16**). Such long-range coupling over five bonds between fluorine and hydrogen



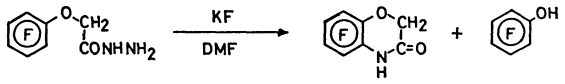
Scheme 6.

has been encountered sometimes in methylaminosubstituted *F*-benzenes.[14] On the other hand, the assignment of the fluorine atom at 5-position in the (*F*-benzo)pyrimidinedione (**16**) is based on its simple double-doublet peak due to the coupling with two unequivalent fluorines. The position of dimethylamino group is, therefore, assigned to 7-position of the product.

On the other hand, the *F*-benzoylurea (**4**) was cyclized into the expected 1,3-dimethyl(*F*-benzo)pyrimidine-2,4(1*H*,3*H*)-dione (**17**), in the presence of potassium fluoride in anhydrous DMF.[15] The ^{19}F-NMR spectrum of the product shows four signals of equal intensity, and their splitting patterns show that the product is of an *ortho*-disubstituted *F*-benzene structure. The long-range coupling (J_{8-H}=9 Hz) between the fluorine at the 8-position and *N*-methyl hydrogens was again observed in both ^{19}F- and ^{1}H-NMR spectra of the heterocyclic compound (**17**).[13]

The dimethylamino group present in the former product (**16**) is considered to come from DMF, where DMF plays the parts of both dimethylaminating agent and solvent in the nucleophilic cyclization reaction at the presence of sodium hydride.

From F-*Phenoxy Compounds*: The reaction of 2-(*F*-phenoxy)acetohydrazide (**11**) with potassium fluoride in DMF gave 1,4-(*F*-benz)oxazin-3(2*H*)-one (**18**), though in a poor yield. A great majority of the product was *F*-phenol, which resulted from the C–O bond cleavage during the reaction. The heterocyclic compound (**18**) was identical with that previously derived from *F*-aniline,[3] and would be formed by cyclization accompanied with the simultaneous cleavage of N–N bond of the terminal hydrazide functions. Under some other basic conditions, such as pyridine and potassium carbonate in DMF, no definite products were obtained except *F*-phenol.

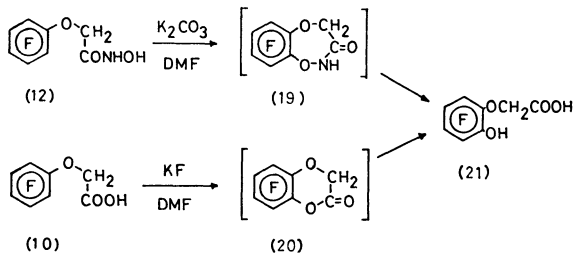


(11) (18)

Scheme 7.

We tried to cyclize the acetohydroxamic acid (**12**) by heating under reflux with potassium carbonate in DMF. The reaction proceeded to give (2-hydroxy-*F*-phenoxy)acetic acid (**21**), while the expected intermediary heterocyclic compound (**19**) could not be isolated. The ^{19}F-NMR spectrum of the product shows four signals of equal intensity; their splitting patterns indicate that the product is of an *ortho*-disubstituted *F*-benzene structure. The assignment of the fluorine atom at the 6-position in the product (**21**) is based upon its multiplet peak, due to the coupling with the adjacent *O*-methylene hydrogens and three other ring-fluorines. The assignment of the fluorine at the 3-position is based upon its doubled double-doublet peak, due to the coupling with three ring-fluorines.

We tried to cyclize the acetic acid (**10**) by refluxing it in the presence of potassium fluoride in DMF.[16,17] The reaction also proceeded to give (2-hydroxy-*F*-phenoxy)acetic acid (**21**); again the expected intermediary heterocyclic compound (**20**) could not be isolated.



(12) (19) (21) (10) (20)

Scheme 8.

The reactions of the two different precursors, (**10**) and (**12**), resulted in the direct formation of the identical *ortho*-disubstituted *F*-benzene (**21**) under basic conditions.

Experimental

Melting points are uncorrected. The spectral data are those obtained on the following instruments and apparatus unless otherwise noted: IR spectra: JASCO DS-403G, A-1, and A-102. UV spectra: Hitachi 124 and 220. ^{1}H-NMR spectra: Varian A-60 and Hitachi R-24B against the internal TMS reference. ^{19}F-NMR spectra: JEOL PS-100 as the positive value downfield from the internal F-benzene reference. Mass spectra: JEOL JMS-07 and 01SG.

N-*Benzyloxy*-F-*benzamide (1)*. *F*-Benzoyl chloride (2.70 g, 12 mmol) was added dropwise to a stirred mixture of *O*-benzylhydroxylamine (31 mmol),[18] anhydrous pyridine (1.96 g, 25 mmol), and absolute ether (50 ml) over a 30-min period. The mixture was refluxed for an additional 1.5 h, cooled, and filtered. The filtrate was washed successively, with water, diluted hydrochloric acid, and water, and dried over magnesium sulfate. The residue obtained after evaporation *in vacuo* was recrystallized from benzene, to give *N*-benzyloxy-*F*-benzamide (**1**) (3.18 g, 85%) in colorless plates, mp 140.0—141.0 °C. IR(KBr): 3120 (NH) and 1670 cm^{-1} (C=O). ^{1}H-NMR (acetone-d_6) δ=5.50 (s, 2H, CH_2), 7.4 (s, 5H, arom.), and 10.7—11.1 (br. s, 1H, NH). Found: C, 52.95; H, 2.52; N, 4.32%. Calcd for $C_{14}H_8NF_5O_2$: C, 53.01; H, 2.54; N, 4.42%.

F-*Benzohydroxamic Acid (2)*. The *N*-(benzyloxy)amide (**1**) (1.73 g, 5.4 mmol) dissolved in methanol (50 ml) was hydrogenated in the presence of 5% palladium on charcoal (0.30 g) under atmospheric pressure at room temperature. The catalyst was filtered out, and the filtrate was evaporated to dryness *in vacuo*. Recrystallization from benzene gave *F*-benzohydroxamic acid (**2**) (1.00 g, 80%) in colorless needles, mp 140.0—141.0 °C. IR(KBr): 3230 (NH, OH) and 1650 cm^{-1} (C=O). ^{1}H-NMR (acetone-d_6) δ=7.35 (s, 1H, OH) and 9.4—10.1 (br. s, 1H, NH). Found: C, 37.04; H, 1.00; N, 6.60%. Calcd for $C_2H_2NF_5O_2$: C, 37.02; H, 0.89; N, 6.17%. The hydroxamic test using iron(III) chloride solution was positive.

N-(p-*Tolyl*)-N-*hydroxy*-F-*benzamide (3)*. *F*-Benzoyl chloride (3.30 g, 14 mmol) was added dropwise to a stirred mixture of ethereal *N*-(*p*-tolyl)hydroxylamine (2.10 g, 17 mmol in 80 ml of ether) and aqueous sodium hydrogencarbonate (2.60 g, 31 mmol in 15 ml of water) over a 1-h period at 0 °C. The mixture was stirred at 0 °C for an additional 2 h, and poured into ether. The ethereal solution was washed with water, dried over sodium sulfate, and evaporated to dryness *in vacuo*. The residue was recrystallized from aqueous methanol to give *N*-(*p*-tolyl)-*N*-hydroxy-*F*-

benzamide (**3**) (3.80 g, 84%) in colorless needles, mp 178—179 °C. IR(KBr): 3200 (OH) and 1650 cm^{-1} (C=O). Found: C, 53.05; H, 2.67; N, 4.40%. Calcd for $C_{14}H_8NF_5O_2$; C, 53.01; H, 2.54; N, 4.42%. The hydroxamic test using iron(III) chloride solution was positive.

Reaction of F-*Benzoyl Chloride with Urea.* *F*-Benzoyl chloride (1.00 g, 4.3 mmol) was added dropwise to a stirred mixture of urea (0.25 g, 4.2 mmol), anhydrous DMF (7 ml), and anhydrous pyridine (2 ml) over a 30-min period at room temperature and under a dry nitrogen atmosphere. The mixture was refluxed for an additional 30 min, cooled, and poured into ether. The ethereal solution was washed with water, dried over sodium sulfate, and evaporated to dryness *in vacuo*. The residue was recrystallized from aqueous methanol to give a white solid (315 mg). MS of the white solid; Found: *m/e*, 448. Calcd for $C_{15}H_2N_2F_{10}O_3$; 448. The solid was chromatographed on a silica-gel column. The fraction eluted with hexane–chloroform was sublimed to give di(*F*-benzoyl)amine (**8**) (27 mg, 3%) in colorless needles, mp 157—158 °C. IR(KBr): 3280, 3200 (NH), and 1750 cm^{-1} (C=O). Found: C, 41.54; H, 0.35; N, 3.56%; M^+, 405. Calcd for $C_{14}HNF_{10}O_2$: C, 41.50; H, 0.25; N, 3.46%; M, 405.

N,N′-*Dimethyl*-N-*(*F-*benzoyl)urea* (**4**). *F*-Benzoyl chloride (4.25 g, 18 mmol) was added dropwise to a stirred mixture of *N,N′*-dimethylurea (2.20 g, 25 mmol) and anhydrous pyridine (15 ml) over a 20-min period at room temperature. The mixture was refluxed for an additional 6 h, cooled, and poured into ether. The ethereal solution was washed with water, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on a silica-gel column. The fraction eluted with hexane–chloroform and that with chloroform–dichloromethane gave *N,N′*-dimethyl-*N*-(*F*-benzoyl)urea (**4**) (2.30 g, 44%). Recrystallization from cyclohexane afforded colorless needles, mp 62—63 °C. IR(KBr): 1720 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ=2.85 (d, J=4 Hz, 3H, NCH_3), 3.15 (s, 3H, CH_3), and 8.15—8.75 (br. s, 1H, NH). Found: C, 42.56; H, 2.50; N, 9.84%; M^+, 282. Calcd for $C_{10}H_7N_2F_5O_2$: C, 42.57; H, 2.50; N, 9.93%; M, 282.

*2-(*F-*Phenoxy)acetohydrazide* (**11**). A solution of ethyl (*F*-phenoxy)acetate (**9**) (8.10 g, 30 mmol) in ethanol (5 ml) was added dropwise to a stirred solution of 100% hydrazine hydrate (4.50 g, 90 mmol) in ethanol (5 ml) over a 10-min period at 0 °C. The mixture was stirred at 0 °C for an additional 20 min, and poured into saturated aqueous sodium chloride. The resulting solid was filtered, washed with water, and air-dried. Sublimation gave 2-(*F*-phenoxy)-acetohydrazide (**11**) (7.20 g, 94%) in colorless needles, mp 67—69 °C. IR(KBr): 3330 cm^{-1} (NH). Found: C, 37.52; H, 1.98; N, 10.94%. Calcd for $C_8H_5N_2F_5O_2$: C, 37.71; H, 2.14; N, 10.85%.

*2-(*F-*Phenoxy)acetohydroxamic Acid* (**12**). A solution of potassium hydroxide (2.40 g, 43 mmol) in methanol (7.5 ml) was added to a stirred solution of hydroxylamine hydrochloride (2.40 g, 35 mmol) in methanol (13.5 ml) at room temperature. Ethyl (*F*-phenoxy)acetate (**9**) (3.50 g, 13 mmol) was added to the stirred mixture, and then the mixture was filtered immediately. The filtrate was left standing overnight at room temperature, poured into water, and acidified with diluted hydrochloric acid. Barium chloride (3.50 g, 15 mmol) was dissolved in the acidified solution, and then the solution was basified with aqueous ammonia. The resulting precipitates were collected by filtration, washed with water, and air-dried. The solid (3.5 g) was warmed to dissolve in 10% aqueous acetic acid (20 ml) for a few minutes, and cooled to room temperature. The resulting precipitates were collected by filtration, washed with water, and air-dried. Recrystallization from petroleum ether–ethyl acetate gave 2-(*F*-phenoxy)acetohydroxamic acid (**12**) (2.10 g, 59%) in colorless plates, mp 106—108 °C. IR (KBr): 3220 (OH, NH) and 1650 cm^{-1} (C=O). Found: C, 37.37; H, 1.57; N, 5.45%. Calcd for $C_8H_4NF_5O_3$: C, 37.31; H, 1.62; N, 5.48%. The hydroxamic test using iron(III) chloride solution was positive.

*1,2-(*F-*Benz)isoxazol-3(2*H*)-one* (**13a**). A mixture of *F*-benzohydroxamic acid (**2**) (1.00 g, 4.4 mmol), potassium carbonate (1.00 g, 1.2 mmol), and water (20 ml) was refluxed for 10 h with stirring and cooled. *F*-Aniline (90 mg, 11%) deposited on the inside of a condencer, and was identified by comparison with an authentic specimen.[3] The reaction mixture was neutralized, and extracted with ether. The ethereal extract was dried over magnesium sulfate, and evaporated *in vacuo*. The residual solid was chromatographed on a silica-gel column by elution with benzene. An earlier fraction gave the starting material (**2**) (75 mg, 7.5%). A later fraction gave 1,2-(*F*-benz)isoxazol-3-(2*H*)-one (**13a**) (55 mg, 6%). Recrystallization from benzene afforded colorless prisms, mp 171.0—172.0 °C. IR (KBr): 3400 (OH), 3000 (NH), and 1665 cm^{-1} (C=N). ^{1}H-NMR (acetone-d_6) δ at 35 °C=6.2 (br. s); δ at −58 °C=5.5 (br. s) and 8.5 (br. s). Found; C, 40.44; H, 0.70; N, 6.25%; M^+, 207. Calcd for $C_7NHF_4O_2$; C, 40.60; H, 0.49; N, 6.77%; M, 207.

The neutral aqueous layer was acidified and then extracted with ether repeatedly. The combined extracts were treated in a similar manner to that described above. Upon elution chromatography with ethyl acetate–chloroform on a silica-gel column, an earlier fraction gave the heterocyclic compound (**13**) (85 mg, 9%). A later fraction gave *F*-benzoic acid (50 mg, 5%), which was identified by comparison with an authentic specimen.[20]

*2-(*p-*Tolyl)-1,2-(*F-*benz)isoxazol-3(2*H*)-one* (**14**). A solution of *N*-(*p*-tolyl)-*N*-hydroxy-*F*-benzamide (**3**) (427 mg, 1.3 mmol) in anhydrous pyridine (15 ml) was refluxed for 10 h with stirring, cooled, and poured into ether. The ethereal solution was washed with water and dried over sodium sulfate. Evaporation *in vacuo* gave a residual oil, which was chromatographed on a silica-gel column.

The fraction eluted with hexane gave 2-(*p*-tolyl)-1,2-(*F*-benz)isoxazol-3(2*H*)-one (**14**) (35 mg, 9%). Sublimation afforded colorless needles, mp 116.0—117.0 °C. IR (KBr): 1780 cm^{-1} (C=O). Found: C, 56.42; H, 2.35; N, 4.62; F, 25.50%; M^+, 297. Calcd for $C_{14}H_7NF_4O_2$: C, 56.58; H, 2.37; N, 4.71; F, 25.59%; M, 297.

The fraction eluted with hexane–chloroform and that with chloroform gave *N*-(*p*-tolyl)-*F*-benzamide (**15**) (80 mg, 20%). Recrystallization from cyclohexane–ethanol afforded colorless needles, mp 198.5—199.5 °C. IR (KBr); 3240 (NH) and 1670 cm^{-1} (C=O). Found: C, 55.89; H, 2.83; N, 4.59%. Calcd for $C_{14}H_8NOF_5$: C, 55.82; H, 2.68; N, 4.65%.

*1,3-Dimethyl-7-dimethylamino(*F-*benzo)pyrimidine-2,4(1*H*,3*H*)-dione* (**16**). A solution of *N,N′*-dimethyl-*N*-(*F*-benzoyl)urea (**4**) (595 mg, 2.1 mmol) in anhydrous DMF (10 ml) was added dropwise to a stirred suspension of sodium hydride (3.3 mmol) and anhydrous DMF (10 ml) over a 15-min period at room temperature. The mixture was refluxed for an additional 5 h, cooled, and poured into ether. The ethereal solution was washed with water, dried over sodium sulfate, and evaporated to dryness *in vacuo*. The residue was chromatographed on a silica-gel column. The fraction eluted with chloroform gave 1,3-dimethyl-7-dimethylamino(*F*-benzo)pyrimidine-2,4(1*H*,3*H*)-dione (**16**) (0.40 g,

66%). Recrystallization from benzene afforded colorless needles, mp 186—187.5 °C. IR (KBr): 1700 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ=3.05 (m, 6H, CH_3), 3.35 (s, 3H, CH_3) and 3.67 (d, J=9 Hz, 3H, CH_3). ^{19}F-NMR ($CHCl_3$) δ=9.5 (d.sep, 1F, F^6), 19.9 (dd, 1F, F^5), and 24.3 (m, 1F, F^8), (J_{5-8}=11.5, J_{5-6}=20.0, J_{H-6}=3.0 Hz). Found: C, 50.19; H, 4.23; N, 14.65; F, 19.6%; M^+, 287. Calcd for $C_{12}H_{12}N_3O_2F_3$: C, 50.18; H, 4.21; N, 14.63; F, 19.8%; M, 287.

*1,3-Dimethyl(F-benzo)pyrimidine-2,4(1H,3H)-dione (**17**).* A solution of *N,N'*-dimethyl-*N*-(*F*-benzoyl)urea (**4**) (2.44 g, 8.7 mmol) in anhydrous DMF (20 ml) was added dropwise to a stirred mixture of potassium fluoride (1.00 g, 18 mmol) and anhydrous DMF (30 ml) over a 30-min period at room temperature. The mixture was refluxed for an additional 7 h, cooled, and poured into ether. The ethereal solution was worked up in a similar manner to that described above. The chromatographic fraction eluted with hexane–chloroform gave 1,3-dimethyl(*F*-benzo)pyrimidine-2,4(1*H*,3*H*)-dione (**17**) (1.12 g, 49%). Recrystallization from cyclohexane afforded colorless needles, mp 102—104 °C. IR (KBr): 1720 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ=3.35 (s, 3H, CH_3) and 3.73 (d, J=9 Hz, 3H, CH_3). ^{19}F-NMR ($CHCl_3$) δ=0.05 (dd, 1F, F^6), 12.8 (ddq, 1F, F^8), 17.3 (ddd, 1F, F^7), and 24.2 (ddd, 1F, F^5), (J_{5-6}=J_{6-7}=23.0, J_{7-8}=21.0, J_{5-8}=13.0, J_{5-7}=11.5, J_{6-8}=1.0, and J_{8-H}=9 Hz). UV (EtOH); λ_{max} (log ε); 218 (4.49) and 313 nm (3.45). Found: C, 45.93; H, 2.34; N, 10.53; F, 29.1%; M^+, 262. Calcd for $C_{10}H_6N_2F_4O_2$: C, 45.82; H, 2.31; N, 10.69; F, 29.0%; M, 262.

*Reaction of 2-(F-Phenoxy)acetohydrazide (**11**) with Potassium Fluoride in DMF.* A mixture of 2-(*F*-phenoxy)acetohydrazide (**11**) (1.04 g, 4.0 mmol), potassium fluoride (0.57 g, 9.8 mmol), and anhydrous DMF (15 ml) was refluxed for 13.5 h with stirring and then, after being cooled, was poured into ether. The ethereal solution was washed with water, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on a silica-gel column. The fraction eluted with chloroform contained *F*-phenol, which was identified by spectral comparisons with an authentic specimen.[7] The residual solid from the fraction eluted with chloroform, was sublimed to give 1,4-(*F*-benz)-oxazin-3(2*H*)-one (**18**) (13 mg, 1.5%) in colorless needles, mp 190—191.5 °C measured in a sealed tube. The product was identified by comparison with an authentic specimen.[3] Found: M^+, 221.012. Calcd for $C_8H_3NF_4O_2$: M, 221.016.

*Reaction of 2-(F-Phenoxy)acetohydroxamic Acid (**12**) with Base.* A mixture of 2-(*F*-phenoxy)acetohydroxamic acid (**12**) (1.00 g, 3.9 mmol), potassium carbonate (0.60 g, 4.3 mmol), and anhydrous DMF (20 ml) was refluxed for 10 h, cooled, and poured into ether. The ethereal solution was washed with 3% hydrochloric acid and water, successively, and dried over magnesium sulfate. The residue from evaporation was sublimed to give (2-hydroxy-*F*-phenoxy)acetic acid (**21**) (95 mg, 11%). Recrystallization from cyclohexane–chloroform afforded colorless needles, mp 114—116 °C. IR (KBr): 3520 and 3460 (phenolic OH), and 1720 cm^{-1} (C=O). ^{19}F-NMR[21] (MeOH) δ=−2.2 (dm, 1F, F^6), 3.1 (ddd, 1F, F^3), 4.8 (ddd, 1F, F^4), and 11.8 (ddd, 1F, F^5), (J_{3-4}=J_{4-5}=J_{5-6}=22.5, J_{4-6}=3.0, J_{3-6}=5.5, and J_{3-5}=6.5 Hz). The phenol test using iron(III) chloride solution was positive.

*Reaction of (F-Phenoxy)acetic Acid (**10**) with Potassium Fluoride.* A mixture of (*F*-phenoxy)acetic acid (**10**)[22] (1.02 g, 4.2 mmol), potassium fluoride (0.57 g, 9.7 mmol), and anhydrous DMF (15 ml) was refluxed for 13.5 h with stirring, cooled, and poured into ether. The ethereal solution was washed with water, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on a silica-gel column. The fraction eluted with dichloromethane gave a solid product. Recrystallization from benzene followed by sublimation afforded (2-hydroxy-*F*-phenoxy)acetic acid (**21**) (56 mg, 6%) in colorless needles, mp 113—114 °C. The product was identified by comparison with an authentic specimen obatained by the above reaction.

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References

1) According to the revised nomenclature of highly fluorinated organic compounds by J. A. Young, *J. Chem. Document.*, **14**, 98 (1974); *J. Fluorine. Chem.*, **6**, 571 (1975).

2) Preceding Part II: Y. Inukai, T. Sonoda, and H. Kobayashi, *Bull. Chem. Soc. Jpn.*, **52**, 2657 (1979).

3) Y. Inukai, Y. Oono, T. Sonoda, and H. Kobayashi, *Bull. Chem. Soc. Jpn.*, **52**, 516 (1979).

4) The synthesis of *F*-benzohydroxamic acid from ethyl *F*-benzoate has been reported by A. Ostaszynski and H. Plenkiewicz, 6th International Symposium on Fluorine Chemistry, Durham, England (1971), Abstr. A-28; they gave no details of the experimental conditions.

5) W. B. Renfrow, Jr., and C. R. Hauser, *J. Am. Chem. Soc.*, **59** 2308 (1937).

6) Y. K. Agrawal and S. G. Tandan, *J. Indian Chem. Soc.*, **48**, 397 (1971).

7) J. M. Birchall and R. N. Haszeldine, *J. Chem. Soc.*, **1959**, 13.

8) R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," John Wiley and Sons, New York (1953), p. 519.

9) E. J. Forbes, R. D. Richardson, M. Stacey, and J. C. Tatlow, *J. Chem. Soc.*, **1959**, 2019.

10) V. M. Vlasov and G. G. Yakobson, *Russ. Chem. Rev.*, **43**, 781 (1974).

11) G. M. Brooke and B. S. Furniss, *J. Chem. Soc.*, **1967**, 869.

12) H. L. Yale, *Chem. Rev.*, **33**, 242 (1943).

13) Two possible schemes of long-range coupling are conceivable between the *N*-methyl hydrogens and the ring-fluorine: one is the coupling with the fluorine atom at the 5-position and the other that at the 8-position. The magnitude of the observed J_{H-F} value, however, indicates the former scheme to be more likely.[14] Assignment of ^{19}F-NMR signals in the text is, therefore, tentative.

14) J. Burdon, *Tetrahedron*, **21**, 1101 (1965); J. G. Allen, J. Burdon, and J. C. Tatlow, *J. Chem. Soc.*, **1965**, 6329; J. Burdon, N. B. Hollyhead, and J. C. Tatlow, *ibid.*, **1965**, 6336.

15) For examples, R. Oda, *Kagaku*, **32**, 179 (1977); **33**, 75 (1978); **34**, 75 (1979); J. H. Clark and J. M. Miller, *J. Am. Chem. Soc.*, **99**, 498 (1977).

16) T. D. Petrova, V. P. Mamaev, G. G. Yakobson, and N. N. Vorozhtsov, Jr., *Khim. Geterotsikl. Soedin.*, **1968**, 771; *Chem. Abstr.*, **71**, 13104c (1969); V. P. Molosnova, V. A. Barkhash, and N. N. Vorozhtsov, *J. Gen. Chem., USSR,*

39, 1937 (1969); E. V. Aroskar, P. J. N. Brown, R. G. Plevey, and R. Stephens, *J. Chem. Soc.*, **1968**, 1569.

17) J. H. Clark, J. Emsley, and O. P. A. Heyte, *J. Chem. Soc., Perkin Trans. 1*, **1977**, 1091; J. H. Clark and J. M. Miller, *Tetrahedron Lett.*, **1977**, 599.

18) Benzyloxyamine was prepared by the neutralization of benzyloxyamine hydrochloride synthesized by A. Janny, *Chem. Ber.*, **16**, 170 (1883).

19) E. Bamberger, *Chem. Ber.*, **34**, 61 (1901).

20) J. M. Birchall and R. N. Haszeldine, *J. Chem. Soc.*, **1961**, 3719.

21) The chemical shifts were measured against the internal *F*-acetic acid reference. The values are given here after being converted against an *F*-benzene reference; the difference between the former reference and the latter one is taken to be 84.4 ppm.

22) (*F*-Phenoxy)acetic acid (**10**) was prepared from ethyl (*F*-phenoxy)acetate.[11]