

# *ortho*-Disubstituted *F*-Benzenes. I. Preparation of (*F*-Benzo)heterocyclic Compounds from *F*-Aniline and the Reactions of Some Intermediate (*F*-Phenyl)amino Compounds†

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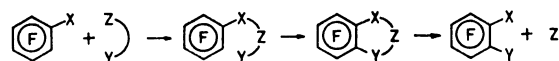
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With the intention of achieving the selective *ortho*-disubstitution of *F*-aniline via intramolecular nucleophilic cyclization, syntheses of some requisite intermediate (*F*-phenyl)amino compounds and (*F*-benzo)heterocyclic compounds were investigated. 2-Phenyl-*F*-benzoxazole, 2-phenyl-*F*-benzimidazole, and 2,3-dihydro-1,4-(*F*-denz)-oxazin-3-one were obtained from the respective precursors: benz-*F*-anilide, *N*-(*F*-phenyl)benzamidine, and hydroxyacet-*F*-anilide. 2-Phenyl-*F*-benzothiazole was obtained by treating benz-*F*-anilide with phosphorus pentasulfide. Hydrolytic dehalogenation of haloacet-*F*-anilide failed to give hydroxyacet-*F*-anilide, but it was obtained successfully by catalytic debenzoylation of benzyloxyacet-*F*-anilide. The reactions of iodoacet-*F*-anilide with silver nitrate and acetate yielded 2-nitrate and 2-acetate, respectively. The reaction with diamminesilver(I) nitrate resulted in a reductive deiodination which gave acet-*F*-anilide. This exceptional reactivity was ascribed to the strong electron-withdrawing effect of the *F*-phenyl group.

There have been reports of several procedures for attaining *ortho*-disubstituted *F*-benzenes;<sup>1)</sup> rather inaccessible starting substances were used, however.<sup>2)</sup> The reactions of monosubstituted *F*-benzenes with nucleophiles yielded predominantly *para*-disubstituted derivatives.<sup>3)</sup> The *ortho*-disubstitution by nucleophilic reactions occurred only in a few cases where the attacking nucleophile was chemically bonded to the preceding substituent group so as to be oriented to the *ortho*-position.<sup>4)</sup> This might constitute another useful procedure for obtaining *ortho*-disubstituted benzenes from readily available monosubstituted ones, if a wide variety of actual or potential nucleophiles could be bonded to the preceding substituent. The nucleophiles include not only actual nucleophilic agents but also their protected derivatives and the functional groups which are readily convertible to effective nucleophilic agents. As shown in Scheme 1, the nucleophile to be introduced into the *ortho*-position is linked to the substituent with one to three atoms in between, so that a five- to seven-membered heterocyclic ring is formed as an intermediate by nucleophilic cyclization. The resulting heterocyclic ring is cleaved to the final *ortho*-disubstituted *F*-benzene.<sup>5,6)</sup>



Scheme 1.

This paper will report on the *F*-benzo-heterocyclic compounds and precursory (*F*-phenyl)amino compounds which were obtained in the course of the investigation of the *ortho*-substitution on *F*-aniline (**1**) via intramolecular nucleophilic cyclization.

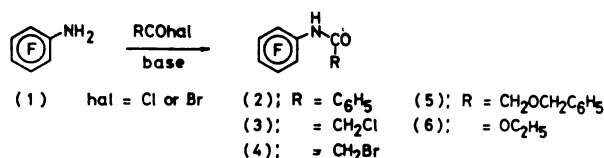
## Results and Discussion

### Preparation of Precursory (*F*-Phenyl)amino Compounds.

Nucleophiles such as amine nitrogen, oxyanion oxygen,

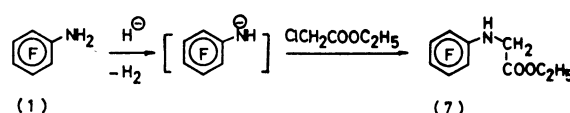
† Presented in part before the 8th International Symposium on Fluorine Chemistry at Kyoto, Japan, 1976.

and thiolate sulfur are regarded as the most effective cyclizing agents for replacing the fluorine atom on an *F*-phenyl nucleus. On the other hand, *F*-aniline nitrogen is also an actual nucleophile, and the linkage formation of *F*-aniline onto a ligand to prepare the precursory(*F*-phenyl)amino compounds can be achieved by nucleophilic attack of *F*-aniline nitrogen onto the carbocationic site of a ligand carrying a nucleophile. In a reaction of this type, the oxygen nucleophile has to be protected in the form of a carbonyl, ester, ether, or some other group containing oxygen, lest it should interfere with the *F*-aniline nitrogen nucleophile. The terminal halides can also be taken as equivalents, because they are hydrolyzable into a hydroxyl group.



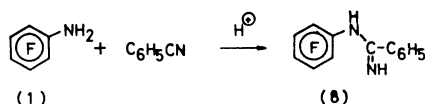
Scheme 2.

Acylation was one of the most convenient methods to afford the requisite precursors. *F*-Aniline (**1**), whose amine nitrogen is much less basic than the ordinary one,<sup>7)</sup> reacted with various acyl halides to give the corresponding amides (**2**—**5**) and carbamate (**6**) in a similar manner to that for ordinary aromatic primary amines. The reactions proceeded in the presence of bases such as pyridine or aqueous alkali generally in good yield.



Scheme 3.

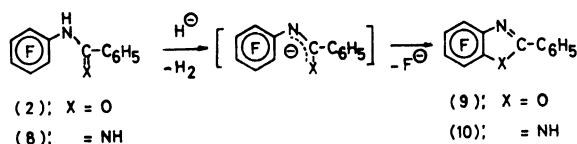
Upon ethoxycarbonylmethylation on the amine nitrogen, *F*-aniline had to be activated by deprotonation; in practice, chloroacetate gave *N*-(*F*-phenyl)glycinate (**7**) by being refluxed with sodium hydride in DMF.



Scheme 4.

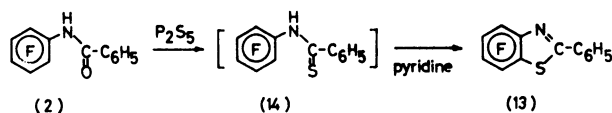
The reaction with the nitrile carbon proceeded by the protonation of the nitrile; thus benzonitrile afforded *N*-(*F*-phenyl)benzamidine (**8**) in the presence of anhydrous *p*-toluenesulfonic acid.<sup>8)</sup>

**Intramolecular Nucleophilic Cyclization.** The carbonyl oxygen in benz-*F*-anilide (**2**) and the imino nitrogen in benzamidine (**8**) could work as nucleophilic agents at the cyclization step. Upon being refluxed in the presence of sodium hydride in DMF, these two compounds gave strongly fluorescent 2-phenyl-*F*-benzoxazole (**9**) and 2-phenyl-*F*-benzimidazole (**10**), respectively, presumably by the nucleophilic attack of anionic intermediates to the *ortho*-fluorine on the *F*-phenyl nucleus. Since acet-*F*-anilide (**11**) yielded 2-methyl-*F*-benzoxazole (**12**) in much lower yield,<sup>9)</sup> the phenyl group on the side chain favored the intramolecular cyclization reaction, probably due to the steric effect of its bulkiness and the resonance stabilization of the conjugated structure of the benzylideneamine type. The same effects have been invoked, in part, to explain the similar trend in the relative ease of formation of polyfluorinated benzofuran and indole derivatives from the base-catalyzed cyclization of the precursory  $\beta$ -(*F*-phenyl)ketones.<sup>10)</sup>



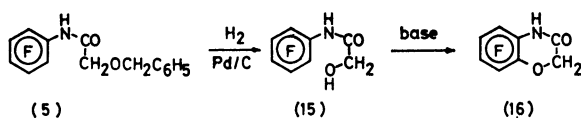
Scheme 5.

Introduction of sulfur atom as a nucleophilic agent was effected by replacing the carbonyl oxygen of benz-*F*-anilide (**2**) by refluxing with phosphorus pentasulfide in pyridine. The reaction proceeded to give directly the cyclized 2-phenyl-*F*-benzothiazole (**13**), without isolation of an expected intermediate, thiobenz-*F*-anilide (**14**).



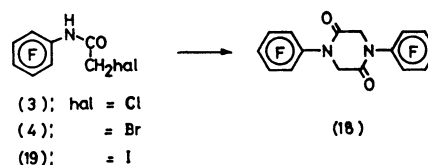
Scheme 6.

The present heteroaromatic compounds were isolated in fairly good yields, but against our purpose they were so stable that the cleavage of these five-membered rings was unsuccessful.



Scheme 7.

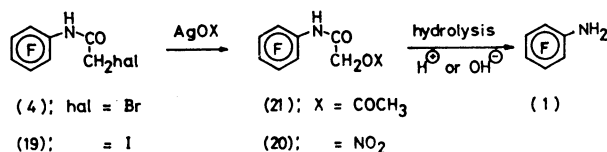
Formation of six-membered heterocyclic rings was attained by the cyclization of hydroxyacet-*F*-anilide (**15**), which was derived from benzyloxyacet-*F*-anilide (**5**) by reductive debenzoylation. Nucleophilic cyclization of the 2-hydroxy compound (**15**) gave 2,3-dihydro-1,4-(*F*-benz)oxazin-3-one (**16**) by way of alcoholate anionic intermediate. The ring fission of this compound seems more facile than the simple 2,3-dihydro-1,4-(*F*-benz)-oxazine (**17**), whose heterocyclic ring could not be cleaved.<sup>5)</sup>



Scheme 8.

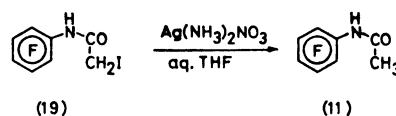
#### Reactions of Haloacet-*F*-anilides with Nucleophiles.

Searching for a shorter route from *F*-aniline to the 2-hydroxy compound (**15**), we attempted to hydrolyze haloacet-*F*-anilides under various conditions. In the reactions of chloroacet-*F*-anilide (**3**) with potassium carbonate in anhydrous DMF, as well as that of bromoacet-*F*-anilide (**4**) with tetrabutylammonium hydroxide in a benzene-water mixture, the only isolated solid product was 1,4-di(*F*-phenyl)-2,5-piperazinedione (**18**). The attempted hydrolysis of haloacet-*F*-anilides (**3**) and (**4**) to the 2-hydroxy compound (**15**) in aqueous alkaline media afforded no definite products. Iodoacet-*F*-anilide (**19**), which was derived from chloroacet-*F*-anilide (**3**) by treatment with sodium iodide in acetone, gave the same result as above when treated with alkali in an aqueous solvent. In the reactions with silver nitrate and acetate, the haloacet-*F*-anilides (**19**) and (**4**) gave the respective esters (**20**) and (**21**). Hydrolytic fission at the O-N or O-C bond of the esters, however, did not proceed either in acidic or in basic media; instead the amide N-C bond was cleaved to give the parent *F*-aniline (**1**).



Scheme 9.

On the other hand, when treated with diamminesilver(I) in aqueous THF at room temperature in the dark, the 2-iodo compound (**19**) afforded unexpectedly acet-*F*-anilide (**11**), accompanied by immediate precipitation of yellow silver iodide, the yield being almost quantitative. This reductive dehalogenation seemed to proceed specifically in aqueous THF; otherwise, for example in aqueous dioxane, the 2-iodo compound (**19**)



Scheme 10.

gave only the piperazinedione derivative (**18**) in poor yield.

This unusual reactivity of the iodoacet-*F*-anilide (**19**), in comparison with unfluorinated iodoacetanilide,<sup>11</sup> suggested that the *F*-phenyl group exerted its electron-withdrawing effect up to the  $\gamma$ -position. Evidence might be adduced for this in the reaction of di(*F*-phenyl)-methyl bromide<sup>12</sup> and bromomethyl *F*-phenyl ketone<sup>13</sup> with nucleophiles. Further studies of the cleavage of the heterocyclic rings and the effects of the *F*-phenyl group are under way in this laboratory.

### Experimental

Melting points were uncorrected. IR spectra were obtained with a JASCO DS-403G spectrometer. <sup>1</sup>H-chemical shifts were recorded on a Varian A-60 against the internal TMS reference. <sup>19</sup>F-NMR shifts were recorded on a JEOL PS-100 as the positive values downfield from the internal *F*-benzene reference. MS were obtained with JEOL JMS-07 and 01SG spectrometers. Electronic absorption and fluorescence spectra were recorded on HITACHI 200-20 and MDF-4 spectrometers, respectively. *F*-Aniline (**1**) was prepared according to the methods by Forbes<sup>14</sup> and Birchall.<sup>15</sup>

**Benz-*F*-anilide (2).** A mixture of *F*-aniline (2.00 g, 11 mmol), benzoyl chloride (5.00 g, 40 mmol), and 20% aqueous potassium carbonate (50 ml) was heated under reflux for 2 h. The cooled mixture was poured into ice-water and a solid product was collected by filtration. Recrystallization from benzene gave white plates of benz-*F*-anilide (**2**) melting at 188–189 °C (2.45 g, 78%). IR (KBr): 1670 cm<sup>-1</sup> (C=O). Found: C, 54.28; H, 2.29; N, 4.89%. Calcd for C<sub>13</sub>H<sub>6</sub>NF<sub>5</sub>O: C, 54.37; H, 2.11; N, 4.88%.

**Chloroacet-*F*-anilide (3).** Into a mixture of *F*-aniline (4.00 g, 22 mmol), anhydrous pyridine (4.05 g, 51 mmol), and absolute ether (70 ml), chloroacetyl chloride (7.00 g, 62 mmol) was added dropwise over 30 min with stirring. The mixture was refluxed for an additional 1 h, cooled, and filtered. The filtrate was washed with water, 10% aqueous sodium hydroxide, and water, successively, and evaporated to dryness after being dried over magnesium sulfate. Recrystallization of the residual solid from cyclohexane gave white needles, mp 108–109 °C, of chloroacet-*F*-anilide (**3**) (4.67 g, 88%). IR (CCl<sub>4</sub>): 2950 and 2920 (CH), 1720 cm<sup>-1</sup> (C=O). Found: C, 37.02; H, 1.17; N, 5.40%. Calcd for C<sub>8</sub>H<sub>5</sub>NCIF<sub>5</sub>O: C, 37.07; H, 1.27; N, 5.26%.

**Bromoaceto-*F*-anilide (4).** *F*-Aniline (5.00 g, 27 mmol) was worked up with bromoacetyl bromide (14.56 g, 72 mmol) in a manner similar to the above. Recrystallization from cyclohexane gave white needles, mp 113–114 °C, of bromoacet-*F*-anilide (**4**) (7.55 g, 91%). IR (CCl<sub>4</sub>): 2950 and 2920 (CH), 1715 cm<sup>-1</sup> (C=O). Found: C, 31.67; H, 1.02; N, 4.49%. Calcd for C<sub>8</sub>H<sub>5</sub>NBrF<sub>5</sub>O: C, 31.61; H, 1.00; N, 4.61%.

**Benzoyloxyacet-*F*-anilide (5).** Into a mixture of *F*-aniline (5.00 g, 27 mmol), anhydrous pyridine (13.7 g, 173 mmol), and absolute ether (50 ml), benzoyloxyacetyl chloride<sup>16</sup> (10.8 g, 58 mmol) was added dropwise over 30 min with stirring. The reaction mixture was refluxed for an additional 1 h, then cooled to room temperature and filtered. The filtrate was washed with water, 10% aqueous sodium hydroxide, diluted hydrochloric acid, and water, successively, and then dried over magnesium sulfate. The residue obtained after evaporation was recrystallized from cyclohexane to give benzoyloxyacet-*F*-anilide (**5**) (8.30 g, 92%) of white plates, mp 129–130 °C. IR (KBr): 3000 (CH), 1670 cm<sup>-1</sup> (C=O). <sup>1</sup>H-NMR

(CDCl<sub>3</sub>): 4.2 (s, 2H, COCH<sub>2</sub>O), 4.7 (s, 2H, OCH<sub>2</sub>), 7.4 (s, 5H, arom.), 7.8–8.1 ppm (br s, 1H, NH). Found: C, 54.62; H, 3.19; N, 4.03%. Calcd for C<sub>15</sub>H<sub>10</sub>NF<sub>5</sub>O<sub>2</sub>: C, 54.39; H, 3.04; N, 4.23%.

**Ethyl (*F*-Phenyl)carbamate (6).** Into an ice-chilled solution of *F*-aniline (2.00 g, 10.9 mmol) in ethanol (20 ml) was added with stirring the separate solutions of ethyl chloroformate (2.00 g, 18.4 mmol) in ethanol (5 ml) and aqueous sodium carbonate (1.20 g in 2 ml) simultaneously over 10 min. The resulting solution was kept stirring for an additional 30 min at 0 °C. It was then diluted with ethanol and the resulting precipitates were filtered out. The filtrate was poured into a large amount of water to give crude precipitates, which were recrystallized from petroleum ether (bp 40–60 °C) to afford white fibrous ethyl (*F*-phenyl)carbamate (**6**), mp 81 °C (sublimable). The yield was up to 40%. Found: C, 42.37; H, 2.37; N, 5.49%. Calcd for C<sub>9</sub>H<sub>8</sub>NF<sub>5</sub>O<sub>2</sub>: C, 42.36; H, 2.51; N, 5.45%.

**Ethyl *N*-(*F*-Phenyl)glycinate (7).** A DMF solution of *F*-aniline (5.00 g, 27.3 mmol in 30 ml) was added dropwise into a suspension of sodium hydride (27.1 mmol) in DMF (20 ml) with stirring. Into the resulting green mixture, after the evolution of hydrogen ceased, was added ethyl chloroacetate (5.00 g, 40.8 mmol). The mixture was refluxed for 1 h with stirring, then cooled and extracted with ether. The ethereal extract was washed with diluted hydrochloric acid and water, successively, and dried over magnesium sulfate. The dried extract was distilled under reduced pressure, and the fraction boiling at 100–135 °C/5 Torr was crystallized from cyclohexane-ethanol to give ethyl *N*-(*F*-phenyl)glycinate (**7**) (1.56 g, 21%) of white needles, mp 64–65 °C. IR (KBr): 2990 (CH), 1728 (C=O), 1265 and 1230 cm<sup>-1</sup> (C–N). Found: C, 44.90; H, 3.11; N, 4.98%. Calcd for C<sub>10</sub>H<sub>8</sub>NF<sub>5</sub>O<sub>2</sub>: C, 44.62; H, 3.00; N, 5.20%.

***N*-(*F*-Phenyl)benzamidine (8).** A mixture of *F*-aniline (3.00 g, 16.4 mmol), benzonitrile (2.70 g, 26.2 mmol), and anhydrous *p*-toluenesulfonic acid (26.5 mmol) was kept stirring at 180–200 °C for 5 h. The resulting solid was washed with ether, 20% aqueous sodium hydroxide, and water, successively, and was recrystallized from cyclohexane-ethanol to give *N*-(*F*-phenyl)benzamidine (**8**) (2.55 g, 55%) in white needles melting at 127–128 °C. IR (CCl<sub>4</sub>): 3500 and 3400 (NH), and 1640 cm<sup>-1</sup> (C=N). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 4.8–5.2 (br s, 2H, NH), 7.0–8.0 ppm (m, 5H, arom.). Found: C, 54.47; H, 2.63; N, 9.76%. Calcd for C<sub>13</sub>H<sub>7</sub>N<sub>2</sub>F<sub>5</sub>: C, 54.56; H, 2.47; N, 9.79%.

**2-Phenyl-*F*-benzoxazole (9).** Benz-*F*-anilide (**2**) (0.50 g, 1.75 mmol) dissolved in anhydrous DMF (15 ml) was added dropwise into a mixture of sodium hydride (2.5 mmol) and anhydrous DMF (15 ml) over 30 min under a dry nitrogen atmosphere. The mixture was refluxed for an additional 2 h, then extracted with ether. The ethereal extract was washed with diluted hydrochloric acid and water, successively, dried over magnesium sulfate, and evaporated to dryness. The residual solid was chromatographed on a neutral alumina column. From the fraction eluted with benzene, 0.43 g (92%) of 2-phenyl-*F*-benzoxazole (**9**) was obtained. Recrystallization from methanol gave white needles melting at 125.2–125.7 °C.<sup>17</sup> IR (KBr): 1540 cm<sup>-1</sup> (C=N). UV:  $\lambda_{\max}$  (EtOH); 293 (log  $\epsilon$  4.40), 287.5 (4.40), 283 (4.40), 236 nm (3.99). Fluorescence spectra (EtOH): emission  $\lambda_{\max}$ ; 349 nm and excitation  $\lambda_{\max}$ ; 295 nm. <sup>19</sup>F-NMR (CDCl<sub>3</sub>): 0.4 (1F), 2.5 (1F), 3.1 (1F), 11.2 ppm (1F). Found: C, 58.68; H, 2.09; N, 5.28; F, 29.3%; M<sup>+</sup>, 267.

**2-Phenyl-*F*-benzimidazole (10).** The benzamidine (**8**) (0.50 g, 1.75 mmol) dissolved in anhydrous DMF (15 ml) was added dropwise into sodium hydride (2.5 mmol) in anhydrous

DMF (15 ml) over 30 min under a dry nitrogen atmosphere. The mixture was refluxed for an additional 2 h, and subsequently worked up in a manner similar to that described in the oxazole (**9**). A chromatographic fraction eluted with THF gave white needles of 2-phenyl-*F*-benzimidazole (**10**) (0.25 g, 54%), mp 221–222 °C after recrystallization from ethanol. UV:  $\lambda_{\max}$  (EtOH); 293 (log  $\epsilon$  4.25), 288 (4.24), 242 nm (4.14). Fluorescence spectra (EtOH): emission  $\lambda_{\max}$ ; 332 nm and excitation  $\lambda_{\max}$ ; 312 nm.  $^{19}\text{F}$ -NMR (ethyl acetate): 5.1 (2F), 8.0 ppm (2F). Found: C, 58.60; H, 2.39; N, 10.41; F, 28.4%;  $M^+$ , 266.055. Calcd for  $\text{C}_{13}\text{H}_8\text{N}_2\text{F}_4$ : C, 58.66; H, 2.27; N, 10.52; F, 28.6%;  $M$ , 266.058.

**2-Phenyl-*F*-benzothiazole (**13**).** A mixture of benz-*F*-anilide (**2**) (1.45 g, 5.0 mmol), phosphorus pentasulfide (2.20 g, 10.0 mmol), and anhydrous pyridine (20 ml) was refluxed for 12 h. The cooled mixture was poured into water. The resulting solid was filtered off, washed with water, and then chromatographed on a silica gel column. Evaporation of the solvent from a hexane–benzene fraction, and recrystallization from cyclohexane resulted in 2-phenyl-*F*-benzothiazole (**13**) (1.10 g, 77%) in a white powder, mp 133.0–133.5 °C. IR (KBr): 1640  $\text{cm}^{-1}$  (C=N), UV:  $\lambda_{\max}$  (EtOH); 295 (log  $\epsilon$  4.30), 253 nm (4.08).  $^{19}\text{F}$ -NMR ( $\text{CDCl}_3$ ): 3.2 (1F), 4.1 (1F), 15.4 (1F), 25.1 ppm (1F). Found: C, 55.19; H, 1.97; N, 4.77; F, 26.3%;  $M^+$ , 283. Calcd for  $\text{C}_{13}\text{H}_8\text{NF}_4\text{S}$ : C, 55.13; H, 4.95; F, 26.8%;  $M$ , 283. The sulfur test using sodium nitroprusside was positive.

**2,3-Dihydro-1,4-(*F*-benz)oxazine-3-one (**16**).** The 2-benzyloxy compound (**5**) (5.40 g, 16 mmol) dissolved in ethyl acetate (50 ml) was hydrogenated in the presence of 5% palladium on charcoal (1.00 g) under atmospheric pressure at room temperature. The catalyst was filtered out and the filtrate was evaporated to dryness. Recrystallization from benzene gave hydroxyacet-*F*-anilide (**15**) (3.50 g, 89%) in a white powder, mp 99–100 °C. IR (KBr): 3240  $\text{cm}^{-1}$  (OH).  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ): 3.0–3.4 (br s, 1H, OH), 4.3 (s, 2H,  $\text{CH}_2$ ), 7.9–8.3 ppm (br s, 1H, NH). Found: C, 39.86; H, 1.81; N, 5.64%. Calcd for  $\text{C}_8\text{H}_4\text{NF}_3\text{O}_2$ : C, 39.85; H, 1.67; N, 5.81%.

A mixture of hydroxyacet-*F*-anilide (**15**) (2.00 g, 8.3 mmol), anhydrous potassium carbonate (2.00 g, 14 mmol), and anhydrous DMSO (50 ml) was kept stirring at 110 °C for 22 h. Then the cooled mixture was poured into ether. The ethereal solution was washed with diluted hydrochloric acid and water, dried over magnesium sulfate, and evaporated to dryness. The resulting solid was purified by chromatography on a silica gel column. A fraction eluted by benzene was recrystallized from benzene to give 2,3-dihydro-1,4-(*F*-benz)oxazine-3-one (**16**) (0.66 g, 36%) in white needles, mp 194.0–195.5 °C measured in a sealed tube.  $^1\text{H}$ -NMR (acetone- $d_6$ ): 4.7 (s, 2H,  $\text{CH}_2$ ), 9.5–10.3 ppm (br s, 1H, NH). UV:  $\lambda_{\max}$  (EtOH); 240 (log  $\epsilon$  4.83), 209 nm (4.18). Found: C, 43.50; H, 1.53; N, 6.15; F, 35.5%;  $M^+$ , 221. Calcd for  $\text{C}_8\text{H}_3\text{NF}_4\text{O}_2$ : C, 43.46; H, 1.37; N, 6.33; F, 34.4%;  $M$ , 221.

**Iodoacet-*F*-anilide (**19**).** Chloroacet-*F*-anilide (**3**) (2.00 g, 8.2 mmol) dissolved in anhydrous acetone (10 ml) was treated with sodium iodide (2.00 g, 13 mmol) in anhydrous acetone (10 ml) for 3 h in the dark. The mixture was poured into ether and filtered. The filtrate was evaporated to give a solid, which was sublimed at 150–160 °C. The sublimate was recrystallized from benzene to give white needles, mp 152.5–153.0 °C, of iodoacet-*F*-anilide (**19**) (2.10 g, 80%). IR ( $\text{CCl}_4$ ): 2910 and 2840 (CH), 1720  $\text{cm}^{-1}$  (C=O). Found: C, 27.67; H, 0.89; N, 3.91%. Calcd for  $\text{C}_8\text{H}_3\text{NF}_5\text{IO}$ : C, 27.37; H, 0.86; N, 3.99%.

**(Nitrooxy)acet-*F*-anilide (**20**).** Into the iodoacet-*F*-anilide (**19**) (1.00 g, 3.0 mmol) in THF (10 ml) was added

silver nitrate (1.00 g, 5.9 mmol) dissolved in water (10 ml). The solution was left standing in the dark for 9 h at room temperature. The mixture was then filtered and the filtrate was extracted with ether. Evaporation of the dried extract and recrystallization of the residue from aqueous methanol resulted in (nitrooxy)acet-*F*-anilide (**20**) (0.35 g, 41%) in white needles, mp 156.8–158.8 °C. IR (KBr): 3080, 3040, and 3000 (CH), 1690 (C=O), 1640 and 1630  $\text{cm}^{-1}$  ( $\text{ONO}_2$ ).  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ): 5.2 (s, 2H,  $\text{CH}_2$ ), 7.2–7.5 ppm (br s, 1H, NH). Found: C, 33.67; H, 1.18; N, 9.87%. Calcd for  $\text{C}_8\text{H}_3\text{N}_2\text{F}_5\text{O}_4$ : C, 33.58; H, 1.06; N, 9.79%.

A mixture of bromoacet-*F*-anilide (**4**) (0.50 g, 1.6 mmol) dissolved in THF (10 ml) and silver nitrate (0.80 g, 4.7 mmol) dissolved in water (10 ml) was refluxed for 5 h in the dark with stirring. The subsequent working up gave the nitrate (**20**) (0.07 g, 15%), while 0.18 g (36%) of the starting material was recovered.

When chloroacet-*F*-anilide (**3**) was treated in the same manner as above, it remained unreacted and was recovered almost quantitatively.

**Acetoxyacet-*F*-anilide (**21**).** A mixture of bromoacet-*F*-anilide (**4**) (2.00 g, 6.6 mmol), silver acetate (2.00 g, 12 mmol), and acetic acid (32 ml) was refluxed with stirring for 5 h in the dark, and then left standing at room temperature overnight. The resulting precipitates were filtered out and the filtrate was evaporated to give an oily residue, which was solidified immediately. The residue was chromatographed on a neutral alumina column. An eluate with benzene–acetone (10:1) was evaporated and the residue was recrystallized from benzene to give acetoxyacet-*F*-anilide (**21**) (1.40 g, 75%) in white needles, mp 85.5–87.0 °C. IR (KBr): 3000 (CH), 1760 (ester C=O), 1690  $\text{cm}^{-1}$  (amide C=O).  $^1\text{H}$ -NMR (acetone- $d_6$ ): 2.1 (s, 3H,  $\text{CH}_3$ ), 4.8 (s, 2H,  $\text{CH}_2$ ), 9.0–9.4 ppm (br s, 1H, NH). Found: C, 42.23; H, 2.29; N, 4.80%.  $\text{C}_{10}\text{H}_6\text{NF}_5\text{O}_3$ : C, 42.41; H, 2.14; N, 4.96%.

**Reactions of Haloacet-*F*-anilides with Bases.** **1:** A mixture of chloroacet-*F*-anilide (**3**) (1.00 g, 4.1 mmol), anhydrous potassium carbonate (0.25 g, 1.8 mmol), and anhydrous DMF (20 ml) was refluxed for 1 h with stirring. The cooled mixture was poured into ether. The ethereal solution was washed with diluted hydrochloric acid and water, successively, and evaporated to dryness. The residue was chromatographed on a neutral alumina column. The benzene eluate was evaporated and the residue was recrystallized from aqueous methanol to afford 1,4-di(*F*-phenyl)2,5-piperazinedione (**18**) (0.35 g, 41%) in white plates, mp 178–179 °C. Further purification was effected by recrystallization from cyclohexane–benzene to afford a specimen of white needles melting at 180.0–180.5 °C.<sup>10b</sup> IR (KBr): 2900 (CH), 1690 (C=O), 1330 and 1130  $\text{cm}^{-1}$  (C–N).  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ): 4.5 ppm (s,  $\text{CH}_2$ ). Found: C, 43.28; H, 1.09; N, 6.10%;  $M^+$ , 446.009.

When treated with potassium hydroxide in aqueous dioxane, chloroacet-*F*-anilide (**3**) was recovered unchanged almost quantitatively.

**2:** A mixture of bromoacet-*F*-anilide (**4**) (0.50 g, 1.6 mmol), benzene (15 ml), and aqueous tetrabutyl ammonium hydroxide (1.6 mmol, 10 ml) was heated for 4 h with stirring. The benzene layer was separated and the aqueous layer was extracted with ether. The organic layer were combined and evaporated to give 0.23 g (63%) of the piperazinedione (**18**) after recrystallization from cyclohexane–benzene.

**3:** Into the iodoacet-*F*-anilide (**19**) (0.50 g, 1.5 mmol) in 50% aqueous THF (10 ml) was added diamminesilver(I) nitrate (5.0 mmol) in 50% aqueous THF (50 ml); the solution was left standing for 20 h in the dark. The mixture was filtered and the filtrate was extracted with ether. Evapo-

ration of the dried extract (crude yield 0.35 g) and recrystallization of the residue from aqueous methanol afforded acet-*F*-anilide (**11**) (0.17 g, 51%) in white needles, mp 135–136 °C. IR(KBr): 3240 (NH), 3060, 3020, and 2980 (CH), 1685 cm<sup>-1</sup> (C=O). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 2.2 (s, 3H, CH<sub>3</sub>), 7.2–7.5 ppm (br s, 1H, NH). Found: C, 42.82; H, 1.81; N, 6.36%. The product was identified by comparison with an authentic specimen.<sup>18)</sup>

4: Bromoacet-*F*-anilide (**4**) (0.50 g, 1.6 mmol) in 50% aqueous THF (10 ml) was added into diamminesilver nitrate (4.2 mmol) in 50% aqueous THF (10 ml); the mixture was refluxed for 5 h in the dark with stirring. After being worked up in the same manner as above, 0.06 g (16%) of the piperazinedione (**18**) was obtained.

5: When treated in the above manner, chloroacet-*F*-anilide (**3**) remained unreacted to be recovered almost quantitatively.

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