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Studies on Fluorinated Pyrimidines. I. A New Method of Synthesizing 5-Fluorouracil and Its Derivatives

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A series of 5-fluoro-6-substituted-5,6-dihydrouracil-5-carboxylic esters (**13**), -5-carboxamides (**15**, **16**), and -5-carbonitriles (**18**, **19**) was prepared by direct fluorination of the corresponding uracil-5-carboxylic esters (**6**), -5-carboxamide (**14**), and -5-carbonitrile (**17**) with fluorine or trifluoromethyl hypofluorite (CF_3OF) in the presence of water, methanol and/or acetic acid. Hydrolysis of the above-mentioned products under mild conditions gave 5-fluorouracil (**1a**) in high yield. Some applications of the present method for the synthesis of 1-(2-tetrahydrofuryl)-5-fluorouracil (**1b**) were also described.[1)]

Keywords——uracil-5-carboxylic esters; uracil-5-carboxamide; uracil-5-carbonitrile; fluorine; CF_3OF; 5-fluoro-6-substituted-5,6-dihydrouracil-5-carboxylic esters; 5-fluorouracil; Ftorafur; methyl ureidomethylenemalonate

The similarity of steric volume between fluorine and hydrogen atoms and the dissimilarity of their behavior due to the difference in electronegativity enable many fluorinated compounds to act as antimetabolites with respect to the corresponding halogen-free natural substrates.

In 1957, Heidelberger *et al.* reported the synthesis[2)] of 5-fluorouracil (**1a**) and its antitumor activity[3)] against murine leukemia. It was clearly shown that **1a** was converted *in vivo* into 5-fluoro-2′-deoxyuridylic acid, an inhibitor of thymidylate synthetase, and prevented the biosynthesis of desoxyribonucleic acid (DNA). At first, **1a** was prepared in rather low overall yield (*ca.* 17%) by a basic ring-construction method consisting of several steps starting from ethyl fluoroacetate.

Recently, direct fluorination methods[4)] starting from uracil (**2a**) have been developed in several solvent systems using fluorine or CF_3OF. These methods have raised the yield of **1a** in small-scale experiments to 76—92%, although large-scale preparations seem less successful (25—78% yields). Fluorination of **2a** goes through an intermediate (**3**) of the type common to other halogenation processes (chlorination, bromination). In contrast to the chloro (**4**) and bromo (**5**) compounds, **3** is stable and removal of HOR^1 from **3** requires a high temperature (Chart 1).

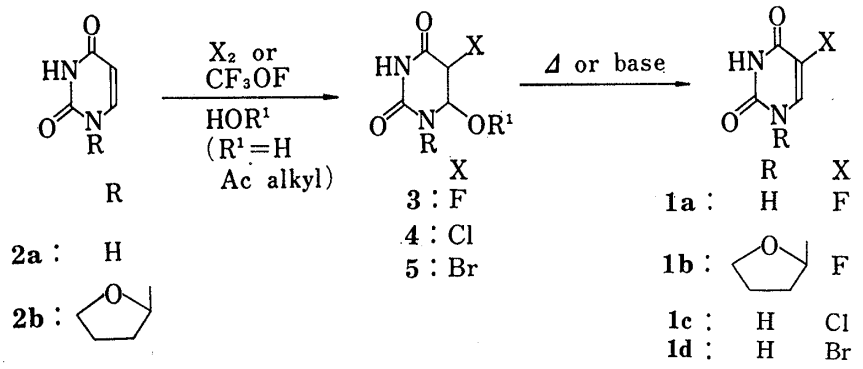

Chart 1

Therefore, we first chose 5-carboxyuracil (**7**) as the starting material to be fluorinated, instead of **2a**, expecting that the 5-carboxyl group would 1) facilitate the fluorination, 2) prevent over-fluorination, and 3) be easily removed by subsequent treatment with an acid (Chart 2).

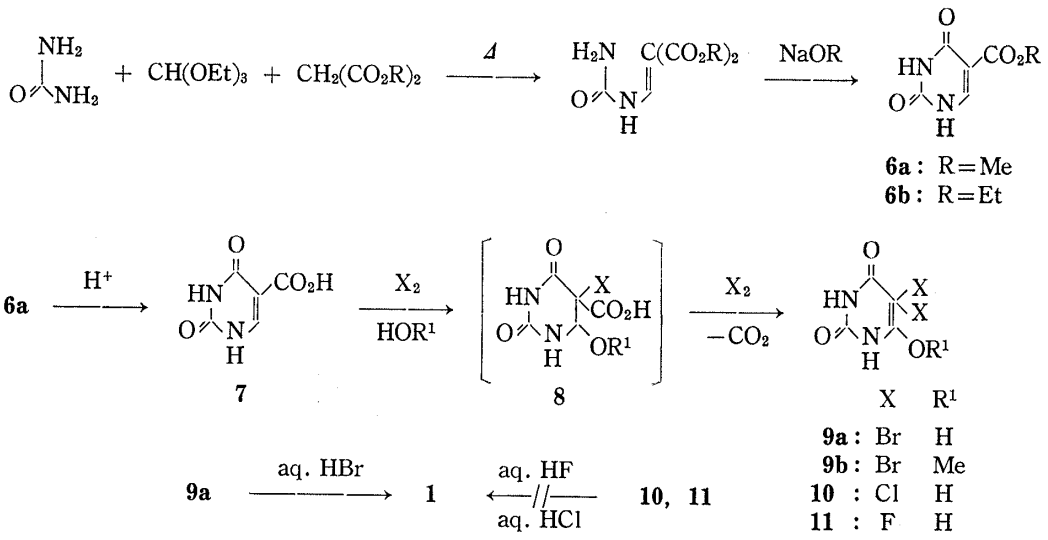

Chart 2

However, halogenation of **7** in water or methanol in preliminary experiments led to 5,5-dihalogeno-6-hydroxy(or methoxy)-5,6-dihydrouracil (**9**, **10**, and **11**). Even when equimolar bromine was added to a suspension of **7** in methanol, 59% of **7** was recovered and 73% (based on **7** consumed) of 5,5-dibromo-6-methoxy-5,6-dihydrouracil (**9b**) was obtained. This showed that the expected halogenation product, the 5-carboxy-5-halogeno intermediate (**8**), was more susceptible to halogenation than the starting material (**7**), presumably after decarboxylation. In contrast to compound **9**, which, on the treatment with hydrobromic acid, gave 5-bromouracil (**1d**),[5] the 5,5-difluoro (**11**) and 5,5-dichloro (**10**) compounds failed to give the corresponding 5-halogenouracils (**1a** and **1c**) on treatment with hydrofluoric and hydrochloric acid, respectively, due to the inability to produce F^+ and Cl^+ from the C–F and C–Cl bonds, and were recovered unchanged. To prevent decarboxylation of **8** during the halogenation reaction, protection of the carboxyl group in **7** as an alkoxycarbonyl group was investigated. Chlorination of 5-methoxycarbonyluracil (**6a**) (prepared by the route shown in Chart 2) in water or methanol gave the 5-chloro-6-hydroxy (**12a**) or 5-chloro-6-methoxy (**12b**) derivative, which, on heating under acidic conditions, gave **1c** in high yield. This method of preparing **1c** from **6a** was manipulated as a one-pot synthesis (Chart 3). It is likely that the reaction proceeds

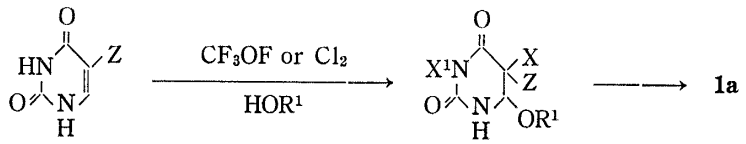

Chart 3

through dealkoxycarbonylation of **12**, which accelerates removal of the 6-substituent with formation of a double bond between C-5 and C-6.

Fluorination of **6a**,[6] with CF_3OF gave the desired 5-fluoro-6-substituted derivative, **13a** or **13b**, depending upon the solvent composition used for the reaction. Fluorination of uracil-5-carboxamide (**14**) under similar conditions gave the 3,5-difluoro-6-hydroxy derivative (**15**), the structure of which was confirmed by the proton magnetic resonance (PMR) analysis. Similarly, fluorination of uracil-5-carbonitrile (**17**)[7] resulted in the formation of nearly equal amounts of 5-fluoro (**18**) and 3,5-difluoro derivatives (**19**) (Chart 3).

Hydrolysis of **13a** in diluted sodium hydroxide solution failed to give **1a**, while that of **13b** provided **1a** in high yield. Hydrolysis of these compounds (**13**, **15**, **18**, and **19**) under acidic conditions gave **1a** in high yields. Under these conditions with hydrochloric acid, reduction of the N–F bond in **15** or **19** to an N–H bond by chloride ion occurred. It seems likely that, in the case of **13a** (6-OH), the C–C bond between the 5 and 6 positions is cleaved by hydroxide ion (a retroaldol reaction) and some ring-opened products are formed, because the reaction mixture showed only an end absorption in its ultraviolet (UV) spectrum. In the case of **13b**, it seems that the hydrolysis proceeds by the initial cleavage of the ester linkage at C-5 followed by decarboxylation and the formation of a double bond between C-5 and C-6 (Chart 4).

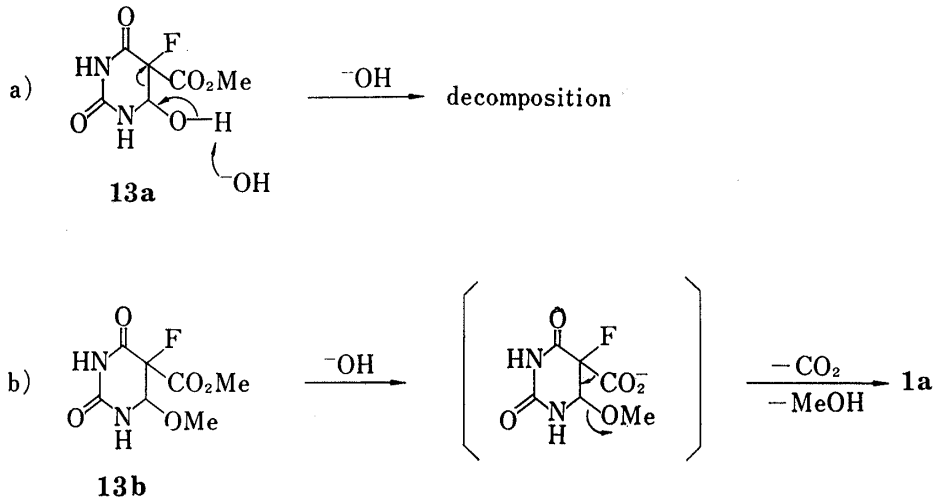

Chart 4

Fluorination with elemental fluorine was carried out by bubbling a gas mixture of fluorine and nitrogen through the reaction mixture. Treatment of the carboxylic acid derivatives (**6**, **14**, and **17**) in water gave the hypofluorite adducts (**13**, **16**, and **18**) as stable crystals which were converted to **1a** as above in excellent yields.

In order to establish a one-pot synthesis of **1a**, we studied these reactions in detail. Without addition of a reducing agent such as sodium bisulfite, the one-pot reaction gave a low yield of **1a**. This result was attributed to formation of peroxides, *e.g.*, hydrogen peroxide, *etc.*, which can be formed by the reaction of water with fluorine.[8] Some chlorine, generated by the reaction of the added hydrochloric acid with hydrogen peroxide[9] in the reaction mixture, must have reacted with a part of **1a** or the probable intermediate **8** giving the 5-chloro-5-fluoro-6-hydroxy derivative (**20**) (Chart 5).

On excluding the influence of the peroxides according to the procedures described in the experimental section, the one-pot synthesis provided an excellent yield of **1a** (92%). In contrast to our procedure, the known method shown in Chart 1 gave **1a** in 57% yield. A higher yield of **1a** from **13** as compared with the case of **3**, appears to be attributable

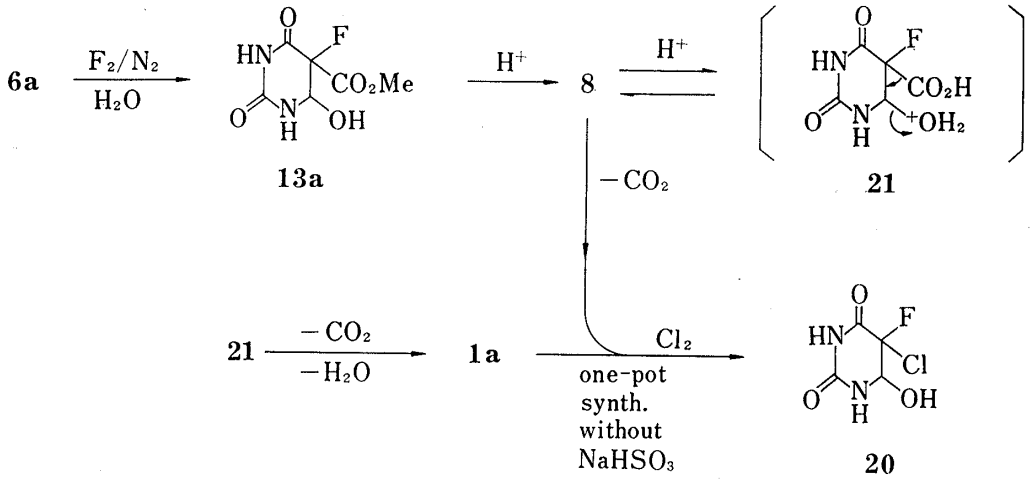

Chart 5

to assistance by the carboxyl function in the elimination of the hydroxyl group at the 6 position *via* the protonated intermediate **21** (Chart 5). The ready hydrolysis of **13** under mild conditions and quantitative conversion of it to **1a**, raise the posibility that **13** is a masked compound of **1a**, which is a useful antitumor agent.

Since the first preparation of 1-(2-tetrahydrofuryl)-5-fluorouracil (**1b**, Ftorafur) by Giller *et al.*[10] (reaction a in Chart 6) as a pro-drug of **1a**, many reports[11] have dealt with improved methods for synthesizing **1b**. Earl *et al.*[12] applied direct fluorination for the first time to prepare **1b** in 1972 (reaction b in Chart 6).

We applied the fluorination reaction shown above for the synthesis of **1b**. Our starting materials were prepared by heating **6** with 2,3-dihydrofuran in pyridine[11] at 155°C or by the condensation of 2-chlorotetrahydrofuran with the silylated intermediate obtained from **6**.

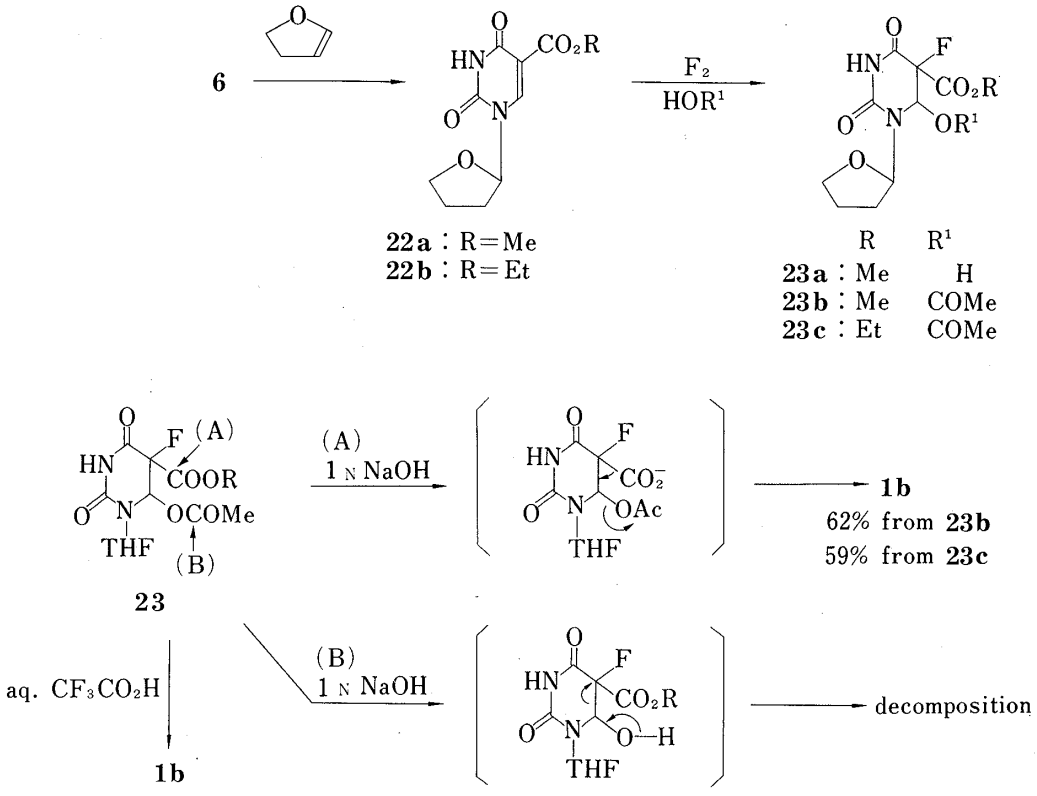

Chart 6

Fluorination of 5-alkoxycarbonyl-1-(2-tetrahydrofuryl)uracil (**22a**) with fluorine in water or acetic acid gave 5-fluoro-1-(2-tetrahydrofuryl)-6-hydroxy-5-methoxycarbonyl-5,6-dihydrouracil (**23a**) or the 6-acetoxy-5-fluoro-1-(2-tetrahydrofuryl) derivative (**23b**), respectively (Chart 6). Alkaline hydrolysis of **23a** gave no UV-positive product, presumably as a result of clevage of the dihydrouracil ring just as in the case of **13a**. However, hydrolysis of **23a** in a chilled aqueous trifluoroacetic acid solution gave **1b** in 84% yield (by UV measurement) after 46 d. It was remarkable to obtain **1b** from **23a** in an acidic solution in spite of the lability of the N^1-(2-tetrahydrofuryl) bond toward acids. However, the conversion was too slow to be practical. Thus, we studied an alkaline hydrolysis of the 6-acetoxy derivatives (**23b** and **23c**). They were prepared by fluorinating a solution of **22** in acetic acid with 2.3 eq of fluorine. The products were characterized by measurement of their PMR spectra. Hydrolysis of **23b** or **23c** with an excess of sodium hydroxide solution afforded **1b** in good yield. As the 6-hydroxy compound (**23a**) gave no **1b** under similar conditions, it seemed that nucleophilic attack by hydroxide ion at the carbonyl of the 6-acetoxy group in **23b** or **23c** [path B in Chart 6] was hindered because of the steric influence of the 1-(2-tetrahydrofuryl) group and that the alkoxycarbonyl group was hydrolyzed preferentially, the resulting carboxylate intermediate being easily decarboxylated to give **1b** [path A in Chart 6].

Experimental

All melting points were determined on a Yanagimoto hot plate apparatus and are uncorrected. PMR spectra were recorded on a Varian T-60 spectrometer. Tetramethylsilane was used as an internal standard for all spectra, and deuterated dimethylsulfoxide was used as the solvent, unless otherwise specified. Chemical shifts were expressed in δ (ppm) values. UV spectra were recorded on a Hitachi EPS-3T spectrometer. Thin-layer chromatography (TLC) was performed using pre-coated Kieselgel 60 F 254 Art. 5715 (Merck) sheets. Column chromatography was carried out with Kieselgel 60 Art. 7734 (Merck).

5-Methoxycarbonyluracil (6a)——A mixture of urea (90 g, 1.5 mol), methyl malonate (132 g, 1.0 mol), and triethyl orthoformate 155 g, 1.1 mol) was heated at 130°C for 4 h with stirring. EtOH liberated during the course of the reaction was distilled off. The reaction mixture was chilled in an ice bath after addition of H_2O (100 ml) while hot. A white precipitate that separated was collected by filtration and washed with H_2O and MeOH successively, then dried over P_2O_5 *in vacuo*, giving methyl ureidomethylenemalonate (130 g, 69%). PMR: 3.67 (3H, s), 3.73 (3H, s), 7.30 (2H, br.), 8.47 (1H, d, J=13 Hz), 10.30 (1H, d, J=13 Hz). mp 223°C. *Anal.* Calcd for $C_7H_{10}N_2O_5$: C, 41.58; H, 4.99; N, 13.86. Found: C, 41.84; H, 5.05; N, 14.26.

Methyl ureidomethylenemalonate (117.0 g, 0.58 mol) was added to a solution of NaOMe prepared from Na (14.1 g, 0.61 mol) and 1.8 l of absolute MeOH, and the mixture was heated under reflux for 10 min, giving a gel after cooling. Ice-water (800 ml) and conc. HCl (60 ml) were added to the above mixtute, giving 83.1 g (84%) of **6a** as colorless needles. PMR: 3.72 (3H, s), 8.12 (1H, s), 11.23 (1H, br.), 11.53 (1H, br.). Crude **6a** was recrystallized from H_2O giving the monohydrate of **6a**. mp 253—256°C. *Anal.* Calcd for $C_6H_6N_2O_4 \cdot H_2O$: C, 38.30; H, 4.28; N, 14.89. Found: C, 38.48; H, 4.15; N, 14.90. UV λ_{max} nm (ε): 271 (11500, pH 1.0), 271 (11400, pH 7.0).

5-Ethoxycarbonyluracil (6b)——In a manner similar to that stated above, **6b** (74%) was prepared *via* ethyl ureidomethylenemalonate (66% from urea). mp 241—242°C. PMR: 1.25 (3H, t, J=7.5 Hz), 4.18 (2H, q, J=7.5 Hz), 8.13 (1H, s), 11.5 (2H, br.). *Anal.* Calcd for $C_7H_8N_2O_4$: C, 45.65; H, 4.38; N, 15.12. Found: C, 45.55; H, 4.36; N, 15.15.

5-Carboxyuracil (7)——A suspension of **6a** (monohydrate, 498 g, 2.6 mol) in a mixture of H_2O (2.4 liter) and conc. HCl (250 ml) was heated under reflux for 16.5 h. Soon a clear solution was obtained and then crystals separated. They were filtered off and washed with H_2O. Anhydrous 5-carboxyuracil (**7**) was obtained after heating them over P_2O_5 at 110—120°C *in vacuo* (399 g, 96%). PMR: 8.28 (1H, s), 12.13 (3H, br.). UV $\lambda_{max}^{pH\ 7.0}$ nm: 271.

5,5-Dibromo-6-hydroxy-5,6-dihydrouracil (9a)——Br_2 (3.1 ml, 60 mmol) was added dropwise to a suspension of **7** (4.68 g, 30 mmol) in H_2O (60 ml) with stirring. After the effervescence of CO_2 had ceased, colorless needles separated from the reaction mixture. They were filtered off and dried giving 6.46 g (79%) of **9a**. PMR: 5.03 (1H, m), 7.43 (1H, m), 8.72 (1H, br.), 10.83 (1H, br.). *Anal.* Calcd for $C_4H_4Br_2N_2O_3$: C, 16.69; H, 1.40; N, 9.37. Found: C, 16.77; H, 1.34; N, 9.82. mp>250°C (from H_2O).

5,5-Dichloro-6-hydroxy-5,6-dihydrouracil (10)——Chlorine gas was bubbled through a suspension of the Na salt of **7** (1.78 g, 10 mmol) in 20 ml of H_2O until a clear solution was obtained. Removal of the solvent *in vacuo* afforded a white solid. Recrystallization of the solid from acetone–hexane gave 1.20 g (60%) of **10** as colorless needles. mp 208—209°C (dec). PMR: 4.97 (1H, m), 7.42 (1H, m), 8.77 (1H, br.), 10.92

(1H, s). *Anal.* Calcd for $C_4H_4Cl_2N_2O_3$: C, 24.14; H, 2.03; N, 14.08; Cl, 35.63. Found: C, 24.19; H, 1.97; N, 14.34; Cl, 35.79.

5-Bromouracil (1d)——The Na salt of **7** (1.79 g, 10 mmol) was treated with Br_2 (1.26 ml, 24 mmol) in H_2O (20 ml), and the mixture was heated under reflux for 7 h, giving 0.76 g (40%) of **1d** as yellow prisms. UV $\lambda_{max}^{pH\ 7.0}$ nm: 278.

5-Chloro-6-hydroxy-5-methoxycarbonyl-5,6-dihydrouracil (12a)——Chlorine gas was bubbled into a suspension of **6a** (14.1 g, 83 mmol) in H_2O (240 ml) until a clear solution was obtained. The mixture was evaporated to one-tenth of the initial volume *in vacuo*, giving 14.8 g (80%) of **12a** as a white solid. mp 179—181°C (colorless needles from acetone–hexane). PMR: 3.78 (3H, s), 4.98 (1H, d, J=4 Hz), 6.5 (1H, br.), 8.57 (1H, br.), 10.80 (1H, br.). *Anal.* Calcd for $C_6H_7ClN_2O_5$: C, 32.37; H, 3.17; N, 12.59. Found: C, 32.24; H, 2.94; N, 12.56.

5-Chloro-6-methoxy-5-methoxycarbonyl-5,6-dihydrouracil (12b)——A suspension of **6a** (3.40 g, 20 mmol) in MeOH (100 ml) was treated with Cl_2 until a clear solution was obtained. The mixture was evaporated to one-tenth of the initial volume *in vacuo*, giving **12b** as a white solid. Recrystallization of the product from acetone–hexane gave 3.55 g (75%) of **12b** as colorless needles. mp 164—166°C. PMR: 3.37 (3H, s), 3.80 (3H, s), 4.73 (1H, d, J=5 Hz), 9.10 (1H, br.), 10.95 (1H, br.). *Anal.* Calcd for $C_7H_9ClN_2O_5$: C, 35.53; H, 3.83; N, 11.84; Cl, 14.99. Found: C, 35.41; H, 3.88; N, 11.76; Cl, 15.22.

5-Chlorouracil (1c)——a) A solution of **12a** (345 mg, 1.6 mmol), in conc. HCl (15 ml) was heated under reflux for 15 h to afford 92 mg (27%) of **1c** as yellow prisms. UV $\lambda_{max}^{pH\ 7.0}$ nm: 275.

b) A suspension of **6a** (2.55 g, 15 mmol) in H_2O (60 ml) was treated with Cl_2. The mixture was heated under reflux for 16 h after addition of conc. HCl (10 ml). It was evaporated to one-fifth of the initial volume *in vacuo*, giving 1.39 g (63%) of **1c** as colorless prisms. mp>300°C. PMR: 7.75 (1H, d, J=6 Hz), 11.17 (1H, br.), 11.48 (1H, br.). *Anal.* Calcd for $C_4H_3ClN_2O_2$: C, 32.78; H, 2.06; N, 19.12; Cl, 24.20. Found: C, 32.54; H, 1.97; N, 19.02; Cl, 24.30. UV $\lambda_{max}^{pH\ 7.0}$ nm: 275.

c) A solution of **10** (300 mg, 1.5 mmol) in conc. HCl (15 ml) was heated under reflux for 3.5 h. No product with a UV absorption maximum at *ca.* 270 nm was observed.

5,5-Dibromo-6-methoxy-5,6-dihydrouracil (9b)——A suspension of **7** (0.77 g, 5 mmol) in MeOH (20 ml) was treated with Br_2 (0.26 ml, 5 mmol) and H_2O (0.18 ml) for 2 d. Unreacted **7** (0.46 g, 59%) was recovered as a precipitate. The mother liquor was diluted with EtOAc (50 ml) and washed with H_2O. The EtOAc solution was evaporated to dryness, giving 0.45 g (73%) of **9b** as a white powder. PMR: 3.37 (3H, s), 4.80 (1H, d, J=4.5 Hz), 9.07 (1H, br.), 10.92 (1H, s).

Uracil-5-carboxamide (14)——A suspension of **6a** (20.0 g, 0.12 mol) in conc. NH_4OH (200 ml) was heated overnight at 60°C. Fine needles were collected on a filter and were washed with H_2O and EtOH, giving 7.1 g of **14**. The mother liquor was concentrated to give another crop of **14** (8.9 g). The total yield of **14** was 16.0 g, (88%). *Anal.* Calcd for $C_5H_5N_3O_3$: C, 38.71; H, 3.25; N, 27.09. Found: C, 38.54; H, 3.19; N, 26.77. mp>300°C.

Uracil-5-carbonitrile (17)——This compound was prepared in a manner similar to that stated in the literature.[7] mp 290°C. (dec., from H_2O). PMR: 8.43 (1H, s), 11.75 (1H, s), 11.98 (1H, s).

Fluorination of 5-(Substituted)uracils with CF_3OF

5-Fluoro-6-hydroxy-5-methoxycarbonyl-5,6-dihydrouracil (13a)——a) A suspension of **6a** (0.51 g, 3 mmol) in 20 ml of H_2O was placed in a pressure-resistant glass tube (100 ml) and frozen in a dry ice–EtOH bath. CCl_3F (20 ml) was added to the frozen mass, then CF_3OF (*ca.* 400 mg) was dissolved into the above mixture chilled in the same bath. Then, the glass tube was stoppered and removed from the cooling bath. The reaction mixture was brought to room temperature, and allowed to stand at that temperature overnight with stirring to yield a colorless solution. N_2 was bubbled into the reaction mixture in order to remove excess CF_3OF, then the mixture was evaporated to dryness *in vacuo* after addition of NaOAc (400 mg). The residue was treated with acetone to remove insoluble inorganic salts. The acetone solution was brought to dryness *in vacuo* and gave 0.7 g of crude **13a** as a yellow glass. PMR: 3.80 (3H, s), 4.90 (1H, m, after addition of D_2O, d, J_{HF}=4 Hz), 7.13 (1H, d, J=5 Hz), 8.53 (1H, br.), 10.85 (1H, br.).

b) Fluorination with CF_3OF (290 mg) was carried out in a manner similar to that described above for **6a** (0.51 g, 3 mmol) in a mixture of H_2O (20 ml) and CF_3COOH (20 ml) giving 1.15 g of a pale yellow syrup containing **13a**.

5-Fluoro-6-methoxy-5-methoxycarbonyl-5,6-dihydrouracil (13b)——CF_3OF (1.1 g) was dissolved in a chilled mixture of MeOH (25 ml) and CCl_3F (50 ml) in a pressure-resistant glass tube (300 ml) cooled in a dry ice–EtOH bath. Then, **6a** (1.36 g, 8 mmol) was suspended in the above mixture, followed by addition of MeOH (80 ml) cooled in the same bath prior to use. The reaction tube was sealed and the mixture was brought to room temperature. The reaction mixture was evaporated to dryness *in vacuo* after being stirred for 16 h, giving a white solid that was chromatographed on silica gel (solv.: $CHCl_3$ containing 1—10% of MeOH) to provide 1.52 g of the crude **13b** and some **6a** (0.31 g). Recrystallization of the solid from acetone–hexane gave 1.26 g (93%) of **13b** as colorless flakes. mp 165—166°C. PMR: 3.38 (3H, s), 3.85 (3H, s), 4.77 (1H, dd, J_{HF}=2 Hz, J=5 Hz, after addition of D_2O, d, J_{HF}=2 Hz), 8.77 (1H, br.), 10.92 (1H, br.). *Anal.* Calcd for $C_7H_9FN_2O_5$: C, 38.19; H, 4.12; N, 12.76; Found: C, 38.49; H, 4.06; N, 12.50.

3,5-Difluoro-6-hydroxy-5,6-dihydrouracil-5-carboxamide (15)——**14** (0.46 g, 3 mmol) was treated with

CF_3OF (0.99 g) in a solvent system composed of H_2O and CCl_3F for 160 h in a pressure-resistant glass tube at room temperature. A part of the starting material (0.23 g) was recovered by filtration, and the filtrate was evaporated to dryness after addition of NaOAc (1.3 g) *in vacuo*, giving a red syrup (1.55 g) that consisted mainly of **15**. PMR: 4.93 (1H, m, after addition of D_2O, d, J_{HF}=2.5 Hz), 8.35 (1H, br.). There was no signal between 10 and 11 ppm assignable to N^3–H.

5-Fluoro- (18) and 3,5-Difluoro-6-hydroxy-5,6-dihydrouracil-5-carbonitrile (19)——**17** (1.10 g, 8 mmol) was treated with CF_3OF (1.2 g) in a solvent system composed of H_2O and CCl_3F for 40 h in a pressure-resistant glass tube at room temperature. Removal of the solvent *in vacuo* gave a brown syrup. It was dissolved in acetone and the insoluble substances were removed by filtration. The filtrate was evaporated to dryness *in vacuo*, giving a mixture of almost equal amounts of **18** and **19** (1.74 g). PMR: 5.33 (1H, m, after addition of D_2O, d, J_{HF}=3 Hz), 7.7—8.2 (1H, br.), 9.00 (1H, br.), 10.3—11.0 (1/2 H, br.).

5-Fluorouracil (1a)——a) A solution of **13a** (1.19 g, 5.8 mmol) in 25 ml of 1N HCl was heated under reflux for 1 h. Then, the reaction mixture was passed through a column of activated carbon which was eluted with MeOH–H_2O–benzene (25/6/3, v/v). The eluate gave **1a** as a white powder (490 mg, 65%) after removal of the solvent *in vacuo*. mp 282—283°C (from H_2O). PMR: 7.70 (1H, dd, J_{HF}=6 Hz, J=5 Hz), 10.68 (1H, br.), 11.47 (1H, br.), *Anal.* Calcd for $C_4H_3FN_2O_2$: C, 36.93; H, 2.24; N, 21.26; F, 14.37. Found: C, 36.90; H, 2.24; N, 21.26; F, 14.37. UV λ_{max} nm: 267 (pH 1.0), 267 (pH 7.0).

b) A solution of **13b** (0.65 g, 3 mmol) in 30 ml of 1.5N HCl was heated under reflux for 2.5 h, and the mixture was treated as above, giving 0.37 g (95%) of **1a** as colorless prisms. UV $\lambda_{max}^{pH\ 7.0}$ nm: 267.

c) A mixture of crude **15** (1.55 g) and 25 ml of conc. HCl was heated under reflux for 5.5 h. The mixture was treated as above, giving 0.23 g (quantitative yield) of **1a** as a white powder. UV $\lambda_{max}^{pH\ 7.0}$ nm: 267.

d) A mixture of crude **18** and **19** (1.70 g) in 40 ml of conc. HCl was heated under reflux for 6.5 h. The mixture was treated as above, giving 0.76 g (81% from **17**) of **1a** as a white powder. UV $\lambda_{max}^{pH\ 7.0}$ nm: 267.

e) A solution of **13b** (102.15 mg, 0.46 mmol) in 20 ml of 1N NaOH was allowed to stand at room temperature for 1 h. The mixture was neutralized with 1N HCl. The yield of **1a** was 89%, calculated from the TOD_{267}.

f) Treatment of **13a** (30.50 mg, 0.14 mmol) in 10 ml of 1N NaOH did not give any product which showed an absorption maximum in the UV spectrum.

Fluorination of 5-(Substituted)uracils with Fluorine

5,5-Difluoro-6-hydroxy-5,6-dihydrouracil (11)——A suspension of **7** (9.36 g, 60 mmol) in 500 ml of H_2O was treated with 4.0 eq. of diluted F_2 (F_2/N_2=30%) with vigorous stirring at room temperature. After filtration of the unchanged **7** (7.74 g, 83% recovery), $CaCO_3$ (12.0 g) and $NaHSO_3$ (15.0 g) were added to the filtrate. Insoluble substances were filtered off and washed with H_2O. The filtrate and the washings were evaporated to dryness *in vacuo*, giving a white solid. It was triturated with 200 ml of acetone and the insoluble substances were filtered off. The filtrate was evaporated to dryness *in vacuo*, giving 0.75 g (45%) of **11** as a white powder. mp 188—189°C (from acetone–$CHCl_3$–hexane). PMR: 5.02 (1H, m; after addition of D_2O, dd, J_{HF}=3 Hz, J_{HF}=6 Hz), 7.2 (1H, br.), 8.9 (1H, br.), 11.0 (1H, br.). *Anal.* Calcd for $C_4H_4F_2N_2O_3$: C, 28.93; H, 2.43; N, 16.87. Found: C, 29.05; H, 2.39; N, 16.83.

An Attempt to convert 11 into 1a——A mixture of **11** (166 mg, 1.0 mmol), H_2O (20 ml), and 46% HF solution (1 ml) was heated under reflux for 4 h. The UV spectrum of the reaction mixture showed only an end absorption, and **11** was recovered as checked by the TLC method.

One-pot Synthesis of 5-Fluorouracil (1a)——a) Without Reducing Procedure: Into a suspension of **6a** (5.10 g, 30 mmol) in H_2O (600 ml) was bubbled 2 eq. of F_2 (F_2/N_2=11%) at room temperature with vigorous stirring. In the course of bubbling, **6a** dissolved gradually giving a clear solution. The end point of the reaction was indicated by the complete loss of the absorption maximum of **6a** at 271 nm in the UV spectrum. Next, 50 ml of 1M $CaCl_2$ solution was added to the mixture in order to remove HF as CaF_2. The mixture was filtered and the filtrate was heated under reflux for 1 h after addition of conc. HCl (100 ml). The mixture was passed through a column of activated carbon (50 g) that was washed with H_2O and eluted with MeOH. Removal of the solvent *in vacuo* gave 1.19 g (31%) of **1a**.

b) The reaction mixture obtained from the fluorination of **6a** (1.96 g, 11.6 mmol) in 345 ml of H_2O with 3.0 eq of diluted F_2 (F_2/N_2=25%) was divided into several portions, which were treated by one of the following procedures.

i) Evaporated to dryness *in vacuo*, then hydrolyzed in 1N HCl by under reflux for 2 h. Yield of **1a**: 70%.

ii) Hydrolyzed directly, after addition of conc. HCl, by refluxing for 2 h. Yield of **1a**: 23%.

iii) Hydrolyzed directly, after addition of 46% HF solution, by refluxing for 2 h. Yield of **1a**: 67%.

iv) Hydrolyzed directly, after addition of conc. HCl and aqueous hydrogen peroxide solution, by refluxing for 2 h. Yield of **1a**: 19%.

v) Hydrolyzed, after addition of conc. HCl and $NaHSO_3$, by refluxing for 2 h. Yield of **1a**: 79%.

vi) Hydrolyzed, after addition of $CaCO_3$ and $NaHSO_3$ followed by acidification with conc. HCl, by heating under reflux for 2 h. Yield of **1a**: 77%.

c) With Reducing Procedure: A suspension of **6a** (7.52 g, 40 mmol) in 200 ml of H_2O was treated with 1.8 eq of F_2 (F_2/N_2=25%). The reaction mixture was treated with 5.55 g of $NaHCO_3$ and 23 ml of 1M

$NaHSO_3$, then heated under reflux for 1 h after addition of 50 ml of conc. HCl. The yield of **1a** was 92% when measured by the UV method. Chromatography on activated carbon (50 g) as before and recrystallization of a white powder thus obtained from H_2O gave 4.12 g (79%) of **1a** as pale yellow prisms. mp 282—283°C. UV $\lambda_{max}^{pH\ 7.0}$ nm: 267.

5-Chloro-5-fluoro-6-hydroxy-5,6-dihydrouracil (20)——A suspension of **6a** (monohydrate, 15.05 g, 80 mmol) in 400 ml of H_2O was treated with 2.2 eq of F_2 ($F_2/N_2=40\%$). The reaction mixture was heated under reflux for 70 min after addition of 50 ml of conc. HCl, giving **1a** in 59% yield (determined by the UV method). The mixture was evaporated to dryness *in vacuo*, giving 13.0 g of a yellow solid that was triturated with 500 ml of acetone. Insoluble substances were filtered off, and the filtrate was brought to dryness *in vacuo*, giving 6.9 g of a yellow solid. The crude products were chromatographed on silica gel (solv.: acetone/$CHCl_3$=1/4), giving 2.0 g (14%) of **20** as a white solid. mp 184—186°C (from EtOAc–hexane). PMR: 5.03 (1H, m, $J_{HF}=2$ Hz), 8.8 (1H, br.), 11.0 (1H, br.). *Anal.* Calcd for $C_4H_4FN_2O_3$: C, 26.32; H, 2.21; N, 15.35. Found: C, 26.40; H, 2.06; N, 15.29

5-Fluoro-6-hydroxy-5-methoxycarbonyl-5,6-dihydrouracil (13a)——A suspension of **6a** (15.04 g, 80 mmol) in H_2O (400 ml) was treated with 1.95 eq of F_2 (25% v/v) at room temperature with vigorous stirring. The reaction mixture was chilled in an ice bath and neutralized with $CaCO_3$ (15.6 g). Insoluble substances were filtered off after addition of $NaHSO_3$ (5.2 g) and the filtrate was evaporated to dryness *in vacuo*, giving a white powder (23.7 g). The crude product was chromatographed on silica gel (solv.: acetone/$CHCl_3$=1/3 v/v), affording 13.00 g (77%) of **13a** as colorless needles. mp 171—172°C. PMR: 3.80 (3H, s), 4.90 (1H, m; after addition of D_2O, d, $J_{HF}=4$ Hz), 7.13 (1H, d, $J=5$ Hz), 8.53 (1H, br.). 10.85 (1H, br.). *Anal.* Calcd for $C_6H_7FN_2O_5$: C, 34.96; H, 3.42; N, 13.59. Found: C, 35.07; H, 3.41; N, 13.58.

5-Ethoxycarbonyl-5-fluoro-6-hydroxy-5,6-dihydrouracil (13c)——A suspension of **6b** (920 mg, 5 mmol) in H_2O (200 ml) was fluorinated and treated as described in the case of **13a**. The crude product was recrystallized from MeOH–$CHCl_3$–hexane, giving 561 mg (51%) of **13c** as colorless prisms. mp 163—165°C. PMR: 1.22 (3H, t, $J=7$ Hz), 4.28 (2H, q, $J=7$ Hz), 4.93 (1H, dd, $J_{HF}=3$ Hz, $J=5$ Hz; after addition of D_2O, d, $J_{HF}=3$ Hz), 6.3 (1H, br.), 8.48 (1H, br.), 10.80 (1H, br.). *Anal.* Calcd for $C_7H_9FN_2O_5$: C, 38.19; H, 4.12; N, 12.73. Found: C, 37.90; H, 3.94; N, 12.87.

5-Fluoro-6-hydroxy-5,6-dihydrouracil-5-carboxamide (16)——A suspension of **14** (1.55 g, 10 mmol) in H_2O (200 ml) was fluorinated and the reaction mixture was treated in the manner described above, giving 0.74 g (39%) of **16** as fine needles. mp 188—189°C (dec. from acetone–$CHCl_3$). PMR: 4.86 (1H, m), 6.82 (1H, d, $J=5$ Hz), 7.75 (1H, br.), 7.93 (1H, br.), 8.48 (1H, br.), 10.63 (1H, br.). *Anal.* Calcd for $C_5H_6FN_3O_4$: C, 31.42; H, 3.16; N, 21.99. Found: C, 31.25; H, 3.21; N, 22.09.

5-Fluoro-6-hydroxy-5,6-dihydrouracil-5-carbonitrile (18)——A suspension of **17** (2.05 g, 15 mmol) in 150 ml of H_2O was treated with 4.5 eq of F_2 and the reaction mixture was treated as above, giving 1.86 g (72%) of **18** as fine needles. mp 158—160°C (dec.). PMR: 5.35 (1H, m), 7.75 (1H, br.), 9.00 (1H, br.), 11.40 (1H, br.). *Anal.* Calcd for $C_5H_4FN_3O_3$: C, 34.69; H, 2.33; N, 24.27. Found: C, 34.39; H, 2.27; N, 24.16.

Hydrolysis of 13a, 16, and 18 under Acidic Conditions giving 1a (Yield of 1a was determined by the UV Method——a) A solution of **13a** (23.15 mg) in 5 ml of 1N HCl was heated under reflux for 1 h, giving 98% yiled of **1a**.

b) A solution of **16** (23.05 mg) in 5 ml of conc. HCl was heated under reflux for 6.5 h, giving 57% yield of **1a**.

c) A solution of **18** (17.85 mg) in 5 ml of conc. HCl was heated under reflux for 6.5 h, giving 71% yield of **1a**.

5-Fluoro-6-hydroxy-5,6-dihydrouracil (3)——A suspension of **2a** (1.12 g, 10 mmol) in H_2O (150 ml) was treated with 1.6 eq of F_2 ($F_2/N_2=25\%$) at room temperature. After addition of $CaCO_3$ (3.0 g) and $NaHSO_3$ (1.0 g) to the reaction mixture, precipitates were filtered off. The filtrate was evaporated to dryness *in vacuo*, giving a pale yellow solid (1.8 g). It was chromatographed on silica gel (solv.: $CHCl_3$/MeOH=8/1 v/v), giving 0.71 g of a white solid that was recrystallized from MeOH to provide 0.62 g (42%) of **3** as colorless prisms. mp 177—178°C (dec.). PMR: 4.95 (1H, m), 5.35 (1H, dd, $J_{HF}=43$ Hz, $J=4$ Hz), 6.62 (1H, d, $J=4$ Hz), 8.43 (1H, br.), 10.42 (1H, br.). *Anal.* Calcd for $C_4H_5FN_2O_3$: C, 32.44; H, 3.40; N, 18.92. Found: C, 32.30; H, 3.29; N, 18.96.

A solution of **3** (148 mg, 1 mmol) in 1N NaOH (10 ml) was allowed to stand at room temperature for 3 h, giving 36% yield of **1a** (determined by the UV method).

A mixture obtained from the fluorination of **2a** (1.12 g, 10 mmol) in H_2O (150 ml) was divided into two portions, one of which was heated at 95°C for 2.5 h (yielding 3% of **1a**), then at 100°C for 15 h (giving 9% yield of **1a**). The other portion was treated similarly after addition of $NaHSO_3$ (1.2 g) and conc. HCl (8 ml), providing **1a** in 20% and 57% yields after the same reaction periods, respectively.

1-(2-Tetrahydrofuryl)-5-methoxycarbonyluracil (22a) and 1-(2-Tetrahydrofuryl)-5-ethoxycarbonyluracil (22b)——The title compounds were prepared according to the method reported by Nomura *et al.*[11] **22a**: mp 191—193°C ($CHCl_3$–hexane). PMR: 1.8—2.4 (4H, m), 3.73 (3H, s), 3.8—4.4 (2H, m), 5.93 (1H, m), 8.18 (1H, s), 11.50 (1H, br.). *Anal.* Calcd for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.04; N, 11.66. Found: C, C, 50.29; H, 4.99; N, 11.48. UV $\lambda_{max}^{pH\ 7.0}$ nm: 278. **22b**: PMR: 1.30 (3H, t, $J=7$ Hz), 1.8—2.5 (4H, m),

3.8—4.4 (2H, m), 4.24 (2H, q, J=7 Hz), 5.93 (1H, m), 8.23 (1H, s), 11.55 (1H, br.).

5-Fluoro-1-(2-tetrahydrofuryl)-6-hydroxy-5-methoxycarbonyl-5,6-dihydrouracil (23a)——A suspension of **22a** (0.98 g, 4.1 mmol) in 200 ml of H_2O was treated with 4 eq of F_2 (F_2/N_2=25%) at room temperature. The mixture was treated with $CaCO_3$ (2.0 g) and $NaHSO_3$ (2.1 g), and a precipitate was filtered off. The filtrate was evaporated to dryness *in vacuo* giving a yellow syrup. The crude products were chromatographed on silica gel (solv.: $CHCl_3$/MeOH=100/1 v/v), giving a white solid that was recrystallized from acetone–$CHCl_3$–hexane to provide 0.49 g (43%) of **23a** as colorless prisms. mp 165—170°C. PMR: 1.7—2.2 (4H, m), 3.75 (3H, s), 3.82 (2H, br.), 5.0—5.2 (1H, m; after addition of D_2O, d, J_{HF}=3.5 Hz), 7.28 and 7.33 (1H, d, J=5 Hz), 11.08 (1H, br.). The sample was a mixture of the geometrical isomers of **23a**. *Anal.* Calcd for $C_{10}H_{13}FN_2O_6$: C, 43.48; H, 4.74; N, 10.14. Found: C, 43.45; H, 4.63; N, 10.02.

6-Acetoxy-5-fluoro-1-(2-tetrahydrofuryl)-5-methoxycarbonyl-5,6-dihydrouracil (23b)——A solution of **22a** (1.20 g, 5 mmol) in 200 ml of glacial acetic acid was treated with 2.3 eq of F_2 (F_2/N_2=15%) with vigorous stirring at room temperature. The reaction mixture was evaporated to dryness, giving **23a** as a colorless syrup. PMR ($CDCl_3$): 2.07 (4H, m), 2.17 (3H, s), 3.92 (3H, s, and 2H, m), 5.90 (1H, m), 6.67 (1H, d, J_{HF}= 2 Hz), 9.40 (1H, br.).

1-(2-Tetrahydrofuryl)-5-fluorouracil (1b)——a) **23a** (30 mg, 0.11 mmol) was added to a chilled mixture of 15 ml of H_2O and 1 ml of CF_3COOH, and the whole was allowed to stand in a refrigerator for 46 d. The progress of the hydrolysis of **23a** was followed by the UV method to determine the yield of **1b** (29%, 58%, 73%, and 84% after 10, 21, 30, and 46 d, respectively).

b) A solution of **23b** (590 mg, 1.9 mmol) in 1N NaOH (40 ml) was allowed to stand at room temperature for 1 h and then the mixture was neutralized with AcOH. The yield of **1b** determined by the UV method was 63%.

c) A solution of **22a** (2.40 g, 10 mmol) in 200 ml of AcOH was treated with 1.7 eq of F_2 (F_2/N_2=15%) at room temperature, and the reaction mixture was concentrated *in vacuo*, giving a syrup that was treated with 200 ml of 1N NaOH for 1 h at room temperature. The whole mixture was then neutralized by careful addition of conc. HCl with cooling in an ice bath. The yield of **1b** was 62%. The reaction mixture was passed through a column of activated carbon (40 g), and the column was eluted with MeOH. The eluate was evaporated to dryness *in vacuo*, giving 1.40 g of a white solid that was found to be a mixture of **1a** and **1b** by TLC. The mixture was passed through a column of XAD-2 resin and the column was washed with H_2O to remove **1a** (12%), then, **1b** was eluted with a mixture of H_2O and EtOH (5/1 v/v). Removal of the solvent *in vacuo* gave a white solid that was recrystallized from EtOH–hexane, giving 0.84 g (42%) of **1b** as colorless prisms. mp 172—173°C. UV $\lambda_{max}^{pH\ 7.0}$ nm: 271. PMR: 2.07 (4H, m), 3.7—4.5 (2H, m), 5.93 (1H, m), 7.80 (1H, d, J_{HF}=7 Hz), 11.77 (1H, br.). *Anal.* Calcd for $C_8H_9FN_2O_3$: C, 48.00; H, 4.53; N, 14.00. Found: C, 48.12; H, 4.43; N, 13.92.

d) A solution of **22b** (0.94 g, 3.7 mmol) in 150 ml of AcOH was treated with 2.0 eq of F_2 (F_2/N_2=15%), and the mixture was treated as in c), giving 59% of **1b** (by the UV method).

e) A solution of **23a** (54.25 g, 0.20 mmol) in 10 ml of 1N NaOH was allowed to stand at room temperature for 1 h, then neutralized with conc. HCl. The UV spectrum of the reaction mixture showed only an end absorption.

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References and Notes

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