Fluorinated Heterocyclic Compounds. 2. 2,4-Difluoro and 4-Amino-2-fluoropyrimidines, Nucleoside Base Analogs

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Nucleoside base analogs in which fluoro substituents replace the enolic hydroxy groups of uracil, thymine and cytosine have been prepared. Improved methods for the preparation and isolation of the known 2,4-difluoropyrimidine, 2,4-difluoro-6-methylpyrimidine and the new 2,4-difluoro-5-methylpyrimidine, 2-fluoro-4-aminopyrimidine, 4-fluoro-2-aminopyrimidine, and other alkylaminofluoropyrimidines are described.

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As outlined in the previous article [1], the possibility of preparing analogs of nucleoside bases in which the *enolic* hydroxy group of pyridone or pyrimidone was replaced by the closely related fluoro group was explored and 4-fluoro-2-pyridone, a deaza analog of uracil in which the 4-hydroxy group of 4-hydroxy-2-pyridone was replaced by a fluoro substituent, was prepared. In this paper we describe the synthesis of fluoro analogs of the nucleoside bases, uracil (**1**), thymine (**2**), isocytosine (**3a**), cytosine (**3b**) and some related substances. If one regards the structures of

1 R = H 3a R = NH_2, R' = OH

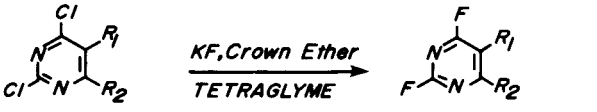
2 R = CH_3 b R = OH, R' = NH_2

Figure 1

1-3 in their enolic form we see from considerations previously discussed [1] that complete replacement of the hydroxy groups by fluoro substituents can give us potential analogs of the common nucleoside bases, which may have potential as antitumor drugs.

Treatment of 2,4-dichloropyrimidine (**4**), 2,4-dichloro-6-methylpyrimidine (**5**) and 2,4-dichloro-5-methylpyrimidine (**6**) with anhydrous potassium fluoride (KF) in tetraglyme and a catalytic amount of dicyclohexano-18-crown-6 [2] at 150-160° [3] for 6 hours gave in high yields the corresponding fluorinated compounds, 2,4-difluoropyrimidine (**7**) [4], 2,4-difluoro-6-methylpyrimidine (**8**) [5], and the unknown 2,4-difluoro-5-methylpyrimidine (**9**) as shown in Scheme I. Previous procedures for these displacement reactions used sealed tubes in an autoclave at 300° [4a] or dimethylformamide (DMF) [5] as solvent. In the former case **7** was obtained in 70% yield but using silver fluoride and in addition difficulties were experienced in separating the volatile **7** from the ether extracting solvent. In the latter example **8** was difficult to separate from DMF. Using tetraglyme (bp 275-276°) as solvent it was possible to distill the more volatile products directly out of the reaction mixtures uncontaminated by *any* solvent. High yields of **7-9** on large scale reactions can readily be obtained. Compounds **7-9** were characterized by spectroscopic methods. The nmr spectra of **8**, however, exhibits a coupling constant $J_{5,4F}$ = 2 Hz while **9** shows $J_{6,4F}$ = 12 Hz. This phenomena whereby the *meta* coupling constant between H and F is larger than the *ortho* coupling constant in heterocyclic nitrogen base compounds such as 2-fluoropyridine ($J_{3,F}$ = 2 Hz, $J_{4,F}$ = 7.5 Hz) has been recorded [6]. On the other hand the *meta* coupling constant through nitrogen, $J_{6,F}$, in 2-fluoropyridine and in **7-9** is <2 Hz.

SCHEME I



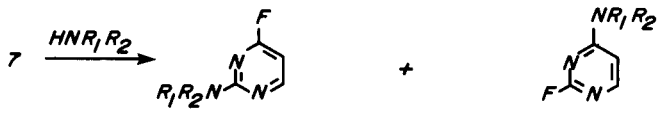
4, R_1 = R_2 = H 7, R_1 = R_2 = H

5, R_1 = H; R_2 = CH_3 8, R_1 = H; R_2 = CH_3

6, R_1 = CH_3; R_2 = H 9, R_1 = CH_3; R_2 = H

Having synthesized **7** and **9** which can be regarded as analogs of **1** and **2** respectively, we were interested in preparing 2-amino-4-fluoropyrimidine (**10a**) and 4-amino-2-fluoropyrimidine (**11a**), fluoro analogs of **3a** and **3b**. Surprisingly, both **10a** and **11a** were unknown despite the fact that some *5 and 6-substituted* 2-amino-4-fluoropyrimidines and 4-amino-2-fluoropyrimidines were known [5,7]. Our facile synthesis of **7** in large quantities allowed us to make the parent fluorinated analogs of **3a** and **3b**, **10a** and **11a** and a large variety of alkylaminofluoropyrimidines, unsubstituted at the 5 or 6 positions as shown in Scheme II. Thus, treatment of **7** with ammonia gas dissolved in ethanol and yielded after column chromatography on silica gel 16% of **10a** and 66% of **11a**. The reactions of **7** in *hex-*

SCHEME II



10a, $R_1 = R_2 = H$
b, $R_1 = R_2 = CH(CH_3)_2$
c, $R_1 = H$; $R_2 = (CH_2)_2CH_3$
d, $R_1 = H$; $R_2 = CH(CH_3)CH_2CH_3$
e, $R_1 = H$; $R_2 = (CH_2)_2N(C_2H_5)_2$

11a, $R_1 = R_2 = H$
b, $R_1 = R_2 = CH(CH_3)_2$
c, $R_1 = H$; $R_2 = (CH_2)_2CH_3$
d, $R_1 = H$; $R_2 = CH(CH_3)CH_2CH_3$
e, $R_1 = H$; $R_2 = (CH_2)_2N(C_2H_5)_2$

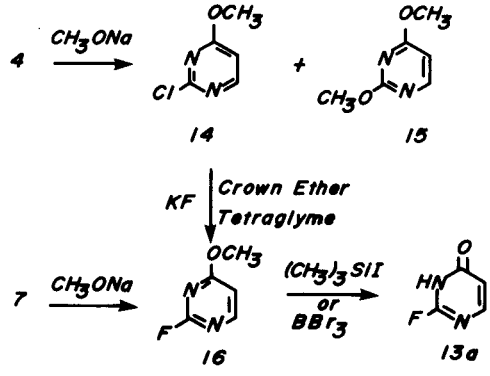
ane gave, with diisopropylamine, 2-diisopropylamino-4-fluoropyrimidine (**10b**) and 4-diisopropylamino-2-fluoropyrimidine (**11b**); with propylamine, 4-fluoro-2-propylaminopyrimidine (**10c**) and 2-fluoro-4-propylaminopyrimidine (**11c**); with *sec*-butylamine, 2-*sec*-butylamino-4-fluoropyrimidine (**10d**) and 4-*sec*-butylamino-2-fluoropyrimidine (**11d**); and with *N,N*-diethylethylenediamine, 2-*N,N*-diethylethylenediamino-4-fluoropyrimidine (**10e**) and 4-*N,N*-diethylethylenediamino-2-fluoropyrimidine (**11e**).

In all cases the amines displaced the 4-fluoro substituent preferentially to the 2-fluoro group of **7** and the ratios of **10a-e** to **11a-e** formed varied from 1:4 to 1:2.5. Mixtures of the corresponding two isomers of **10** and **11** could be easily separated by column chromatography on silica gel without degradation or hydrolysis. In the separation of **10c** from **11c**, some 2,4-di(propylamino)pyrimidine (**12**) was isolated.

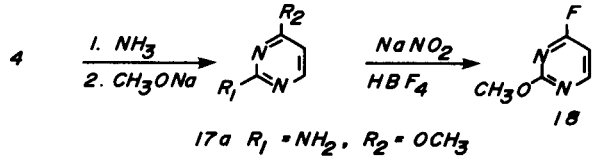
Since we had prepared 4-fluoro-2-pyridone [1], a fluorodeaza analog of uracil (**1**), it seemed reasonable to attempt the preparation of the more closely related fluoro analogs of **1**, 2-fluoro-4-pyrimidone (**13a**) and 4-fluoro-2-pyrimidone (**13b**). Treatment of **4** with sodium methoxide in methanol yielded 2-chloro-4-methoxypyrimidine (**14**). In the preparation of **14** some 2,4-dimethoxypyrimidine was also isolated. The displacement of the 2-chloro group of **14** with KF proceeded as before except that higher reaction temperatures (190-200°) and longer times (14 hours) wer required to give the desired 2-fluoro-4-methoxypyrimidine (**16**). Compound **16** was also prepared by direct displacement of **7** with sodium methoxide (Scheme III). Attempts to cleave the methyl ether linkage of **16** as before using trimethylsilyl iodide [8] or boron tribromide [10] to give **13a** failed, although 75-85% of **16** was consumed. Uracil (**1**) was detected in the crude reaction mixture.

Treatment of **4** with ammonia gas in methanol and subsequent reaction of the crude mixture with sodium methoxide gave a mixture of 4-amino-2-methoxypyrimidine (**17b**) and 2-amino-4-methoxypyrimidine (**17a**). Diazotization of **17b** with sodium nitrite followed by treatment with tetrafluoroboric acid [10] yielded 4-fluoro-2-methoxypyrimidine (**18**) in only 10% isolated yield (Scheme IV) [11,12].

SCHEME III



SCHEME IV



17a $R_1 = NH_2$, $R_2 = OCH_3$
b $R_1 = OCH_3$, $R_2 = NH_2$

We have shown that fluorinated analogs of uracil (**1**), thymine (**2**), isocytosine (**3a**) and cytosine (**3b**) in which all of the enolic hydroxy groups have been replaced by fluoro substituents as in **7**, **9**, **10**, and **11** are readily prepared but that compounds such as **13a** and **13b** in which only one of two enolic hydroxy groups have been replaced by fluoro substituents still eludes us. Compounds **7-11** are undergoing biological testing as antitumor agents.

EXPERIMENTAL

Nuclear magnetic resonance (nmr) spectra for protons were recorded on a Varian EM 360 spectrometer; nmr spectra for carbon were recorded on a Varian FT-80A spectrometer at 20 MHz using deuteriochloroform as solvent and tetramethylsilane as the internal standard. Fluorine-19 nmr spectra were obtained on a Bruker WP 60 FT nmr spectrometer operating at 56.45 MHz in the quad detection mode using 30° pulses (1.3 μ sec) and no time delay between acquisition of the 8K FIDs. The chemical shifts are recorded in ppm upfield from fluorotrichloromethane. Infrared spectra (ir) were recorded on a Unicam SP 1000 IR spectrophotometer as Nujol films between sodium chloride discs. Vapour phase chromatographic (vpc) analyses for **7-9** were performed using a 30 m × 0.25 i.d. column coated with CBW. Analysis (vpc) of **10a-e** and **11a-e** were done using a 15 m × 0.25 i.d. column coated with CAM and vpc analysis on **16** and **18** were done using a 15 m × 0.25 mm i.d. column coated with DB-5. All columns had a film thickness of 0.25 μ. The temperature conditions were programmed so that the column was held at 70-120° for 1-2 minutes and then heated to 180-200° at a rate of 6-8°/minute. Computer acquired mass spectral data were recorded through a VG2025 data system interfaced to the gcms system at an ionizing energy of 70 eV in the EI mode at an ion source temperature of 200° and a scan rate of 1.5 second per decade. Solvents were removed on a rotary evaporator, unless otherwise specified. Silica gel was used for all thin and preparative layer chromatography (tlc) and column chromatography. All melting and boiling points are uncorrected. Microanalysis were performed by Dr. C. Daesslé, Montreal, Quebec.

2,4-Difluoropyrimidine (**7**).

To a stirred solution of 7.45 g (0.05 mole) of 2,4-dichloropyrimidine (**4**) (Aldrich Chemical Co.) in 20 ml of tetraglyme (tetraethylene glycol dimethyl ether) was added 0.3 g of dicyclohexano-18-crown-6 and 12-18 g (0.2-0.3 mole) of finely ground anhydrous potassium fluoride. The slurry was heated at 150° under argon for 6-12 hours. An efficient Davies type condenser was used to ensure that the volatile product did not escape from the reaction mixture. After the reaction was completed the condenser was changed to a 15 cm Vigreux column and direct distillation *in vacuo* from the reaction flask, heated to 40-60°, gave in the receiver flask, cooled with a dry ice acetone bath, 4.8 g (82% yield) of 2,4-difluoropyrimidine (**7**) as a clear colourless liquid, bp 20-22° (1-2 torr) (68-70° (135 torr) [4a]) (53° (45 torr [4b]); ^{1}H nmr (deuteriochloroform): δ 7.09 (ddd, $J_{5,2F} = J_{5,4F} = 2.0$ Hz, $J_{5,6} = 6.0$ Hz, 1 H, H-5), 8.72 (d, dd, $J_{6,2F} = 2.0$ Hz, $J_{6,4F} = 12.0$ Hz, $J_{5,6} = 6.0$ Hz, 1 H, H-6). Analysis (vpc) showed the product to be >99% pure. In the absence of water pure **7** was stable and could be kept at room temperature for months without decomposition.

2,4-Difluoro-6-methylpyrimidine (**8**).

In a manner similar to that described for the preparation of **7**, 2,4-dichloro-6-methylpyrimidine (**5**) (Aldrich Chemical Co.) was converted to 2,4-difluoro-6-methylpyrimidine (**8**) [13] in 85% yield (>99% pure by vpc) as a colourless liquid: bp 27-28° (1-2 torr) (145° [5]); ^{1}H-nmr (deuteriochloroform): δ 2.64 (s, 3 H, CH_3), 6.80 (t, $J_{5,2F} = J_{5,4F} = 2.0$ Hz, 1 H, H-5).

2,4-Difluoro-5-methylpyrimidine (**9**).

In a manner similar to that described for the preparation of **7**, 2,4-dichloro-5-methylpyrimidine (**6**) was converted in 85% yield to 2,4-difluoro-5-methylpyrimidine (**9**) [13] as a colourless oil, bp 27-28° (1-2 torr); ^{1}H-nmr (deuteriochloroform): δ 2.34 (s, 3 H, CH_3), 8.40 (dd, $J_{6,2F} = 2.0$ Hz, $J_{6,4F} = 12.0$ Hz, 1 H, H-6); ms: (70 eV), m/e (relative intensity) 130 (M^+, 100), 103 (39), 90 (15), 65 (63).

Anal. Calcd. for $C_5H_4F_2N_2$: C, 46.15; H, 3.10; F, 29.21; N, 21.54. Found: C, 46.20; H, 3.29; F, 29.00; N, 21.37.

Analysis (vpc-ms) of **9** showed **9** to be 97.5% pure, containing 1% chlorofluoropyrimidines and 1.4% of **6**.

2-Amino-4-fluoropyrimidine (**10a**) and 4-Amino-2-fluoropyrimidine (**11a**).

To a stirred solution of 6.4 g (0.055 mole) of **7** in 15 ml of absolute ethanol, kept below 0°, was added 35 ml of a solution of ammonia gas in ethanol at −50 to −30°. The absolute ethanol (35 ml) contained 6 g of ammonia (10*M*). The solution was stirred for 1-1.5 hours at 25-30°. The solvent was evaporated using the rotary evaporator and the white crystalline product (8 g) was separated by column chromatography on silica gel.

Elution with dry ether yielded, after recrystallization from ether-hexane, 1.1 g (16%) of **10a**, mp 158° [14]; uv (methanol): λ max 228 nm (log ε 4.17), 287 nm (log ε 3.49); ^{1}H nmr (DMSO-d_6): δ 6.28 (dd, $J_{5,6} = 7.0$ Hz, $J_{5,F} = 1.7$ Hz, 1 H, H-5), 6.68 (br s, 2 H, NH_2), 8.34 (dd, $J_{6,5} = 7.0$ Hz, $J_{6,F} = 12.3$ Hz, 1 H, H-6); ^{13}C nmr (DMSO-d_6): 93.90 (d, $J_{5,F} = 29$ Hz, C-5), 162.62 (C-6), 164.07 (d, $J_{2,F} = 15$ Hz, C-2), 169.73 (d, $J_{4,F} = 246$ Hz, C-4); ^{19}F nmr (DMSO-d_6): 61.23 (dd, $J_{F,5} = 3$ Hz, $J_{F,6} = 12$ Hz); ms: (70 eV), m/e (relative intensity) 113 (M^+, 100), 86 (78), 67 (44), 41 (63).

Anal. Calcd. for $C_4H_4FN_3$: C, 42.15; H, 3.55; F, 16.80; N, 37.15. Found: C, 42.48; H, 3.56; F, 16.60; N, 36.96.

Further elution with dry ether yielded some fractions containing 0.6 g (9%) of two components by tlc (ether as eluant). Elution with 1:50 to 1:10 absolute methanol:dry ether gave after recrystallization from methanol-ether 4.0 g (66%) of **11a**, mp 212° [14]; uv (methanol): λ max 228 nm (log ε 4.05), 269 nm (log ε 3.74); ^{1}H nmr (DMSO-d_6): δ 6.44 (dd, $J_{5,6} = 5.0$ Hz, $J_{5,F} = 4.5$ Hz, 1 H, H-5), 7.18 (br s, 2 H, NH_2), 8.03 (dd, $J_{6,5} = 5.5$ Hz, $J_{6,F} = 2.0$ Hz, 1 H, H-6); ^{13}C nmr (DMSO-d_6): 103.43 (C-5), 157.40 (C-6), 163.03 (d, $J_{2,F} = 208$ Hz, C-2), 167.20 (d, $J_{4,F} = 17$ Hz, C-4); ^{19}F nmr (DMSO-d_6): δ 46.18 (br s); ms: (70 eV), m/e (relative intensity) 113 (M^+, 100), 86 (26), 67 (17), 41 (21).

Anal. Calcd. for $C_4H_4FN_3$: C, 42.15; H, 3.55; F, 16.80; N, 37.15. Found: C, 42.15; H, 3.68; F, 17.05; N, 36.88.

2-Diisopropylamino-4-fluoropyrimidine (**10b**) and 4-Diisopropylamino-2-fluoropyrimidine (**11b**).

To a solution of 2.9 g (0.025 mole) of **7** in 25 ml of dry hexane was added 5.05 g (0.05 mole) of diisopropylamine. The reaction mixture was stirred at 22-25° for 4 hours and finally at 70-80° overnight. The solvent was evaporated *in vauo* and the crude product was separated by column chromatography using 200 g of silica gel. Elution with dichloromethane:hexane (1:1) yielded an oil which on distillation in a Kugelrohr apparatus gave 1.0 g (20%) of **10b**, bp 80-85° (0.01 torr); uv (methanol): λ max 247 nm (log ε 4.32), 306 nm (log ε 3.40); ^{1}H nmr (deuteriochloroform): δ 1.31 (d, J = 6.0 Hz, 12 H, CH_3), 4.80 (septet, J = 6.0 Hz, 2 H, CH), 6.06 (dd $J_{5,6} = 5.0$ Hz, $J_{5,F} = 1.5$ Hz, 1 H, H-5), 8.28 (dd, $J_{6,5} = 4.5$ Hz, $J_{6,F} = 12.0$ Hz, 1 H, H-6); ms: (70 eV), m/e (relative intensity) 197 (M^+, 32), 182 (58), 154 (72), 140 (100), 70 (36), 41 (72).

Anal. Calcd. for $C_{10}H_{16}FN_3$: C, 60.88; H, 8.17; F, 9.63; N, 21.30. Found: C, 60.78; H, 8.07; F, 9.68; N, 21.56.

Further elution with ether yielded in the middle fractions 0.8 g of a mixture of two components (tlc, ether eluant). Elution with methanol:ether (1:20) gave 2.5 g (53%) of **11b**, mp 57-58°; uv (methanol): λ max 244 nm (log ε 4.35), 284 nm (log ε 4.06); ^{1}H nmr (deuteriochloroform): δ 1.10 (d, J = 6.0 Hz, 12 H, CH_3), 4.3 (septet, J = 6.0 Hz, 2 H, CH), 6.35 (dd, $J_{5,6} = 5.5$ Hz, $J_{5,F} = 4.5$ Hz, 1 H, H-5), 8.00 (dd, $J_{6,5} = 5.5$ Hz, $J_{6,F} = 2.0$ Hz, 1 H, H-6); ms: (70 eV), m/e (relative intensity) 197 (21), 182 (39), 154 (70), 140 (100), 70 (21), 41 (54).

Anal. Calcd. for $C_{10}H_{16}FN_3$: C, 60.88; H, 8.17; F, 9.63; N, 21.30. Found: C, 60.75; H, 8.10; F, 9.87; N, 21.45.

2-Fluoro-4-propylaminopyrimidine (**10c**) and 4-Fluoro-2-propylaminopyrimidine (**11c**).

To 1.8 g (0.015 mole) of **7** in 25 ml of dry hexane was added 1.8 g (0.03 mole) of *n*-propylamine at 0-20°. Only this reaction among those used for the preparation of **10b-e** and **11b-e** proved to be very exothermic. The mixture was stirred at room temperature for an additional 1.5 hours. Analysis by tlc exhibited two new spots using hexane:ether (1:1) as eluant and no remaining **7**. The reaction was worked up as for **10b** and **11b**. Chromatography on silica gel and elution with hexane:ether (1:1) yielded 1.3 g (fraction 1) of a mixture of two isomers. Further elution with dry ether yielded 0.68 g pure component (fraction 2) and finally elution with

absolute methanol:ether (1:9) gave 0.5 g of fraction 3. Flash chromatography [15] of fraction 1 using ether as eluant yielded 0.2 g (10%) of **10c** as an oil; uv (methanol): λ max 238 nm (log ε 4.21), 297 nm (log ε 3.49); ^{1}H nmr (deuteriochloroform): δ 0.9 (t, J = 8 Hz, 3 H, CH_3), 1.4-1.9 (m, 2 H, CH_2), 3.30 (m, 2 H, CH_2), 5.68 (br, 1 H, NH), 6.1 (dd, $J_{5,6}$ = 7 Hz, $J_{5,F}$ = 1.7 Hz, 1 H, H-5), 8.22 (dd, $J_{6,5}$ = 7 Hz, $J_{6,F}$ = 12, 3 Hz, 1 H, H-6); ms: (70 eV), m/e (relative intensity) 155 (M^+, 51), 126 (100), 97 (43), 70 (33), 41 (30).

Further elution with ether gave 1.0 g of a substance identical with fraction 2 above for a total yield of 69% of **11c**, mp 56-57°; uv (methanol): λ max 238 nm (log ε 4.14), 277 nm (log ε 3.77); ^{1}H nmr (deuteriochloroform): δ 0.9 (t, J = 8 Hz, 3 H, CH_3), 1.4-1.9 (m, 2 H, CH_2), 3.31 (m, 2 H, CH_2N), 6.22 (dd, $J_{5,6}$ = 5.5 Hz, $J_{5,F}$ = 4.5 Hz, 1 H, H-5), 6.68 (br 1 H, NH), 8.00 (dd, $J_{6,5}$ = 5.5 Hz, $J_{6,F}$ = 2 Hz, 1 H, H-6); ms: (70 eV), m/e (relative intensity) 155 (M^+, 57), 126 (100), 97 (43), 70 (33), 41 (30).

Anal. Calcd. for $C_7H_{10}FN_2$: C, 54.18; H, 6.49; F, 12.24; N, 27.08. Found: C, 54.30; H, 6.69; F, 12.41; N, 27.01.

Fraction 3 was distilled in a Kugelrohr distillation apparatus to give **12** as a colorless oil, bp 160-170° (0.02 torr); uv (methanol): λ max 227 nm (log ε 4.59), 290 nm (log ε 4.06); ^{1}H nmr (deuteriochloroform): δ 0.9 (t, J = 8 Hz, 3 H, CH_3), 1.1 (t, J = 8 Hz, 3 H, CH_3), 1.4-1.9 (m, 4 H, CH_2), 3.31 (m, 4 H, CH_2N), 5.8 (d, J = 6.0 Hz, 1 H, H-5), 6.2 (br s, 2 H, NH), 7.78 (d, J = 6.0 Hz, 1 H, 6-H); ms: (70 eV), m/e (relative intensity) 194 (M^+, 50), 165 (100), 137 (33), 110 (67), 78 (11), 39 (53).

Anal. Calcd. for $C_{10}H_{18}N_4$: C, 61.82; H, 9.34; N, 28.84. Found: C, 61.62; H, 9.53; N, 28.66.

2-*sec*-Butylamino-4-fluoropyrimidine (**10d**) and 4-*sec*-Butylamino-2-fluoropyrimidine (**11d**).

In a manner similar to that described for **10c** and **11c**, 2.32 g (0.02 mole) of **7** reacted with 2.9 g of *sec*-butylamine to give a mixture of two components which on column chromatography and elution with ether yielded 0.5 g (15%) of **10d** as a colorless liquid: bp 80-85° (0.01 torr); uv (methanol): λ max 238 nm (log ε 4.26), 292 nm (log ε 3.58); ^{1}H nmr (deuteriochloroform): δ 0.9 (t, J = 8 Hz, 3 H, CH_3), 1.25 (d, J = 8 Hz, 3 H, CH_3), 1.4-1.9 (m, 2 H, CH_2), 3.82 (m, 1 H, CH), 5.74 (br 1 H, NH), 6.26 (dd, $J_{5,6}$ = 7 Hz, $J_{5,F}$ = 1.7 Hz, 1 H, H-5), 8.28 (1 H, dd, $J_{6,5}$ = 7 Hz, $J_{6,F}$ = 12 Hz, 1 H, H-6); ms: (70 eV), m/e (relative intensity) 169 (50), 154 (60), 140 (100), 113 (18), 92 (10), 70 (10), 41 (38).

Anal. Calcd. for $C_8H_{12}FN_3$: C, 56.78; H, 7.15; F, 11.23; N, 24.83. Found: C, 56.83; H, 7.03; F, 11.27; N, 24.48.

Further elution with methanol:ether (1:50) gave 1.7 g (50%) of **11d** as a clear oil: bp 105-110° (0.01 torr); uv (methanol): λ max 238 nm (log ε 4.06), 277 nm (log ε 3.72); ^{1}H nmr (deuteriochloroform): δ 0.9 (t, J = 8 Hz, 3 H, CH_3), 1.25 (d, J = 8 Hz, 3H, CH_3), 1.4-1.9 (m, 2 H, CH_2), 4.01 (m, 1 H, CH), 5.70 (br, 1 H, NH), 6.11 (dd, $J_{5,6}$ = 5.5 Hz, $J_{5,F}$ = 4.5 Hz, 1 H, H-5), 8.0 (dd, $J_{5,6}$ = 5.5 Hz, $J_{6,F}$ = 2 Hz, 1 H, H-6); ms: (70 eV), m/e (relative intensity) 169 (57), 154 (66), 140 (100), 113 (23), 92 (14), 70 (14), 41 (41).

Anal. Calcd. for $C_8H_{12}FN_3$: C, 56.78; H, 7.15; F, 11.23; N, 24.83. Found: C, 56.80; H, 7.42; F, 11.27; N, 24.75.

2-*N,N*-Diethylethylenediamino-4-fluoropyrimidine (**10e**) and 4-*N,N*-Diethylethylenediamino-2-fluoropyrimidine (**11e**).

By the procedure similar to the describe above for **10d** and **11d**, compounds **10e** and **11e** were prepared as colorless oils. Thus **10e** was obtained in 16% yield; bp 90-100° (0.01 torr); uv (methanol): λ max 238 nm (log ε 4.26), 292 nm (log ε 3.46); ^{1}H nmr (deuteriochloroform): δ 1.01 (t, J = 8 Hz, 6 H, CH_3), 2.26 (m, 6 H, CH_2N), 3.2-3.6 (m, 2 H, CH_2NH), 5.90 (br s, 1 H, NH), 6.19 (dd, $J_{5,6}$ = 5.5 Hz, $J_{5,F}$ = 1.5 Hz, 1 H, H-5), 8.31 (dd, $J_{6,5}$ = 5.5 Hz, $J_{6,F}$ = 12 Hz, 1 H, H-6); ms: (70 eV), m/e (relative intensity) 212 (M^+, 2), 140 (87), 86 (100), 58 (12).

Anal. Calcd. for $C_{10}H_{17}FN_4$: C, 56.58; H, 8.07; F, 8.95; N, 26.39. Found: C, 56.83; H, 8.45; F, 9.11; N, 26.10.

Compound **11e** was isolated in 60% yield: bp 120-130° (0.01 torr); uv (methanol): λ max 238 nm (log ε 4.10), 277 nm (log ε 3.73); ^{1}H nmr (deuteriochloroform): δ 1.03 (t, J = 8 Hz, 6 H, CH_3), 2.64 (m, 6 H, CH_2N), 3.6-3.2 (m, 2 H, CH_2NH), 6.2-6.45 (m, 2 H, H-5 and NH), 8.05 (dd, $J_{6,5}$ = 5.5 Hz, $J_{6,F}$ = 2 Hz, 1 H, H-6); ms: (70 eV), m/e (relative intensity) 212 (M^+, 4), 140 (76), 86 (100), 58 (15).

Anal. Calcd. for $C_{10}H_{17}FN_4$: C, 56.58; H, 8.07; F, 8.95; N, 26.39. Found: C, 56.44; H, 8.33; F, 8.75; N, 26.53.

2-Fluoro-4-methoxypyrimidine (**16**). Method A.

A mixture of 1.44 g (0.01 mole) of 2-chloro-4-methoxypyrimidine (**14**) [16], 0.01 g of dicyclohexano-18-crown-6 and 2.32 g (0.04 mole) of anhydrous potassium fluoride in 10 ml of tetraglyme was heated under argon for 14 hours at 190-200° and then cooled to room temperature. Vacuum distillation using a Vigreux column gave 0.7 g (55%) of **16** (>99% pure by vpc), bp 28-30°, 10 torr (76-79° (135 torr) [4a]); ^{13}C nmr (deuteriochloroform): 54.75 (OCH_3), 106.51 (C-5), 159.82 (d, $J_{6,F}$ = 12 Hz, C-6), 162.80 (d, $J_{2,F}$ = 217 Hz, C-2), 173.31 (d, $J_{4,F}$ = 12 Hz, C-4).

Method B.

A solution fo sodium methoxide in absolute methanol was prepared using 0.4 g (0.02 mole) of sodium. The methanol was evaporated *in vacuo* and 10 ml of tetraglyme was added to form a slurry. To the slurry at 0° was added 2.32 g (0.02 mole) of **7** in 10 ml of tetraglyme at 0°. The mixture was stirred at 0° for 4-5 hours. Vacuum distillation of the reaction mixture yielded in the 1st fraction 1.55 g (60%) of a colorless oil, bp 20-40° (10 torr). Analysis (vpc) of the 1st fraction showed that it contained **7** (10%) and **16** (90%). The second fraction yielded a mixture of **16** (15%) and 2,4-dimethoxypyrimidine (**15**). Fractional distillation of the 1st faction gave **7** in the forerun, bp 20° (10 torr) and 1.2 g (45%) of pure **16** identical to that prepared by Method A.

4-Fluoro-2-methoxypyrimidine (**18**).

To a solution of 1.25 g (0.01 mole) of 4-amino-2-methoxypyrimidine (**17b**) [17] in 10 ml of 48% fluoroboric acid at −8 to −5° was added 1.2 g (0.017 mole) of sodium nitrite. The mixture was kept at 0° for 30 minutes, removed from the ice bath during which the temperature quickly rose to 33°, and finally stirred for 1 hour. The mixture was cooled to −15° and 3*N* sodium hydroxide at 0° was added until the solution was neutral. The mixture was extracted with ether and dried over potassium fluoride. Distillation yielded 0.13 g of pure **18** in 10% yield as a colorless oil; bp 25-26° (10 torr) 65-66° (135 torr) [19]); ms: (70 eV), m/e (relative intensity) 142 (M^+, 16), 128 (68), 127 (21), 98 (100), 71 (53).

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[2] Dibenzo-18-crown-6 or no catalyst gives lower yields.

[3] Reactions conducted at lower temperatures using **4** as a test substrate yielded mixtures of 2-chloro-4-fluoropyrimidine and 4-chloro-2-fluoropyrimidine as shown by vpc-ms analysis but these pyrimidines were not further characterized.

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[11] Diazotization followed by treatment with hexafluorophosphoric acid yielded only 2-methoxy-4-pyrimidone. The formation, however, of 2-methoxy-4-pyrimidone suggested to us that direct diazotization of **10a** may give us **13**. The only product isolated from such preliminary experiments was **1**.

[12] The low yield of **18** precluded studies aimed at the cleavage of the methyl ether of **18** to give the desired **13**.

[13] Both **8** and **9** but not **7** suffered some decomposition on storage.

[14] Before melting **10a** exhibited crystal deformation at 138°. Compound **11a** showed similar behaviour at 158°.

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