Aromatic Fluorine Compounds. X. The 2,3- and 2,6-Difluoropyridines[1]

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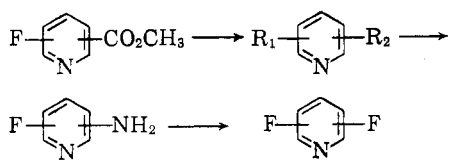
The preparation of difluoropyridines by the Schiemann reaction was investigated. 2-Amino-6-fluoropyridine (IIIa), necessary for the synthesis of 2,6-difluoropyridine (IVa) by the Schiemann reaction, was conveniently prepared by the Curtius degradation of 6-fluoropicolinic hydrazide (IIa) and by the Hofmann reaction on 6-fluoropicolinamide (IId). Since an α-fluorine on a pyridine nucleus is preferentially replaced by hydrazine when it is either adjacent to or opposite a carbomethoxy group, the hydrazides necessary for the synthesis of 3-amino-2- and 6-fluoropyridine could not be prepared. These amines were prepared from the appropriate 2-fluoropyridinecarboxamide by the Hofmann reaction. The preparation of difluoropyridines was successful with two of the aminofluoropyridines and led to the following new compounds: 2,3-difluoro- (IVb) and 2,6-difluoropyridine (IVa).

The chemistry of nuclear fluorinated pyridines has been limited to the monofluoropyridines,[6] their derivatives,[6] and pentafluoropyridine.[7] As information on the other polyfluoropyridines was needed, our attention was directed to the difluoropyridines. This communication describes the preparation of 2,6-difluoropyridine (IVa),[8] 2,3-difluoropyridine (IVb), and the attempted synthesis of 2,5-difluoropyridine.

The reaction scheme selected for the synthesis of 2,6-difluoropyridine (IVa), based on a related reaction sequence originally used to prepare 2-amino-6-chloropyridine,[9] is outlined as illustrated. The



Ia. 6-F, 2-CO_2CH_3
b. 2-F, 3-CO_2CH_3
c. 6-F, 3-CO_2CH_3

IIa. 6-F, 2-CON_2H_3
b. 2-N_2H_3, 3-CO_2CH_3
c. 6-N_2H_3, 3-CO_2CH_3
d. 6-F, 2-$CONH_2$
e. 2-F, 3-$CONH_2$
f. 6-F, 3-$CONH_2$

IIIa. 6-F, 2-NH_2
b. 2-F, 3-NH_2
c. 6-F, 3-NH_2

IVa. 2-F, 6-F
b. 2-F, 3-F

advantages of this method lie in the fact that it employs standard laboratory procedures and readily available starting materials. Methyl 6-fluoropicolinate (Ia) was treated with hydrazine to give 6-fluoropicolinic hydrazide (IIa). Only equimolecular amounts of the ester and hydrazine should be used because excess hydrazine replaces the fluorine to give 6-hydrazinopicolinic hydrazide. Diazotization of 6-fluoropicolinic hydrazide and decomposition of the resulting azide in 50% aqueous acetic acid in a Curtius reaction[9,10] gave a low yield of 2-amino-6-fluoropyridine (IIIa). The low yield was most likely due to the hydrolysis of the α-fluorine under prolonged exposure to acid during the decomposition of the azide. The fact that fluorine atoms adjacent to aromatic ring nitrogens are easily hydrolyzed in acid solution[11] lends support to this conclusion. This facile hydrolysis is further illustrated with 6-fluoropicolinic acid which was hydrolyzed to 6-carboxy-2-pyridone when heated under reflux with water. Apparently the ionization of 6-fluoropicolinic acid in water produces a concentration of hydrogen ions sufficient to catalyze the hydrolysis of the fluorine, for under similar conditions 6-fluoro-2-picoline remains unchanged. It also was found that methyl 6-fluoropicolinate and 6-fluoropicolinic hydrazide are inert to the action of hot methanol. Hydrolysis of 2-halopyridines in mild acid conditions appears to be peculiar to fluorine, for 6-chloropicolinic acid was recovered unchanged after heating under reflux with water.[12] It is interesting to note that 6-fluoropicolinic acid is relatively stable in aqueous potassium hydroxide,[13] and sodium methoxide is needed to replace the fluorine of methyl 6-fluoropicolinate.

An improved method for the preparation of 2-

(1) The Curtius reaction route was done by G. C. F. and L. D. S. at the I. S. G. S. laboratories, and the Hofmann route was done by A. R. and W. J. L. at the University of North Carolina.

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(5) Abstracted in part from the M.A. dissertation of William J. Link, University of North Carolina, August, 1953. Present address, Sun Oil Co., Marcus Hook, Pa.

(6) A comprehensive review of halogenated pyridines, including the monofluoropyridines, is given by H. E. Mertel in "The Chemistry of Heterocyclic Compounds," Vol. 14, Pt. 2, E. Klingsberg, ed., Interscience Publishers, Inc., New York, N. Y., 1961, pp. 299–419.

(7) M. Stacey and J. C. Tatlow, *Nature*, **186**, 231 (1960); R. N. Haszeldine, *et al.*, *Proc. Chem. Soc.*, 211 (1960).

(8) A preliminary note on this work was published in *Nature*, **191**, 595 (1961).

(9) M. P. Cava and N. K. Bhattacharyya, *J. Org. Chem.*, **23**, 1287 (1958).

(10) P. A. S. Smith, "Organic Reactions," Vol. III, R. Adams, ed., John Wiley & Sons, Inc., New York, N. Y., 1946, p. 379.

(11) W. K. Miller, S. B. Knight, and A. Roe, *J. Am. Chem. Soc.*, **72**, 4765 (1950).

(12) R. R. Bishop, E. A. S. Cavell, and N. B. Chapman [*J. Chem. Soc.*, 437 (1952)] have found it necessary to heat 2,6-dibromopyridine for 6 hr. at 160° in 70% sulfuric acid to effect acid hydrolysis of only one bromine to give 6-bromo-2-pyridone.

(13) In the permanganate oxidation of 6-fluoro-2-picoline to 6-fluoropicolinic acid [A. Roe, P. H. Cheek, and G. F. Hawkins, *J. Am. Chem. Soc.*, **71**, 4152 (1949)], one mole of potassium hydroxide is produced for each mole of potassium 6-fluoropicolinate. This potassium salt was exposed to the potassium hydroxide at reflux temperatures for an extended period of time without excessive decomposition.

amino-6-fluoropyridine (IIIa) involved the inverse addition of the reagents in the diazotization step. 6-Fluoropicolinic azide, which resulted from the addition of hydrochloric acid to a stirred slurry of ether, sodium nitrite, and 6-fluoropicolinic hydrazide (IIa) in water, was decomposed in warm chloroform to give 6-fluoropicolinic isocyanate. This was subsequently hydrolyzed as before in 50% aqueous acetic acid, giving 2-amino-6-fluoropyridine (IIIa). This compound also can be prepared by treatment of 6-fluoropicolinamide (IId) with potassium hypobromite under Hofmann conditions.

Subsequent diazotization of 2-amino-6-fluoropyridine (IIIa) in fluoboric acid via the Schiemann reaction gave 2,6-difluoropyridine (IVa) in a 27% yield.

2,6-Difluoropyridine, b.p. 124.5° (743 mm.), is a colorless, exceptionally volatile liquid with a pronounced pyridine-like odor. It forms neither an isolable hydrochloride in ethereal hydrogen chloride nor a picrate in ethanol. However, titration against 0.01 *N* hydrochloric acid provided evidence that 2,6-difluoropyridine is a weak base. By contrast, pentafluoropyridine has been reported to be neutral.[7]

An attempt to prepare the hydrazides of methyl 2-fluoro- and 6-fluoronicotinate failed and prevented the preparation of 3-amino-2-fluoropyridine and 3-amino-6-fluoropyridine by the Curtius method. In both methyl 2-fluoronicotinate (Ib) and methyl 6-fluoronicotinate (Ic), where a carbomethoxy group is either adjacent to or opposite an α-fluorine on the pyridine ring, fluorine is preferentially replaced by hydrazine, giving not the anticipated hydrazide, but methyl 2-hydrazinonicotinate (IIb) and methyl 6-hydrazinonicotinate (IIc). The unlikely possibility that the latter two compounds were the isomeric 2-methoxypicolinic hydrazide and 6-methoxypicolinic hydrazide was ruled out by the synthesis of these compounds from the corresponding methyl 2- (and 6-) methoxypicolinates. It has been reported, also, that hydrazine reacts with methyl 2-fluorobenzoate to give the expected 2-fluorobenzoic hydrazide.[14] Therefore, a carbomethoxy group adjacent to or opposite an α-fluorine in a pyridine ring causes sufficient activation of the fluorine for replacement with hydrazine.

The action of hypobromite on 2-fluoronicotinamide (IIe) and 6-fluoronicotinamide (IIf) provided a synthetic route for the preparation of 3-amino-2-fluoropyridine (IIIb) and 3-amino-6-fluoropyridine (IIIc). Subsequent diazotization of 3-amino-2-fluoropyridine with ethyl nitrite in fluoboric acid gave 2,3-difluoropyridine (IVb) in low (20%) yield. All attempts to prepare solid derivatives of 2,3-difluoropyridine with ethereal hydrogen chloride, methyl iodide, picric acid, and 2,4,7-trinitrofluorenone were unsuccessful. All attempts to prepare 2,5-difluoropyridine by diazotization of IIIc in fluoboric acid failed.

(14) E. L. Bennett and C. Niemann, *J. Am. Chem. Soc.*, **72**, 1800 (1950).

Experimental[15,16]

6-Fluoropicolinic Hydrazide (IIa).—Hydrazine (12.3 g., 0.39 mole) dissolved in methanol (120 ml.) was added dropwise at 0° to a stirred solution of methyl 6-fluoropicolinate[17] (60.0 g., 0.39 mole) in methanol (240 ml.) during a 30-min. period. The mixture was heated under reflux for 30 min., cooled to 0°, and the precipitated hydrazide was collected and washed with cold methanol. Additional hydrazide was obtained from the filtrate and washings. 6-Fluoropicolinic hydrazide was obtained as white needles; yield, 51.2 g. (85.4%), m.p. 120–122°. Recrystallization from methanol gave the pure hydrazide, m.p. 120.5–121.5°.

Anal. Calcd. for $C_6H_6FN_3O$: C, 46.45; H, 3.90; N, 27.08. Found: C, 46.68; H, 4.02; N, 27.15.

6-Hydrazinopicolinic Hydrazide.—A mixture of 6-fluoropicolinic hydrazide (1.0 g., 6.4 mmoles), absolute ethanol (15 ml.) and hydrazine (1.5 g., 46.8 mmoles) was heated under reflux for 1 hr. The mixture was evaporated to give tan needles (1.6 g.) which were recrystallized from ethanol to give off-white needles of 6-hydrazinopicolinic hydrazide; yield, 0.88 g. (82%), m.p. 194–195°. Two more recrystallizations from ethanol raised the melting point to 198–199°.

Anal. Calcd. for $C_6H_9N_5O$: C, 43.11; H, 5.43; N, 41.89. Found: C, 43.13; H, 5.58; N, 41.89.

Methyl 6-Methoxypicolinate.—Methyl 6-fluoropicolinate[17] (10.0 g., 65 mmoles) was added to sodium methoxide (3.5 g., 65 mmoles, prepared from 1.5 g. of sodium) in methanol (50 ml.). The solution was heated under reflux for 8.5 hr. and then evaporated. The remaining oil was treated with cold petroleum ether which gave a solid phase and a petroleum ether extract. The extract was evaporated and the resulting residue was treated as before with cold petroleum ether giving an additional solid phase and another petroleum ether extract. Repetition of this procedure gave several solid fractions that were combined and sublimed (45–50°, 0.1 mm.) to give a colorless sublimate of methyl 6-methoxypicolinate; yield, 8.1 g. (75%), m.p. 37–39°. Recrystallization from petroleum ether did not change the melting point.

Anal. Calcd. for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.75; H, 5.36; N, 8.08.

6-Carboxy-2-pyridone.—6-Fluoropicolinic acid[17] (10.0 g., 71 mmoles) was heated under reflux with water (25 ml.) for 8 hr. The mixture was cooled and the colorless 6-carboxy-2-pyridone was collected and dried; yield, 9.7 g. (98%), m.p. 264.5° (cor.) (lit.,[18] m.p. 267°). Recrystallization from water raised the melting point to 268.8–269.3° (cor.).

6-Chloropicolinic acid was recovered (88%) unchanged after heating under reflux in water for 18.5 hr. At no time did the mixture give a precipitate with silver nitrate solution after acidification with nitric acid. This indicates that hydrolysis of the chlorine was negligible.

2-Amino-6-fluoropyridine (IIIa).—*N* Hydrochloric acid (170 ml.) was added to a slurry of sodium nitrite (12.0 g., 0.17 mole), 6-fluoropicolinic hydrazide (20.0 g., 0.13 mole), water (200 ml.), and ether (100 ml.) over a 45-min. period at −2 to +1°. Stirring was continued for 30 min. at this temperature. Additional ether was added as needed. The ether layer was decanted and the aqueous layer was extracted twice with ether. The combined ether layers were dried over magnesium sulfate and filtered. Chloroform (100 ml.) was added and the stirred solution was evaporated on a

(15) Unless otherwise specified, all boiling points and melting points are uncorrected.

(16) Analysis in part by W. J. Link, and the remainder along with infrared spectra by D. R. Dickerson, Illinois State Geological Survey.

(17) A. Roe, P. H. Cheek, and G. F. Hawkins, *J. Am. Chem. Soc.*, **71**, 4152 (1949).

(18) H. Ost, *J. prakt. Chem.*, [2] **27**, 289 (1883).

water bath until only a chloroform solution remained. This solution was heated under reflux for 2 hr. and then evaporated, leaving the crude isocyanate (average about 18 g.). This was heated on a steam bath with 50% aqueous acetic acid (280 ml.) for 1 hr. The precipitated solid (3.6 g.) was removed and the filtrate was treated with Norit, filtered, and cooled. The pH was adjusted to 7 with 20% aqueous sodium hydroxide, keeping the temperature less than 10°. The neutralized solution was extracted three times with chloroform. The organic layers were combined, dried over magnesium sulfate, and evaporated. Sublimation (45°, 0.1 mm.) of the residue gave 2-amino-6-fluoropyridine; yield, 7.2 g. (50%), m.p. 53–54.5°. Similar material (2.6 g.) from another preparation was recrystallized from petroleum ether and chloroform to give colorless plates of pure 2-amino-6-fluoropyridine (2.1 g., m.p. 58–59°).

Anal. Calcd. for $C_5H_5FN_2$: C, 53.57; H, 4.50; N, 24.99. Found: C, 53.59; H, 4.32; N, 24.87.

The 2-amino-6-fluoropyridine was prepared also in a 53% yield by the Hofmann hypobromite method as described for 2-fluoro-3-aminopyridine except that the product was collected by filtration.

6-Fluoro-2-pyridylphenylthiourea, prepared from the amine and phenyl isothiocyanate[19a] was recrystallized from ethanol; m.p. 192–193°.

Anal. Calcd. for $C_{12}H_{10}FN_3S$: N, 16.99. Found: N, 16.75.

2,6-Difluoropyridine (IVa).—Sodium nitrite (10.2 g., 0.15 mole) was added in small portions to a stirred mixture of 2-amino-6-fluoropyridine (10.0 g., 89 mmoles) and 50% fluoroboric acid (65 ml.) at −8 to −10° during 1 hr. The green mixture was stirred for 30 min. at 0°, heated to 50°, cooled, poured onto ice, neutralized with sodium carbonate, and subjected to steam distillation. The steam distillate (500 ml. which contained 3 ml. of colorless oil) was extracted three times with ether. The combined ether extracts were dried with magnesium sulfate, evaporated, and the residue (5.5 g.) was distilled to give three fractions of 2,6-difluoropyridine as a colorless oil; total yield, 2.75 g. (27%), b.p. 122–124.5° (743 mm.), $n^{25}D$ 1.4338–1.4349. A center cut, b.p. 124.5°, $n^{25}D$ 1.4349, was used for an analytical sample.

Anal. Calcd. for $C_5H_3F_2N$: C, 52.18; H, 2.63; N, 12.17. Found: C, 52.15; H, 2.59; N, 12.06.[20]

The infrared spectrum of the pure liquid showed absorptions at 1493 cm.$^{-1}$ and a double maximum at 1607 and 1592 cm.$^{-1}$. Additional absorptions were found at 3110, 1447, 1308, 1232, 993, and 717 cm.$^{-1}$.

A differential plot of the data obtained by a potentiometric titration of 2,6-difluoropyridine in 50% aqueous ethanol against 0.011 *N* hydrochloric acid showed an end point at approximately pH 5.

Methyl 2-Fluoronicotinate (Ib).—Excess diazomethane in ether was added to a cold mixture of 2-fluoronicotinic acid[21] (20.0 g., 0.14 mole) in ether (500 ml.). Evaporation of the mixture and distillation of the remaining oil gave methyl 2-fluoronicotinate; yield, 21.2 g. (96%), b.p. 103–104° (10 mm.), $n^{25}D$ 1.4979.[22] Redistillation of this material gave an analytical sample; b.p. 101° (10 mm.), $n^{25}D$ 1.4979.

Anal. Calcd. for $C_7H_6FNO_2$: C, 54.19; H, 3.90; N, 9.03. Found: C, 54.43; H, 3.85; N, 9.11.

Methyl 2-Hydrazinonicotinate (IIb).—Hydrazine (2.1 g., 65 mmoles) in anhydrous ethanol (15 ml.) was added dropwise to methyl 2-fluoronicotinate (10.0 g., 65 mmoles) in ethanol (40 ml.) at 0°. The mixture was evaporated under diminished pressure at room temperature. The residue (4.8 g.) was recrystallized twice from methanol to give near-white needles of methyl 2-hydrazinonicotinate; yield, 1.3 g. (10%), m.p. 106–106.5°. During the recrystallization it was found necessary to keep the solvent temperature less than 40° to avoid excessive decomposition.

Anal. Calcd. for $C_7H_9N_3O_2$: C, 50.29; H, 5.43; N, 25.14. Found: C, 50.36; H, 5.45; N, 25.39.

2-Methoxynicotinic Hydrazide.—Methyl 2-fluoronicotinate (6.0 g., 39 mmoles) in methanol (20 ml.) was added dropwise to a stirred solution of sodium methoxide (2.1 g., 39 mmoles, prepared from 0.9 g. of sodium) in methanol (30 ml.) at 0°. The mixture was heated under reflux for 2 hr. and then cooled in an ice bath. Hydrazine (1.25 g., 39 mmoles) in methanol (12.5 ml.) was added dropwise and the mixture was heated under reflux for 30 min. The solvent was evaporated and the residue (8.0 g.) was recrystallized twice from methanol, Norit being used to give near-white prisms of 2-methoxynicotinic hydrazide; yield, 3.3 g. (51%), m.p. 137–139°. Another recrystallization from methanol raised the melting point to 138.5–140°.

Anal. Calcd. for $C_7H_9N_3O_2$: C, 50.29; H, 5.43; N, 25.14. Found: C, 50.23; H, 5.40; N, 25.20.

3-Amino-2-fluoropyridine (IIIb).—This compound was prepared by the Hofmann reaction[23] on 2-fluoronicotinamide (IIe).

Bromine (14 ml., 0.26 mole) was added at 0° to a solution of potassium hydroxide (77 g., 1.37 moles) dissolved in water (460 ml.). 2-Fluoronicotinamide[21] (32 g., 0.2 mole) was added at 10° and stirring was continued at ice bath temperature until all of the amide had dissolved. After the solution had been heated to 75–80° for 15–20 min., which produced a color change from yellow to dark red, it was cooled to 0°, acidified with acetic acid, made basic with dilute potassium hydroxide, and continually extracted with ether for 2 days. Evaporation of the ether, after drying, left a liquid which was distilled to give 3-amino-2-fluoropyridine; yield, 23.9 g. (87%), b.p. 116–117° (24 mm.), $n^{25}D$ 1.5518.

Anal. Calcd. for $C_5H_5FN_2$: N, 24.99. Found: N, 24.87; F, positive by calcium chloride test.[19b]

A monohydrochloride, prepared by saturating a solution of the amine in anhydrous ether with dry hydrogen chloride, was dried *in vacuo*: m.p. 187–188° dec.

Anal. Calcd. for $C_5H_6ClFN_2$: N, 18.86. Found: N, 18.93.

2,3-Difluoropyridine (IVb).—2-Fluoro-3-aminopyridine (4.8 g., 43 mmoles) was dissolved in a mixture of 40% fluoboric acid (20.1 ml.) and absolute ethanol (40 ml.). This solution was stirred mechanically and cooled to −5° by means of a Dry Ice–acetone bath. Ethyl nitrite was introduced into this cold solution for 30 min. Upon addition of absolute ethanol (30 ml.) and anhydrous ether (40 ml.) and subsequent cooling to Dry Ice–acetone temperature, precipitation occurred. The light yellow precipitate was filtered through a chilled Büchner funnel, washed twice with cold absolute ethanol and twice with cold anhydrous ether. The salt was sucked as dry as possible on the Büchner funnel, during which time the shade of yellow darkened. The salt was transferred rapidly to a round-bottomed flask equipped with a reflux condenser and was thermally decomposed by heating with a small luminous flame. After decomposition appeared complete, dilute sodium hydroxide was added and the mixture was steam distilled. An oil was removed from the distillate, following saturation with sodium chloride, and purified in a micro-distillation apparatus; yield, 1 g. (20%), b.p. 118° (755 mm.), $n^{25}D$ 1.4420.

Anal. Calcd. for $C_5H_3F_2N$: N, 12.17. Found: N, 12.09.

Attempts to prepare the hydrochloride, methyl iodide, picrate, and 2,4,7-trinitrofluorenone derivatives all failed.

Methyl 6-Fluoronicotinate (Ic).—Diazomethane (10.5 g.,

(19) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd ed., John Wiley & Sons, Inc., New York, N. Y., 1948: (a) p. 179; (b) p. 57.

(20) A modified Dumas method was used for the nitrogen analysis.

(21) J. T. Minor, G. F. Hawkins, C. A. VanderWerf, and A. Roe, *J. Am. Chem. Soc.*, **71**, 1125 (1949).

(22) R. D. Beaty and W. K. R. Musgrave, *J. Chem. Soc.*, 3512 (1961), report a melting point of 74–75° for methyl 2-fluoronicotinate. All attempts to convert our material to a solid have failed.

(23) E. S. Wallis and J. F. Lane, "Organic Reactions," Vol. III, R. Adams, ed., John Wiley & Sons, Inc., New York, N.Y., 1946, p. 267.

0.25 mole) in ether (970 ml.) was added to a cooled solution of 6-fluoronicotinic acid[21] (35.1 g., 0.25 mole) in ether (1.5 l.). When the mixture became colorless, the ether was evaporated, and the remaining solid (36.4 g., 94% yield, m.p. 47–49.5°) was vacuum sublimed (50°, 0.1 mm.) to give methyl 6-fluoronicotinate; yield, 34.8 g. (90%), m.p. 49–50°. Recrystallization from petroleum ether and chloroform raised the melting point to 49.5–50.5°.

Anal. Calcd. for $C_7H_6FNO_2$: C, 54.19; H, 3.90; N, 9.03. Found: C, 53.98; H, 4.07; N, 9.21.

Methyl 6-Hydrazinonicotinate (IIc).—Anhydrous hydrazine (4.1 g., 0.13 mole) in methanol (40 ml.) was added dropwise during 40 min. to a stirred solution of methyl 6-fluoronicotinate (20.0 g., 0.13 mole) in methanol (80 ml.). The mixture was heated under reflux for 15 min., cooled, and the crude product (10.3 g., m.p. 134.5–136°) was collected and washed with cold methanol. An additional amount of product (10.6 g.) was obtained when the mother liquor was evaporated. The crude combined product was recrystallized from methanol, Norit being used to give white needles of methyl 6-hydrazinonicotinate; yield, 10.4 g. (48%), m.p. 138–139°.

Anal. Calcd. for $C_7H_9N_3O_2$: C, 50.29; H, 5.43; N, 25.14. Found: C, 50.18; H, 5.38; N, 25.08.

Methyl 6-Methoxynicotinate.—Methyl 6-fluoronicotinate (10.0 g., 64 mmoles) was added to sodium methoxide (8.1 g., 0.15 mole, prepared from 3.5 g. of sodium) in anhydrous methanol (50 ml.). The mixture was heated under reflux for 2 hr., cooled, and evaporated. The remaining solid was washed three times with hot carbon tetrachloride. These washings were combined and evaporated to give a white solid (8.3 g., m.p. 50–51°). This was vacuum sublimed (50°, 0.1 mm.) to give pure methyl 6-methoxynicotinate; yield, 7.1 g. (66%), m.p. 51–52°. Recrystallization from petroleum ether gave white plates, m.p. 51–51.8°.

Anal. Calcd. for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.21; H, 5.44; N, 8.37.

6-Methoxynicotinic Hydrazide.—Following the procedure used in the preparation of 6-fluoropicolinic hydrazide, hydrazine (1.0 g., 31 mmoles) in methanol (10 ml.) was added to methyl 6-methoxynicotinate (2.0 g., 12 mmoles) in methanol (20 ml.). Evaporation of this mixture gave the crude product (1.7 g.) which was recrystallized from methanol to give white micro needles of 6-methoxynicotinic hydrazide; yield, 0.93 g. (47%), m.p. 156.5–157.5°.

Anal. Calcd. for $C_7H_9N_3O_2$: C, 50.29; H, 5.43; N, 25.14. Found: C, 50.32; H, 5.34; N, 24.97.

3-Amino-6-fluoropyridine (IIIc).—Sodium hydroxide (6.6 g., 0.16 mole) was dissolved in water (80 ml.) and cooled to 0°, whereupon bromine (8.4 g., 52 mmoles) was added. 6-Fluoronicotinamide[21] (6 g., 40 mmoles) was added and the solution mechanically stirred for 15 min. at ice bath temperature. The ice bath then was replaced by a water bath at 75° and the solution was held at this temperature for 45 min. During the heating period a color change from yellow to dark red was observed.

The solution was allowed to cool to room temperature, acidified with acetic acid, and then made alkaline by addition of dilute sodium hydroxide. This solution was saturated with sodium chloride and continuously extracted with ether for 24 hr. in a liquid–liquid extractor. After the extract had been dried overnight, the ether was evaporated and a red residue was obtained (crude yield, 4 g.). Purification was effected by vacuum sublimation; yield 1.6 g. (35%), m.p. 87–87.5°.

Anal. Calcd. for $C_5H_5FN_2$: N, 24.99. Found: N, 24.96; F, positive by calcium chloride test.[19b]

3-Acetamido-6-fluoropyridine.—A small amount of 3-amino-6-fluoropyridine was dissolved in anhydrous ether. Ketene was bubbled through the solution for 30 min. without any noticeable effect. Removal of the ether gave a product which was recrystallized from water. When no crystals formed after the product had stood for 2 days, the solution was found to be acid to litmus. It was made basic and, after it had stood overnight in an ice bath, deposited long, white needles, m.p. 131–132°.

Anal. Calcd. for $C_7H_7FN_2O$: N, 18.18. Found: N, 18.38; F, positive by calcium chloride test.[19b]

Attempted Preparation of 2,5-Difluoropyridine.—All attempts to prepare 2,5-difluoropyridine from 2-fluoro-5-aminopyridine by methods identical to those previously described failed. On one trial, some apparent diazonium fluoborate was obtained and it appeared fairly stable, although the yield was rather poor. Thermal decomposition proceeded smoothly, but the product obtained from steam distillation was lost before it was characterized. Several more trials under the same conditions did not yield the diazonium fluoborate.

Reactions of Trihalogenated Esters with Triethylamine and Anions[1]

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The reactions of several trihalogenated esters with triethylamine were studied at room temperature. All the trihalogenated esters formed quaternary ammonium compounds with triethylamine. In the case of the trifluoro esters, the formation of N,N-diethyltrifluoroacetamide and an ether was a competing reaction. Amide formation was not observed for the tribromo and trichloro esters, at room temperature, but occurred with methyl thioltrichloroacetate. During this study, it was observed that methyl trichloroacetate behaved as an alkylating agent toward sodium phenoxide, while ethyl trifluoroacetate behaved as an acylating agent. A significant feature of this work is the alkylating ability of alkyl trichloroacetates, at room temperature. This property makes methyl trichloroacetate a potentially useful methylating agent to replace toxic compounds such as diazomethane or dimethyl sulfate.

Our interest in the reactions of primary and secondary amines with trihalogenated acetates[3] has led us to investigate the behavior of triethylamine with similar esters. The purpose of the present work was to determine the products formed when triethylamine reacted with some trihalogenated esters at room temperature.

(1) Abstracted in part from the Ph.D. dissertation of A. C. Pierce, University of Pennsylvania, 1962.

(2) Recipient of W. T. Taggart and E. F. Smith Memorial Scholarships, 1961–1962.

(3) (a) M. M. Joullié and A. R. Day, *J. Am. Chem. Soc.*, **76**, 2990 (1954); (b) M. M. Joullié, *ibid.*, **77**, 6662 (1955); (c) A. C. Pierce, Ph.D. dissertation, University of Pennsylvania, 1962.