Pyrimidines. 6.
6-Trifluoromethyl Chloropyrimidines and Related Compounds

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A study of the chlorination of 6-trifluoromethylpyrimidines was made. On sequential treatment of 6-trifluoromethyluracil (**6**) with phosphorus oxychloride and phosphorus pentachloride, 2,4-dichloro-6-trifluoromethylpyrimidine (**7**) (25%) and 4-chloro-6-trifluoromethylpyrimidin-2-yldichlorophosphate (**8**) (53%) were obtained. Compound **8** was converted to **7** by treatment with hydrogen chloride in phosphorus oxychloride in 72% yield. In a one-pot synthesis, 77% of **7** was obtained from **6**. The preparation of 2,4,5-trichloro-6-trifluoromethyluracil (**16**) proceeded similarly. Although the pyrimidinyldichlorophosphate ester has been proposed as the intermediate in converting a pyrimidinol to a chloropyrimidine, these are the first examples of such compounds to be isolated, characterized, and made to yield the ring-chlorinated pyrimidines.

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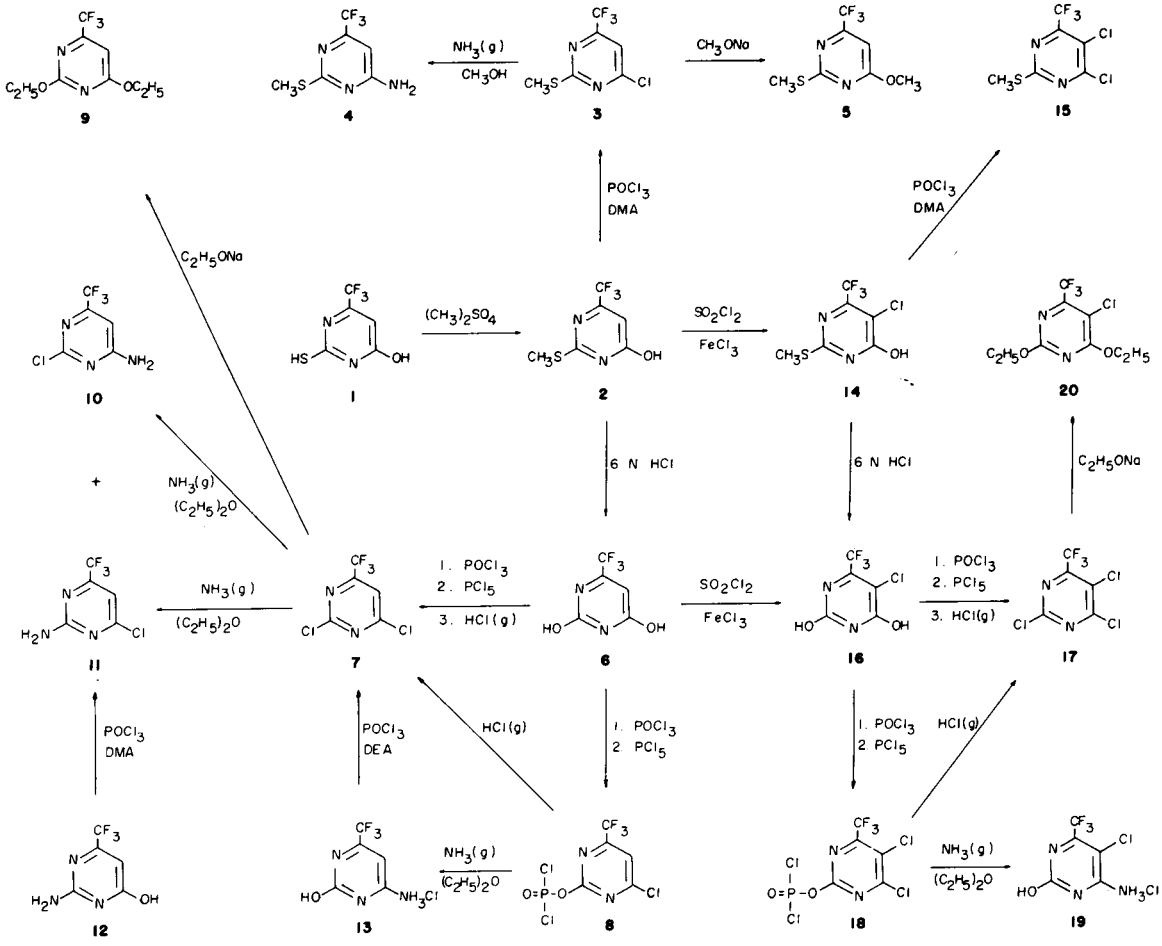
Ring-chlorinated pyrimidines were reported to exhibit antifungal activity (1-4). It was of interest to determine the effect of a trifluoromethyl group in the 6 position of the ring on fungitoxicity.

2,4-Dichloro-6-trifluoromethylpyrimidine had been reported previously (5). It was prepared from the corresponding uracil in 41% yield by heating with phosphorus oxychloride in the presence of dimethylaniline.

Scheme I



Earlier work (6,7) had shown that a series of 6 substituted ring chlorinated pyrimidines could be prepared in substantially higher yield by treatment with phosphorus oxychloride alone. An attempt was made to prepare 2,4-dichloro-6-trifluoromethylpyrimidine by prolonged heating with phosphorus oxychloride, but only minor amounts of product were obtained.

Phosphorus pentachloride in conjunction with phosphorus oxychloride was used successfully to prepare ring-chlorinated pyrimidines, but there was also the danger of *C*-chlorination in the 5 position (8). This method was employed successfully for the preparation of a number of such pyrimidines in good yield (6,9). The present work concerns an examination of the use of phosphorus pentachloride in conjunction with phosphorus oxychloride for the preparation of 2,4- and 2,4,5-chlorinated 6-trifluoromethylpyrimidines. A summary of the reactions carried out is depicted in Scheme I (10).

6-Trifluoromethyl-2-thiouracil (**1**) (11) was converted to the methylthio compound **2** which was subsequently hydrolyzed to 6-trifluoromethyluracil (**6**). Compound **6** was treated sequentially with phosphorus oxychloride and phosphorus pentachloride. Two products were obtained, 2,4-dichloro-6-trifluoromethylpyrimidine (**7**) in 25% yield and a compound which analyzed for chlorotrifluoromethylpyrimidinyldichlorophosphate in 56% yield. Upon treatment of this compound with ammonia gas in ether, another compound was obtained which had the elemental composition of an aminotrifluoromethylpyrimidinol hydrochloride. Its silylated derivative was distinct from that of 2-amino-6-trifluoromethylpyrimidin-4-ol (**12**) (12). Therefore, the pyrimidine obtained by ammonolysis was assigned structure **13** and the dichlorophosphate had structure **8**.

Compound **8** dissolved in phosphorus oxychloride was treated with gaseous hydrogen chloride. Product **7** was obtained in 72% yield. On carrying out the two steps in one pot, an overall yield of 77% of **7** resulted.

When ammonia gas was added to a solution of **7** in ether, a mixture of two products **A** (40%) and *B* (60%) was found, as determined by gas chromatography. The mass spectra of both products showed similar fragmentation patterns and parent peaks m/e 197, suggesting that they were isomers: 4-amino-2-chloro-6-trifluoromethylpyrimidine (**10**) and 2-amino-4-chloro-6-trifluoromethylpyrimidine (**11**). The properties of **A** coincided with those of a sample prepared by chlorinating (5) 2-amino-6-trifluoromethylpyrimidin-4-ol (**12**) (12). It was thus evident that **B** was the reverse isomer **10**. Upon heating **13** with phosphorus oxychloride in the presence of diethylaniline, 83% **7** resulted. It is apparent that the amino group in the 2 position is relatively stable, whereas the amino group in the 4 position is relatively labile.

The reactions with 5-chloro-6-trifluoromethyluracil (**16**) paralleled those with 6-trifluoromethyluracil (**6**). Compound **16** yielded the dichlorophosphate **18** on sequential chlorination with phosphorus oxychloride and phosphorus pentachloride. Compound **18** yielded 2,4,5-trichloro-6-trifluoromethylpyrimidin-2-ol hydrochloride (**19**) on ammonolysis in ether. The chlorine in the 5 position was stable to 48 hours refluxing with constant boiling hydrochloric acid and was not displaced by excess sodium ethoxide under reflux in ethanol for 48 hours, whereas the chlorines in the 2 and 4 positions were replaced by ethoxyl groups in **20**.

To our knowledge, no example of a pyrimidinyldichlorophosphate has been characterized. The stability of compounds **8** and **18** is the result of the low electron densities of the 2 positions due both to the resonance of the ring and the inductive effect of the trifluoromethyl group in position 6. These compounds were stable in sealed glass vials for over one year, as determined by gc and ir analyses.

The conversion of a hydroxyl function to a chloro functionality on a pyrimidine ring by phosphorus oxychloride is usually considered to proceed by rearrangement of the dichlorophosphoryl intermediate by an S_Ni mechanism. When treated with gaseous hydrogen chloride in phosphorus oxychloride solution, compounds **8** and **18** were converted to the chloro analogs **7** and **17**, respectively. It would appear that the chlorination proceeded by a bimolecular nucleophilic substitution mechanism.

Upon treatment of the dichlorophosphates **8** and **18** with gaseous ammonia in ether, the reaction appeared to go by a nucleophilic attack on the phosphorus. This must have been preceded by replacement of the chlorines attached to the phosphorus by amino groups.

When 2,4-dichloro-6-trifluoromethylpyrimidine was subjected to ammonolysis in ethereal ammonia, 40% of 2-amino-4-chloro-6-trifluoromethylpyrimidine and 60% of the reverse isomer were obtained. The results of comparable ammonolysis reactions with 2,4-dichloropyrimidine yielded 60% of 2-amino-4-chloropyrimidine and 40% of the isomer (13), and when treated similarly, 2,4-dichloro-6-methylpyrimidine yielded 28% of 2-amino-4-chloro-6-methylpyrimidine and 33% of 4-amino-6-chloro-6-methylpyrimidine (14). These results are consistent with the π electron distribution around the ring, as influenced by the substituent in the 6 position.

2,4,5-Trichloro-6-trifluoromethylpyrimidine (**17**) and 2,4-dichloro-6-trifluoromethylpyrimidine (**7**) afforded protection, respectively, against the fungi *Rhizoctonia solani* on cotton plants (90% at 6.3 lb/acre; none at 25 lb/acre), *Pythium sp.* on peas (90% at 6.3 lb/acre; 70% at 3.1 lb/acre), and *Thielaviopsis basicola* on mung bean (60% at 25 lb/acre; 100% at 6.3 lb/acre) (15). Details of these

studies will be published elsewhere.

EXPERIMENTAL

Infrared spectra were obtained with a Perkin-Elmer Model 221 spectrophotometer. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Ultraviolet spectra were gotten with a Cary Model 15 spectrophotometer, and refractive indices were taken with an Abbe-3L, B & L refractometer. The purity of samples and the course of reactions were established by gas chromatography which was performed on a Varian Aerograph Model 1200 gas chromatograph with a flame ionization detector to which is attached a Varian Model 20 recorder. The column employed was 5 feet × 1/8 inch o.d., packed with 3% Dexsil 400 on Anachrom A (90-100 mesh) purchased from Analabs, New Haven, CT. Nitrogen was used as the carrier gas. Gas chromatographic mass spectrometric results were obtained with a Hewlett-Packard 5985 gc/ms system using helium as the carrier gas, and the column employed was that described for gas chromatography.

6-Trifluoromethyl-2-thiouracil (**1**).

The title compound was prepared by condensing thiourea with ethyl 4,4,4-trifluoroacetoacetate in ethanol in the presence of sodium ethoxide according to Miller, *et al.*, (11). The yield of product was 83%, mp 242-243.5° (lit (11) mp 247-249°, yield 40%); uv (methanol): λ max 212.5 nm (ε 28085), 270 (32595); ir (potassium bromide): ν CF_3 1169 cm^{-1}.

2-Methylthio-6-trifluoromethylpyrimidin-4-ol (**2**).

6-Trifluoromethyl-2-thiouracil (11) (58.8 g, 0.3 mole) was added to 750 ml of water containing sodium hydroxide (60 g, 1.5 mole) with stirring. The solution was decolorized with Norit A, and dimethyl sulfate (37.8 g, 0.3 mole) was added over 1 hour. Stirring was continued for an additional 3 hours at room temperature, after which the solution was heated to near boiling for 5 minutes. Norit A was added again with stirring. After 0.5 hour, the mixture was filtered and brought to *p*H 1-2 with 12 *N* hydrochloric acid and refrigerated overnight. The product was removed by filtration, washed free of acid with water and dried at 80° overnight. The yield of compound was 59.5 g (87%), mp 176-177.5°. A pure sample was crystallized from 2-propanol, mp 179-180°, (lit (5) mp 181-182°, prepared by condensing *S*-methylisothiuronium sulfate wiuth ethyl 4,4,4-trifluoroacetoacetate); uv (methanol): λ max 226 nm (ε 6388), 296 (8552); ir (potassium bromide): ν CF_3 1160 cm^{-1}.

4-Chloro-2-methylthio-6-trifluoromethylpyrimidine (**3**).

The title compound was prepared from **2** by chlorination with phosphorus oxychloride in the presence of dimethylaniline as reported previously (5). The yield of product was 70%, bp 83.5° (9.3 mm) [lit (5) bp 105° (25 mm)]; n_D^{25} 1.5050; uv (acetonitrile): λ max 224 nm (ε 4106), 2.59 (16423), 305 (2053); ir (neat): ν CF_3 1153 cm^{-1}.

4-Amino-2-methylthio-6-trifluoromethylpyrimidine (**4**).

To a solution of about 20 g of ammonia in 100 ml of methanol at 0° was added compound **3** (11.5 g, 0.05 mole) with stirring. Stirring was continued for an additional 0.5 hour, and the mixture was kept at -15° for 4 hours. The solvent was removed under vacuum in a rotary evaporator, and the residue was slurried in acetone. The insoluble salts were removed by filtation, the acetone was removed under vacuum, and the residue was slurried twice in hexane. The yield of product was 6.0 g (60%), and the analytical sample was crystallized from isopropanol, mp 223-224°; uv (methanol): λ max 229 nm (ε 21716), 246 (106622), 295 (5547); ir (potassium bromide): ν CF_3 1146 cm^{-1}.

Anal. Calcd. for $C_6H_6N_3F_3S$: C, 34.47; H, 2.89; N, 20.11. Found: C, 34.71; H, 2.83; N, 20.04.

4-Methoxy-2-methylthio-6-trifluoromethylpyrimidine (**5**).

Compounds **3** (11.5 g, 0.05 mole) was added during 15 minutes to a solution of sodium (1.15 g 0.05 g-atom) in 100 ml of methanol with stirring at room temperature. Stirring was continued overnight. The solvent was evaporated under vacuum, and the residue was partitioned between methylene chloride and water. The organic layer was dried over sodium sulfate, and the solvent was removed under vacuum in a rotary evaporator. The residue was distilled, and the yield of product was 11.2 g (98%), bp 86.5-87.0° (7.2 mm). An analytical sample was crystallized from 2-propanol, mp 36-37°; uv (methanol): λ max 228 nm (ε 5430), 251 (13438), 284 (4168); ir (neat): ν CF_3 1155 cm^{-1}.

Anal. Calcd. for $C_7H_7N_2F_3OS$: C, 37.49; H, 3.15; N, 12.50. Found: C, 37.75; H, 3.25; N, 12.22.

6-Trifluoromethyluracil (**6**).

Compound **2** (84 g, 0.4 mole) was heated under reflux with stirring in 900 ml of 10% hydrochloric acid for 8 hours. After cooling, the crystalline product was removed by filtration, washed with 12 *N* hydrochloric acid, and dried at 80°. The yield of product was 57 g (79%), mp 229-230° [lit (12) mp 218-220°], prepared by hydrolysis of 2-carboxymethylthio-4-hydroxy-6-trifluoromethylpyrimidine with 6 *N* hydrochloric acid, uv (methanol): λ max 260 nm (ε 7505), 307 (390); ir (potassium bromide): ν CF_3 1163 cm^{-1}.

2,4-Dichloro-6-trifluoromethylpyrimidine (**7**).

A mixture of **6** (108 g, 0.6 mole) in 950 ml of phosphorus oxychloride was heated under reflux with stirring overnight. After cooling, phosphorus pentachloride (250 g, 1.2 mole) was added and heating and stirring were resumed overnight, until very little hydrogen chloride evolved. The phosphorus oxychloride was removed by atmospheric distillation, and the residue was distilled under vacuum. The product boiling at 30° (0.5 mm) was collected in 32.5 g (25%) yield as 2,4-dichloro-6-trifluoromethylpyrimidine. The spectral properties, uv (acetonitrile): λ max 262 nm (ε 5475); ir (neat): ν CF_3 1155 cm^{-1}; n_D^{25} 1.4638 were consistent with those of a sample prepared according to lit (5) yield 41%, bp 92° (65 mm), prepared from **6** with phosphorus oxychloride and dimethylaniline.

4-Chloro-6-trifluoromethylpyrimidin-2-yldichlorophosphate (**8**).

The residue from **7** was distilled further to yield 106.4 g (56%) of the title compound, bp 98-100.5° (0.5 mm). An analytical sample boiled at 118° (4.2 mm), n_D^{25} 1.4757; uv (acetonitrile): λ max 262 nm (ε 5475); ir (neat): ν CF_3 1172 cm^{-1}.

Anal. Calcd. for $C_5HN_2Cl_3F_3O_2P$: C, 19.04; H, 0.32; N, 8.88; Cl, 33.72; P, 9.82. Found: C, 18.93; H, 0.42; N, 8.92; Cl, 33.55; P, 9.88.

Conversion of **8** to **7**.

To 80 g (0.25 mole) of **8** dissolved in 800 ml of phosphorus oxychloride kept at 15-20° was added hydrogen chloride gas in a rapid stream with stirring over 2 hours. The mixture was allowed to come to room temperature with continued stirring overnight. The phosphorus oxychloride was removed by atmospheric distillation and the residue was poured onto a slurry of ice and water. The aqueous material was extracted with chloroform several times. The chloroform extract was washed with water, dried over sodium sulfate, and freed of chloroform in a vacuum rotary evaporator. On distillation, the residue yielded 38.9 g (72%) of **7**, bp 82° (0.5 mm).

Conversion of **6** to **7** in One Pot.

A mixture of **6** (36 g, 0.2 mole) and phosphorus oxychloride (360 ml) was heated with stirring under reflux overnight. To the cooled mixture was added phosphorus pentachloride (83.3 g, 0.4 mole) and heating with stirring was continued, until very little hydrogen chloride evolved. The mixture was worked up as for the conversion of **8** to **7**. The yield of product was 33.2 g (77%), bp 43-44° (1.5 mm).

4-Amino-6-trifluoromethylpyrimidin-2-ol Hydrochloride (**13**).

Compound **8** (15.8 g, 0.05 mole) dissolved in 200 ml of ether was subjected to a stream of gaseous ammonia at 5-10° with stirring. When no further heat of reaction was apparent, stirring was continued 2 hours longer, and the mixture was kept at -15° overnight. The inorganic salts were removed by filtration, and the ether was evaporated under a stream

of air. The residue weighed 7.5 g (70%) and decomposed over a wide range of temperature. An analytical sample was prepared by recrystallization of 1 g of material from a mixture of 30 ml of ether and 1.25 ml of methanol, mp 160° dec and 238-240° dec, successively; uv (methanol): λ max 230 nm (ε 10916), 307.5 (4153); ir (potassium bromide): ν CF_3 1152 cm^{-1}.

Anal. Calcd. for $C_5H_5N_3ClF_3O$: C, 27.86; H, 2.34; N, 19.49; Cl, 16.45. Found: C, 27.98; H, 2.52; N, 19.28; Cl, 16.44.

2,4-Diethoxy-6-trifluoromethylpyrimidine (**9**).

To a solution of sodium (4.6 g, 0.2 g-atom) in 460 ml of ethanol, **7** (21.7 g, 0.1 mole) was added dropwise with stirring at room temperature. After continued stirring overnight, the mixture was heated to boiling for 1 hour. The salts were removed by filtration, the alcohol evaporated under vacuum, and the residue was partitioned between chloroform and water. The chloroform layer was dried over sodium sulfate and removed by vacuum distillation, and upon further distillation, the product was obtained in 22 g (93%) yield, bp 36° (0.05 mm); n_D^{25} 1.4325; uv (acetonitrile): λ max 212 nm (ε 7632), 264 (5943); ir (neat): ν CF_3 1152 cm^{-1}.

Anal. Calcd. for $C_9H_{11}N_2F_3O_2$: C, 45.76; H, 4.79; N, 11.86; F, 24.13. Found: C, 45.66; H, 4.81; N, 11.99; F, 24.38.

Ammonolysis of **7**.

To **7** (10.9 g, 0.05 mole) dissolved in 10 ml of ether was added gaseous ammonia at -5 to 0° with stirring. Gas addition was interrupted when there was no further apparent heat of reaction. The mixture was stirred 1 hour longer and kept at -15° overnight. Ammonium chloride was removed by filtration, and the solvent was evaporated under vacuum. The yield of product was 9.9 g, mp 93° (soften) 140-189°, and was mixture of two compounds: **A** (40%) and **B** (60%) by gas chromatographic analysis.

4-Amino-2-chloro-6-trifluoromethylpyrimidine (**10**).

The mixture of **A** and **B** was slurried in 10 ml volumes of cold acetonitrile until the insoluble residue was pure by gas chromatographic determination. The yield of compound was 4.7 g (47%), mp 191-192° and was shown to be the **B** fraction by gas chromatography. Recrystallization from acetonitrile did not alter the melting point; uv (methanol): λ max 270 nm (ε 12521), 285 (4220); ir (potassium bromide): ν CF_3 1146 cm^{-1}.

Anal. Calcd. for $C_5H_3N_3ClF_3$: C, 30.40; H, 1.53; N, 21.23; Cl, 17.95. Found: C, 30.43; H, 1.77; N, 21.22; Cl, 17.73.

2-Amino-4-chloro-6-trifluoromethylpyrimidine (**11**).

The acetonitrile solution was kept at -15° overnight, freed of a small quantity of **10** by filtration, evaporated to a small volume, and kept at -15° overnight. A yield of 2.0 g (20%) of product, mp 92-93° (lit (5) mp 93°) was obtained which was component **A**; uv (methanol): λ max 234 nm (ε 15775), 306 (3725); ir (potassium bromide): ν CF_3 1144 cm^{-1}.

2-Amino-6-trifluoromethylpyrimidin-4-ol (**12**).

The title compound was prepared from guanidine hydrochloride and ethyl 4,4,4-trifluoroacetoacetate in the presence of sodium butoxide in 45% yield, mp 291-292° (lit (12) yield 72%, mp 282°); uv (methanol): λ max 220 nm (ε 8414), 295 (8945); ir (potassium bromide): ν CF_3 1154 cm^{-1}.

Reaction of **13** with Phosphorus Oxychloride.

Compound **13** (5.5 g, 0.025 mole) dissolved in phosphorus oxychloride (55 ml) to which was added diethylaniline (7.5 g, 0.05 mole) was heated under reflux with stirring for 3 hours. The major part of the phosphorus oxychloride was distilled off at atmospheric pressure, and the residue was poured onto an ice water slurry. After stirring for several minutes, the mixture was extracted with chloroform. The organic layer was washed with water, dried over sodium sulfate, and freed of chloroform in a rotary evaporator under vacuum. The residue was distilled under vacuum to yield 4.5 g (83%) of **7**, bp 32° (0.5 mm).

5-Chloro-2-methylthio-6-trifluoromethylpyrimidin-4-ol (**14**).

Compound **2** (21.0 g, 0.1 mole) was added to a mixture of acetic acid (200 ml), acetic anhdyride (10 ml) and ferric chloride (1.6 g, 0.01 mole). The mixture was heated to 100° and sulfuryl chloride (14.9 g, 0.11 mole) was added dropwise with stirring. After completion of addition of the sulfuryl chloride, the mixture was heated slowly to boiling and kept under reflux overnight. The course of the reaction was monitored by gc, and additional increments of sulfuryl chloride and ferric chloride were added with heating, until the starting pyrimidine was nearly completely chlorinated. The solvents were removed in a rotary evaporator and the residue was slurried in water. The product was removed by filtration, washed free of color with water, and dried at 80° overnight. the yield of compound was 22.4 g (91.5%), mp 195-196°. An analytical sample was crystallized from isopropanol, mp 200-201°; uv (methanol): λ max 237 nm (ε 5845), 306 (9687), 315 (9579); ir (potassium bromide): ν CF_3 1158 cm^{-1}.

Anal. Calcd. for $C_6H_4N_2ClF_3OS$: C, 29.46; H, 1.65; N, 11.45; Cl, 14.49. Found: C, 29.74; H, 1.89; N, 11.42; Cl, 14.33.

4,5-Dichloro-2-methylthio-6-trifluoromethylpyrimidine (**15**).

The title compound was prepared from **14** in the same manner as **3**. The yield of product was 78%, bp 103° (7.2 mm); uv (acetonitrile): λ max 238 nm (ε 3903), 270 (2.883), 320 (2484); ir (neat): ν CF_3 1154 cm^{-1}.

Anal. Calcd. for $C_6H_3N_2Cl_2F_3S$: C, 27.39; H, 1.15; N, 10.65; Cl, 26.95. Found: C, 27.65; H, 1.29; N, 10.74; Cl, 26.94.

5-Chloro-6-trifluoromethyluracil (**16**).

Compound **16** was prepared from **6** by a procedure similar to that employed for the preparation of **14**. The yield of product was 88%, mp 224-225°. The compound did not decompose by heating with 6 *N* hydrochloric acid under reflux overnight. An analytical sample was crystallized from 2-propanol, mp 230-231°; uv (methanol): λ max 278 nm (ε 6725), 329 (ε 492); ir (potassium bromide): ν CF_3 1178 cm^{-1}.

Anal. Calcd. for $C_5H_2N_2ClF_3O_2$: C, 27.99; H, 0.94; N, 13.06; Cl, 16.52. Found: C, 28.08; H, 1.05; N, 13.22; Cl, 16.36.

2,4,5-Trichloro-6-trifluoromethylpyrimidine (**17**).

Compound **17** was prepared from **16** in the same manner as **7**. The yield of product was 19% (23% on a conversion basis), bp 40° (0.5 mm), n_D^{25} 1.4906 in a run of 0.51 mole; uv (acetonitrile): λ max 226 nm (ε 11008), 281 (4433); ir (neat): ν CF_3 1165 cm^{-1}.

Anal. Calcd. for $C_5N_2Cl_3F_3$: C, 23.88; N, 11.14; Cl, 42.90. Found: C, 24.02; N, 11.38; Cl, 42.65.

4,5-Dichloro-6-trifluoromethylpyrimidin-2-yldichlorophosphate (**18**).

The residue from **17** was distilled to yield 48% (59% on a conversion basis) of **18**, bp 107-108° (0.5 mm), n_D^{25} 1.4924; uv (acetonitrile): λ max 222 nm (ε 10151), 279 (5075); ir (neat): ν CF_3 1169 cm^{-1}.

Anal. Calcd. for $C_5H_2Cl_4F_3O_2P$: C, 17.16; N, 8.01; Cl, 40.54; P, 8.85. Found: C, 16.99; N, 8.08; Cl, 40.81; P, 8.59.

The residue from the last distillation was hydrolyzed by heating with 6 *N* hydrochloric acid overnight, and 20% of **16** was recovered.

4-Amino-5-chloro-6-trifluoromethylpyrimidin-4-ol Hydrochloride (**19**).

The title compound was prepared from **18** in the same manner as **13**. The yield of product was 43%, mp 140-141° dec and 223° dec, successively, crystallized from a mixture of acetone and hexane (1:3 v/v), uv (methanol): λ max 240 nm (ε 11037), 323 (3472); ir (potassium bromide): ν CF_3 1151 cm^{-1}.

Anal. Calcd. for $C_5H_4N_3Cl_2F_3O$: C, 24.02; H, 1.61; N, 16.81; Cl, 28.36. Found: C, 24.24; H, 1.91; N, 16.60; Cl, 28.15.

Conversion of **18** to **17**.

To **18** (15.0 g, 0.043 mole) dissolved in phosphorus oxychloride (150 ml) was added gaseous hydrogen chloride over 2 hours with stirring. The remainder of the procedure was the same as for the conversion of **8** to **7**. The yield of **16** was 8.1 g (75%), bp 44° (0.7 mm).

Conversion of **16** to **17** in One Pot.

Compound **16** (42.9 g, 0.2 mole) was treated with phosphorus oxy-

chloride (430 ml), phosphorus pentachloride (83.3 g, 0.4 mole), and gaseous hydrogen chloride sequentially as in the conversion of **6** to **7**. The yield of **17** was 54.6 g (78%), bp 40° (0.5 mm).

5-Chloro-2,4-diethoxy-6-trifluoromethylpyrimidine (**20**).

The title compound was prepared from **16** (25.1 g, 0.1 mole) in the same manner as **9** was prepared from **7**. The yield of product was 18.1 g (67%) bp 61-62° (0.08 mm); n_D^{25} 1.4569; uv (methanol): λ max 223 nm (ε 9871), 281 (6342); ir (neat): ν CF_3 1152 cm^{-1}.

Anal. Calcd. for $C_9H_{10}N_2ClF_3O_2$: C, 39.94; H, 3.72; N, 10.35; Cl, 13.10. Found: C, 40.02; H, 4.01; N, 10.11; Cl, 13.03.

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