Pyrimidines. 7. A Study of the Chlorination of Pyrimidines with Phosphorus Oxychloride in the Presence of *N,N*-Dimethylaniline

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The chlorination of 6-trifluoromethyluracils by phosphorus oxychloride in the presence of *N,N*-dimethylaniline was studied and compared with results obtained with 6-methyluracils. 6-Trifluoromethyluracil and its 5-chloro analog afforded moderate yields of the di- and trichloropyrimidines, accompanied by good yields of the 2-*N*-methylanilino by-products, after a 3-hour reaction time. After 24 hours, the 2-*N*-methylanilinopyrimidines were the primary or sole products. A small yield of 2,4-*bis*(*N*-methylanilino)-6-trifluoromethylpyrimidine was also obtained. The 6-methyluracils afforded high yields of the di- and trichloropyrimidines, after 3 and 24 hours, along with minor amounts of the 2-*N*-methylanilino by-products. After 48 hours, the proportion of 2,4-dichloro-6-methylpyrimidine decreased, and the 2-*N*-methylanilino product increased. 2-Chloro-4-methylanilino-6-methylpyrimidine and *bis*(2-*N*-methylanilino)-6-methylpyrimidine were also formed in small amounts. The chlorination products from 5-chloro-6-methyluracil remained constant over 188 hours of reaction time.

It appears that the π electron distribution around the ring, as influenced by the substituents, controls the course of the chlorination and by-product formation. Since the amination by a tertiary amine is a type of Hofmann reaction, the presence of the chlorine in the 5 position of the ring adds steric hindrance and thus enhances the regiospecificity of the formation of by-products.

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In a recent paper, a study of the ring-chlorination of 6-trifluoromethylpyrimidines was reported along with our interest in these compounds [1]. It was shown that on chlorination of 6-trifluoromethyluracil and its 5-chloro analog with phosphorus oxychloride in the presence of phosphorus pentachloride, yields of 77 and 78% of the respective chloropyrimidines were obtained. A 2-pyrimidyldichlorophosphate was isolated in each case and converted to the 2-chloropyrimidine by means of gaseous hydrogen chloride.

2,4-Dichloro-6-trifluoromethylpyrimidine had been prepared earlier by chlorination of the uracil with phosphorus oxychloride in the presence of *N,N*-dimethylaniline (DMA) [2]. The yield reported was 41%. The essence of the present study was to determine the basis for the low yield of product from the reaction which should have been superior to the treatment with phosphorus oxychloride and phosphorus pentachloride by virtue of the short reaction time.

As a result of the preparation of 2,4,5-trichloropyrimidine from barbituric acid, phosphorus oxychloride and DMA, a by-product (5%) was obtained which was shown to be 4,6-dichloro-2-*N*-methylanilinopyrimidine [3]. 2,4,6-*Tris*(*N*-methylanilino)pyrimidine was also known [4]. On heating 5-nitro-4-styryluracil with phosphorus oxychloride and DMA, it was claimed that 2-chloro-4-*N*-methylanilino-5-nitro-6-styrylpyrimidine was obtained as the major product [5]. When 6-methyl-5-nitrouracil was chlorinated in the same manner, 6% of 2(4)-chloro-6-methyl-4(2)-*N*-methylanilinopyrimidine was obtained [6]. Upon chlorinating 5-phenylbarbituric acid similarly, 8% of the by-product, 4,6-dichloro-2-*N*-methylanilino-5-phenylpyrimidine, was recovered. The structure was not established [7]. A minor by-product, 4-chloro-6-*N*-methylanilino-5-nitropyrimidine was recovered from the chlorination of 4,6-dihydroxy-5-nitropyrimidine using phosphorus oxychloride and DMA [8].

A search for by-products resulting from the reaction of phosphorus oxychloride and DMA on the trifluoromethyluracils was undertaken. A comparison of the results obtained with the corresponding 6-methyluracils was included. The reactions carried out are summarized in Scheme 1 [9].

6-Trifluoromethyluracil (**1a**) was treated with phosphorus oxychloride and DMA, and two products were obtained, 2,4-dichloro-6-trifluoromethylpyrimidine (**2a**) in 46% yield, which was comparable to the reported yield [2]. The second product was 4-chloro-2-*N*-methylanilido-6-trifluoromethylpyrimidine (**3a**) (31%). The structure of **3a** was established by acid hydrolysis to replace the chlorine with a hydroxyl group (**5a**). Compound **5a** was prepared independently by condensing α-methyl-α-phenylguanidine with ethyl 4,4,4-trifluoroacetoacetate. When **2a** was treated with *N*-methylaniline, 2-chloro-4-*N*-methylanilino-6-trifluoromethylpyrimidine (**6a**) was formed. When **3a** was treated with *N*-methylaniline for 16 hours, 2,4-*bis*-(*N*-methylanilino)trifluoromethylpyrimidine (**4a**) was formed in 85% yield. The same product was obtained from **2a** in 57% yield, after 96 hours of heating. Compound **6a** was hydrolyzed to **12a** by heating with 20% hydrochloric acid. An independent approach was used to prove the structures of **6a** and **12a**. 4-*N*-Methylanilino-6-trifluoromethylpyrim-

SCHEME I

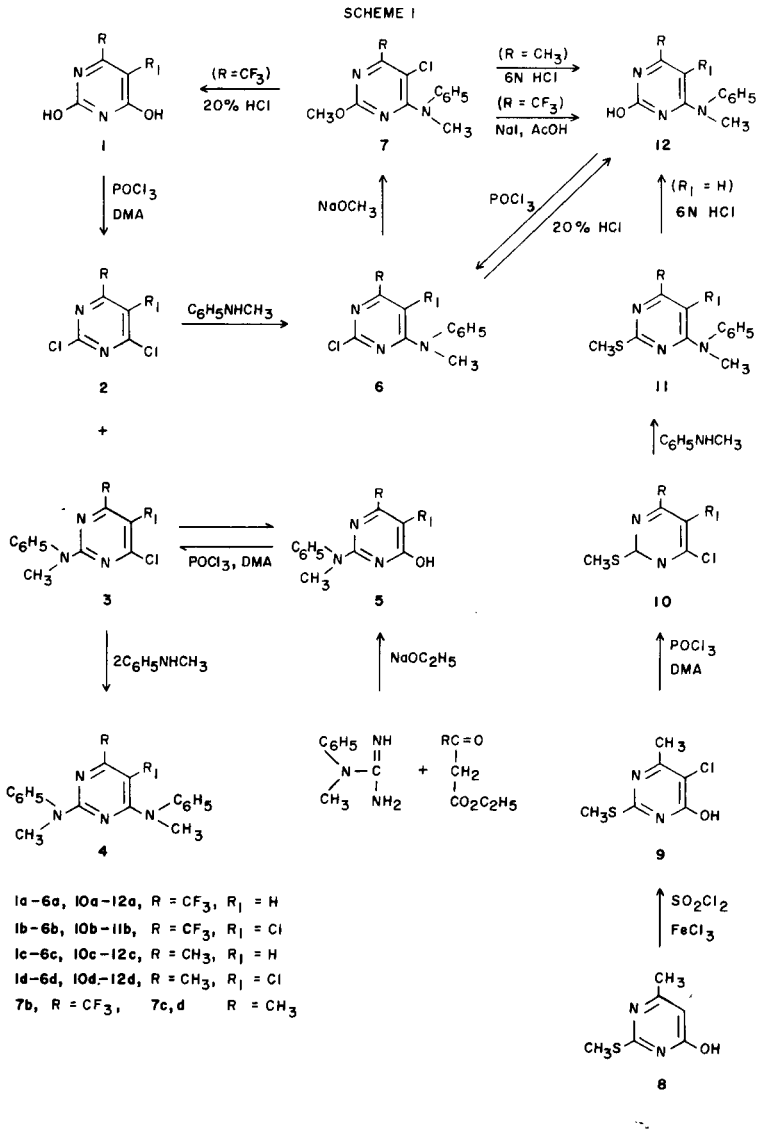
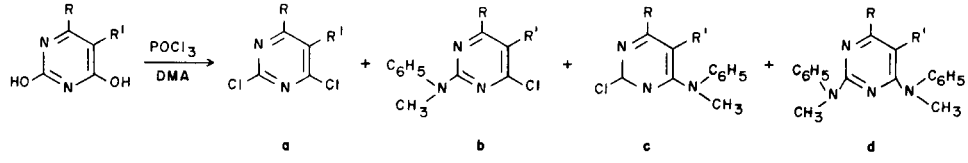


Table 1

Reaction of Substituted Uracils with Phosphorus Oxychloride in the Presence of Dimethylaniline (DMA)



Starting R	Starting R'	Reflux Time, hours: 3				24				48				188			
		Composition of Mixture, % [a]															
		a	b	c	d	a	b	c	d	a	b	c	d	a	b	c	d
CF_3	H	33	62	0	5	9	80	0	11	9	81	0	10	7	81	0	12
CF_3	Cl	28	72	0	0	0	100	0	0	0	100	0	0	0	100	0	0
CH_3	H	93	7	0	0	91	9	0	0	68	18	4	9	66	23	6	5
CH_3	Cl	96	4	0	0	95	5	0	0	95	5	0	0	94	6	0	0

[a] Quantitation by gas chromatography.

idine (**11a**) was prepared from 4-chloro-2-methylthio-6-trifluoromethylpyrimidine (**10a**) [1] and subsequently hydrolyzed with 6 *N* hydrochloric acid to **12a** in 17% yield accompanied by 63% of **1a**.

The reactions with 5-chloro-6-trifluoromethyluracil (**1b**) paralleled those with 6-trifluoromethyluracil (**1a**). 2,4,5-Trichloro-6-trifluoromethylpyrimidine (**2b**) was prepared in 47% yield along with 36% 4,5-dichloro-2-*N*-methylanilino-6-trifluoromethylpyrimidine (**3b**). Compound **4b** was prepared from **3b** in 80% yield after heating overnight, but when **4b** was obtained from **2b**, the yield was 58% after 96 hours of heating. Attempts to hydrolyze **3b** to **5b** by prolonged heating with constant boiling hydrochloric acid failed. Compound **5b** was prepared by the chlorination of **5a** with sulfuryl chloride. The preparation of **6b** was achieved by reacting **2b** with *N*-methylaniline, but attempts to hydrolyze **6b** to **12b** by prolonged heating with constant boiling hydrochloric acid were unsuccessful. Other attempts to prepare **12b** were carried out by preparing **11b** from **10b** [1] and *N*-methylaniline. Compound **12b** was stable to prolonged heating with constant boiling hydrochloric acid. On reacting **6b** with sodium methoxide, **7b** was formed which on heating for 20 hours with constant boiling hydrochloric acid yielded 95% of **1b**. When **7b** was treated with sodium iodide in acetic acid [10], 24% of **12a** was obtained. In addition to converting the methoxy to a hydroxy substitutent, the chlorine in the 5 position was replaced by hydrogen. Thus **12b** remains unknown.

A similar chlorination study was carried out on 6-methyluracil and its 5-chloro analog for comparison with the results obtained with the 6-trifluoromethyluracils.

In the preparation of 2,4-dichloro-6-methylpyrimidine (**2c**) from **1c** using phosphorus oxychloride and DMA, a small amount of by-product was detected in the gas chromatogram of the crude material. No attempt was made to isolate and identify it, although later experiments indicated that this compound was 4-chloro-6-methyl-2-methylanilinopyrimidine (**3c**). 6-Methyl-2,4,5-trichloropyrimidine (**2d**) was prepared in 86% yield from **1d** [11] by chlorination with phosphorus oxychloride and DMA. The by-product **3d** was recovered in 5% yield. The structures of the by-products were established by preparing 4-methoxy-6-methyl-2-*N*-methylanilinopyrimidine from 2-chloro-4-methoxy-6-methylpyrimidine [12] and *N*-methylaniline followed by acid hydrolysis to **5c** and chlorination to **3c**. Compound **5d** was prepared from **5c** by chlorination with sulfuryl chloride, and then converted to **3d**. Compounds **4c** and **4d** were prepared from **2c** and **2d**, respectively. Whereas it took 3 hours to prepare **4c**, 168 hours of heating were required to obtain **4d**.

6-Methyl-4-*N*-methylanilino-2-methylthiopyrimidine (**11c**) was prepared from **10c** [13] and *N*-methylaniline in 97% yield. The corresponding 5-chloro analog (**11d**) was obtained by the sequence **8** [14] to **9** by chlorination with sulfuryl chloride, to **10d** by chlorination with phosphorus oxychloride and DMA, and to **11d** by reaction with *N*-methylaniline. The conversion of **11c** to **12c** was by 6 *N* hydrochloric acid hydrolysis, whereas the attempted hydrolysis of **11d** to **12d** by prolonged heating with constant boiling hydrochloric acid failed.

Since the methylthio group could not be hydrolyzed in the case of **11d**, the more labile methoxy group was examined. 2-Methoxy-6-methylpyrimidin-4-ol [15] was chlorinated in the 5 position with *N*-chlorosuccinimide. The product was further chlorinated with phosphorus oxychloride to yield 4,5-dichloro-2-methoxy-6-methylpyrimidine, which in turn was treated with *N*-methylaniline to form **7d**. Compound **7d** was hydrolyzed to **12d** in 80% yield with 6 *N* hydrochloric acid.

Compounds **6c** and **6d** were prepared from **2c** and **2d**, respectively, by treatment with *N*-methylaniline. Both **6c** and **6d** were resistant to hydrochloric acid hydrolysis. The low yields of products **2a** and **2b** are explained on the basis of the formation of the by-products **3a** and **3b**, respectively.

It was of further interest to investigate the effect of reaction time on by-product formation. All of the possible products that could be anticipated from this type of chlorination were available (**2a-d, 3a-d, 4a-d,** and **6a-d**). The study was carried out by heating **1a-d** with phosphorus oxychloride and DMA. Samples of the reaction mixtures were assayed by gas chromatography after 3, 24, 48 and 188 hours. When there was doubt as to the identity of a product in a gas chromatogram, it was characterized by gc/ms. Even though the fragmentation patterns of isomeric pairs were similar, the compounds could be identified by the mass abundances of the fragments. The results obtained are shown in Table 1. With the exception of 6-methyluracil (**1c**) none of the starting compounds yielded the 4-*N*-methylanilinopyrimidine (**6**). Compound **6c** appeared after 48 hours of boiling in about 5% yield. The 2,4-*bis*(*N*-methylanilino)pyrimidine (**4a**) was detected after 3 hours (5%) and increased to 12% after 188 hours in the reaction with **1a**. The *bis*(*N*-methylanilino)pyrimidine (**4c**) appeared after 48 hours. The major products resulting from **1a** were **2a** (33%) and **3a** (62%) after 3 hours. After 24 hours the composition changed to **2a** (9%) and **3a** (80%), and this mixture was stable over 188 hours of heating. The products resulting from **1b** were **2b** (28%) and **3b** (72%) after 3 hours, and **3b** (100%) after 24 hours. The chlorination of **1c** yielded **2c** (93%) and **3c** (7%) after 3 hours. After 48 hours, the composition of the mixture changed to **2c** (68%) and **3c** (18%). This was essentially the same over 188 hours. The reaction of **1d** with phosphorus oxychloride and DMA was completed in 3 hours and remained the same over 188 hours. The products formed were **2d** (96%)

and **3d** (4%).

It is apparent that the π electron distribution around the ring, as further influenced by the substituents, controls the course of the chlorination and by-product formation. The mechanism of amination with tertiary amines (DMA) and secondary amines (*N*-methylanilino) are different. The amination of the chloropyrimidine with the tertiary amine is by a Hofmann type reaction where the quarternary compound is formed followed by release of methyl chloride. That an alkyl halide was released in this type of reaction was demonstrated by Kober and Raetz and substitution was surmized to take place in the 2 position [16]. The present work establishes unequivocally that the amination of the chloropyrimidines occurs primarily in the 2 position, after short reaction times. The amination with the secondary amine is by a bimolecular nucleophilic substitution and favors the 4 and 6 positions at moderately low reaction temperatures. Halogen in the 4 or 6 position is a better leaving group than the corresponding halogen in the 2 position. It is for these reasons that the high degree of regiospecificity was observed. It was also found that low yields of products were formed by amination of the 4 position of the chloropyrimidines by the tertiary amine, when the 5 position was occupied by hydrogen. When the 5 position was occupied by chlorine, no such product was detected. This may be due to the steric hindrance of the chlorine for the Hofmann amination, whereas with the S_N2 type amination, this steric hindrance plays no role.

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 Perkin-Elmer Lambda 5 uv/vis 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 ionizaiton detector to which was 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 5 feet × 1/8 inch o.d. packed with 5% OV-101 on 80-100 mesh Gas Chrom Q.

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

A mixture of **1a** [1] (50 g, 0.28 mole), phosphorus oxychloride (518 ml) and DMA (67 g, 0.56 mole) was heated under reflux for 3 hours. A major portion of the phosphorus oxychloride was removed by atmospheric distillation, and the residue was poured into an ice water slurry. After stirring for several minutes, the mixture was extracted with ether. The organic layer was washed with water, dried over sodium sulfate, and freed of solvent in a rotary evaporator under mild vacuum. The residue was distilled under reduced pressure to yield 27.9 g (46%) of the dichloro compound **2a**, bp 21° (0.1 mm) (lit [2], bp 92° (6.5 mm), yield 41%).

4-Chloro-2-*N*-methylanilino-6-trifluoromethylpyrimidine (**3a**).

The residue from the previous reaction was dissolved in hexane decolorized with Norite A and refrigerated overnight. The product was obtained by filtration (25 g, 31%), mp 59-60°. An analytical sample was crystallized from hexane, mp 59.5-60°; uv (methanol): λ max 224 nm (ε 3595), 255 (6413), 322 (746); ir (potassium bromide): ν CF_3 1154 cm^{-1}.

Anal. Calcd. for $C_{12}H_9ClF_3N_3$: C, 50.10; H, 3.15; N, 14.61; Cl, 12.33; F. 19.81. Found: C, 49.89; H, 3.33; N, 14.77; Cl, 12.06; F, 19.97.

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

5-Chloro-6-trifluoromethyluracil [1] (49 g, 0.23 mole) was treated with 500 ml of phosphorus oxychloride and DMA (60 g, 0.5 mole) in the same manner as **1a**. The yield of **2b** was 27 g (47%), bp 42° (1.0 mm) (lit [1], bp 40° (0.5 mm), yield 78%).

4,5-Dichloro-2-*N*-methylanilino-6-trifluoromethylpyrimidine (**3b**).

The residue from **2b** was worked up in the same manner as **3a**. The yield of product was 26.9 g (36%), mp 81-81.5° crystallized from hexane; uv (methanol): λ max 222 nm (ε 3558), 265 (8230), 344 (975); ir (potassium bromide): ν CF_3 1153 cm^{-1}.

Anal. Calcd. for $C_{12}H_8Cl_2F_3N_3$: C, 44.74; H, 2.50; N, 13.05; Cl, 22.01. Found: C, 44.61; H, 2.68; N, 13.01; Cl, 21.92.

2,4-bis(*N,M*ethylanilino)-6-trifluoromethylpyrimidine (**4a**).

To 50 ml of ethanol were added 10.7 g (0.1 mole) of *N*-methylaniline and 14.4 g (0.05 mole) of **3a**. The mixture was heated under reflux with stirring overnight. The product was poured into water, adjusted to *p*H 7 with sodium bicarbonate and extracted with ether. The extract was washed with water, dried over sodium sulfate, and the ether was removed in a rotary evaporator. The residue was distilled to yield 15.2 g (85%) of product, bp 154° (0.02 mm). The product was pure enough for analysis; uv (methanol): λ max 224 nm (ε 4562), 257 (4266), 311 (1962); ir (neat): ν CF_3 1149 cm^{-1}.

Anal. Calcd. for $C_{19}H_{17}F_3N_4$: C, 63.68; H, 4.78; N, 15.65. Found: C, 63.40; H, 4.51; N, 15.88.

When **4a** was prepared from **2a**, the reflux time was 96 hours and the yield of product was 57%.

5-Chloro-2,4-bis(*N*-methyanilino)-6-trifluoromethylpyrimidine (**4b**).

Compound **4b** was prepared from **3b** in 80% yield in the same manner as **3b** was prepared from **3a**. The product boiled at 180° (0.08 mm); uv (methanol): λ max 234 nm (ε 6557), 270 (9443), 314 (4328); ir (neat): ν CF_3 1149 cm^{-1}.

Anal. Calcd. for $C_{19}H_{16}ClF_3N_4$: C, 58.09; H, 4.11; N, 14.26. Found: C, 57.93; H, 4.24; N, 14.45.

When **4b** was prepared from **2b**, 96 hours of reflux time was required, and the yield of product was 58%.

2-*N*-Methylanilino-6-trifluoromethylpyrimidin-4-ol (**5a**).

A suspension of 26.1 g (0.09 mole) of **3a** in 250 ml of concentrated hydrochloric acid was heated under reflux with stirring for 60 hours. Upon cooling overnight, 21.3 g (88%) of crystalline product was obtained. The crystals were washed with water and dried, mp 170°. The analytical sample was crystallized from water, mp 170°; uv (methanol): λ max 216 nm (ε 5639), 233 (3644), 305 (3947); ir (potassium bromide): ν CF_3 1145 cm^{-1}.

Anal. Calcd. for $C_{12}H_{10}F_3N_3O$: C, 53.53; H, 3.74; N, 15.61. Found: C, 53.54; H, 3.72; N, 15.64.

5a Prepared from α-Methyl-α-phenylguanidine and Ethyl 4,4,4-Trifluoroacetoacetate.

To a solution of sodium ethoxide prepared from sodium (3.4 g, 0.147 g-atom) in ethanol (250 ml) was added ethyl 4,4,4-trifluoroacetoacetate (24.8 g, 0.134 mole) and α-methyl-α-phenylguanidine hydrochloride (25 g, 0.134 mole). The mixture was heated under reflux for 1 hour and stirred at room temperature overnight. The solvent was removed by evaporation, and the residue was dissolved in water and acidified with acetic acid. After refrigeration overnight, the crystals were obtained by filtration, washed with water and dried, yield 2.7 g (7.5%), mp 170°. The spectral and chromatographic properties of this product were indistinguishable from those prepared by hydrolysis of **3a**.

5-Chloro-2-*N*-methylanilino-6-trifluoromethylpyrimidin-4-ol (**5b**).

Compound **5a** (13.5 g, 0.05 mole) was dissolved in a mixture of acetic acid (125 ml) and acetic anhydride (6 ml). A catalytic quantity of ferric chloride was added, and sulfuryl chloride (7.5 g, 0.056 mole) was added dropwise with stirring at near the boiling point of the solvent mixture. After completion of addition of the sulfuryl chloride, the mixture was kept under reflux overnight. The solvent was removed under vacuum in a rotary evaporator and the residue dried at 70°. The yield of crude product was 14.5 g (95%), mp 160-162°. The analytical sample was crystallized from aqueous acetone, mp 166-166.5°; uv (methanol): λ max 216 nm (ε 7284), 254 (3739), 315 (3852); ir (potassium bromide): ν CF_3 1143 cm^{-1}.

Anal. Calcd. for $C_{12}H_9ClF_3N_3O$: C, 47.46; H, 2.99; N, 13.84; Cl, 11.68. Found: C, 47.19; H, 3.11; N, 13.87; Cl, 11.65.

Attempts to hydrolyze **3b** in the same manner as **3a** failed.

2-Chloro-4-*N*-methylanilino-6-trifluoromethylpyrimidine (**6a**).

To 24 ml of ethanol were added *N*-methylaniline (6.4 g, 0.06 mole) and 2,4-dichloro-6-trifluoromethylpyrimidine (**2a**) (6.5 g, 0.03 mole). The mixture was allowed to stand at ambient temperatures for 3 hours. The solvent was removed under vacuum, and the residue was dissolved in chloroform. After washing with water and drying over sodium sulfate, the chloroform was vacuum evaporated. The product was dissolved in ethanol, decolorized with Nuchar, and allowed to crystallize in the refrigerator overnight. The yield of compound was 13.8 g (80%), mp 79-80°; uv (methanol): λ max 255 nm (ε 5234), 294 (2714); ir (potassium bromide): ν CF_3 1157 cm^{-1}.

Anal. Calcd. for $C_{12}H_9ClF_3N_3$: C, 50.10; H, 3.15; N, 14.61; Cl, 12.33. Found: C, 49.83; H, 3.44; N, 14.70; Cl, 12.40.

2,5-Dichloro-4-*N*-methylanilino-6-trifluoromethylpyrimidine (**6b**).

Compound **6b** was prepared from **2b** in 85% yield in the same manner as **6a** was obtained from **2a**. The analytical sample was prepared by dissolving in ethanol, decolorizing with Nuchar, and refrigerating, mp 91-92°; uv (methanol): λ max 220 nm (ε 6495), 272 (3799), 315 (3069); ir (potassium bromide): ν CF_3 1152 cm^{-1}.

Anal. Calcd. for $C_{12}H_8Cl_2F_3N_3$: C, 44.74; H, 2.50; N, 13.05; Cl, 22.01. Found: C, 44.80; H, 2.77; N, 13.25; Cl, 21.72.

5-Chloro-2-methoxy-4-*N*-methylanilino-6-trifluoromethylpyrimidine (**7b**).

Compound **6b** (31.8 g, 0.1 mole) was added to a solution of 2.3 g (0.1 g-atom) of sodium in 240 ml of methanol. The mixture was heated under reflux with stirring overnight. Sodium chloride was removed by filtration and the solvent vacuum evaporated. The residue was partitioned between ether and water, and the ether layer was dried over sodium sulfate and removed under vacuum. The yield of product was 31 g (97%) mp 70-71°. An analytical sample was crystallized from ethanol, mp 73.5-74.5°; uv (methanol): λ max 259 nm (ε 2821), 313 (4194); ir (potassium bromide): ν CF_3 1142 cm^{-1}.

Anal. Calcd. for $C_{13}H_{11}ClF_3N_3O$: C, 49.14; H, 3.49; N, 13.23; Cl, 11.16. Found: C, 49.45; H, 3.71; N, 13.57; Cl, 10.85.

4-*N*-Methylanilino-2-methylthio-6-trifluoromethylpyrimidine (**11a**).

A mixture of 4-chloro-2-methylthio-6-trifluoromethylpyrimidine [1] (34.4 g, 0.15 mole), *N*-methylaniline (16.1 g, 0.15 mole) and ethanol (60 ml) was allowed to stir at room temperature overnight. The solvent was removed under vacuum, and the residue was slurried in acetone and filtered free of the insoluble material. The filtrate was reduced to a small volume and cooled in the refrigerator overnight. A yield of 28 g (62%) of product, mp 95-98°, was obtained by filtration. An analytical sample was prepared by crystallization from ethanol, mp 99-100°; uv (methanol): λ max 245 nm (ε 10346), 308 (3289); ir (potassium bromide): ν CF_3 1155 cm^{-1}.

Anal. Calcd. for $C_{13}H_{12}F_3N_3S$: C, 51.16; H, 4.04; N, 14.04; S, 10.71. Found: C, 51.36; H, 4.20; N, 13.92; S, 10.97.

5-Chloro-4-*N*-methylanilino-2-methylthio-6-trifluoromethylpyrimidine (**11b**).

The title compound was prepared from 4,5-dichloro-2-methylthio-6-trifluoromethylpyrimidine [1] in the same manner as **11a**. The yield of product was 84% and the analytical sample was prepared from isopropanol, mp 86.5-87.5°; uv (methanol): λ max 255 nm (ε 9740), 326 (3399); ir (potassium bromide): ν CF_3 1144 cm^{-1}.

Anal. Calcd. for $C_{13}H_{11}ClF_3N_3S$: C, 46.78; H, 3.32; N, 12.58; Cl, 10.62. Found: C, 46.87; H, 3.57; N, 12.49; Cl, 10.58.

4-*N*-Methylanilino-6-trifluoromethylpyrimidin-2-ol (**12a**).

Compound **11a** (6 g, 0.02 mole) was heated under reflux in 60 ml of concentrated hydrochloric acid for 64 hours. The hydrolyzate was kept at -20° overnight, and 0.8 g (22%) of **1a**, mp 227-228°, was recovered. The filtrate was evaporated to dryness under vacuum, and the residue was dissolved in a minimal volume of water and refrigerated overnight. A second crop of **1a** was recovered (1.5 g, 41%), mp 220°. The mother liquor was evaporated to dryness under vacuum, and the residue (0.9 g, 17%) of **12a** was obtained, mp 178-180°. An analytical sample was crystallized from water, mp 181.5-182°; uv (methanol): λ max 207 nm (ε 12212), 265 (3317), 288 (4337); ir (potassium bromide): ν CF_3 1142 cm^{-1}.

Anal. Calcd. for $C_{12}H_{10}F_3N_3O$: C, 53.53; H, 3.74; N, 15.61. Found: C, 53.78; H, 3.88; N, 15.33.

Compound **12a** from **7b**.

To **7b** (2.6 g, 0.008 mole) dissolved in 10 ml of acetic acid was added sodium iodide (2 g, 0.013 mole), and the mixture was kept at 110° for 4 hours in a teflon lined pressure vessel with occasional shaking [10]. After cooling, the solvent was removed under vacuum, and the residue was extracted by boiling twice with 100 ml portions of water which on cooling yielded 0.35 g of product, mp 177-178°. The filtrate was concentrated to a small volume by vacuum evaporation and refrigerated overnight. An additional 0.3 g of product was obtained, mp 177-178°. An analytical sample was crystallized from aqueous alcohol, mp 180°. The product was indistinguishable from **12a** by elemental, chromatographic and spectral analyses and the yield was 24%.

Hydrolysis of **7b** to **1b**.

Compound **7b** (10 g, 0.031 mole) was heated under reflux with 100 ml of concentrated hydrochloric acid for 20 hours. The hydrochloric acid was removed by vacuum evaporation, and the residue was triturated with acetone. The acetone was evaporated under vacuum, and the residue of **1b** was recovered in a yield of 7 g (95%), mp 210-213°. On recrystallization from water, the product melted at 231-232° and was indistinguishable from an authentic sample [1].

6-Methyl-2,4,5-trichloropyrimidine (**2d**).

The title compound was prepared from **1d** [11] in the same manner as **2b**. The yield of product was 80%, bp 86° (1.0 mm) (lit [4], bp 115-120° 12 mm).

4,5-Dichloro-2-*N*-methylanilino-6-methylpyrimidine (**3d**).

The residue from **2d** was worked up in the same manner as **3a**. The yield of product was 5%, mp 61-62°. The analytical sample was crystallized from ethanol, mp 64-65°; uv (methanol): λ max 236 nm (ε 4443), 264 (8309), 318 (1371).

Anal. Calcd. for $C_{12}H_{11}Cl_2N_3$: C, 53.75; H, 4.14; N, 15.67; Cl, 26.45. Found: C, 53.96; H, 4.11; N, 15.64; Cl, 26.49.

4-Methoxy-6-methyl-2-*N*-methylanilinopyrimidine.

2-Chloro-4-methoxy-6-methylpyrimidine [12] (31.7 g, 0.2 mole), *N*-methylaniline (23.5 g, 0.22 mole) and 50 ml of ethanol were heated at 88° for 2.5 hours in a teflon lined pressure vessel. The reaction mixture was poured into water, extracted with ether, the ether layer washed with water and dried over sodium sulfate. The ether was evaporated under vacuum and the residue vacuum distilled. The product boiled at 112° (0.05 mm) and yielded 27.5 g (60%) of compound n_D^{25} 1.5832; uv (methanol): λ max 224 nm (ε 1630), 266 (2224).

Anal. Calcd. for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33. Found: C, 68.09; H, 6.75; N, 18.61.

2-*N*-Methylanilino-6-methylpyrimidin-4-ol (**5c**).

4-Methoxy-6-methyl-2-*N*-methylanilinopyrimidine (16.7 g, 0.073 mole) was heated with 170 ml of 6 *N* hydrochloric acid under reflux overnight. The free acid was removed by vacuum distillation, and the residue was dissolved in water and freed of chloride by passage through a column of Amberlite IR-4B. The eluate was reduced to a small volume, and the crystals were removed, washed with water, and dried at 70°. The yield of product was 9 g, mp 119-120°. An additional yield of 0.8 g, mp 121-122°, was obtained from the mother liquor. The combined yields were 62%, and the analytical sample was crystallized from water, mp 121-122°; uv (methanol): λ max 220 nm (ε 5931), 240 (4282), 296 (3446).

Anal. Calcd. for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52. Found: C, 66.91; H, 6.17; N, 19.43.

5-Chloro-2-*N*-methylanilino-6-methylpyrimidin-4-ol (**5d**).

The title compound was prepared from **5c** in the same manner as **5b** was prepared from **3a**. The yield of product was 62%, and an analytical sample was crystallized from aqueous ethanol, mp 178-179°; uv (methanol): λ max 218 nm (ε 5463), 246 (4338), 307 (3931).

Anal. Calcd. for $C_{12}H_{12}ClN_3O$: C, 57.22; H, 4.85; N, 16.83; Cl, 14.20. Found: C, 57.52; H, 5.00; N, 16.68; Cl, 14.31.

4-Chloro-2-*N*-methylanilino-6-methylpyrimidine (**3c**).

Compound **5c** (6.5 g, 0.03 mole) was heated under reflux with 65 ml of phosphorus oxychloride for 3 hours. The excess phosphorus oxychloride was distilled under vacuum, and the residue was poured into an ice water slurry. The remainder of the workup procedure was the same as for **2a**. The yield of product was 5.6 g (80%), bp 104° (0.02 mm); n_D^{25} 1.6080; uv (methanol): λ max 227 nm (ε 3519), 262 (6016), 310 (1524).

Anal. Calcd. for $C_{12}H_{12}ClN_3$: C, 61.67; H, 5.18; N, 17.98; Cl, 15.17. Found: C, 61.61; H, 5.42; N, 17.87; Cl, 15.18.

Conversion of **5d** to **3d**.

Compound **5d** was obtained from **3d** in 85% yield by chlorination with phosphorus oxychloride and DMA.

6-Methyl-2,4,-bis(*N*-methylanilino)pyrimidine (**4c**).

The title compound was obtained from **2c** in the same manner as **4a** was prepared from **2a**. The reflux time was 3 hours, and the yield of product was 62%, bp 174° (0.012 mm) (lit [8], bp 182°, 0.8 mm); uv (methanol): λ max 229 nm (ε 4584), 265 (4121), 296 (3011).

Anal. Calcd. for $C_{19}H_{20}N_4$: C, 74.94; H, 6.62; N, 18.41. Found: C, 74.68; H, 6.44; N, 18.50.

5-Chloro-6-methyl-2,4-bis(*N*-methylanilino)pyrimidine (**4d**).

The title compound was prepared from **2d** as above. The reflux time was 168 hours, and the yield of product was 62%, bp 179-182° (0.012 mm); uv (methanol): λ max 234 nm (ε 6557), 270 (9443), 314 (4328).

Anal. Calcd. for $C_{19}H_{19}ClN_4$: C, 67.35; H, 5.65; N, 16.54. Found: C, 67.37; H, 5.54; N, 16.64.

6-Methyl-4-*N*-methylanilino-2-methylthiopyrimidine Hydrochloride (**11c**).

A mixture of 4-chloro-6-methyl-2-methylthiopyrimidine (**10c**) [13] (60 g, 0.34 mole), *N*-methylaniline (36.3 g, 0.34 mole) and 65 ml of ethanol was made, and after 3 hours, the material solidified. The mixture was allowed to stand overnight after which acetone was added with stirring, and stirring was continued for 1 hour. The product was removed by filtration and dried at 70° (yield 78.5 g, 82%), mp 216-217°. The filtrate was reduced to a small volume, and an additional quantity of product was recovered (12.5 g, 15%), mp 216-217°. An analytical sample was crystallized from (1:1) ethanol, acetone, mp 217-218.5°; uv (methanol): λ max 237 nm (ε 9233), 246 (9838), 291 (4964).

Anal. Calcd. for $C_{13}H_{16}ClN_3S$: C, 55.40; H, 5.72; N, 14.91; Cl, 12.58. Found: C, 55.63; H, 5.49; N, 14.85; Cl, 12.46.

5-Chloro-6-methyl-2-methylthiopyrimidin-4-ol (**9**).

The title compound was prepared from **8** [14] in the same manner as **5b** was obtained from **3a**. The yield of product was 79%, and the analytical sample was crystallized from isopropanol, mp 260-261°; uv (methanol): λ max 218 nm (ε 4396), 246 (8275), 289 (3129).

Anal. Calcd. for $C_6H_7ClN_2OS$: C, 37.80; H, 3.70; N, 14.70; Cl, 18.60. Found: C, 37.72; H, 3.70; N, 14.65; Cl, 18.88.

4,5-Dichloro-6-methyl-2-methylthiopyrimidine (**10d**).

Compound **10d** was prepared from **9** in the same manner as **2d** was obtained from **1d**. The yield of **10d** was 76%, and an analytical sample was obtained by distillation, bp 83-84° (0.02 mm), and crystallization from 2-propanol, mp 51-51.5°; uv (methanol): λ max 220 nm (ε 367), 261 (2068), 300 (274).

Anal. Calcd. for $C_6H_6Cl_2N_2S$: C, 34.46; H, 2.89; N, 13.46; Cl, 33.91. Found: C, 34.58; H, 2.77; N, 13.35; Cl, 34.04.

5-Chloro-6-methyl-4-*N*-methylanilino-2-methylthiopyrimidine (**11d**).

The title compound was prepared from **10d** in the same manner as **11c**. The product was obtained in 96% yield, and the analytical sample was crystallized from ethanol, mp 92°; uv (methanol): λ max 252 nm (ε 10113), 308 (4802).

Anal. Calcd. for $C_{13}H_{14}ClN_3S$: C, 55.81; H, 5.04; N, 15.02; Cl, 12.67. Found: C, 55.70; H, 5.09; N, 15.08; Cl, 12.60.

6-Methyl-4-*N*-methylanilinopyrimidin-2-ol (**12c**).

To 400 ml of 6 *N* hydrochloric acid was added **11c** (40 g, 0.14 mole), and the mixture was heated under reflux with stirring overnight. The aqueous acid was removed in a rotary evaporator under vacuum, and the residue was dissolved in water and passed through a column of Amberlite IR-4B to remove chloride. The resulting aqueous solution was vacuum evaporated to a small volume. After cooling overnight in the refrigerator, the crystals were obtained by filtration, washed with acetone and dried at 70°. The yield of product was 34.4 g (91%), mp 251-252°. The analytical sample was crystallized from water, mp 251.5-252°; uv (methanol): λ max 208 nm (ε 14109), 260 (5086), 278 (5826).

Anal. Calcd. for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52. Found: C, 66.79; H, 6.19; N, 19.26.

5-Chloro-2-methoxy-6-methylpyrimidin-4-ol.

A mixture of 2-methoxy-6-methylpyrimidin-4-ol (28 g, 0.2 mole) (15), *N*-chlorosuccinimide (26.8 g, 0.2 mole), and 280 ml of chloroform was heated under reflux overnight. The solution was cooled to room temperature, filtered free of succinimide, washed with water, and the chloroform layer was dried over sodium sulfate. The chloroform solution was evaporated to a small volume and cooled in the refrigerator. A yield of 20 g (57%) of product, mp 217-218°, was obtained by filtration. The mother liquor was taken to dryness and the residue slurried with water and dried at 70° to yield a further crop of product (9.3 g, 27%) mp 212-214°. The total yield of product was 84%, and the analytical sample was obtained from ethanol, mp 218.5-219.5°; uv (methanol): λ max 224 nm (ε 2463), 275 (2957).

Anal. Calcd. for $C_6H_7ClN_2O_2$: C, 41.27; H, 4.04; N, 16.05; Cl, 20.30. Found: C, 41.35; H, 4.21; N, 15.92; Cl, 20.31.

4,5-Dichloro-2-methoxy-6-methylpyrimidine.

A mixture of phosphorus oxychloride (32 ml) and DMA (13.8 g, 0.114 mole) was added dropwise with stirring to 5-chloro-2-methoxy-6-methylpyrimidin-4-ol (10 g, 0.057 mole) at ambient temperatures. Upon completion of addition of the chlorinating mixture, the solution was kept under reflux for 2 hours. It was then cooled and poured onto ice and extracted with ether. The ether layer was washed with water, dried over sodium sulfate, and the ether was evaporated under vacuum. The residue was distilled, and a yield of title compound (8.8 g, 80%) was obtained, bp 61.5-62.5°; uv (methanol): λ max 222 nm (ε 4281), 280 (2380).

Anal. Calcd. for $C_6H_6Cl_2N_2O$: C, 37.33; H, 3.13; N, 14.52; Cl, 36.73. Found: C, 37.26; H, 3.08; N, 14.53; Cl, 36.89.

5-Chloro-2-methoxy-6-methyl-4-*N*-methylanilinopyrimidine (**7d**).

Compound **7d** was obtained from 4,5-dichloro-2-methoxy-6-methylpyr-

imidine in the same manner as **6b** was prepared from **2b**. The yield of product was 89%, and the analytical sample was crystallized from ethanol, mp 94-95°; uv (methanol): λ max 228 nm (ε 4765), 256 (2158), 299 (5605).

Anal. Calcd. for $C_{13}H_{14}ClN_3O$: C, 59.20; H, 5.35; N, 15.93; Cl, 13.85. Found: C, 59.23; H, 5.53; N, 15.65; Cl, 13.77.

2-Chloro-6-methyl-4-*N*-methylanilinopyrimidine (**6c**).

Compound **6c** was prepared from **12c** in the same manner as **3c** was from **5c**. The yield of product was nearly quantitative, and an analytical sample was prepared by crystallization from ethanol, mp 94-95°; uv (methanol): λ max 235 nm (ε 2823), 257 (4959), 274 (4603).

Anal. Calcd for $C_{12}H_{13}N_3O$: C, 61.67; H, 5.18; N, 17.98; Cl, 15.17. Found: C, 61.66; H, 4.88; N, 17.69; Cl, 15.21.

Attempts to hydrolyze **6c** to **12c** with hydrochloric acid failed.

2,5-Dichloro-6-methyl-4-methylanilinopyrimidine (**6d**).

Compound **6d** was prepared from **2d** in the same manner as **6b** was obtained from **2b**. The yield of product was 31%, and the analytical sample was crystallized from ethanol, mp 100-100.5°; uv (methanol): λ max 228 nm (ε 5200), 268 (2927), 296 (4824).

Anal. Calcd. for $C_{12}H_{11}Cl_2N_3$: C, 53.75; H, 4.14; N, 15.67; Cl, 26.45. Found: C, 53.62; H, 4.10; N, 15.67; Cl, 26.34.

Attempts to hydrolyze **6d** to **12d** with hydrochloric acid failed.

5-Chloro-6-methyl-4-methylanilinopyrimidin-2-ol (**12d**).

The title compound was prepared from **11d** in the same manner as **12c** was obtained from **11c**. The yield of product was 80%, and the analytical sample was gotten after two recrystallizations from aqueous ethanol, mp 226-227° dec; uv (methanol): λ max 608 nm (ε 67892), 275 (3687).

Anal. Calcd. for $C_{12}H_{12}ClN_3O$: C, 57.72; H, 4.85; N, 16.83; Cl, 14.20. Found: C, 57.51; H, 4.81; N, 16.71; Cl, 14.43.

Products Identified by Heating **1a-d** Under Reflux With Phosphorus Oxychloride in the Presence of DMA for 3, 24, 48, and 188 hours.

To 25 ml portions of phosphorus oxychloride were added **1a-d** (2.5 g) together with 2 molar equivalents of DMA. The mixtures were heated under reflux, and 1 ml samples were removed after each time period. The samples were poured onto ice and extracted with ether (3 × 10 ml). The extract was dried over calcium chloride and gas chromatographed. Quantitation was done by integrating the areas under the curves. The data are summarized in Table 1.

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