chloride, then hot petroleum ether (b.p. 30–60°) was added to the point of turbidity. The solution was chilled in an acetone–Dry Ice bath and the supernatant solvent decanted to leave an oily precipitate. This was dried *in vacuo* at 35–40° (0.5 mm.) to afford 2.30 g. (84%) of VII as a white hygroscopic foam; $\lambda_{max(\mu)}^{Nujol}$ 2.99 (NH), 3.6–4.5 (R_4N^+), 5.90 (amide C—O), 6.50 (amide II, NO_2), 7.35 (NO_2), free of absorption at 9.60 (C—OH). It moved as a single spot in solvent C with R_f 0.94 but could not be separated here or in other solvent systems from starting material.

Anal. Calcd. for $C_{19}H_{21}Cl_2N_3O_4 \cdot HCl$: C, 49.3; H, 4.78; N, 9.08; Cl, 23.0. Found: C, 49.4; H, 4.83; N, 9.22; Cl, 22.8.

m-[Bis-(2-chloroethyl)aminomethyl]phenoxyacetic acid hydrochloride (VIII). To a hot solution of 0.50 g. (1.08 mmoles) of VII in 5 ml. of 1,2-dimethoxyethane was added 15 ml. of hot 4*N*-hydrochloric acid solution. After being heated at 80° (bath temperature) for 2.25 hr., the mixture was evaporated to dryness *in vacuo* (up to 50°/0.5 mm.). The residue was dissolved in 15 ml. of 0.1*N* hydrochloric acid solution, then continuously extracted with chloroform until the lower chloroform layer was free of the yellow color of *m*-nitroaniline. The aqueous phase was separated and evaporated to dryness *in vacuo* (40° '0.5 mm.) to afford 0.25 g. (65%) of VIII as a yellow amber oil which could not be crystallized.

The analytical sample of VIII was obtained by dissolving 120 mg. of the oil in acetone, filtering to remove a trace of insoluble material, diluting the filtrate with ether and allowing an oil to precipitate overnight. The supernatant solvent was removed by decantation and the oil was dried *in vacuo* to afford 100 mg. of VIII as a light amber oil; λ_{max}^{film} 3.0–4.2 (CO_2H and NR_4H^+), 5.70 (carboxyl C=O), 7.80 (aryl C—O—C), 12.6 (*m*-substituted benzene), 13.4 (C—Cl). It moved as a single spot in solvents D with R_1 0.82 (starting material streaks to R_f 0.7) and F with R_f 0.79 (R_f 1.0 for starting material) and could be detected by ultraviolet light, diazotized sulfanilic acid or iodoplatinate spray.[19] Freshly prepared solutions of VIII in acetone gave single spots. On standing, these solutions gave streaks on paper chromatograms.

Anal. Calcd. for $C_{13}H_{17}Cl_2NO_3 \cdot HCl$: C, 45.6; H, 5.29; Cl, 31.0; N, 4.09. Found: C, 45.7; H, 5.21; Cl, 30.4; N, 4.42.

Acknowledgment. The authors wish to thank Dr. Peter Lim for interpretation of the infrared absorption spectra and his staff for the paper chromatography and spectrophotometry. The authors are also indebted to Mr. O. P. Crews and his staff for large-scale preparation of certain intermediates.

MENLO PARK, CALIF.

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[CONTRIBUTION FROM THE RESEARCH INSTITUTE OF TEMPLE UNIVERSITY]

Fluorine-Containing Potential Anticancer Agents. I. Synthesis of Some Trifluoromethylpyrimidines[1]

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Various 2- and 6-trifluoromethylpyrimidines have been synthesized for evaluation as cancer chemotherapeutic agents.

Recent investigations have shown that the introduction of fluorine into some pyrimidines produces compounds which inhibit tumor growth[3,4]

Despite this discovery, very few new fluoropyrimidines[5–10] have been prepared for screening against neoplasms. A program has therefore been initiated in this laboratory to synthesize various new fluorine-containing pyrimidines and condensed pyrimidine systems for evaluation as cancer chemotherapeutic agents.

As the first stage in this program, a series of 2-trifluoromethylpyrimidines was prepared as shown in schemes A and B.

Trifluoroacetamidine (I) was prepared in 95% yield from trifluoroacetonitrile and ammonia by the method of Reilly and Brown.[11] The condensation of I with ethyl formylacetate, ethyl acetoacetate, ethyl trifluoroacetoacetate, diethyl malonate and ethyl cyanoacetate afforded 4-hydroxy-2-trifluoromethylpyrimidine (II), 4-hydroxy-6-methyl-2-trifluoromethylpyrimidine (III), 2,6-bistrifluoromethyl - 4 - hydroxypyrimidine (IV), 4,6 - dihydroxy-2-trifluoromethylpyrimidine (V) 6-amino-4-hydroxy-2-trifluoromethylpyrimidine (VI), respectively. The chlorination of II, III, IV, V, and VI with phosphorus oxychloride in dimethylaniline gave the corresponding chloro compounds VII, VIII, IX, X and XI, respectively. The derivatives VII,

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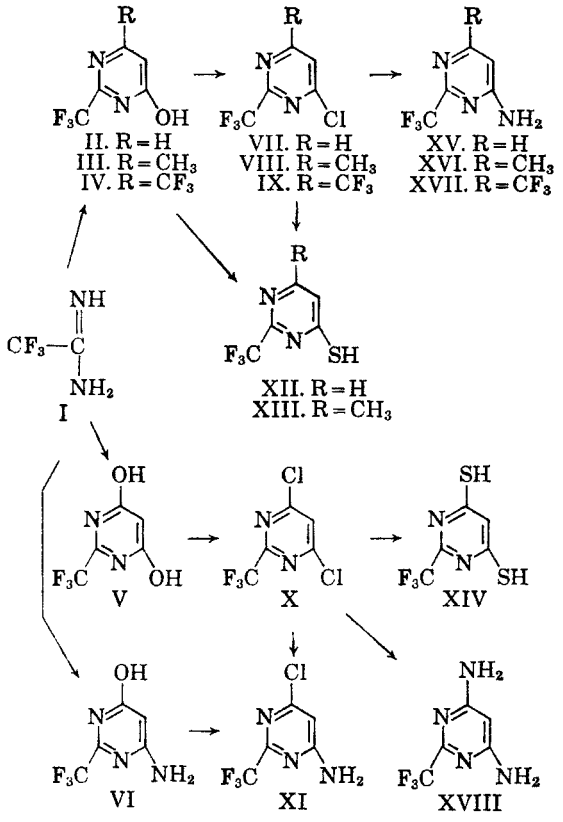
SCHEME A

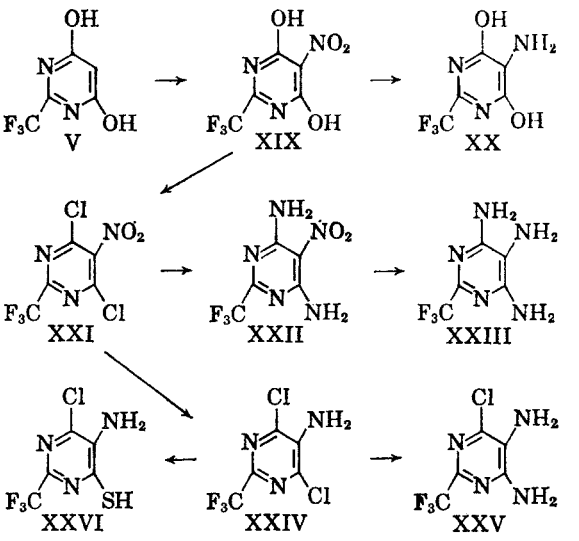


VIII and X were treated with potassium hydrogen sulfide and converted into the mercapto compounds, 4-mercapto-2-trifluoromethylpyrimidine (XII), 4-mercapto - 6 - methyl - 2 - trifluoromethylpyrimidine (XIII) and 4,6-dimercapto-2-trifluoromethylpyrimidine (XIV). The mercapto compounds (XII, XIII and XIV) were also prepared from the reaction between the corresponding hydroxy derivatives and phosphorus pentasulfide in xylene. The amination of VII, VIII and IX with alcoholic ammonia at 100° gave the amines XV, XVI, and XVII, respectively. The diamine, XVIII, was prepared from X with alcoholic ammonia at 150–170°, whereas XI was obtained by introducing ammonia gas into an ethereal solution of X.

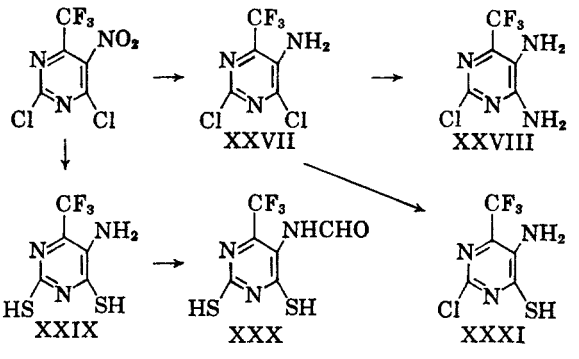
In Scheme B, an attempt to introduce an amine group at the 5-position of V, *via* initial nitrosation, was unsuccessful. The usual nitrosation techniques were ineffective. However, 4,6-dihydroxy-5-nitro-2-trifluoromethylpyrimidine (XIX), was prepared by simply evaporating a solution of V in 70% nitric acid on the water bath. The 5-amino compound, XX, was then prepared by reduction of XIX with alkaline sodium dithionite.

Compound XIX was converted into 4,6-dichloro-5-nitro-2-trifluoromethylpyrimidine (XXI), in good yield, by treatment with phosphorus oxychloride in dimethylaniline at 70–80°. Conversion of XXI to 4,6-diamino-5-nitro-2-trifluoromethylpyrimidine (XXII) was carried out by reaction with ammonia in benzene solution. 4,5,6-Triamino-2-trifluoromethylpyrimidine (XXIII) was obtained by reducing XXII with iron and acetic acid. Similar reduction, with iron-acetic acid, converted XXI to 5-amino-4,6-dichloro-2-trifluoromethylpyrimidine (XXIV). Subsequent treatment of XXIV with ethanolic ammonia, at 100°, gave 4,5-diamino-6-chloro-2-trifluoromethylpyrimidine. The reaction of XXIV with one equivalent of potassium hydrogen sulfide afforded XXVI.

SCHEME B



SCHEME C



2,4 - Dichloro - 5 - nitro - 6 - trifluoromethylpyrimidine[10] (scheme C) was reduced to XXVII with iron and acetic acid. Conversion of XXVII to XXVIII was accomplished with ethanolic ammonia at 100°. 5-Amino-2,4-dimercapto-6-trifluoromethylpyrimidine (XXIX) was prepared from 2,4 - dichloro - 5 - nitro - 6 - trifluoromethylpyrimidine through reaction with a mixture of potassium hydrogen sulfide and hydrogen sulfide. Heating XXIX with formic acid gave the formyl derivative XXX. The treatment of XXVII with an equivalent of potassium hydrogen sulfide afforded the compound XXXI.

All of these compounds are being screened, at present, through the Cancer Chemotherapy National Service Center of the National Institutes of Health.

The synthesis of various condensed pyrimidines, from the intermediates reported herein, will be described in future publications.

EXPERIMENTAL[12]

4-Hydroxy-2-trifluoromethylpyrimidine (II). A mixture of 10 g. (0.09 mole) of I and 17 g. (0.12 mole) of sodium ethyl formylacetate in 60 ml. of water was kept overnight at room temperature and then acidified with hydrochloric acid. The deposited colorless crystals were collected. From the filtrate, another crop of colorless crystals was obtained which was combined with the above to give 8.2 g. of II (55.6% yield).

A small sample was recrystallized from water to give II as colorless prisms, m.p. 167–168°.

Anal. Calcd. for $C_5H_3F_3N_2O$: C, 36.59; H, 1.83; N, 17.07. Found: C, 36.54; H, 2.04; N, 16.50.

4-Hydroxy-6-methyl-2-trifluoromethylpyrimidine (III). To a solution of 4.68 g. (0.036 mole) of ethyl acetoacetate in 25 ml. of ethanol, containing 0.8 g. of sodium metal (0.035 g.-atom), was added 3.36 g. (0.03 mole) of I. The mixture was refluxed for 3 hr. with stirring. After evaporation of the solvent, the residue was dissolved in 20 ml. of water and acidified with hydrochloric acid. The colorless crystals were collected. From the filtrate another crop of crystals was obtained which was combined with the above. Recrystallization from benzene gave III as colorless plates (3.2 g., 60%), m.p. 140–141°.

Anal. Calcd. for $C_6H_5F_3N_2O$: C, 40.49; H, 2.81; N, 15.73. Found: C, 40.43; H, 2.75; N, 15.34.

2,6-Bistrifluoromethyl-4-hydroxypyrimidine (IV). This synthesis was identical with that used for the preparation of compound III, using 25 g. (0.22 mole) of I, 42 g. (0.23 mole) of ethyl trifluoroacetoacetate and 5.5 g. (0.24 g.-atom) of sodium metal. Recrystallization from ligroin gave IV as colorless prisms (18 g. 35.3%), m.p. 117–118°.

Anal. Calcd. for $C_6H_2F_6N_2O$: C, 31.03; H, 0.86. Found: C, 31.34; H, 1.20.

4,6-Dihydroxy-2-trifluoromethylpyrimidine (V). V was prepared in 62% yield as described above for III using 62 g. (0.55 mole) of I, 84 g. of diethyl malonate (0.525 mole) and 13 g. (0.56 g.-atom) of sodium metal. A small sample was purified by atmospheric sublimation; m.p. 265°.

Anal. Calcd. for $C_5H_3F_3N_2O_2$: C, 33.33; H, 1.67. Found: C, 33.77; H, 1.73.

6-Amino-4-hydroxy-2-trifluoromethylpyrimidine (VI). This synthesis was the same as described for compound III, using 6.9 g. of I (0.06 mole), the same amount of ethyl cyanoacetate and 2.8 g. (0.12 g.-atom) of sodium metal; yield, 8 g. (74%). Recrystallization from 50% ethanol gave VI as colorless needles or prisms; m.p. 252°.

Anal. Calcd. for $C_5H_4F_3N_3O$: C, 33.52; H, 2.23. Found: C, 33.64; H, 1.90.

Chlorination of 4-hydroxy-2-trifluoromethylpyrimidines. A mixture of 1 g. of 4,6-dihydroxy-2-trifluoromethylpyrimidine (V), 5 ml. of phosphorus oxychlorde and 1 ml. of dimethylaniline was refluxed for 2 hr. The excess of phosphorus oxychloride was removed *in vacuo*. The residue was poured on crushed ice, and then extracted with ether. The extract was washed with a small amount of water and dried over sodium sulfate. After removal of the solvent, the oily residue was distilled *in vacuo* to give 0.7 g. of a colorless oil (X). The other chloro compounds, shown in Table I, were prepared by the same method.

Preparation of 4-mercapto-2-trifluoromethylpyrimidines. Method (A). A mixture of 2 g. (0.0092 mole) of 4,6-dichloro-2-trifluoromethylpyrimidine (X) and 4 g. of potassium hydrogen sulfide (0.055 mole) in 30 ml. of methanol, containing a small amount of water, was refluxed for a short time. The solvent was removed. The residue was diluted with a small amount of water and acidified with hydrochloric acid. The resulting yellow needles were collected. The filtrate was extracted with ether and a second crop of crystals was obtained from the ether extract. Recrystallization of the second crop from ligroin afforded yellow needles which were combined with the first crop of crystals to give 1.7 g. of XIV (87%). A small sample was recrystallized from ligroin to give XIV as yellow needles which melted at 150–151°. The other mercapto compounds, shown in Table II, were prepared by essentially the same method.

Method (B). An intimate mixture of 1.5 g. of 4,6-dihydroxy-2-trifluoromethylpyrimidine (V) and 7.5 g. of phosphorus pentasulfide was suspended in 50 ml. of xylene and heated at 130–140° for 7 hr. with intermittent stirring. After cooling, the resulting cake was extracted with ether and the filtrate was extracted with dilute sodium hydroxide. The sodium hydroxide extract was acidified with hydrochloric acid and then extracted with ether. Both ether extracts were combined and dried over sodium sulfate. Upon removal of the solvent, there were obtained yellow needles which were recrystallized from ligroin; yield, 1.1 g. (64.7%). The product was identical with 4,6-dimercapto-2-trifluoromethylpyrimidine (XIV) prepared by Method (A); mixed m.p. 149–151°. Compounds XII and XIII were also obtained in the same manner from the corresponding hydroxypyrimidines.

Preparation of 4-amino-2-trifluoromethylpyrimidines. Three grams (0.014 mole) of 4,6-dichloro-2-trifluoromethylpyrimidine (X) was dissolved in 50 ml. of ethanol containing 3 g. (0.176 mole) of ammonia and heated in an autoclave at 170° for 5 hr. The solvent was removed and to the residue a small amount of water was added. The mixture was extracted with ethyl acetate and dried over sodium sulfate. From the extract there was obtained 2.5 g. (99.6%) of colorless crystals. Further recrystallization from dilute methanol gave colorless needles of XVIII; m.p. 243°.

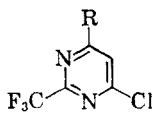
Anal. Calcd. for $C_5H_5F_3N_4$: C, 33.71; H, 2.81. Found: C, 33.39; H, 2.98.

All the other 4-amino derivatives were prepared by the same method. See Table III.

4,6-Dihydroxy-5-nitro-2-trifluoromethylpyrimidine (XIX). Four and two-tenths grams of 4,6-dihydroxy-2-trifluoromethylpyrimidine (V) was added to 80 ml. of 70% nitric acid. Upon evaporation to dryness, slightly greenish yellow crystals of XIX were obtained, m.p. 148–150° dec. A small sample was sublimed *in vacuo* for microanalysis.

Anal. Calcd. for $C_6H_2F_3N_3O_4$: C, 26.67; H, 0.89. Found: C, 26.86; H, 1.26.

TABLE I

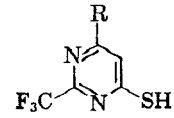


No.	R	Reflux Time (Hr.)	Yield, %	B.P. (Mm.)	Appearance[a]
VII	H	1.5	70	45 (4)	Colorless oil
VIII	CH_3	1	64	48 (2)	Colorless oil
IX	CF_3	1	48	43–44 (15)	Colorless oil
X	Cl	2	59	38 (1)	Colorless oil
XI	NH_2	1.5	27	m.p. 148–151°	Colorless prisms or plates from benzene

[a] Compounds VII, VIII, IX, and X solidified when stored in the freezer.

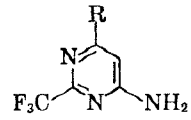
(12) All melting points are uncorrected. Elemental analyses are by Huffman Microanalytical Lab., Wheatridge, Colo., and Schwarzkopf Microanalytical Lab., Woodside 77, N. Y.

TABLE II



No.	R	Yield, %	Appearance	M.P.	Calcd., %	Found, %
XII	H	84	Yellow prisms (ligroin)	87–90	C, 33.3 H, 1.66	33.62 1.73
XIII	CH_3	70	Yellow prisms (ligroin)	86–87	C, 37.1 H, 2.58	37.45 2.86
XIV	SH	87	Yellow needles (ligroin)	150–151	C, 28.3 H, 1.41 S, 30.2	27.76 1.44 30.61

TABLE III



No.	R	Reaction Temp.	Time (Hr.)	Appearance	M.P.	Yield, %	Calcd., %	Found, %
XV	H	100	2	Colorless needles (dil. methanol)	180–181	95.8	C, 36.81 H, 2.45 F, 34.97	36.82 2.62 34.69
XVI	CH_3	100	2	Colorless prisms (benzene)	173–174	87.8	C, 40.68 H, 3.39	41.09 3.33
XVII	CF_3	100	2	Colorless prisms (ligroin)	149–150	93.9	C, 31.17 H, 1.30 F, 49.35	31.06 1.40 49.76

5-Amino-4,6-dihydroxy-2-trifluoromethylpyrimidine (XX). One gram (0.0044 mole) of 4,6-dihydroxy-5-nitro-2-trifluoromethylpyrimidine (XIX) was dissolved in 10 ml. of water containing 0.5 g. (0.0090 mole) of potassium hydroxide. To this solution sodium dithionite was added until the color of the reaction mixture remained constant, (slightly yellow). After cooling, it was extracted with ethyl acetate and dried over sodium sulfate. From the extract, 0.8 g. (93%) of crystalline XX was obtained.

A small sample purified by sublimation gave XX as colorless crystals, m.p. 257–259° dec.

Anal. Calcd. for $C_5H_4F_3N_3O_2$: C, 30.77; H, 2.05; F, 29.23. Found: C, 30.78; H, 2.05; F, 29.54.

4,6-Dichloro-5-nitro-2-trifluoromethylpyrimidine (XXI). To a mixture of 34 g. (0.15 mole) of 4,6-dihydroxy-5-nitro-2-trifluoromethylpyrimidine (XIX) and 170 ml. of phosphorus oxychloride, 34 ml. of dimethylaniline was added gradually and the reaction mixture was heated at 70–80° for 1.5 hr. The excess of phosphorus oxychloride was removed, the residue was poured onto crushed ice (*ca.* 800 g.), extracted with ether and dried over sodium sulfate. After removal of the solvent, the oily residue was taken up in ligroin, and treated with charcoal to give XXI as pale yellow prisms, (35 g., 89%).

Small samples were purified by vacuum distillation (b.p. 72°/6 mm.) or sublimation; slightly colored prisms, m.p. 49–50°.

Anal. Calcd. for $C_5Cl_2F_3N_3O_2$: C, 22.90; H, 0. Found: C, 22.71; H, 0.

4,6-Diamino-5-nitro-2-trifluoromethylpyrimidine (XXII). To a solution of 8 g. of 4,6-dichloro-5-nitro-2-trifluoromethylpyrimidine (XXI) in 150 ml. of benzene, ammonia gas was introduced at 50–60° for 2 hr. The reaction mixture was evaporated and the residue was washed with water. Recrystallization from methanol gave XXII as slightly colored needles (6.2 g., 92%), m.p. 293°.

Anal. Calcd. for $C_5H_4F_3N_5O_2$: C, 26.90; H, 1.79; F, 25.56. Found: C, 27.36; H, 1.82; F, 26.08.

4,5,6-Triamino-2-trifluoromethylpyrimidines (XXIII). A mixture of 3.1 g. of 4,6-diamino-5-nitro-2-trifluoromethylpyrimidine (XXII), 3.5 g. of iron and 250 ml. of acetic acid was heated at 50° for 3 hr. with stirring. The reaction mixture was filtered and the filtrate was evaporated. To the residue 100 ml. of water was added and the mixture was extracted with ethyl acetate. The extract was washed with dilute sodium hydroxide, then water, and dried over sodium sulfate. From the extract, there was obtained 2.5 g. (92.6%) of yellow crystals which were recrystallized from water to give XXIII as colorless needles, m.p. 263–264°. In another experiment, a small amount of colorless scales was also obtained. Recrystallization from methanol gave colorless scales which melted *ca.* 315°. This was probably an acetyl derivative.

Analysis of the main product is shown as follows:

Anal. Calcd. for $C_5H_6F_3N_5$: C, 31.08; H, 3.10; F, 29.53. Found: C, 31.69; H, 3.50; F, 29.50.

5-Amino-4,6-dichloro-2-trifluoromethylpyrimidine (XXIV). A mixture of 24 g. of 4,6-dichloro-5-nitro-2-trifluoromethylpyrimidine (XXI), 20 g. of iron powder and 500 ml. of acetic acid was heated at 40–50° for 2 hr. When the reaction was exothermic, it was necessary to moderate it with a cooling bath.

After filtering the reaction mixture, the filtrate was evaporated *in vacuo*. The residue was diluted with water and extracted with ether. The extract was washed with dilute sodium hydroxide and dried over sodium sulfate. After removal of the solvent, there was obtained a pale yellow oil which soon solidified. The solid was recrystallized from ligroin to give XXIV as colorless needles, (16 g., 76%), m.p. 56–59°.

Anal. Calcd. for $C_5H_2Cl_2F_3N_3$: C, 25.86; H, 0.86; F, 24.57. Found: C, 25.63; H, 0.91; F, 24.80.

4,5-Diamino-6-chloro-2-trifluoromethylpyrimidine (XXV). Sixteen grams of 5-amino-4,6-dichloro-2-trifluoromethylpyrimidine (XXIV) was dissolved in 100 ml. of ethanol containing 10 g. of ammonia and heated in an autoclave for 4 hr. at 100°. The reaction mixture was evaporated, the residue was washed with water and dried; yield, 14.3 g. (96%). A small sample was purified by sublimation to give XXV as colorless crystals, m.p. 243–244°

Anal. Calcd. for $C_5H_4ClF_3N_4$: C, 28.24; H, 1.88. Found: C, 28.83; H, 1.94.

5-Amino-6-chloro-4-mercapto-2-trifluoromethylpyrimidine (XXVI). To a solution of 7 g. of potassium hydrogen sulfide (0.10 mole) in 20 ml. of water and 130 ml. of methanol, 11 g. (0.05 mole) of 5-amino-4,6-dichloro-2-trifluoromethylpyrimidine (XXIV) was added and the reaction mixture was heated at 50–60° for 1.5 hr. The solvent was removed and to the residue 100 ml. of water was added. The mixture was slightly acidified with acetic acid, extracted with ether and dried with sodium sulfate. Removal of the solvent gave XXVI as yellow needles (9.3 g., 81%). Recrystallization from methanol-benzene gave yellow needles, m.p. 175–176° dec.

Anal. Calcd. for $C_5H_3ClF_3N_3S$: C, 26.14; H, 1.31. Found: C, 26.19; H, 1.24.

5-Amino-2,4-dichloro-6-trifluoromethylpyrimidine (XXVII). A mixture of 12.5 g. of 2,4-dichloro-5-nitro-6-trifluoromethylpyrimidine[10] 100 ml. of acetic acid, and 12 g. of iron powder was heated at 60° for 1 hr. with stirring. The reaction mixture was evaporated. To the residue 100 ml. of water was added, the mixture was extracted with ether, and the extract was washed with dilute sodium hydroxide and dried over sodium sulfate. From the extract, there was obtained 10 g. (86.6%) of XXVII as slightly colored crystals which were recrystallized from ligroin to colorless crystals, m.p. 72°.

Anal. Calcd. for $C_5H_2Cl_2F_3N_3$: C, 25.86; H, 0.86. Found: C, 26.46; H, 0.98.

2-Chloro-4,5-diamino-6-trifluoromethylpyrimidine (XXVIII). Ten grams of 5-amino-2,4-dichloro-6-trifluoromethylpyrimidine (XXVII) was dissolved in 100 ml. of ethanol containing 10 g. of ammonia and the solution was heated at 100° for 4 hr. The solvent was evaporated, and the residue was washed with water and dried to yield 8.6 g. (99%) of XXVIII. Recrystallization from methanol-benzene gave colorless prisms; m.p. 226–227°.

Anal. Calcd. for $C_5H_4ClF_3N_4$: C, 28.24; H, 1.88. Found: C, 28.23; H, 2.07.

5-Amino-2,4-dimercapto-6-trifluoromethylpyrimidine (XXIX). Ten grams of freshly distilled 2,4-dichloro-5-nitro-6-trifluoromethylpyrimidine[10] was added to a solution of 13 g. (0.18 mole) of potassium hydrogen sulfide in 200 ml. of water. The reaction mixture was stirred at room temperature to form a dark red solution. (After about 1.5 hr. a yellow precipitate began to separate). Hydrogen sulfide gas was introduced slowly to this reaction mixture and it was heated on a water bath. After heating for 2 hr. the reaction mixture was decolorized and the filtrate was neutralized with acetic acid. It was extracted with ethyl acetate and dried over sodium sulfate. From the extract, there was obtained 8 g. (93%) of XXIX as yellow crystals. Recrystallization from benzene containing methanol gave yellow needles. This product decomposed gradually above 240°.

Reaction of XXIX with formic acid. A mixture of 1 g. (0.0044 mole) of 5-amino-2,4-dimercapto-6-trifluoromethylpyrimidine (XXIX) and 30 ml. of formic acid was refluxed for 2 hr. The yellow reaction mixture was evaporated almost to dryness, and a small amount of water was added. The insoluble yellow crystals were collected and washed with water to give *ca.* 1 g. (89%), m.p. *ca.* 250°. Recrystallization from dilute methanol gave yellow needles, m.p. 255–256°. This compound did not change on heating at its melting point. A small sample was sublimed and microanalysis indicated that it was 2,4-dimercapto-5-formamido-6-trifluoromethylpyrimidine (XXX).

Anal. Calcd. for $C_6H_4F_3N_3OS_2$: C, 28.24; H, 1.57. Found: C, 28.70; H, 1.58.

5-Amino-2-chloro-4-mercapto-6-trifluoromethylpyrimidine (XXXI). To a solution of 5 g. (0.069 mole) of potassium hydrogen sulfide hemihydrate in 50 ml. of methanol, containing a small amount of water, 7.6 g. (0.033 mole) of 5-amino-2,4-dichloro-6-trifluoromethylpyrimidine (XXVII) was added, and the reaction mixture was heated at 60° for 3 hr. The solvent was removed and 100 ml. of water was added to the residue. It was neutralized with acetic acid, extracted with ether and dried over sodium sulfate. From the extract, 5.8 g. (76.6%) of yellow needles was obtained. Recrystallization from ligroin provided XXXI as yellow needles, m.p. 132° dec.

Anal. Calcd. for $C_5H_3ClF_3N_3S$: C, 26.14; H, 1.31. Found: C, 26.64; H, 1.56.

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