—A mixture of 4 g. (0.032 mole) of II and 2.65 g. (0.035 mole) of chloroacetonitrile in 20 ml. of benzene was refluxed for 90 min. The separated hydrochloride was collected, the base liberated with 10% sodium hydroxide, extracted with ether and distilled.

3-β-Aminoethyl-8-methyl-3,8-diazabicyclo[3.2.1]octane (XXIV).—To a stirred suspension of 2.3 g. (0.06 mole) of lithium aluminum hydride in 150 ml. of dry tetrahydrofuran at 0°, 3.2 g. (0.0197 mole) of XXIII diluted with 10 ml. of tetrahydrofuran was added. The reaction mixture was refluxed for 3 hr., cooled to −5° and cautiously decomposed with 8 ml. of water. After stirring for 1 hr. at room temperature, the inorganic material was filtered and thoroughly washed with tetrahydrofuran. The filtrate was dried over sodium sulfate, the solvent evaporated and the residue distilled.

3-Guanidinoethyl-8-methyl-3,8-diazabicyclo[3.2.1]octane (XXV).—A stirred mixture of 2.2 g. (0.013 mole) of XXIV, 4.8 g. (0.026 mole) of S-ethylisothiuronium bromide and 30 ml. of chloroform was refluxed for 5 hr., under an efficient hood. A viscous oil separated and solidified on cooling. The chloroform solution was decanted and stored. The solid crop (4 g.) after washing with ether was crystallized twice from isopropyl alcohol (200 ml.) to give 1.7 g. (35%) of the dihydrobromide of XXV, m.p. 230–233°. The chloroform solution was evaporated and the oily residue was crystallized from isopropyl alcohol to give 1.7 g. (45%) of XXV monohydrobromide.

8-Methyl-3-nitroso-3,8-diazabicyclo[3.2.1]octane (XXVI).—To a stirred solution at 0° of 7.3 g. (0.058 mole) of II in 29 ml. of 2 *N* hydrochloric acid, was added dropwise a solution of 4.5 g. (0.065 mole) of sodium nitrite in 10 ml. of water. The reaction mixture was kept at room temperature for 2 hr., cooled, made alkaline with 50% sodium hydroxide solution and extracted with ether. The extract was dried over sodium sulfate, the solvent evaporated and the residue distilled.

3-Amino-8-methyl-3,8-diazabicyclo[3.2.1]octane (XXVII).—To a stirred suspension of 3.8 g. (0.1 mole) of lithium aluminum hydride in 200 ml. of dry tetrahydrofuran, a solution of 7.6 g. (0.049 mole) of XXVI in 40 ml. of tetrahydrofuran was added at such a rate that the temperature was kept at 40–45°. At the end of the addition, the mixture was refluxed for 6 hr., then cooled to −5° and cautiously decomposed with 13 ml. of water. After stirring for 1 hr. at room temperature, the reaction mass was filtered, washed with ether, the filtrate was collected and dried over sodium sulfate. The solvent was evaporated, the oily residue diluted with 20 ml. ether and dried again over sodium hydroxide. After evaporation of the solvent, the oil was distilled to yield 5.5 g. (82%) of XXVII, b.p. 110–115° (20 mm.). The product was highly hygroscopic. The *dihydrochloride* was obtained by adding the base to alcoholic hydrogen chloride. By mixing an ether solution of the base with an ethanol solution of *p*-nitrobenzaldehyde, yellow crystals of the *3-p-nitrobenzalamino derivative* separated, m.p. 96–98°. It was transformed to the corresponding *hydrochloride*, m.p. 250–252° (ethanol).

Anal. Calcd. for $C_{14}H_{19}ClN_4O_2$: N, 18.05; Cl, 11.45. Found: N, 17.99; Cl, 11.40.

3-Carbethoxy-8-methyl-3,8-diazabicyclo[3.2.1]octane (XXVIII).—To a mixture of 2.1 g. (0.0166 mole) of II and 10 ml. of 2 *N* sodium hydroxide stirred at 0°, 2.2 g. (0.02 mole) of ethyl chlorocarbonate was added dropwise. The mixture was stirred for 2 hr. at room temperature, the reaction product was extracted with ether, dried and distilled.

3-Diethylcarbamyl-8-methyl-3,8-diazabicyclo[3.2.1]octane (XXIX).—A suspension of 3.65 g. (0.029 mole) of II in 15 ml. of 2 *N* sodium hydroxide was treated dropwise and with stirring at 0°, with 4 g. (0.03 mole) of diethyl chloroformamide.[27] The temperature was allowed to rise to 40° and after 1 hr. the mixture was extracted with ether. The extract was dried over solid sodium hydroxide and distilled. *The citrate* (XXIXb) was prepared by mixing an ethanolic solution of citric acid and an ether solution of the base.

3-Phenylcarbamyl-8-methyl-3,8-diazabicyclo[3.2.1]octane (XXX).—A mixture of 2.52 g. (0.02 mole) of II, 2.4 g. (0.02 mole) of phenyl isocyanate and 10 ml. of benzene was refluxed for 30 min. After cooling the solid product was collected and crystallized from ethanol.

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The Synthesis and Antineoplastic Properties of Selenoguanine, Selenocytosine and Related Compounds[1]

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Selenoguanine, selenocytosine, diselenothymine, and 5-methylselenocytosine have been synthesized. In several experimental murine neoplasms selenoguanine and thioguanine showed comparable antitumor activities; however, some differences were noted. These compounds exhibited cross-resistance.

During a course of study of selenium analogs of physiologically active sulfur compounds, 2-selenouracil, 2-selenothymine, and 6-selenopurine (I) were synthesized.[2] As an inhibitor of the growth of the mouse lymphoma L-1210, the activity of (I) was equivalent to that of 6-mercaptopurine,[3] a clinically useful antileukemic agent.[4] In the other mouse tumors studied[3] (I) was less active than mercaptopurine. On the other hand, (I) had greater antibacterial activity[5] and greater ability to inhibit the incorporation of formate into purines[5] than did its sulfur analog.

Selenopurine is rather unstable, its half-life in pH 7 phosphate-citrate buffer being only 6 hours.[6] 6-Selenopurine-9-β-D-ribonucleoside has a half-life of only 1 hour under these conditions.[6]

The synthesis of 2-amino-6-selenopurine (selenoguanine) (II) was undertaken in the hope that resonance

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stabilization would make this compound more stable than is I.

6-Thioguanine has been studied extensively as an antitumor agent in animals and to a lesser extent as an antileukemic agent in man. It has been suggested that the antineoplastic action of thioguanine is related to the ability of this compound to be incorporated into deoxyribonucleic acid (DNA),[7] while the postulate has been presented that the strength of hydrogen-bonding between the sulfur of thioguanine and the amino group of cytosine facing it in the double helix of DNA might be implicated in the mechanism of action of this compound.[8] Since polarization increases in passing from carbamoyl to thiocarbamoyl to selenocarbamoyl compounds[2,9,10] and since such polarization should affect the strength of hydrogen-bonding involving sulfur and selenium, respectively, the synthesis and study of selenocytosine and of selenoguanine were of interest; if incorporated into DNA, each of these compounds might form unusual hydrogen bonds with amino groups facing the polarized carbon-selenium bond. That selenocarbamoyl compounds are capable of hydrogen-bonding has been demonstrated recently.[11]

Selenoguanine was synthesized in excellent yield by the addition of sodium hydroselenide to 2-amino-6-chloropurine, 4-amino-2-selenopyrimidine by the reaction of diselenouracil[2] with ammonia in a fashion analogous to the synthesis of thiocytosine from dithiouracil.[12] Diselenothymine was made by the addition of sodium hydroselenide to 2,4-dichloro-5-methylpyrimidine.[13] Addition of ammonia converted the product to seleno-5-methylcytosine. While the reaction of uracil with formaldehyde readily yields 5-hydroxymethyluracil,[14] attempts to cause formaldehyde to react with diselenouracil or with selenocytosine were unsuccessful.

Table I indicates the effect of (II), when administered by different routes, on the growth of the L5178Y lymphoma in mice. Intraperitoneal and subcutaneous injections of (II) produced essentially the same degree of tumor-inhibition, while oral doses were less effective. The relative potencies of 6-mercaptopurine (II) and 6-thioguanine on three transplantable tumors are shown in Table II; each of the agents was capable of inhibiting the growth of the three neoplasms. Selenoguanine and thioguanine appeared to be the most potent in this respect, with II producing comparable inhibition with the least toxicity. These results suggest that II has a higher therapeutic index than thioguanine and agree with the findings that the maximum tolerated dose of II was 8 times that of thioguanine.[5]

Cross-resistance between mercaptopurine II and thioguanine was exhibited by these compounds on a mercaptopurine-resistant subline of the L1210 lymphoma (Table III). Similar results were also obtained using 6C3HED lymphosarcoma ascites cells, a finding which suggests that these drugs have similar modes of action.

TABLE I

THE EFFECT OF SELENOGUANINE ADMINISTERED BY DIFFERENT ROUTES ON THE GROWTH OF SUBCUTANEOUS IMPLANTS OF THE L5178Y LYMPHOMA IN BDF_1 MICE

I. Efficacy of 8 mg./kg. daily for 6 days

Route of administrations	Av. Δ in body wt., g.[b]	Mortality	Av. tumor wt., mg.[c]	Approx. % tumor inhibition
...	+1.6	0/10	262 ± 19	..
I.P.	−2.9	0/10	69 ± 6	77
S.C.	−0.4	0/10	77 ± 8	71
P.O.[a]	+0.6	0/10	219 ± 22	16

II. Efficacy of Graded Oral Doses

Daily dosage, mg./kg.	Av. Δ in body wt., g.[b]	Mortality	Av. tumor wt., mg.[c]	Approx. % tumor inhibition
..	+2.0	0/10	420 ± 30	..
8	+0.7	0/10	295 ± 26	30
16	−0.2	0/10	354 ± 28	16
24	−0.6	0/10	276 ± 30	34
32	−1.8	0/10	163 ± 12	61

[a] The volume of each dose, administered once daily by gastric intubation for 6 consecutive days was in every case 0.2 ml. per mouse per day. [b] Average weight change from onset to termination of therapy. [c] The average weight of the tumors, together with the standard error of the mean, ($\sqrt{\Sigma d^2/n(n-1)}$), is given for each group.

The comparative effects of II and thioguanine on the survival time of mice bearing an ascites cell form of sarcoma 180 are shown in Table IV. The magnitude of the carcinostatic effects of both agents was similar; however, II was capable of producing tumor-inhibition over a wider dose range, again indicating a better therapeutic index.

The data in Table V show that II in daily doses ranging from 3.9 to 6.5 mg./kg. did not enhance the tumor-inhibitory properties of azaserine in the Ehrlich ascites carcinoma, although 1 mg. of thioguanine/kg. daily markedly potentiates the carcinostatic properties of azaserine in this neoplasm.[15] The biochemical basis for this difference is unknown, but it may be related to the degree of incorporation of each analog into DNA.

Selenocytosine and thiocytosine were tested at levels of 50 and 100 mg./kg. daily for 6 consecutive days in mice bearing ascites cell growths of lymphoma L5178Y; neither compound significantly prolonged the survival time of mice bearing this neoplasm.

Experimental[16]

2-Amino-6-selenopurine (Selenoguanine) (II).—Freshly prepared hydrogen selenide was bubbled through a solution of 0.64 g. (0.028 mole) of sodium in 120 ml. of absolute ethanol for 1 hr. Into the clear orange solution was introduced 2.0 g. (0.0106 mole) of 2-amino-6-chloropurine[17] (90% pure). The mixture was heated to reflux for 19 hr. After cooling, addition of 60 ml. of water and 5 ml. of glacial acetic acid resulted in the precipitation of product mixed with colloidal selenium. The solid was removed by filtration after refrigeration. The mixture was placed in 30

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(17) We are indebted to G. B. Elion, Wellcome Research Laboratories, Tuckahoe, N. Y., for generously supplying this compound.

TABLE II

EFFECTS OF 6-MERCAPTOPURINE, SELENOGUANINE, AND THIOGUANINE ON THE GROWTH OF SUBCUTANEOUS IMPLANTS OF L1210 LYMPHOMA, L5178Y LYMPHOMA, AND SARCOMA 180

		Sarcoma 180					L1210 Lymphoma				L5178Y Lymphoma			
Treatment	Daily dosage,[a] mg./kg.	Av. Δ in body weight,[b] g.	Mortality 1st week	Mortality 2nd week	Av. tumor weight 1st week,[c] mg.	Approx. % tumor inhibition	Av. Δ in body weight,[b] g.	Mortality	Av. tumor weight,[c] mg.	Approx. % tumor inhibition	Av. Δ in body weight,[b] g.	Mortality	Av. tumor weight,[c] mg.	Approx. % tumor inhibition
Mercaptopurine	64						−2.0	0/10	663 ± 27 303 ± 16	54				
	40	+3.4	0/10	0/10	1001 ± 88 349 ± 37	65	−0.5	0/10	663 ± 27 410 ± 27	38	−1.3	0/10	426 ± 47 251 ± 32	41
	32	+3.0	0/10	0/10	1001 ± 88 443 ± 28	56	+0.2	0/10	663 ± 27 452 ± 23	32				
	16	+3.5	0/10	0/10	1001 ± 88 511 ± 32	49								
	8	+3.6	0/10	0/10	1001 ± 88 575 ± 32	43								
Selenoguanine	16	−2.0	0/10	2/10	1001 ± 88 438 ± 54	56	−2.6	0/10	365 ± 17 58 ± 9	84	−4.0	0/10	427 ± 47 33 ± 3	92
	8	+2.0	0/10	1/10	1001 ± 88 955 ± 89	5	−2.3	0/20	365 ± 17 179 ± 15	51	−1.9	0/10	427 ± 47 70 ± 9	84
	4						−1.5	0/10	365 ± 17 302 ± 14	17				
Thioguanine	8						−5.4	5/10	365 ± 17 41 ± 3	89				
	4	−2.2	0/10	7/10	1001 ± 88 388 ± 48	61	−3.8	1/10	365 ± 17 150 ± 23	59	−2.7	0/10	427 ± 47 42 ± 4	90
	2	+1.4	0/10	1/10	1001 ± 88 602 ± 49	40	−2.5	0/20	365 ± 17 269 ± 16	26	−1.8	0/10	427 ± 47 199 ± 23	53

[a] The compounds were suspended in 0.25% carboxymethylcellulose and injected starting 24 hr. after implantation of the tumors, intraperitoneally once daily for 6 days in the case of the two lymphomas and once daily for 7 days in the case of sarcoma 180. [b] Average weight change from onset to termination of therapy. [c] The average weight of the tumors, together with the standard error of the mean ($\sqrt{\Sigma d^2/n(n-1)}$) is given for each group of animals in comparison with its control group; in each case, the latter figure is placed above that of the experimental group.

TABLE III

THE EFFECT OF SELENOGUANINE AND RELATED COMPOUNDS ON THE GROWTH OF SUBCUTANEOUS IMPLANTS OF A 6-MERCAPTOPURINE-RESISTANT SUBLINE OF THE L1210 LYMPHOMA

Treatment	Daily dosage, mg./kg.[a]	Av. Δ in body wt., g.[b]	Av. tumor wt., mg.[c]	Approx. % inhibition
...	..	+0.4	342 ± 28	..
6MP	40	−0.6	316 ± 30	8
SeG	16	−3.4	354 ± 30	0
TG	4	−3.8	306 ± 27	13

[a] Selenoguanine (SeG) and thioguanine (TG) were suspended in 0.25% carboxymethylcellulose; 6-mercaptopurine (6MP) was dissolved in pH 8 phosphate–citrate buffer. All compounds were injected intraperitoneally once daily for 6 consecutive days, starting 24 hr. after implantation of the tumors. [b] Average weight change from onset to termination of therapy. [c] The average weight of the tumors, together with the standard error of the mean, ($\sqrt{\Sigma d^2/n(n-1)}$), is given for each group.

TABLE IV

THE EFFECT OF SELENOGUANINE AND THIOGUANINE ON THE SURVIVAL TIME OF MICE BEARING SARCOMA 180 ASCITES CELLS

Treatment	Daily dosage, mg./kg.[a]	Av. survival, days	No. of 50-day survivors[b]	No. of regressions	Av. Δ body wt., g.[c]
Control	...	10.9	0/10	0/10	+4.1
Selenoguanine	1.3	14.2	0/10	0/10	+7.2
	3.9	17.2	0/9	0/9	+7.4
	6.5	15.8	0/10	0/10	+4.5
	13.0	21.6	0/10	0/10	+1.6
	19.5	17.2	0/10	0/10	0.0
Thioguanine	1.0	18.0	1/10	0/10	+4.0
	3.0	16.7	1/10	1/10	−0.6
	5.0	10.9	0/10	0/10	+0.8

[a] Therapy was indicated 24 hr. after implantation of tumor cells, with the indicated daily dosage given for 6 consecutive days. [b] Mice surviving over 50 days and tumor-free animals were calculated as 50-day survivors in the determination of the average survival time. [c] Average weight change from onset to termination of therapy.

ml. of warm 3% sodium carbonate solution. Selenium was filtered off and the clear, bright yellow filtrate acidified with acetic acid. A yield of 2.15 g. (94.7%) of light orange crystalline product separated. The product, which did not show a m.p., was analytically pure. Ultraviolet Spectrum: pH 10, $\lambda_{max.}$ 318 mμ, $\epsilon_{max.}$ 6,890; pH 8, $\lambda_{max.}$ 326 mμ, $\epsilon_{max.}$ 5,400; pH 1, $\lambda_{max.}$ 263 mμ, 372 mμ; $\epsilon_{max.}$ 5,620, 16,500.

Anal. Calcd. for $C_5H_5N_5Se$: C, 28.05; H, 2.35; N, 32.72. Found: C, 28.16; H, 2.55; N, 32.72.

4-Amino-2-selenopyrimidine (Selenocytosine).—A solution of 3.0 g. (0.0126 mole) of 2,4-diselenopyrimidine[3] in 30 ml. of concd. ammonium hydroxide was heated in a pressure bottle to 100° for 17 hr. After cooling, the solution was filtered and the volume of the filtrate was reduced to 10 ml. After chilling, the white product was recrystallized from boiling water with the aid of Norite. On cooling 1.1 g. (50%) of white, stubby needles melting at 248–250° dec. was obtained. Ultraviolet Spectrum: pH 1, $\lambda_{max.}$ 308 mμ; $\epsilon_{max.}$ 17,600.

Anal. Calcd. for $C_4H_5N_3Se$: C, 27.59; H, 2.89; N, 24.14. Found: C, 27.86; H, 3.11; N, 24.09.

2,4-Diseleno-5-methylpyrimidine (Diselenothymine).—A solution of 3.0 g. (0.13 mole) of sodium in 100 ml. of absolute ethanol was saturated with hydrogen selenide for 3 hr. After addition of 8.0 g. (0.0486 mole) of 2,4-dichloro-5-methylpyrimidine[14] the mixture was heated to reflux for 3 hr. After cooling, 100 ml. of water was added and the solution was chilled and filtered. Acidification of the filtrate with 20 ml. of acetic acid resulted in the formation of an orange precipitate that was removed by filtration. The product was dissolved in warm 3% sodium carbonate solution and reprecipitated with acetic acid. A yield of 6.0 g. (48.9%) of material melting at 186° dec. was obtained. The analytical sample was recrystallized from ethanol. Ultraviolet Spectrum: ethanol, $\lambda_{max.}$ 314 mμ, 350 mμ; $\epsilon_{max.}$ 19,200, 12,600.

TABLE V

THE EFFECT OF COMBINATIONS OF SELENOGUANINE AND AZASERINE ON THE SURVIVAL TIME OF MICE BEARING EHRLICH ASCITES CELLS

Treatment	Daily dosage, mg./kg.[a]	Av. survival, days	Av. Δ body wt., g.[b]
Control	...	10.0	+2.7
Selenoguanine	3.9	12.0	+4.4
	6.5	10.6	+4.2
	13.0	11.0	−3.3
Azaserine	0.2	19.8	+4.2
Azaserine[b] + SeG	0.2 + 3.9	23.8	−0.6
	0.2 + 6.5	23.4	−1.3

[a] Therapy was initiated 24 hr. after implantation of tumor cells, with the indicated daily dosage given for 6 consecutive days. Ten mice were used in each experimental group. [b] Average weight change from onset to termination of therapy.

Anal. Calcd. for $C_5H_6N_2Se_2$: C, 23.82; H, 2.30; N, 11.11. Found: C, 24.10; H, 2.58; N, 11.06.

4-Amino-5-methyl-2-selenopyrimidine (5-Methylselenocytosine).—A solution of 3.0 g. (0.012 mole) of 2,4-diseleno-5-methylpyrimidine in 30 ml. of concd. ammonium hydroxide was heated in a pressure bottle over a steam bath for 17 hr. The product was isolated in a fashion analogous to the preparation of selenocytosine. A yield of 1.2 g. (53.2%) of white needles melting at 227–229° dec. was obtained. Ultraviolet Spectrum: pH 1, λ_{max} 308 mμ; ϵ_{max}. 15,000.

Anal. Calcd. for $C_5H_7N_3Se$: C, 31.92; H, 3.75; N, 22.34. Found: C, 32.04; H, 4.00; N, 22.34.

Antitumor Testing.—These transplantable tumors were used in the studies: Sarcoma 180 and Ehrlich carcinoma in Ha/ICR Swiss mice, 6C3HED lymphosarcoma in C3H mice (A. R. Schmidt Co., Madison, Wis.), L-1210 lymphoma and L-5178Y lymphoblastoma in BDF_1 mice (Cumberland View Farms, Clinton, Tenn.). Tumor transplantations were carried out by withdrawing ascites fluid from donor mice bearing 7-day tumor growths. The fluid was centrifuged for 2 min. (at 1,600 *g*), the supernatant fluid decanted and the cells diluted ten-fold with an isotonic solution of sodium chloride. Into each mouse 0.1 ml. of this suspension was inoculated, either subcutaneously or intraperitoneally. Mice were maintained on a diet of Rockland rat chow pellets; water was available *ad libitum*.

Thioguanine II and selenocytosine were dissolved in 1.6% sodium carbonate; the solutions were adjusted to pH 7 with hydrochloric acid. Fresh solutions of II and 2-selenocytosine were prepared daily. Therapy was initiated 24 hr. after tumor implantation and was continued daily for 6 consecutive days; tumor-bearing animals receiving injections of isotonic saline served as controls. Animals were weighed daily, with weight-changes being used as an indication of drug toxicity. Both prolongation of life and reduction of tumor weight were studied.

Trifluoromethyl Compounds Related to Nucleic Acid Bases[1,2]

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In a continuing program designed to prepare potential antimetabolites, a number of trifluoromethylpyrimidines were synthesized by conventional means and used to obtain trifluoromethyl analogs of a *v*-triazolo[d]-pyrimidine, a pyrazolo[3,4-d]pyrimidine, and a pyrimido[4,5-d]pyrimidine. The rearrangement of a 4-(N-nitroamino)-2-trifluoromethylpyrimidine to a 4-amino-5-nitro-2-trifluoromethylpyrimidine and ring closure of 4-amino-2-trifluoromethyl-5-pyrimidinecarboxamide to a purine under conditions for a Hofmann reaction are reported. Some of the compounds prepared were evaluated and found to be inactive as tumor inhibitors.

In previous work,[3a,b,c] certain 2-trifluoromethylpyrimidines related to the thiamine pyrimidine were prepared and found to inhibit the growth of *Bacillus subtilis* and transplanted Leukemia L-1210. This activity was enhanced when the pyrimidine was incorporated into a thiamine analog, and it has since been found[4] that 40 mg./kg. daily doses of "trifluorothiamine" to mice on a thiamine-deficient diet gave up to 64% inhibition of transplanted Leukemia L-1210 without toxicity. The biological activity with *B. subtilis* and Leukemia L-1210 was reversed by thiamine and was decreased substantially[4,5] when pentafluoroethyl and heptafluoro-*n*-propyl groups were introduced in place of the trifluoromethyl group.

In view of these results, it seemed desirable to continue a program aimed at substituting the trifluoromethyl group for groups of similar size in natural products. It was hoped (but not subsequently realized) that the synthesis of 2-trifluoromethylpyrimidines and other trifluoromethyl compounds related to the nucleic acid bases would yield agents that would be active as tumor inhibitors. Moreover, the possible electronic effect of the trifluoromethyl group on other groups and positions could be further observed.[3c,6]

The fact that trifluoroacetamidine (I) would undergo conventional pyrimidine syntheses already has been described.[3a,7] Related cyclization reactions were carried out in the preparation of four new 2-trifluoromethylpyrimidines from I and the appropriate reagents. These pyrimidines were 4-hydroxy-6-dimethoxymethyl - 2 - trifluoromethylpyrimidine (II), 4,6-diamino - 5 - phenylazo - 2 - trifluoromethylpyrimidine (IV), 4 - amino - 2,6 - bis(trifluoromethyl) - 5 - pyrimidinecarbonitrile (VI), and 4-amino-6-hydroxy-5-nitroso-2-trifluoromethylpyrimidine (IX).

The hydrolysis of II and oxidation with chromic acid[8]

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(2) Presented in part before the Division of Medicinal Chemistry, 140th Meeting of the American Chemical Society, Chicago, Ill., September 1961, Abstracts of Papers, p. 25-O.

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