was recrystallized from 5 ml. of benzene to give 1.14 g. (27%) of product, m.p. 131–136°. An analytical sample, m.p. 137–138.5°, was obtained similarly.

Anal. Calcd. for $C_{20}H_{20}Cl_2N_2O_2$: C, 61.5; H, 5.17; N, 7.17; Cl, 18.2. Found: C, 61.8; H, 5.40; N, 6.95; Cl, 17.8.

5-[Bis(2-chloroethyl)amino]indole-3-carboxylic Acid (XIII).—To a solution of 300 mg. of the benzyl ester (XII) in 10 ml. of tetrahydrofuran was added 0.1 ml. of concentrated hydrochloric acid and 50 mg. of platinum oxide. The mixture was stirred under an atmosphere of hydrogen at room temperature, consuming the theoretical amount of gas during 35 min. The product, which had crystallized from solution as its hydrochloride, was collected along with the catalyst. The mixture was stirred in a solution of 5 ml. of water and 5 ml. of ethyl acetate, followed by removal of the catalyst by filtration. The ethyl acetate extract was evaporated to dryness *in vacuo* to leave 200 mg. (87%) of a sirup which crystallized when stirred with 2 ml. of water. The white crystals were collected, washed with water, and dried. Recrystallization of this material from 50% ethyl acetate–Skellysolve B afforded 93 mg. (40%), m.p. 150–152°. Another recrystallization gave an analytical sample, m.p. 151.5–152.5°.

Anal. Calcd. for $C_{13}H_{14}Cl_2N_2O_2$: Cl, 51.8; H, 4.68; N, 9.30; Cl, 23.55. Found: C, 51.9; H, 5.21; N, 9.07; Cl, 23.16.

Acknowledgments.—The authors wish to thank Dr. Peter Lim for interpretation of the infrared spectra and Mr. O. P. Crews and staff for the large-scale preparation of certain intermediates.

Fluorine-Containing Potential Anticancer Agents. II.[1a] Syntheses of Some Trifluoromethylpurines and Trifluoromethylthiazolopyrimidines[1b]

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As part of a search for improved cancer chemotherapeutic agents, various trifluoromethylpyrimidines were prepared and cyclized by standard techniques to the corresponding trifluoromethyl analogs of purine and thiazolopyrimidine. The compounds were evaluated in the routine three-tumor mouse screen of the Cancer Chemotherapy National Service Center. All were ineffective as tumor inhibitors.

Paper I[1a] of this series described the synthesis of various trifluoromethylpyrimidines as the first stage in a program for the preparation of potential antimetabolites. This program has now been extended to include trifluoromethyl analogs of purines and thiazolopyrimidines.

The syntheses of 5-amino-4,6-dichloro-2-trifluoromethylpyrimidine (XXV) and 5-amino-2,4-dichloro-6-trifluoromethylpyrimidine (XXVI) were reported previously. These intermediates have been converted to various purines in the standard preparative sequence shown in Schemes A and B.

Refluxing XXV and XXVI in methanol with various alkylamines provided the corresponding 4-alkylaminopyrimidines (I–IV and XI–XIV). Ring closure of the 4-alkylaminopyrimidines to the 2- and 6-trifluoromethylpurines (V–VII and XV–XVII) was effected by heating either with a mixture of ethyl orthoformate and acetic anhydride (method A), with 97% formic acid (method B), or with pure ethyl orthoformate (method C).

Method A, applied to the 2-trifluoromethyl series gave the 5-acetamido-6-chloro-4-alkylamino-2-trifluoromethylpyrimidines as side products. With method B, the side products were the corresponding 5-formamidopyrimidines. No side product was isolated when using method C on the 2-trifluoromethyl compounds or when using any of the methods on the 6-trifluoromethyl series.

No attempt was made to cyclize the butylamino pyrimidines (III and XIII).

The 2- and 6-aminopurines (VIII–X and XVIII–XX) were obtained by heating the chloropurines in an autoclave with ethanolic ammonia. The 2-chloropurines (XV–XVII) were converted with potassium hydrogen sulfide in methanol to the 2-mercapto derivatives (XXI). These were difficult to purify. They were therefore treated with ethyl bromide and ethanolic potassium hydroxide, and isolated as the ethyl derivatives (XXII–XXIV).

The reaction of ethanolic ammonia with XXV and XXVI gave the corresponding 4,5-diaminopyrimidines (XXXI and XXVII). In Scheme B, cyclization of XXVII and XXXI, using method A, produced 2-chloro-6-trifluoromethylpurine (XXVIII) and 6-chloro-2-trifluoromethylpurine (XXXIV), respectively. When cyclization of XXVII was carried out with trifluoroacetic anhydride in trifluoroacetic acid the product was 2-chloro-6,8-bis(trifluoromethyl)purine (XXIX).

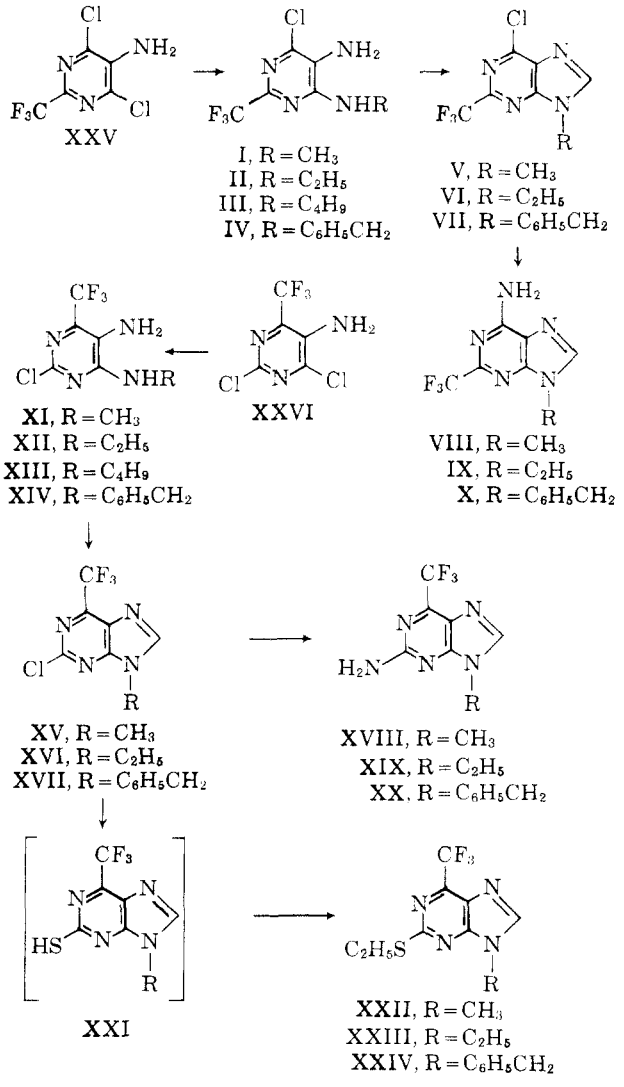
Thiourea and the chloropurine (XXXIV) provided 6-mercapto-2-trifluoromethylpurine (XXXV). Condensation of XXXIV with ethylamine, butylamine, aniline, and benzylamine gave the corresponding alkylamino derivatives (XXXVI–XXXIX).

Various trifluoromethyl[5,4-*d*]thiazolopyrimidines were prepared as outlined in Scheme C.

2,4-Dichloro-5-nitro-6-trifluoromethylpyrimidine (XL) was converted *via* XXVI to 5-amino-2-chloro-4-mercapto-6-trifluoromethylpyrimidine (XLI) as described previously.[1a] Ring closure of XLI to form 5-chloro-7-trifluoromethylthiazolo[5,4-*d*]pyrimidine (XLII) was brought about by heating with ethyl orthoformate. The conversion of 5-amino-6-chloro-4-mercapto-2-trifluoromethylpyrimidine (XLVI)[1a] to 7-chloro-5-trifluoromethylthiazolo[5,4-*d*]pyrimidine (XLVII) was carried out in the same fashion. Reaction of XL with 1 mole of potassium thiocyanate in acetic acid afforded the 4-thiocyano derivative (XLIII). Treatment of XLIII with aniline then gave the 2-

(1) (a) Paper I of this series: S. Inoue, A. J. Saggiomo, and E. A. Nodiff, *J. Org. Chem.*, **26**, 4504 (1961); (b) this investigation was supported by Research Grant CY-4270, from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service; (c) to whom inquiries should be addressed.

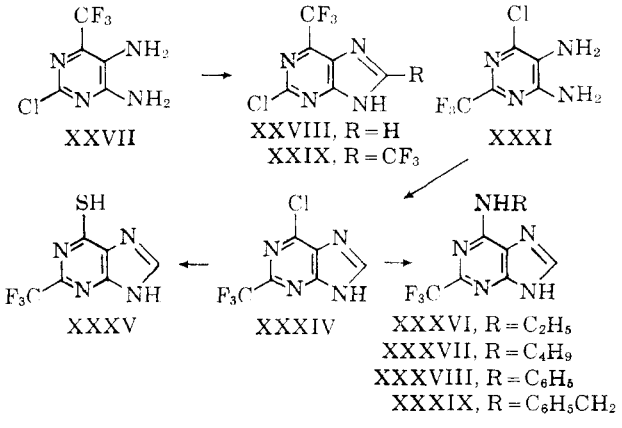
SCHEME A



anilino derivative (XLIV). Cyclization of XLIV occurred during reduction with iron and acetic acid to give a 10% yield of 2-amino-5-anilino-7-trifluoromethylthiazolo[5,4-*d*]pyrimidine (XLV).

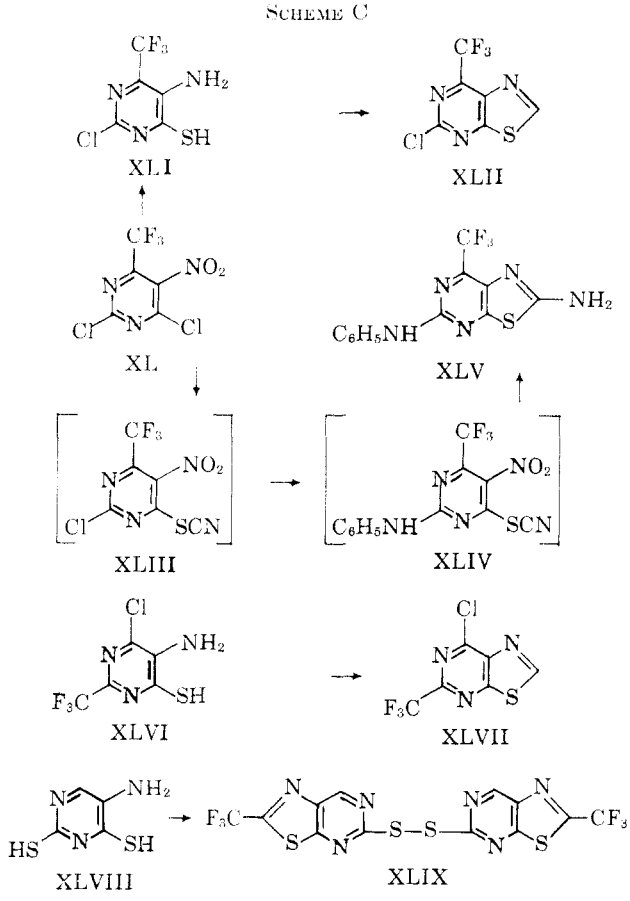
Ring closure of 5-amino-2,4-dimercaptopyrimidine (XLVIII) was effected by heating under reflux with a mixture of trifluoroacetic acid and trifluoroacetic anhydride. However, simultaneous oxidation occurred and the compound isolated was bis(2-trifluoromethylthiazolo[5,4-*d*]pyrimidyl) 5-disulfide (XLIX).

SCHEME B



Most of the compounds described in papers I and II of this series were evaluated in at least one system of the routine three tumor mouse screen of the Cancer Chemotherapy National Service Center. None showed antineoplastic activity. A summary of the data is presented in Table VII.

SCHEME C



Experimental[2]

Synthesis of the 4-Alkylaminopyrimidines (I–IV and XI–XIV).—To a solution of 1.0 g. (0.0043 mole) of 5-amino-4,6-dichloro-2-trifluoromethylpyrimidine (XXV) in 10 ml. of methanol was added a solution of 0.9 g. (0.0087 mole) of 30% methylamine in 10 ml. of methanol. The mixture was heated under reflux for 2 hr. The solvent was then evaporated and the residue was washed with water and dried. Recrystallization from benzene gave colorless prisms of 5-amino-6-chloro-4-methylamino-2-trifluoromethylpyrimidine (I).

The other 4-alkylaminopyrimidines, included in Table I, were prepared by essentially the same method.

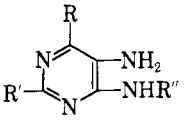
Synthesis of the 9-Alkylpurines (V–VII and XV–XVII). *A.*—To a solution of 30 ml. of ethyl orthoformate in 30 ml. of acetic anhydride was added 5.9 g. (0.016 mole) of 5-amino-4-benzylamino-6-chloro-2-trifluoromethylpyrimidine (IV). The mixture was refluxed for 2 hr. and evaporated *in vacuo*. The residue was shaken with ether and the insoluble crystals (2.1 g., m.p. 183–184°) were filtered. The filtrate was evaporated and the oily residue was crystallized from ligroin (Darco). An additional crystallization from ligroin gave 0.9 g. of 9-benzyl-6-chloro-2-trifluoromethylpurine (VII). See Table II for analytical and physical data.

Crystallization of the ether-insoluble solid (m.p. 183–184°) from 60% methanol gave colorless needles of 5-acetamido-4-benzylamino-6-chloro-2-trifluoromethylpyrimidine, m.p. 187–188°.

(2) All melting points were taken in a Thiele-Dennis apparatus. Much of this work was completed in 1961 and samples and melting point apparatus then used were not available for melting point correction at the date of submission of this manuscript.

TABLE I

TRIFLUOROMETHYLPYRIMIDINES



No.	R	R′	R″	Yield, %	Appearance[c]	M.p., °C.	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found
I	Cl	CF_3	CH_3	92	Prisms (benzene)	140–142	31.80	32.09	2.66	2.75	24.72	24 90
II	Cl	CF_3	C_2H_5	96	Plates (ligroin)	91–92	34.94	35.21	3.34	3.41	23.28	23.21
III	Cl	CF_3	C_4H_9	69	Plates (ligroin)	98–100.5	40.23	40.39	4.50	4.39	20.85	21.10
IV[a]	Cl	CF_3	$C_6H_5CH_2$	98	Needles (70% methanol)	184–185	47.61	47.61	3.33	3.46	18.51	18.51
XI	CF_3	Cl	CH_3	90	Needles (benzene)	185–187	31.80	31.95	2.66	2.70		
XII	CF_3	Cl	C_2H_5	87	Prisms (benzene)	159–161	34.94	35.16	3.34	3.62		
XIII[b]	CF_3	Cl	C_4H_9	85	Yellow oil		40.23	40.06	4.50	4.70	20.85	20.69
XIV	CF_3	Cl	$C_6H_5CH_2$	96	Needles (benzene)	179–180.5	47.61	47.69	3.33	3.19	18.51	18.98

[a] *Anal.* Calcd. for Cl: 11.71. Found: 11.63. [b] B.p. 172° (2 mm.). [c] All compounds except XIII were colorless.

Anal. Calcd. for $C_{14}H_{12}ClF_3N_4O$: C, 48.77; H, 3.50; N, 16.25. Found: C, 48.70; H, 3.55; N, 16.07.

Method B.—A solution of 6.5 g. (0.022 mole) of IV and 120 ml. of 97% formic acid was heated under reflux for 3 hr. The yellow reaction mixture was evaporated *in vacuo*. The oily residue was treated with a small amount of water and then evaporated almost to dryness. The residue was heated with hot ligroin and the insoluble crystals were filtered giving 5.1 g., m.p. 158–160°. From the filtrate 1.2 g. of VII was obtained. Mixture melting point and infrared data indicated that this material was identical with VII obtained *via* method A.

Crystallization of the ligroin-insoluble solid (m.p. 158–160°) from aqueous methanol gave colorless prisms of 4-benzylamino-6-chloro-5-formamido-2-trifluoromethylpyrimidine, m.p. 182–183°.

Anal. Calcd. for $C_{13}H_{10}ClF_3N_4O$: C, 47.25; H, 3.02. Found: C, 47.28; H, 3.76.

C.—A solution of 4 g. (0.013 mole) of IV in 50 ml. of ethyl orthoformate was heated under reflux for 2 hr. and then evaporated under reduced pressure. The residue was treated with 20 ml. of 5% sodium hydroxide and extracted with ether. The extracts were dried over sodium sulfate and concentrated to leave a green oil. Crystallization gave 1 g. of VII.

The other 9-alkylpurines, listed in Table II, were prepared using the foregoing methods.

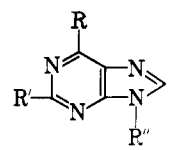
Synthesis of the 2- and 6-Aminopurines (VIII–X and XVIII–XX).—To a solution of 6.0 g. (0.35 mole) of ammonia in 60 ml. of ethanol was added 2.4 g. (0.01 mole) of 2-chloro-9-methyl-6-trifluoromethylpurine (XV). The mixture was heated in an autoclave for 5 hr. at 170° and the solvent was removed under reduced pressure. Recrystallization of the residue gave 2.1 g. of 2-amino-9-methyl-6-trifluoromethylpurine (XVIII).

The same procedure produced the remaining aminopurines included in Table III.

2-Ethylmercapto-9-methyl-6-trifluoromethylpurine (XXII).—A solution was prepared containing 0.9 g. (0.012 mole) of potassium hydrogen sulfide hemihydrate in a mixture of 30 ml. of methanol and 6 ml. of water. To this solution was added 1.4 g. (0.0059 mole) of 2-chloro-9-methyl-6-trifluoromethylpurine (XV) and the mixture was heated at 60° for 3 hr. Concentration almost to dryness was followed by dilution with 10 ml. of water. An unidentified solid (m.p. 115°) was removed by filtration. The filtrate was decolorized and neutralized with acetic acid to give 0.5 g. (36%) of yellow needles of crude 9-methyl-2-mercapto-6-trifluoromethylpurine (XXI, R = CH_3), m.p. 136–139°. This

TABLE II

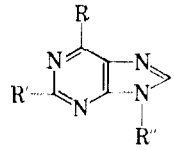
CHLOROTRIFLUOROMETHYLPURINES



No.	R	R′	R″	% yield—Method— A	B	C	Appearance[e]	M.p., °C.	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found
V	Cl	CF_3	CH_3	77	36		Needles (ligroin)	73–74	35.53	35.88	1.70	1.76	23.68	23.98
VI	Cl	CF_3	C_2H_5	33	54[a]		Plates (ligroin)	63–65	38.33	38.57	2.41	2.51	22.35	22.45
VII[b]	Cl	CF_3	$C_6H_5CH_2$	14	18	24	Needles (ligroin)	98–99	49.86	50.05	2.58	2.75		
XV	CF_3	Cl	CH_3	59	71		Needles (water)	126–127	35.53	35.72	1.70	1.93	23.68	23.85
XVI	CF_3	Cl	C_2H_5	81	74		*c*	78–79	38.33	38.34	2.41	2.61	22.35	22.10
XVII[d]	CF_3	Cl	$C_6H_5CH_2$	88			Needles (ligroin)	118–120	49.86	50.05	2.58	2.80		

[a] 6-Chloro-4-ethylamino-5-formamido-2-trifluoromethylpyrimidine formed as side product, m.p. 110–111°. *Anal.* Calcd. for $C_8H_8ClF_3N_4O$: C, 35.75; H, 2.98; N, 20.80. Found: C, 35.50; H, 4.06; N, 20.20. [b] *Anal.* Calcd. for Cl: 11.35. Found: 11.00. [c] B.p. 136–138° (1 mm.). [d] *Anal.* Calcd. for Cl: 11.34. Found: 11.27. [e] All compounds were colorless.

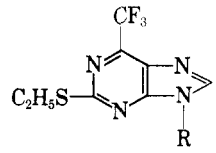
TABLE III
AMINOTRIFLUOROMETHYLPURINES



No.	R	R′	R″	% yield	Appearance[b]	M.p., °C.	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found
VIII	NH_2	CF_3	CH_3	77	Prisms (methanol)	232–235	38.71	38.94	2.78	2.79	32.25	32.45
IX	NH_2	CF_3	C_2H_5	94	Prisms (water)	191–192	41.55	41.61	3.48	3.52	30.29	30.10
X[a]	NH_2	CF_3	$C_6H_5CH_2$	78	Prisms (70% methanol)	181–183	53.24	53.33	3.42	2.64	23.88	23.70
XVIII	CF_3	NH_2	CH_3	90	Needles (methanol)	243–244	38.71	38.98	2.78	2.99	32.25	32.00
XIX	CF_3	NH_2	C_2H_5	74	Prisms (water)	162–164	41.55	41.80	3.49	3.53	30.29	30.15
XX	CF_3	NH_2	$C_6H_5CH_2$	83	Needles (benzene)	183–184	53.24	53.37	3.43	3.35	23.88	23.70

[a] *Anal.* Calcd. for F: 19.42. Found: 19.30. [b] All compounds were colorless.

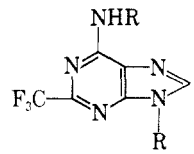
TABLE IV
ETHYLMERCAPTOTRIFLUOROMETHYLPURINES



No.	R	% yield	Appearance	M.p., °C.	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found	% S Calcd.	% S Found
XXII[a]	CH_3	95	Colorless needles (ligroin)	107–109	41.21	41.50	3.45	3.55	21.36	21.50	12.22	11.89
XXIII	C_2H_5	95	Yellow prisms (ligroin)	79–80	43.51	43.68	3.98	4.00	20.28	20.07	11.60	11.65
XXIV	$C_6H_5CH_2$	92	Colorless needles (methanol–water)	103–105	53.20	53.29	3.86	3.65	16.56	16.60	9.48	9.55

[a] *Anal.* Calcd. for F: 21.73. Found: 22.00.

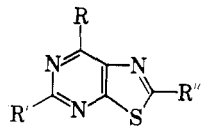
TABLE V
ALKYLAMINOTRIFLUOROMETHYLPURINES



No.	R	% yield	Appearance[a]	M.p., °C.	% C Calcd.	% C Found	% H Calcd.	% H Found	% F Calcd.	% F Found
XXXVI	C_2H_5	48	Needles (water)	285	41.56	41.54	3.46	3.52	24.68	24.58
XXXVII	C_4H_9	74	Needles (methanol)	255	46.33	46.75	4.63	4.70	22.00	21.75
XXXVIII	C_6H_5	95	Needles (methanol)	289–290					20.43	20.42
XXXIX	$C_6H_5CH_2$	80	Plates (methyl ethyl ketone)	271–272	53.24	53.22	3.41	3.35	19.45	18.85

[a] All compounds were colorless.

TABLE VI
TRIFLUOROMETHYLTHIAZOLO[5,4-*d*]PYRIMIDINES



No.	R	R′	R″	% yield	Appearance (solvent)	M.p., °C.	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found
XLII	CF_3	Cl	H	89	Colorless needles (ligroin)	99–100	30.06	30.39	0.42	0.71		
XLVII	Cl	CF_3	H	95	Colorless prisms (sublimation)	87–88	30.06	30.40	0.42	0.64		
XLV	CF_3	C_6H_5NH	NH_2	10	Chloroform	203–204	46.30	46.15	2.57	2.89	22.51	22.34

TABLE VII

C.C.N.S.C. THREE-TUMOR MOUSE SCREEN DATA

	S-180				Ca-755				L-1210			
Compound	Daily dose, mg./kg.	Survivors	Test[a]/control	Test control, %	Daily dose, mg./kg.	Survivors	Test[a]/control	Test control, %	Daily dose, mg./kg.	Survivors	Test[b]/control	Test control, %
I									250	06/06	9.0/8.4	107
II	125	05/06	770/849	90	100	10/10	1066/1327	80	100	06/06	8.0/7.9	101
IV	125	06/06	787/753	104	113	09/10	925/1144	80	113	06/06	7.3/8.0	91
					240	00/10						
V					120	00/10						
					60	04/10	653/527					
					30	08/10	426/527	80				
XI									250	00/06		
									62.5	06/06	8.5/9.2	92
XII									200	05/06	7.4/9.3	79
									100	06/06	9.1/9.2	98
XIII	125	06/06	842/886	95	100	09/10	1599/1486	107	100	06/06	7.5/8.1	92
XIV									250	03/06	9.0/8.7	101
									125	06/06	8.5/8.3	102
XV					240	00/10						
					120	00/10						
					60	09/10	1587/1740	91				
					30	09/10	1714/1740	98				
XVI	125	05/06	1506/1400	107	87.5	09/10	784/552	142	100	03/06	8.3/9.0	
									50	06/06	7.8/8.7	89
XVII					240	05/10	1096/1179					
					120	09/10	1151/1179	97				
					60	09/10	1150/1179	97				
					30	10/10	668/1179	56				
XX					240	03/10	1013/1740					
					120	10/10	2155/1740	123				
					60	08/10	1608/1740	92				
					30	06/10	1672/1740	96				
XXV									250	00/06		
									125	00/06		
XXVI									100	03/06	7.0/10.0	
									66	05/06	8.0/10.0	70
									44	06/06	9.5/10.0	80
									29	05/06	9.2/10.0	95
XXVII									100	06/06	9.1/8.0	192
XXVIII					100	00/10						13
					50	08/10	262/542	48				
					50	12/12	1520/876	173				
XXXI									250	06/06	8.7/9.3	
XXXV	250	06/06	1371/1555	88	250	10/10	833/1022	81	225	06/06	7.7/8.2	93
					225	09/10	996/1047	95				93
					100	10/10	912/1022	89				
					60	09/10	724/1022	70				
XXXVI					100	09/10	512/748	68				
XXXVII	100	06/06	1192/1130	105	100	10/10	682/775	88	100	06/06	8.8/10.7	
XXXVIII	100	06/06	777/1130	68	100	10/10	632/775	81	100	06/06	9.3/10.7	82
XXXIX	100	06/06	1175/1130	103	100	10/10	664/775	85	100	06/06	9.1/10.7	86
									50	06/06	7.6/9.8	
									25	06/06	8.0/11.0	
									12.5	06/06	10.1/10.4	97
XLI	100	01/06	300/1045		100	04/10	906/1267		100	05/06	8.2/10 0	82
	25	06/06	804/827	97					66	05/06	9.4/10.0	94
									44	06/06	8.3/10.0	83
									29	06/06	10.5/10.0	105
XLII	125	06/06	700/779	89	113	06/10	1525/1267		113	05/06	8.6/9.6	89
					57	10/10	1403/1336	105				
XLVI									100	06/06	8.6/9.3	92
XLVII									100	06/06	8.0/8.0	100

[a] Mean tumor weight of test animals over mean tumor weight of control animals. [b] Mean survival time of test animals over mean survival time of control animals.

material was difficult to purify and it was therefore ethylated as follows.

To a solution of 0.7 g. (0.003 mole) of the mercaptopurine, 20 ml. of ethanol, and 0.17 g. (0.003 mole) of potassium hydroxide, was added 0.33 g. (0.003 mole) of ethyl bromide. The solution was warmed for 30 min. and the solvent was removed. The yellow residue was diluted with 10 ml. of water and extracted with ether, and the extracts were dried over sodium sulfate. Concentration of the ether gave 0.75 g. of XXII. Purification, analytical, and physical data for this compound and the others in its class are given in Table IV.

2-Chloro-6-trifluoromethylpurine (XXVIII).—A mixture

of 6.5 g. of 2-chloro-4,5-diamino-6-trifluoromethylpyrimidine (XXVII), 70 ml. of ethyl orthoformate, and 70 ml. of acetic anhydride was heated under reflux for 2 hr. The reaction mixture was evaporated *in vacuo* and to the residue was added 150 ml. of 5% sodium hydroxide solution. The mixture was stirred until clear, treated with Darco, and filtered. The filtrate was acidified with hydrochloric acid and the resulting colorless prisms were collected; yield, 6 g. (90%). Recrystallization from methanol–benzene gave colorless prisms, m.p. 240°.

Anal. Calcd. for $C_6H_2ClF_3N_4$: C, 32.36; H, 0.90; Cl, 15.74; F, 25.62. Found: C, 32.23; H, 1.20; Cl, 15.72; F, 25.15.

2-Chloro-6,8-bis(trifluoromethyl)purine (XXIX).—A solution of 10 ml. of trifluoroacetic acid, 10 ml. of trifluoroacetic anhydride, and 1.0 g. (0.0047 mole) of 4,5-diamino-2-chloro-6-trifluoromethylpyrimidine[1a] (XXVII) was heated under reflux for 2 hr. The mixture was concentrated almost to dryness and the residue was diluted with 5 ml. of 5% sodium hydroxide. This mixture was extracted with ethyl acetate and the extract was dried over sodium sulfate. Concentration provided 0.25 g. (22%) of white crystals of XXIX. Vacuum sublimation gave an analytical sample as colorless prisms, m.p. 149°.

Anal. Calcd. for $C_7HClF_6N_4$: C, 28.93; H, 0.34. Found: C, 28.92; H, 0.55.

6-Chloro-2-trifluoromethylpurine (XXXIV).—This compound was prepared from XXXI in the manner described for the synthesis of XXVIII. Crystallization from water gave an 83% yield of colorless prisms, m.p. 200–201°.

Anal. Calcd. for $C_6H_2ClF_3N_4$: C, 32.36; H, 0.90; Cl, 15.74; F, 25.62. Found: C, 32.58; H, 1.22; Cl, 16.00; F, 25.50.

6-Mercapto-2-trifluoromethylpurine (XXXV).—A solution of 2 g. (0.009 mole) of 6-chloro-2-trifluoromethylpurine (XXXIV) and 0.8 g. (0.011 mole) of thiourea in 20 ml. of methanol was heated under reflux for 3 hr. The solvent was removed and a small amount of water was added to the residue. Insoluble crystals (0.7 g., m.p. 239°) were filtered. The filtrate was made basic with sodium hydroxide solution and then acidified to give another crop of crystals for a total yield of 1.2 g. Recrystallization from aqueous methanol gave colorless plates of XXXV, m.p. 274–275°.

Anal. Calcd. for $C_6H_3F_3N_4S$: C, 32.73; H, 1.36; S, 14.54. Found: C, 32.70; H, 1.58; S, 14.98.

Synthesis of the 6-Alkylamino-2-trifluoromethylpurines (XXXVI–XXXIX).—A mixture of 0.5 g. (0.002 mole) of 6-chloro-2-trifluoromethylpurine (XXXIV), 20 ml. of methanol, and an excess of 70% ethylamine was heated under reflux for 2 hr. The mixture was concentrated and the residue was crystallized from water to give 0.22 g. of 6-ethylamino-2-trifluoromethylpurine (XXXVII). The other 6-alkylaminopurines (Table V) were prepared in the same manner.

5-Chloro-7-trifluoromethylthiazolo[5,4-*d*]pyrimidine (XLII).—A solution of 3 g. of 5-amino-2-chloro-4-mercapto-6-trifluoromethylpyrimidine (XLI)[1a] in 150 ml. of ethyl orthoformate was heated under reflux for 2 hr. The mixture was concentrated *in vacuo* and the residue was treated with 5% sodium hydroxide and extracted with ether. Concentration provided 2.8 g. of XLII. Purification data for this compound and the identically prepared 7-chloro-5-trifluoromethylthiazolo[5,4-*d*]pyrimidine (XLVII) are included in Table VI.

2-Amino-5-anilino-7-trifluoromethylthiazolo[5,4-*d*]pyrimidine (XLV).—To a solution of 4.7 g. (0.018 mole) of 2,4-dichloro-5-nitro-6-trifluoromethylpyrimidine (XL) in 30 ml. of acetic acid was added 1.7 g. (0.018 mole) of potassium thiocyanate. The mixture was stirred for 30 min. and 3.4 g. (0.036 mole) of aniline was then added dropwise, with cooling. After an additional 20 min., 3 g. of iron powder and 100 ml. of acetic acid were added. The mixture was stirred at 60° for 1.5 hr. and filtered. The filtrate was poured into 300 ml. of water and 0.55 g. of XLV was collected (Table VI).

Bis(2-trifluoromethylthiazolo[5,4-*d*]pyrimidyl 5-Disulfide (XLIX).—A mixture of 20 ml. of trifluoroacetic acid, 20 ml. of trifluoroacetic anhydride, and 2 g. of 5-amino-2,4-dimercaptopyrimidine (XLVIII) was heated under reflux for 2 hr. The reaction mixture was evaporated under reduced pressure and the residue was diluted with 40 ml. of water. The water-insoluble solid was dissolved in ethyl acetate. Concentration gave yellow-green crystals which were crystallized from methanol to provide 1.3 g. (22%) of XLIX as colorless plates, m.p. 150–151°.

Anal. Calcd. for $C_{12}H_2F_6N_6S_4$: C, 30.51; H, 0.42. Found: C, 30.43; H, 0.52.

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Hydrazino Acids. II. Alkyl-, Aralkyl-, and Hydroxyalkyl-α-hydrazino Acids

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The reaction of α-halo aliphatic acids with some substituted hydrazines was studied. Ethyl-, butyl-, phenethyl-, and 1,1-dimethylhydrazines have been observed to yield 1,1-disubstituted α-hydrazino acids, while isopropyl-, β-hydroxyethyl-, β-hydroxypropyl-, and benzylhydrazines gave 1,2-disubstituted products. 1-Isopropyl- and 1-benzyl-α-hydrazino acids were prepared by reduction of the corresponding nitrosoamino acids.

The preliminary screening results of some hydrazino and 1-methylhydrazino aliphatic acids tested on Sarcoma 180 in mice at the Sloan Kettering Institute for Cancer Research, N. Y., justified further synthetic exploration in the field of hydrazino acids.

In the first paper of this series,[1] methylhydrazine has been shown to react with halo acids to give α-(1-methylhydrazino) acids. Numerous attempts have now been made to obtain α-(2-methylhydrazino) acids but most of them proved unsuccessful. These included the reduction of the methylene derivatives of some α-hydrazino acids with sodium borohydride, the reduction of the methylhydrazone of pyruvic acid and ethylidene-α-hydrazino acids in the presence of platinum oxide catalyst, the reaction of chloroamino acids with methylamine and the reaction of 1-methyl-2-benzoyl hydrazine with α-halo acids. However, the methylation of the benzylidene derivatives of α-hydrazino acids with dimethyl sulfate led to the desired compounds in low yields. By this method we prepared the α-(2-methylhydrazino)propionic (I) and caproic (II) acids. Although an attempt to repeat these preparations failed, we record the results in the experimental part.

Other alkylhydrazines, owing to the electron-releasing properties of the alkyl group,[2] were expected to behave

(1) A. Carmi, G. Pollak, and H. Yellin, *J. Org. Chem.*, **25**, 44 (1960).

(2) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, New York, N. Y., 1953, p. 316.