which separated was extracted thoroughly with ether, and the combined ether extracts were washed successively with several portions of dilute sodium hydroxide and water. The base was thoroughly extracted from the ether with *N* acetic acid solution and the extract was filtered and made strongly alkaline with sodium hydroxide. The base was again extracted with ether, the combined ether extracts were dried over anhydrous potassium carbonate, and the ether was removed. Crystallization of the residues from the solvents indicated gave the desired bases as bright yellow solids.

7,7′-Ethylenebis(iminoethyleneimino)bis[3-chlorodibenzo[b,h][1,6]naphthyridine] (XVI).—A mixture of 2.92 g. (0.02 mole) of triethylenetetramine (Eastman Kodak Co.) and 40 g. of phenol was heated *in vacuo* on the steam-bath for 3 hr. to remove traces of moisture; 11.96 g. (0.04 mole) of 3,7-dichlorobenzo[b,h][1,6]naphthyridine (XIV) subsequently was added, and the mixture was stirred and heated at 110–125° for 4 hr. The warm reaction mixture was diluted with ethanol and stirred into a solution of 25 ml. of concentrated hydrochloric acid in 250 ml. of acetone. The mixture was further diluted with 500 ml. of acetone, and allowed to stand for 18 hr. The crude yellow hydrochloride salt was collected by filtration, dried, suspended in ethanol, and made strongly alkaline with concentrated ammonium hydroxide. The mixture was shaken with chloroform, filtered, and the aqueous layer discarded. The residue and chloroform layer were combined and evaporated to dryness. The residue was triturated with several portions of boiling ethanol and filtered. The bright yellow residue weighed 6.0 g. (45%), m.p. 248–252°. Recrystallization from a mixture of dimethylformamide, 2-propanol and petroleum ether (b.p. 80–110°) (decolorizing charcoal) raised the melting point to 256–257°.

Anal. Calcd. for $C_{38}H_{36}Cl_2N_8$: C, 67.95; H, 4.80; N, 16.69. Found: C, 68.14; H, 4.59; N, 16.92.

Potential Purine Antagonists. XXXI. The Preparation of Certain 9-Alkyl-2-amino-6-purinethiols and Related Derivatives as Antitumor Agents[1]

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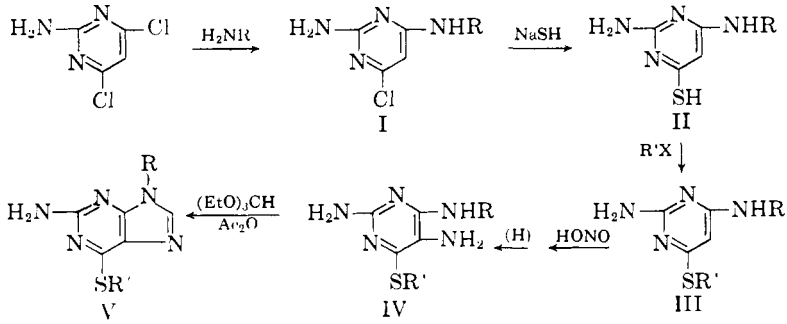
A new, convenient preparation has been achieved for certain 9-alkyl-2-amino-6-purinethiols and their 6-alkylthio derivatives. A number of these compounds exhibit complete tumor inhibition of Adenocarcinoma 755 *in vivo* at varied dosage levels. These data are presented and discussed.

Studies of the antitumor activity of 2-amino-9-methyl-6-purine-

thiol[2] by LePage and Jones[3] have stimulated the synthesis of additional derivatives of 2-amino-6-purinethiol possessing an alkyl substituent at position 9. The inhibition of Adenocarcinoma 755 by various 6-alkylthio-2-aminopurines[4] suggested extension of previous work to include the preparation of a number of 9-alkyl-6-alkylthio-2-aminopurines (V).

Previous synthetic routes[2,5] to 9-substituted 2-amino-6-purinethiols were found to be rather involved and cumbersome for the large quantities of material required for the present study. Thus, a direct route to the preparation of 9-alkyl-6-alkylthio-2-aminopurines (V) was devised.



The preparation of 2-amino-6-chloro-4-substituted aminopyrimidines (I) was readily accomplished when 2-amino-4,6-dichloropyrimidine[6] was refluxed with the proper primary amine in ethanol. The 4-alkylamino-2-amino-6-chloropyrimidines prepared are listed in Table VI. 2-Amino-6-chloro-4-ethylaminopyrimidine has previously been reported[7] from 2-amino-4,6-dichloropyrimidine and aqueous ethylamine at 100°.

To obtain the appropriate 2-amino-4-substituted amino-6-pyrimidinethiol (II) from I, sodium hydrosulfide in ethylene glycol was employed. The use of this reagent for the replacement of an unreactive chlorine atom by mercapto has been reported[4,8] recently for

(1) This investigation was supported by Contract No. SA-43-ph-1928 with the Cancer Chemotherapy National Service Center of the National Cancer Institute, National Institutes of Health.

(2) H. C. Koppel and R. K. Robins, *J. Am. Chem. Soc.*, **80**, 2751 (1958).

(3) G. A. LePage and M. Jones, *Cancer Research*, **21**, 642 (1961).

(4) G. D. Daves, Jr., C. W. Noell, R. K. Robins, H. C. Koppel, and A. G. Beaman, *J. Am. Chem. Soc.*, **82**, 2633 (1960).

(5) H. C. Koppel, D. E. O'Brien, and R. K. Robins, *ibid.*, **81**, 3046 (1959).

(6) E. Buttner, *Ber.*, **36**, 2227 (1903).

(7) H. S. Forrest, R. Hull, H. J. Rodda, and A. R. Todd, *J. Chem. Soc.*, 3 (1951).

(8) H. C. Koppel, R. H. Springer, R. K. Robins, and C. C. Cheng, *J. Org. Chem.*, **26**, 792 (1961).

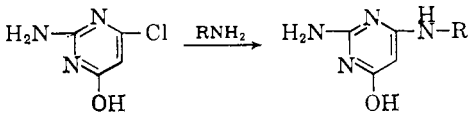
TABLE I

VI R	M.p., °C.	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	—Nitrogen, %— Calcd.	Found
n-Propyl $C_7H_{12}N_4O$	257	49.9	49.7	7.14	6.45	33.3	33.1
Cyclohexyl $C_{10}H_{16}N_4O$	280	57.7	57.4	7.18	7.64	26.9	26.5
n-Butyl $C_8H_{14}N_4O$	230	52.7	52.8	7.68	7.3	30.8	30.8
Benzyl $C_{11}H_{12}N_4O$	223	61.1	60.8	5.55	5.68	25.9	25.8
Isoamyl $C_9H_{16}N_4O$	258	55.1	55.14	8.17	8.48	28.6	28.6
Cyclopentyl $C_9H_{14}N_4O$	273	55.8	55.7	7.2	7.39	28.8	28.5

TABLE II

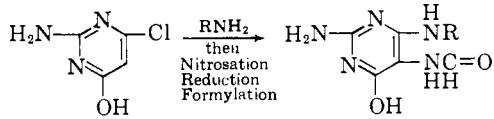
VII R	M.p., °C.	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	—Nitrogen, %— Calcd.	Found	Prepn
n-Propyl $C_9H_{13}N_5O_2$	277–279[a]	45.6	45.34	6.2	6.43	33.3	33.3	A
n-Butyl $C_9H_{14}N_5O_2$	237–238[a]	48.3	48.9	6.26	6.82	31.25	30.8	A
Isobutyl $C_9H_{14}N_5O_2$	250–252[a]	48.3	48.07	6.26	6.58	31.25	30.8	A
Benzyl $C_{12}H_{13}N_5O_2 \cdot H_2O$	250[b]	52.0	52.31	5.4	5.36	25.25	25.6	B
Cyclohexyl $C_{11}H_{17}N_5O_2$	254–255[a]	52.6	52.5	6.78	6.98	27.8	27.6	B
Isoamyl $C_{10}H_{16}N_5O_2 \cdot H_2O$	230[b]	46.9	46.56	7.03	7.35	27.4	27.6	A
2-Methyl-*n*-butyl $C_{10}H_{16}N_5O_2$	243[b]	50.4	50.63	6.73	7.34	29.4	29.45	A
n-Amyl $C_{10}H_{16}N_5O_2 \cdot H_2O$	233[a]	46.9	46.99	7.03	7.65	27.4	27.0	A
Cyclopentyl $C_{10}H_{15}N_5O_2 \cdot 0.5H_2O$	256[a]	48.8	48.59	6.5	6.24	28.45	28.2	B
Methyl $C_6H_9N_5O_2$	350	39.3	39.63	4.92	4.98	38.25	37.6	A

[a] These compounds decompose and then melt at the temperature recorded.



VI

Prepn.	Recryst. solvent	Yield, %	pH 1 λ_{max}, mμ	pH 1 ε	pH 11 λ_{max}, mμ	pH 11 ε	RNH_2
A	Water	42	269	22,700	267	14,900	*n*-Propylamine
B	2-Ethoxy-ethanol	80	270	24,500	268	17,100	Cyclohexyl-amine
A	Water	64	269	22,800	267	15,600	*n*-Butylamine
B	Water	81	269	23,000	268	15,000	Benzylamine
A	MeOH + H_2O	80	269	23,200	267	15,500	Isoamylamine
B	Methanol	86	270	24,000	268	16,500	Cyclopentyl-amine



VII

Equiv. water of hydration	Recryst. solvent	Overall % yield from 4-Cl-derivative	pH 1 λ_{max}, mμ	pH 1 ε	pH 11 λ_{max}, mμ	pH 11 ε	RNH_2
0	Water	40	271	22,000	267	14,500	*n*-Propyl-amine
0	Water	52	272	21,300	268	14,200	*n*-Butylamine
0	Water	37	272	22,100	268	14,300	Isobutyl-amine
1	Water	62	272	21,900	268	15,500	Benzylamine
0	Water	45	270	27,900	268	19,300	Cyclohexyl-amine
1	Water	56	272	22,300	268	14,600	Isoamylamine
0	Water-ethanol	71	272	21,900	268	14,300	2-Methyl-*n*-butylamine
1	Water	70	272	22,200	268	14,400	*n*-Amylamine
½	Water	57	273	23,900	268	15,000	Cyclopentyl-amine
0	Water	45	271	20,500	267	13,200	40% methyl-amine in water

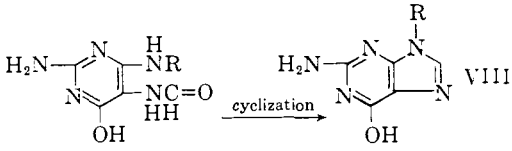
These compounds melted sharply at the temperature recorded.

TABLE III

VIII R	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
n-Propyl $C_8H_{11}N_5O$	373–375	49.7	50.0	5.7	6.2
n-Butyl $C_9H_{13}N_5O$	347–349	52.2	52.7	6.28	6.17
Isobutyl $C_9H_{13}N_5O$	362–365	52.2	52.48	6.28	6.05
Benzyl $C_{12}H_{11}N_5O$	303–304	59.5	59.3	4.56	4.7
Cyclohexyl $C_{11}H_{15}N_5O$	>380	56.7	56.87	6.42	6.49
Isoamyl $C_{10}H_{15}N_5O$	357–359	54.3	54.1	6.78	6.75
2-Methylbutyl $C_{10}H_{15}N_5O$	368–369	54.3	54.3	6.78	7.06
n-Amyl $C_{10}H_{15}N_5O$	303–305	54.3	54.5	6.78	6.70
Cyclopentyl $C_{10}H_{13}N_5O$	>380	54.8	55.11	5.94	6.10
Methyl $C_6H_{17}N_5O$	>380	43.6	43.92	4.24	4.43

similarly substituted pyrimidines. The 4-alkylamino-2-amino-6-pyrimidinethiols (II) prepared by this method are listed in Table VII.

Treatment of the 2-amino-4-substituted amino-6-pyrimidinethiols (II) with various alkyl halides in basic solution or in the presence of N,N-dimethylformamide gave the appropriate 6-alkylthio-2-amino-4-substituted aminopyrimidines (III). Seven different compounds of the general type III were prepared for further systematic study and are listed in Table VIII. These compounds were subjected to nitrosation followed by the usual reduction with sodium hydrosulfite in aqueous solution. The nitrosation and reduction steps were successful for the preparation of only two of the desired compounds, 2,5-diamino-4-methylamino-6-methylthiopyrimidine and 2,5-diamino-4-ethylamino-6-methylthiopyrimidine. These two compounds were readily oxidized in air and were therefore cyclized rapidly with ethyl orthoformate and acetic anhydride to give the two 2-amino-9-methyl-



—Nitrogen, %— Calcd.	Found	Recryst. solvent	Yield, %	pH 1 λmax, mμ	pH 1 ε	pH 11 λmax, mμ	pH 11 ε
36.2	36.1	Reppt.	76	253	15,800	269	11,100
				279	10,200		
33.8	33.5	Reppt.	67	253	13,800	269	10,400
				279	9,100		
33.8	34.0	Reppt.	60	253	12,400	269	11,200
				278	8,500		
29.0	29.0	Reppt.	76	254	12,800	270	11,800
				280	8,500		
30.0	30.2	Reppt.	81	255	11,600	270	11,900
				280	7,900		
31.7	31.8	Reppt.	68	254	11,700	269	10,700
				280	7,900		
31.7	31.7	Reppt.	65	254	12,100	270	10,700
				280	8,200		
31.7	31.6	Reppt.	76	254	11,200	270	10,600
				280	7,500		
31.9	32.1	Reppt.	87	253	12,000	269	10,900
				279	8,100		
42.4	42.3	Reppt.	62	252	12,200	268	10,900
				278	8,800		

6-methylthio- and 2-amino-9-ethyl-6-methylthiopurines (V) listed in Table Va. Attempts to nitrosate the remaining 4-alkylamino-6-alkylthio-2-aminopyrimidines (III) provided only intractable, tarry products.

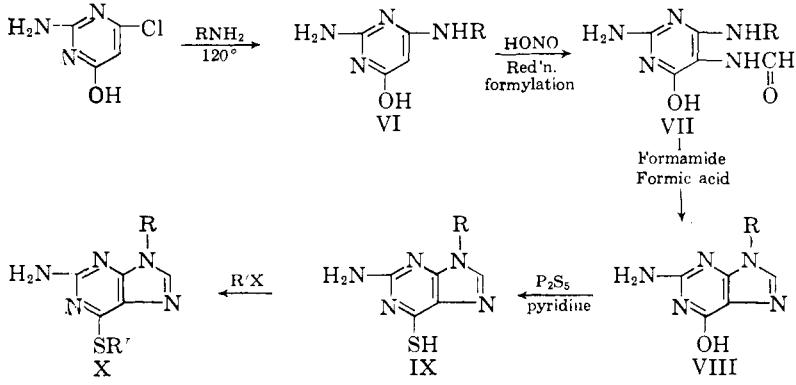
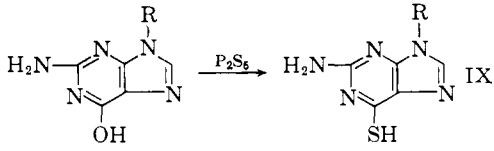


TABLE IV

IX R	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
n-Propyl $C_8H_{11}N_5S$	313–315	45.9	45.52	5.26	5.32
n-Butyl $C_9H_{13}N_5S$	290–291	48.5	49.0	5.82	6.04
Isobutyl $C_9H_{13}N_5S$	330–332	48.5	48.23	5.82	5.55
Isoamyl $C_{10}H_{15}N_5S$	317–319	50.6	50.43	6.33	6.04
2-Methylbutyl $C_{10}H_{15}N_5S$	322–325	50.6	50.6	6.33	6.31
n-Amyl $C_{10}H_{15}N_5S$	302–304	50.6	50.4	6.32	6.49
Cyclopentyl $C_{10}H_{13}N_5S$	340–342	51.1	50.64	5.52	5.30
Cyclohexyl $C_{11}H_{15}N_5S$	357–359	53.0	53.08	6.02	5.91
Ethyl $C_7H_9N_5S$	299–302	43.1	42.76	4.62	4.37

Benzyl prepared by the method of Koppel.[5]
[a] Dimethylformamide.

In view of this work another synthetic route was envisioned. 2-Amino-4-chloro-6-hydroxypyrimidine[7] in 2-ethoxyethanol when treated with the appropriate primary amines gave the desired 2-amino-6-hydroxy-4-substituted aminopyrimidines (VI) (see Table I). The 4-alkylamino-2-amino-6-hydroxypyrimidines (VI) were nitrosated, reduced, and formylated, giving in this four-step process the important 2-amino-5-formamido-6-hydroxy-4-substituted aminopyrimidines (VII) shown in Table II. The preparation of VII was



IX

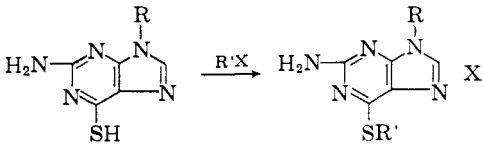
Nitrogen, % Calcd.	Found	Prepn.	Recryst. solvent	Yield, %	pH 1 λ_{max}, mμ	pH 1 ε	pH 11 λ_{max}, mμ	pH 11 ε
33.5	34.0	A	DMF[a] + H_2O	60	259	8,600	251	11,300
					350	17,600	269	8,400
							318	15,600
31.3	31.3	A	DMF + H_2O	70	260	9,500	252	13,000
					349	24,500	270	8,800
							320	21,500
31.3	31.0	A	DMF + H_2O	58	263	8,000	252	11,800
					350	20,800	270	7,100
							320	19,200
29.5	29.1	A	DMF + H_2O	30	263	7,800	248	13,600
					352	22,000	271	8,300
							320	20,000
29.5	29.7	A	DMF + H_2O	50	262	8,100	249	11,800
					350	22,000	270	7,600
							319	20,100
29.5	29.0	C	DMF + H_2O	63	262	8,000	251	11,600
					350	21,800	269	7,300
							319	19,400
29.8	29.8	B	Reppt.	62	262	7,500	251	11,500
					350	22,300	269	7,500
							319	19,800
28.1	27.9	B	Reppt.	50	262	7,700	251	11,000
					350	22,000	270	7,200
							319	19,700
36.0	36.4	See exptl.	Water	53	261	7,600	251	11,300
					350	20,000	269	7,400
							319	18,200

patterned after the method of Bredereck and Edenhofer.[9] 2-Amino-4-chloro-6-hydroxypyrimidine has previously been treated with methylamine[10] and ethylamine[7] in a sealed tube at 120° to give the corresponding 4-substituted amino derivatives. A sealed tube was found to be unnecessary. When the primary alkylamine (or aqueous solution of the amine) was passed into the 2-amino-4-chloro-6-hydroxy-

(9) H. Bredereck and A. Edenhofer, *Ber.*, **88**, 1306 (1955).
(10) W. E. Fidler and H. C. S. Wood, *J. Chem. Soc.*, 4157 (1957).

TABLE V

X R	R'	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
n-Propyl $C_{15}H_{17}N_5S$	Benzyl	154	60.2	60.12	5.68	5.67
n-Propyl $C_{15}H_{16}N_6O_2S$	*o*-Nitrobenzyl	120	52.3	52.35	4.65	4.64
n-Propyl $C_{15}H_{15}Cl_2N_5S$	2,4-Dichlorobenzyl	104	48.8	48.71	4.07	4.05
n-Propyl $C_{12}H_{14}N_6O_2S$	1-Methyl-4-nitroimidazole	208	43.2	43.6	4.19	4.29
n-Propyl $C_{15}H_{16}ClN_5S$	*o*-Chlorobenzyl	155	54.0	54.04	4.8	4.5
n-Propyl $C_{15}H_{16}ClN_5S$	*p*-Chlorobenzyl	148	54.0	54.2	4.8	4.96
n-Propyl $C_{16}H_{19}N_5S$	Phenethyl	132	61.3	61.67	6.08	5.93
n-Propyl $C_{11}H_{17}N_5S$	Isopropyl	98	52.6	52.98	6.76	6.66
n-Propyl $C_{15}H_{16}FN_5S$	*o*-Fluorobenzyl	151	56.8	56.7	5.05	5.24
n-Propyl $C_{15}H_{16}BrN_5S$	*p*-Bromobenzyl	167	47.6	47.9	4.24	4.24
n-Propyl $C_{10}H_{13}N_5O_2S \cdot H_2O$	α-Acetic acid	200 d.	42.1	41.8	5.27	5.22
n-Propyl $C_{14}H_{16}N_6S$	2 Picolyl	139	56.0	55.8	5.34	5.51
n-Butyl $C_{10}H_{15}N_5S$	Methyl	109	50.7	50.24	6.33	6.12
n-Butyl $C_{16}H_{19}N_5S$	Benzyl	163	61.4	61.3	6.07	6.03



Nitrogen, % Calcd.	Nitrogen, % Found	Prepn.	Recryst. solvent	Yield, %	MeOH λ_{max}, mμ	MeOH ε	R'X
23.4	23.7	A	Pet. ether (60–110°) + acetone	87	222 247 314	28,500 15,500 14,300	Benzyl chloride
24.4	24.4	A	Pet. ether + acetone	56	222 245 314	30,000 19,000 14,800	*o*-Nitrobenzyl chloride
19.0	19.1	A	Pet. ether + acetone	61	223 246 314	33,200 17,100 14,000	2,4-Dichlorobenzyl chloride
33.6	33.4	A	Pet. ether + acetone	77	224 314	33,000 14,000	1-Methyl-4-nitro-5-chloroimidazole
21.0	21.1	A	Pet. ether + acetone	78	222 246 314	30,000 15,500 14,000	*o*-Chlorobenzyl chloride
21.0	20.9	A	Pet. ether + acetone	80	223 245 312	33,350 15,000 13,400	*p*-Chlorobenzyl chloride
22.4	22.3	A	Pet. ether + acetone	65	222 246 313	29,100 18,200 16,600	Phenethyl-bromide
27.8	27.8	A	Pet. ether + acetone	65	223 247 314	22,000 14,000 12,800	Isopropyl iodide
22.1	21.9	A	Pet. ether + acetone	68	221 245 312	26,000 15,200 13,300	*p*-Fluorobenzyl chloride
18.5	18.5	A	Pet. ether + acetone	64	223 245 313	30,600 15,500 12,800	*p*-Bromobenzyl bromide
24.55	24.8	B	Water + methanol	31	223 246 312	22,800 14,200 13,100	Chloroacetic acid
28.0	27.7	A	Pet. ether + acetone	74	223 246 314	24,600 15,600 13,500	2-Picolyl chloride hydrochloride
29.5	29.7	C	Pet. ether + acetone	80	223 246 312	23,300 14,700 11,600	Dimethyl sulfate
22.4	22.5	A	Pet. ether + acetone	94	222 247 314	27,000 14,800 14,100	Benzyl chloride

TABLE V

X R	R′	M.p., °C.	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found
n-Butyl $C_{16}H_{18}ClN_5S$	*o*-Chlorobenzyl	190	55.2	55.18	5.17	5.28
n-Butyl $C_{16}H_{18}N_6O_2S$	*p*-Nitrobenzyl	140	53.6	53.21	5.02	4.92
n-Butyl $C_{16}H_{18}N_6O_2S$	*o*-Nitrobenzyl	133	53.6	53.92	5.02	5.12
n-Butyl $C_{13}H_{16}N_8O_2S$	1-Methyl-4-nitro-imidazole	153	44.8	45.25	4.59	4.64
n-Butyl $C_{16}H_{18}ClN_5S$	*p*-Chlorobenzyl	173	55.2	55.27	5.18	5.36
n-Butyl $C_{17}H_{21}N_5S$	Phenethyl	113	62.3	62.73	6.42	6.33
n-Butyl $C_{12}H_{19}N_5S$	Isopropyl	112	54.3	54.3	7.17	6.94
n-Butyl $C_{16}H_{17}Cl_2N_5S$	2,4-Dichloro-benzyl	168	50.2	50.33	4.45	4.2
n-Butyl $C_{16}H_{18}FN_5S$	*o*-Fluorobenzyl	171	58.0	57.83	5.43	5.5
n-Butyl $C_{16}H_{18}FN_5S$	*m*-Fluorobenzyl	136	58.0	58.2	5.43	5.3
n-Butyl $C_{16}H_{18}FN_5S$	*p*-Fluorobenzyl	132	58.0	58.0	5.43	5.65
n-Butyl $C_{16}H_{18}BrN_5S$	*p*-Bromobenzyl	187	49.0	49.16	4.59	4.85
n-Butyl $C_{11}B_{15}N_5O_2S$	α-Acetic acid	199	46.6	46.9	5.34	5.4
n-Butyl $C_{15}H_{18}N_6S$	2-Picolyl	115	57.4	57.4	5.74	5.92
n-Butyl $C_{15}H_{13}N_6S$	4-Picolyl	180	57.4	57.4	5.74	6.03

(*continued*)

Nitrogen, % Calcd.	Found	Prepn.	Recryst. solvent	Yield, %	MeOH $\lambda_{max.}$ mμ	ϵ	R′X
20.1	19.8	A	Pet. ether + acetone	86	222 246 314	29,400 15,100 13,900	*o*-Chlorobenzyl chloride
23.5	23.6	A	Pet. ether + acetone	97	222 246 313	27,800 17,900 16,500	*p*-Nitrobenzyl chloride
23.5	23.2	A	Pet. ether + acetone	63	222 245 314	29,000 18,600 14,700	*o*-Nitrobenzyl chloride
32.2	32.1	A	Pet. ether + acetone	77	224 312	34,500 14,000	1-Methyl-4-nitro-5-chloroimidazole
20.1	20.3	A	Pet. ether + acetone	89	223 246 314	34,000 14,200 13,700	*p*-Chlorobenzyl chloride
21.4	21.2	A	Pet. ether + acetone	40	222 243 313	19,900 13,700 13,700	β-Phenethyl bromide
26.4	26.1	A	Pet. ether (60–110°)	56	223 247 314	21,600 13,800 12,600	Isopropyl iodide
18.3	18.3	A	Pet. ether + acetone	77	223 245 314	32,900 16,800 14,300	2,4-Dichlorobenzyl chloride
21.1	21.0	A	Pet. ether + acetone	72	222 246 314	26,600 15,200 13,900	*o*-Fluorobenzyl chloride
21.1	20.9	A	Pet. ether + acetone	72	222 246 314	30,500 16,200 14,200	*m*-Fluorobenzyl chloride
21.1	20.8	A	Pet. ether + acetone	49	222 247 314	23,400 14,200 13,400	*p*-Fluorobenzyl chloride
17.9	17.7	A	Pet. ether + acetone	42	223 245 314	33,400 16,800 13,900	*p*-Bromobenzyl bromide
24.9	25.0	B	Water + methanol	56	223 247 313	21,300 13,500 12,900	Chloroacetic acid
26.8	26.4	A	Pet. ether + acetone	76	223 246 314	23,500 15,100 13,200	2-Picolyl chloride hydrochloride
26.8	26.3	A	Pet. ether + acetone	78	224 245 314	24,800 15,700 13,800	4-Picolyl chloride hydrochloride

TABLE V

X R	R′	M.p., °C.	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found
Cyclohexyl $C_{18}H_{21}N_5S$	Benzyl	213	63.8	64.03	6.2	6.2
Cyclohexyl $C_{18}H_{20}ClN_5S$	*o*-Chlorobenzyl	218	57.8	57.9	5.36	5.41
Isobutyl $C_{16}H_{19}N_5S$	Benzyl	185	61.4	61.9	6.07	6.28
Isobutyl $C_{16}H_{18}ClN_5S$	*o*-Chlorobenzyl	167	55.2	55.53	5.17	5.19
Isobutyl $C_{16}H_{18}ClN_5S$	*p*-Chlorobenzyl	188	55.2	55.34	5.17	4.98
Isobutyl $C_{16}H_{17}Cl_2N_5S$	2,4-Dichlorobenzyl	140	50.2	50.63	4.45	4.35
Isobutyl $C_{13}H_{16}N_5O_2S$	1-Methyl-4-nitroimidazole	180	44.8	45.1	4.59	4.72
Isobutyl $C_{16}H_{18}N_6O_2S$	*o*-Nitrobenzyl	120	53.7	53.86	5.01	4.84
Isobutyl $C_{17}H_{21}N_5S$	Phenethyl	123	62.3	62.59	6.42	6.17
Isobutyl $C_{12}H_{19}N_5S$	Isopropyl	149	54.3	54.44	7.17	7.03
Isobutyl $C_{12}H_{19}N_5S$	*n*-Propyl	103	54.3	53.75	7.17	6.83
Isobutyl $C_{16}H_{18}FN_5S$	*o*-Fluorobenzyl	184	58.0	58.3	5.43	5.71
Isobutyl $C_{13}H_{21}N_5S$	Isobutyl	113	55.9	56.21	7.53	7.53
Isobutyl $C_{18}H_{23}N_5S$	γ-Phenylpropyl	164	63.2	63.72	6.73	6.36
Isobutyl $C_{16}H_{18}BrN_5S$	*p*-Bromobenzyl	199	49.0	49.45	4.59	4.47

(*continued*)

—Nitrogen, %— Calcd.	Found	Prepn.	Recryst. solvent	Yield, %	—MeOH— $\lambda_{max.}$ mμ	ε	R′X
20.6	20.3	A	Pet. ether + acetone	74	222 246 312	27,100 14,900 14,600	Benzyl chloride
18.8	18.85	A	Pet. ether + acetone	53	222 245 312	29,100 15,000 14,000	*o*-Chlorobenzyl chloride
22.4	22.6	A	Pet. ether + acetone	57	222 247 314	29,800 16,000 14,700	Benzyl chloride
20.1	19.7	A	Pet. ether + acetone	82	222 246 314	29,200 15,300 13,600	*o*-Chlorobenzyl chloride
20.1	20.2	A	Pet. ether + acetone	69	224 247 314	34,000 16,000 13,900	*p*-Chlorobenzyl chloride
18.3	18.2	A	Pet. ether + acetone	85	223 245 314	32,800 16,800 14,200	2,4-Dichlorobenzyl chloride
32.2	31.9	A	Benzene + methanol	78	224 311	31,700 14,000	1-Methyl-4-nitro-5-chloroimidazole
23.4	23.4	A	Pet. ether + acetone	57	222 245 314	29,000 18,600 14,700	*o*-Nitrobenzyl chloride
21.4	21.4	A	Pet. ether + acetone	67	221 247 312	23,700 14,700 13,900	β-Phenethyl bromide
26.4	26.2	A	Pet. ether + acetone	87	223 247 314	22,800 14,300 13,200	Isopropyl iodide
26.4	26.2	A	Pet. ether (60–100°)	97	223 247 313	21,800 14,600 13,000	*n*-Propyl iodide
21.1	21.0	A	Pet. ether + acetone	86	222 246 314	25,900 14,900 13,700	*o*-Fluorobenzyl chloride
25.1	24.9	A	Pet. ether (60–110°)	34	223 247 312	21,800 14,500 13,400	Isobutyl iodide
20.5	20.5	A	Pet. ether + acetone	57	221 247 312	22,800 15,000 13,800	γ-Phenylpropyl bromide
17.9	17.4	A	Pet. ether + acetone	91	223 245 314	34,000 17,200 14,500	*p*-Bromobenzyl bromide

TABLE V

R	R′	M.p., °C.	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found
Isobutyl $C_{16}H_{18}FN_5S$	*m*-Fluorobenzyl	138	58.0	58.24	5.43	5.39
Isobutyl $C_{15}H_{18}N_6S$	2-Picolyl	146	57.4	57.1	5.74	5.89
Isobutyl $C_{11}H_{15}N_5O_2S$	α-Acetic acid	197	47.0	47.4	5.33	5.5
Cyclopentyl $C_{17}H_{19}N_5S$	Benzyl	215	62.8	62.89	5.26	5.78
Cyclopentyl $C_{16}H_{18}N_6S$	2-Picolyl	148	58.9	59.12	5.52	5.48
Benzyl $C_{13}H_{13}N_5S$	Methyl	210	57.7	57.51	4.8	5.03
Benzyl $C_{19}H_{17}N_5S$	Benzyl	157	65.8	65.89	4.9	4.98
Benzyl $C_{19}H_{16}N_6O_2S$	*o*-Nitrobenzyl	152	58.3	58.19	4.08	3.92
Benzyl $C_{16}H_{14}N_8O_2S$	1-Methyl-4-nitro-imidazole	245	50.3	50.9	3.67	3.8
2-Methyl-butyl $C_{17}H_{20}FN_5S$	*o*-Fluorobenzyl	177	59.1	59.2	5.7	5.88
2-Methyl-butyl $C_{12}H_{17}N_5O_2S$	α-Acetic acid	165	48.8	48.8	5.76	5.76
2-Methyl-butyl $C_{16}H_{20}N_6S$	2-Picolyl	127	58.5	58.5	6.09	6.02
2-Methyl-butyl $C_{14}H_{18}N_8O_2S$	1-Methyl-4-nitro-imidazole	200	46.4	46.2	4.97	5.2
2-Methyl-butyl $C_{17}H_{21}N_5S$	Benzyl	168	62.3	62.05	6.41	6.23
2-Methyl-butyl $C_{14}H_{23}N_5S$	*n*-Butyl	103	57.3	56.85	7.86	7.75

(continued)

—Nitrogen, %— Calcd	Found	Prepn.	Recryst. solvent	Yield, %	—MeOH— λ_{max}, mμ	ε	R′X
21.1	21.3	A	Pet. ether + acetone	88	222 246 314	26,000 14,600 13,600	*m*-Fluorobenzyl chloride
26.8	26.4	A	Pet. ether + acetone	91	223 246 314	24,000 15,600 13,500	2-Picolyl chloride hydrochloride
24.9	24.5	B	Water + methanol	91	222 246 310	23,000 14,300 13,400	Chloroacetic acid
21.5	21.8	A	Water + methanol	55	222 247 313	26,800 14,600 14,300	Benzyl chloride
25.75	25.7	A	Water + methanol	79	223 246 313	25,000 15,400 14,000	2-Picolyl chloride hydrochloride
25.8	26.0	C	Methanol	67	247 312	16,000 13,600	Dimethyl sulfate
20.2	20.4	A	Pet. ether + acetone	82	247 314	14,600 15,200	Benzyl chloride
21.4	21.1	A	Pet. ether + acetone	81	246 314	19,200 15,500	*o*-Nitrobenzyl chloride
29.3	29.5	A	Methanol	85	224 313	28,000 12,800	1-Methyl-4-nitro-5-chloroimidazole
20.3	20.0	A	Pet. ether + acetone	76	222 246 314	26,000 15,200 13,800	*o*-Fluorobenzyl chloride
23.7	23.8	B	Water + methanol	83	222 246 312	21,000 13,200 13,200	Chloroacetic acid
25.6	25.5	A	Pet. ether + acetone	68	223 246 314	23,500 15,200 13,400	2-Picolyl chloride hydrochloride
30.95	30.7	A	Pet. ether + acetone	80	225 314	30,000 14,100	1-Methyl-4-nitro-5-chloroimidazole
21.4	21.5	A	Pet. ether + acetone	64	222 247 313	26,200 14,700 14,000	Benzyl chloride
23.85	23.85	A	Pet. ether	36	223 247 312	22,000 14,400 13,200	*n*-Butyl iodide

TABLE V

X R	R'	M.p., °C.	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found
n-Amyl $C_{17}H_{21}N_5S$	Benzyl	149	62.3	62.37	6.41	6.23
Isoamyl $C_{17}H_{20}FN_5S$	*o*-Fluorobenzyl	175	59.1	59.0	5.7	5.91
Isoamyl $C_{12}H_{17}N_5O_2S$	α-Acetic acid	209	48.8	49.15	5.76	5.8

TABLE VA

X R	M.p., °C.	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found
Methyl $C_7H_9N_5S$	190	43.0	43.22	4.6	4.55
Ethyl $C_8H_{11}N_5S$	165	46.0	46.11	5.27	5.31

pyrimidine in refluxing ethoxyethanol, a good yield of the desired product, VI, was obtained. This procedure was found to be especially useful for large-scale runs.

The 5-formamido derivatives (VII) were cyclized readily to the appropriate 9-alkylguanines (VIII) by the use of formamide in the presence of a small amount of formic acid. These 9-alkylguanines (VIII) are listed in Table III. Several of these 9-alkylguanines (R = isobutyl, benzyl, cyclohexyl, and isoamyl[11]) have been prepared previously.[5] The 9-alkylguanines (VIII) were then converted to corresponding 9-alkyl-2-amino-6-purinethiols (IX) by use of phosphorus pentasulfide in pyridine.[4] These derivatives are listed in Table IV. Treatment of the 9-alkyl-2-amino-6-purinethiols (IX) with the appropriate alkyl halide (Table V) in the presence of base gave the desired 9-alkyl-6-alkylthio-2-aminopurines listed in Table V.

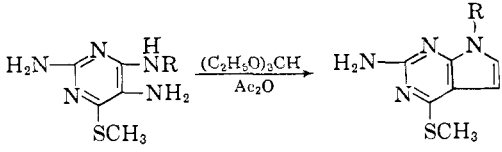
Discussion of Antitumor Testing Data

The testing procedures employed have been adequately described

(11) Ref. 5, Table III, the fourth compound listed, "R" actually should be isoamyl.

(*continued*)

—Nitrogen, %— Calcd.	Found	Prepn.	Recryst. solvent	Yield, %	—MeOH— λ_{max}, mμ	ε	R′X
21.4	20.7	A	Pet. ether + acetone	75	222	23,000	Benzyl chloride
					247	13,000	
					313	12,400	
20.3	20.3	A	Pet. ether + acetone	79	222	26,000	*o*-Fluorobenzyl chloride
					246	14,900	
					314	13,800	
23.7	23.9	B	Water + methanol	86	222	22,400	Chloroacetic acid
					246	14,200	
					310	13,600	



—Nitrogen, %— Calcd.	Found	Recryst. solvent	Yield, %	—pH 1— λ_{max}, mμ	ε	—pH 11— λ_{max}, mμ	ε
35.9	36.0	Benzene	42	247	8,600	246	11,000
				321	9,300	311	10,400
33.5	33.7	Benzene	55	248	8,600	246	12,200
				322	10,600	312	12,100

previously.[12] All testing was conducted under the auspices of the Cancer Chemotherapy National Service Center. 2-Amino-6-purinethiol (thioguanine) has been found to be a potent inhibitor of animal neoplasms[13] and human leukemia.[14] The therapeutic index of thioguanine is approximately 4 against Adenocarcinoma 755.[15] Inspection of Table X would reveal that a rather large number of the 9-alkyl and 9-alkyl-6-alkylthio derivatives of thioguanine possess a therapeutic index much *superior* to the parent compounds.

The compound 2-amino-9-*n*-propyl-6-purinethiol (NSC 40669) is especially noteworthy since it possesses a therapeutic index of 64 against the same tumor line. It is of considerable interest that NSC 40669 is also active at a lower dosage than thioguanine itself (see Table IX).

(12) J. Leiter, A. R. Bourke, S. A. Schepartz, and I. Wodinsky, *Cancer Res.* **20**, 734 (1960).

(13) D. A. Clarke, F. S. Philips, S. S. Sternberg, and C. C. Stock, *Ann. N. Y. Acad. Sci.*, **60**, 235 (1954).

(14) M. L. Murphy, C. T. C. Tan, R. R. Ellison, D. A. Karnofsky, and J. H. Burchenal, *Proc. Am. Assoc. Cancer Research*, **2**, 36 (1955).

(15) H. E. Skipper, J. A. Montgomery, J. R. Thomson, and F. M. Schabel, Jr., *Cancer Research*, **19**, 425 (1959).

TABLE VI

I R	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Methyl $C_5H_7ClN_4$	160	37.8	38.0	4.42	4.28	35.3	35.1
Ethyl $C_6H_9ClN_4$	153	41.7	42.3	5.21	5.31	32.5	36.6
n-Propyl $C_7H_{11}ClN_4$	105	45.0	45.29	5.9	5.96	30.0	30.4
n-Butyl $C_8H_{13}ClN_4$	95	47.8	48.0	6.5	6.83	27.9	28.0
Allyl $C_7H_9ClN_4$	120	45.5	45.9	4.87	4.65	30.3	30.3
Benzyl $C_{11}H_{11}ClN_4$	129	56.3	56.34	4.7	4.62	23.8	23.9

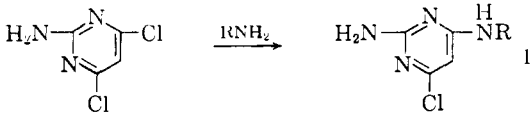
TABLE VII

II R	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Methyl $C_5H_8N_4S$	295[a]	38.5	38.86	5.12	5.13
Ethyl $C_6H_2N_4S\cdot H_2O$	224[a]	38.3	38.58	6.39	6.39
n-Propyl $C_7H_{12}N_4S$	268[a]	45.6	45.65	6.52	6.75
n-Butyl $C_8H_{14}N_4S$	231[a]	48.5	48.96	7.08	7.18
Benzyl $C_{11}H_{12}N_4S$	212[b]	56.9	56.78	5.17	5.10

[a] All of these compounds showed a gradual decomposition and finally melted at the temperature recorded. [b] This compound melted sharply with no decom-

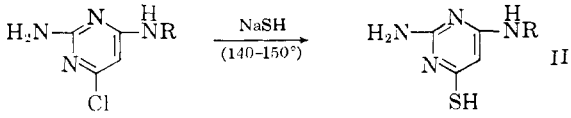
LePage and Jones[3] have found 2-amino-9-methyl-6-purinethiol and 2-amino-9-*n*-butyl-6-purinethiol to inhibit Ehrlich ascites tumor. These 9-alkyl derivatives of thioguanine were found[3] *not* to be converted to the nucleotide form *in vivo*. Since Sartorelli and LePage[16,17] have shown that thioguanine acts at more than one site in purine

(16) A. C. Sartorelli and G. A. LePage, *Cancer Research*, **18**, 1329 (1958).
(17) G. A. LePage, *ibid.*, **20**, 403 (1960).



I

Recryst. solvent	Yield, %	pH 1 λ_{max}, mμ	pH 1 ε	pH 11 λ_{max}, mμ	pH 11 ε	RNH_2
Water	91	276	6,000	237	8,700	40% Methylamine
		302	4,800	287	7,500	in water
Benzene	98	277	7,100	238	9,500	70% Ethylamine
		303	5,400	288	8,800	in water
Heptane–benzene	95	278	7,500	238	9,800	*n*-Propylamine
		304	5,800	288	9,000	
Heptane	85	277	7,400	239	9,800	*n*-Butylamine
		304	5,600	288	9,000	
Heptane–benzene	92	276	8,700	237	10,700	Allylamine
		304	5,000	288	9,900	
Heptane–methanol	99	275	9,100	237	13,100	Benzylamine
		305	4,000	288	10,500	



II

Nitrogen, % Calcd.	Found	Prepn.	Recryst. solvent	Yield, %	pH 1 λ_{max}, mμ	pH 1 ε	pH 11 λ_{max}, mμ	pH 11 ε
35.8	35.6	B	Water	56	330	24,000	232	18,800
							303	19,500
29.75	30.2	B	Water	83	330	24,600	233	16,600
							304	18,500
30.4	30.7	A	Water	79	330	28,100	234	19,600
							305	20,400
28.3	28.6	A	Water	94	330	29,100	233	21,800
							304	19,800
24.1	24.0	B	Water	79	330	20,400	234	18,100
							304	20,400

position range.

metabolism, it is quite possible that the 9-alkyl derivatives described in the present work act at only one site. Thus, the superior therapeutic indices (see Table X) of a number of these derivatives over that of thioguanine in Ad 775 probably result from a more selective action of the antitumor drug. Thus, according to LePage[3] the 9-alkylated 2-amino-6-purinethiols appear to have an entirely different mechanism of action from that of thioguanine. Support for this

TABLE VIII

III

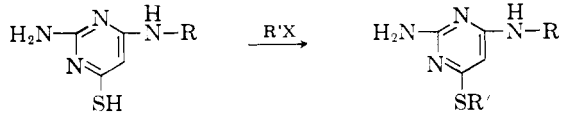
R	R′	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3	CH_3	134	42.3	42.29	5.9	5.75	32.9	33.1
$C_6H_{10}N_4S$								
CH_3	C_2H_5	118	45.6	45.04	6.52	6.67	30.5	30.8
$C_7H_{12}N_4S$								
CH_3	$C_6H_5CH_2$	180	58.5	58.24	5.7	5.74	22.7	22.5
$C_{12}H_{14}N_4S$								
C_2H_5	CH_3	168	45.6	45.24	6.52	6.19	30.5	30.3
$C_7H_{12}N_4S$								
C_2H_5	C_2H_5	120	48.5	49.02	7.06	7.15	28.4	28.6
$C_8H_{14}N_4S$								
C_2H_5	$C_6H_5CH_2$	113	60.0	60.04	6.16	6.54	21.6	21.8
$C_{13}H_{16}N_4S$								
$C_6H_5CH_2$	CH_3	115	58.4	58.6	5.68	5.69	22.7	22.5
$C_{12}H_{14}NS$								

statement was found[3] in that a thioguanine-resistant line of ascites tumor cells was not completely cross-resistant to 2-amino-9-methyl-6-purinethiol.

It might be argued that *in vivo* dealkylation at position 9 is responsible for antitumor activity since such dealkylation would give rise to thioguanine. With mice bearing Ehrlich and Mecca ascites tumors, LePage and Jones[3] have investigated this possibility and reported that no dealkylation took place. The antitumor activity of two of these compounds has been studied in Sarcoma 180 (see Table XI). In several experiments the inhibition by 2-amino-9-*n*-propyl-6-purinethiol (NSC 40669) is greater than that observed for thioguanine with the same tumor[18]; however, additional testing is required to verify these data.

It would appear that the 9-alkyl derivatives of thioguanine described in the present work represent a class of antitumor agents which are worthy of further investigation. These agents should be examined carefully for their activity against a variety of tumors. It would be especially interesting to evaluate these agents against 6-mercaptopurine- and 6-thioguanine-resistant tumor lines. It is also possible that the 9-alkyl derivatives may act synergistically with the usual purine antagonists since the formation of the purine ribotide is

(18) D. A. Clarke, G. B. Elion, G. H. Hitchings, and C. C. Stock, *Cancer Research*, **18**, 445 (1958).



II III

Prepn.	Recryst. solvent	Yield, %	pH 1 λ_{max} mμ	pH 1 ε	pH 11 λ_{max}, mμ	pH 11 ε	R′X
A	Water	80	228	19,800	232	21,600	CH_3I
			286	15,200	290	11,000	
A	Water	93	230	17,100	233	21,200	C_2H_5I
			288	14,400	291	11,400	
B	Benzene	83	290	12,000	234	20,700	$C_6H_5CH_2Cl$
					293	10,400	
A	Water	84	229	17,700	232	22,800	CH_3I
			287	15,400	290	11,800	
A	Water	83	230	17,200	233	21,100	C_2H_5I
			288	14,800	291	11,600	
B	Benzene	85	289	12,600	234	18,200	$C_6H_5CH_2Cl$
					293	9,100	
A	Pet. ether (60–110°) + acetone	94	230	20,400	232	29,500	CH_3I
			288	17,200	290	14,000	

blocked due to the presence of the 9-alkyl group. The use of combination therapy utilizing more than one purine derivative at one time should be carefully examined, especially where there is evidence of difference of mechanism of action among the purines. This would seem to be a particularly attractive area for further investigation, especially since these various active purine derivatives are quite likely to exert their antitumor action at different points along the same metabolic pathway.

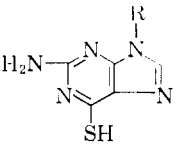
Experimental[19]

Preparation of 2-Amino-6-hydroxy-4-substituted Aminopyrimidines (VI) (Table I): **Method A.**—To 25 g. of 2-amino-4-chloro-6-hydroxypyrimidine[7] placed in a flask equipped with a special Friedrichs condenser designed to remove a low boiling component, and a dropping funnel extending to the bottom of the flask was added 150 ml. of 2-ethoxyethanol, and the mixture was stirred and brought to a moderate reflux. The appropriate amine (50–60 g.) (Table I) was added in a steady stream. The excess amine, which vaporized and passed through the solution, was collected along with a small amount of 2-ethoxyethanol. It is important that the amine be added at such a rate that the temperature of the solution does not fall greatly below that of the boiling 2-ethoxyethanol. After all the amine had been added and all solid material had dissolved, the collected amine was once again passed through the boiling solution. The clear, red solution was then

(19) All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected unless otherwise indicated.

TABLE IX

COMPARISON OF DOSAGE REQUIRED FOR EFFECTIVE INHIBITION OF ADENOCARCINOMA 755

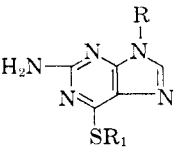


NSC No.	R	Minimum dosage (mg./kg./day) necessary to achieve 90% inhibition of Adenocarcinoma 755
(Thioguanine)	H	≈0.5[a]
26290	CH_3	125
40660	C_2H_5	≈3.5
40669	n-C_3H_7	<0.2
39336	n-C_4H_9	1.0
42378	iso-C_4H_9	≈3.0
58907	n-C_5H_{11}	12.5
50717	iso-C_5H_{11}	12.5
52446	C_5H_{11} (2-methylbutyl)	≈12.5
56455	Cyclopentyl	≈5.0
29609	$CH_2C_6H_5$[b]	≈400
56456	Cyclohexyl	Inactive
29608	n-$C_{10}H_{21}$[b]	Inactive
27611	C_6H_5[b]	Inactive
29576	p-ClC_6H_4[b]	Inactive

[a] Ref. 15. [b] Ref. 5.

TABLE X

COMPARISON OF THERAPEUTIC INDICES OF 9-ALKYL-2-AMINO-6-PURINETHIOLS AND RELATED DERIVATIVES AGAINST CARCINOMA 755



NSC No.	R	R_1	Therapeutic index[a]	Max. degree of effectiveness T/C at MTD
40669	n-Propyl	H	64	0.01
51473	n-Butyl	2-Pyridylmethyl	35	0.00
44580	n-Propyl	o-Chlorobenzyl	32	0.00
39336	n-Butyl	H	30	0.00
47781	n-Butyl	1-Methyl-4-nitro-5-imidazolyl	17	0.03
51471	n-Propyl	2-Pyridylmethyl	17	0.00
59486	Cyclopentyl	2-Pyridylmethyl	16	0.00
44585	Isobutyl	1-Methyl-4-nitro-5-imidazolyl	16	0.00

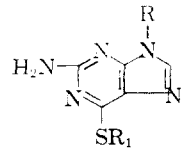
TABLE X (*continued*)

NSC No.	R	R_1	Therapeutic index[a]	Max degree of effectiveness T/C at MTD
48719	Isobutyl	*n*-Propyl	16	0.00
49820	*n*-Butyl	*p*-Fluorobenzyl	16	0.00
43414	*n*-Propyl	*p*-Chlorobenzyl	16	0.00
49817	*n*-Propyl	*o*-Fluorobenzyl	16	0.00
51478	2-Methylbutyl	1-Methyl-4-nitro-5-imidazolyl	9	0.01
56455	Cyclopentyl	H	8	0.00
42381	Isobutyl	Benzyl	8	0.04
48724	Isobutyl	*m*-Fluorobenzyl	8	0.00
48721	Isobutyl	Isobutyl	8	0.00
48720	Isobutyl	*o*-Fluorobenzyl	8	0.00
47780	*n*-Butyl	Isopropyl	8	0.00
42382	*n*-Butyl	Benzyl	8	0.00
49818	*n*-Butyl	*o*-Fluorobenzyl	8	0.01
44584	*n*-Propyl	1-Methyl-4-nitro-5-imidazolyl	8	0.00
51472	*n*-Propyl	*p*-Bromobenzyl	8	0.00
42379	*n*-Propyl	Benzyl	8	0.01
40660	Ethyl	H	8	0.05
36836	Ethyl	Methyl	8	0.01
52445	Isobutyl	2-Pyridylmethyl	6	0.01
42378	Isobutyl	H	4	0.00
48723	Isobutyl	*p*-Bromobenzyl	4	0.18
48722	Isobutyl	3-Phenylpropyl	4	0.08
47784	Isobutyl	Isopropyl	4	0.01
47783	Isobutyl	Phenethyl	4	0.03
42383	*n*-Butyl	*o*-Chlorobenzyl	4	0.05
48718	*n*-Butyl	2,4-Dichlorobenzyl	4	0.05
49819	*n*-Butyl	*m*-Fluorobenzyl	4	0.00
47778	*n*-Propyl	Isopropyl	4	0.00
51477	2-Methylbutyl	2-Pyridylmethyl	4	0.23
50717	Isopentyl	H	4	0.01
42384	Benzyl	Benzyl	4	0.07
51474	*n*-Butyl	4-Pyridylmethyl	2	0.01
52446	2-Methylbutyl	H	2	0.02

[a] Therapeutic index is defined by the Cancer Chemotherapy National Service Center for Adenocarcinoma 755 as: Therapeutic Index $= \frac{\text{MTD}}{\text{MED}}$, where M.T.D. = (Maximum Tolerated Dose) killing not more than 3 out of 10 animals (LD_{30}) with a weight loss between treated and control animals of 5 g. or less. M.E.D. = lowest dosage having a T/C of 40% or less.

TABLE XI

EVALUATION OF THE ANTITUMOR ACTIVITY OF 9-ALKYLTHIOGUANINE DERIVATIVES AGAINST CARCINOMA 755



R	R_1	Dose (mg./kg.)	Survivors	Wt. change (test/control)	Tumor wt. (test/control)	T/C
$(CH_2)_3CH_3$	H	500	0/10	toxic		
		125	0/10	toxic		
		60	0/10	toxic		
		30	0/10	toxic		
		15	1/10	−3.6/−1.2	/1242	toxic
		7.5	7/10	−3.6/−0.6	0/475	0.00
		3.75	8/10	−3.3/−0.9	0/1042	0.00
		3.75	9/10	−2.4/−0.6	17/475	0.03
		1.87	9/10	−2.4/−0.6	50/475	0.10
		1	9/10	−2.4/−0.1	139/1163	0.11
		0.50	10/10	−2.1/−0.1	190/1163	0.16
		0.25	10/10	−0.4/−0.1	694/1163	0.59
		0.12	8/10	−0.8/−0.1	694/1163	0.59
$(CH_2)_3CH_3$	H	14	2/10	−5.1/1.7	12/1136	toxic
		7	8/10	−3.7/1.7	20/1136	0.01
		6.75	10/10	−4.1/0.6	24/1140	0.02
		6.75	3/10	−3.4/0.7	100/1352	toxic
		3.5	8/10	−2.8/1.7	37/1136	0.03
		1.75	10/10	−2.2/1.7	30/1136	0.02
		1.75	10/10	−0.5/2.9	91/1830	0.04
		0.88	10/10	−0.1/2.9	77/1830	0.04
		0.44	9/10	−0.5/2.9	151/1830	0.08
		0.22	10/10	−1.1/2.9	143/1830	0.07
		0.22	10/10	1.2/2.4	107/1587	0.06
		0.11	10/10	0.6/2.4	723/1587	0.45
		0.06	10/10	1.8/2.4	1315/1587	0.82
$CH_2CH(CH_3)_2$	H	31.25	8/10	−4.3/−0.4	0/1032	0.00
		15.62	2/10	−5.6/−0.3	0/1120	toxic
		7.81	8/10	−4.2/−0.4	0/1032	0.00
		7.81	8/10	−2.0/−0.3	0/1120	0.00
		3.9	10/10	−1.8/−0.4	60/1032	0.05
		3.9	10/10	−2.0/−0.3	30/1120	0.02
		1.95	10/10	−1.8/−0.3	422/1120	0.37
		0.98	10/10	−1.3/−0.3	525/1120	0.46
$(CH_2)_2CH_3$	$CH_2C_6H_4Cl$-*p*	200	1/10	−2.2/0.5	/996	toxic
		200	0/10	toxic		
		100	8/10	−2.4/0.5	0/996	0.00
		100	10/10	−2.3/0.1	0/1573	0.00
		50	10/10	−1.9/0.5	10/996	0.01
		50	10/10	−1.7/0.1	15/1573	0.00
		25	10/10	−2.2/0.5	65/996	0.06
		25	7/10	−1.6/0.4	7/1033	0.00
		25	10/10	−1.2/0.1	122/1573	0.07
		12.5	10/10	−1.8/0.4	15/1033	0.01
		12.5	10/10	−1.2/0.1	680/1573	0.43
		6.25	10/10	−1.1/0.4	239/1033	0.23
		6.25	8/10	−0.7/0.1	950/1573	0.60
		3.12	10/10	−0.1/0.4	500/1033	0.48
		3.12	10/10	−0.3/0.1	980/1573	0.62
		1.56	9/10	−0.9/0.4	363/1033	0.35

TABLE XI (*continued*)

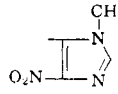
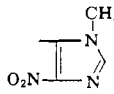
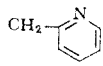
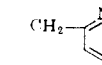
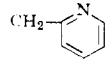
R	R_1	Dose (mg./kg.)	Survivors	Wt. change (test/control)	Tumor wt. (test/control)	T/C
		1.56	10/10	−0.5/0.1	1140/1573	0.72
		0.78	9/10	−0.1/0.1	1350/1573	0.85
$CH_2CH(CH_3)_2$		200	0/10	toxic		
		100	5/10	−2.2/2.8	50/1669	toxic
		100	1/10	−4.9/0.1	/1573	toxic
		50	8/10	−1.3/2.8	44/1669	0.02
		50	5/10	−3.4/−1.9	0/311	toxic
		50	7/10	−2.4/−0.3	0/731	0.00
		50	8/10	−4.1/0.1	0/1573	0.00
		25	8/10	−2.2/2.8	38/1669	0.02
		25	8/10	−2.4/−1.9	13/311	0.04
		25	9/10	−1.6/−0.3	0/731	0.00
		25	10/10	−2.5/0.1	35/1573	0.02
		12.5	8/10	−1.7/−1.9	13/311	0.04
		12.5	9/10	−1.9/−0.3	17/731	0.02
		12.5	9/10	−1.3/0.1	119/1573	0.07
		6.25	9/10	−1.2/−1.9	250/311	0.80
		6.25	10/10	−1.4/−0.3	75/731	0.10
		6.25	9/10	−1.4/0.1	356/1573	0.22
		3.12	10/10	−1.4/−1.9	135/311	0.43
		3.12	8/10	−1.7/−0.3	69/731	0.09
		3.12	7/10	−1.9/−2.0	257/523	0.49
		3.12	9/10	−1.1/0.1	761/1573	0.48
		1.56	10/10	−1.6/−2.0	240/523	0.45
		1.56	3/10	−0.3/0.1	1217/1573	toxic
		0.78	8/10	−1.4/−2.0	431/523	0.82
		0.78	9/10	−1.1/0.1	1083/1573	0.68
		0.39	9/10	−1.4/−2.0	200/523	0.38
		0.39	9/10	−0.8/0.1	1111/1573	0.70
		0.195	10/10	−0.3/0.1	1125/1573	0.71
$(CH_2)_3CH_3$		200	0/10	toxic		
		100	0/10	toxic		
		50	0/10	toxic		
		25	1/10	−6.7/0.6	toxic	
		25	3/10	−2.9/−1.3	0/1045	toxic
		25	10/10	−2.7/−1.3	30/1045	0.02
		12.5	7/10	−4.2/−1.3	36/1045	0.03
		6.25	7/10	−1.8/−1.3	36/1045	0.03
		3	9/10	−2.1/−0.2	72/848	0.08
		1.5	9/10	−0.6/−0.2	433/848	0.51
		0.75	10/10	−2.0/−0.2	255/848	0.30
		0.375	9/10	−0.1/−0.2	756/848	0.89
$CH_2CH(CH_3)_2$	$(CH_2)_2CH_3$	400	0/10	toxic		
		200	0/10	toxic		
		100	7/10	−3.3/−1.0	0/960	0.00
		50	9/10	−3.0/−1.0	17/960	0.01
		50	8/10	−2.6/−0.6	13/1100	0.01
		25	10/10	−2.1/−0.6	45/1100	0.04
		12.5	9/10	−1.2/−0.6	283/1100	0.25
		6.25	9/10	−1.3/−0.6	350/1100	0.31
$(CH_2)_3CH_3$	$CH_2C_6H_4F$-*p*	200	3/10	−3.7/−0.2	0/1256	toxic
		100	9/10	−3.8/−0.2	0/1256	0.00
		50	10/10	−2.9/−0.2	30/1256	0.02
		25	10/10	−2.0/−0.2	130/1256	0.10
		25	10/10	−2.0/−1.1	145/980	0.14
		12.5	10/10	−2.4/−1.1	220/980	0.22

TABLE XI (*continued*)

R	R_1	Dose (mg./kg.)	Survivors	Wt. change (test/control)	Tumor wt. (test/control)	T/C
		6.25	10/10	−2.0/−1.1	470/980	0.47
		3.1	10/10	−1.6/−1.1	585/980	0.59
$(CH_2)_2CH_3$		250	1/10	−1.2/1.9	toxic	
		125	4/10	−1.9/1.9	0/1102	toxic
		62.5	7/10	−2.8/1.9	0/1102	0.00
		31.25	9/10	−0.6/1.9	6/1102	0.00
		31.25	7/10	−0.7/1.7	0/683	0.00
		15.5	7/10	0.3/1.7	7/683	0.01
		7.25	7/10	−0.7/1.7	29/683	0.04
		3.6	9/10	0.7/1.7	83/683	0.12
$(CH_2)_3CH_3$		250	2/10	−2.8/1.9	0/1102	toxic
		125	8/10	−2.7/1.9	0/1102	0.00
		62.5	7/10	−2.5/1.9	0/1102	0.00
		31.25	8/10	−0.9/1.9	6/1102	0.00
		31.25	3/10	−0.7/1.7	17/683	toxic
		15.5	8/10	−2.0/1.7	6/683	0.00
		7.25	8/10	−1.2/1.7	19/683	0.02
		3.6	7/10	0.3/1.7	43/683	0.06
	H	225	0/10	toxic		
		75	5/10	−5.5/−0.2	0/412	toxic
		50	9/10	−2.6/−0.7	0/645	0.00
		25	9/10	−4.3/−0.2	0/412	0.00
		25	10/10	−5.0/−0.7	0/645	0.00
		12.5	8/10	−3.3/−0.7	0/645	0.00
		6.2	10/10	−2.1/−0.7	57/645	0.08
		3.1	9/10	−1.4/−0.7	244/645	0.37
		150	9/10	−4.2/1.7	8/1577	0.00
		75	10/10	−3.3/1.7	10/1577	0.00
		37.5	10/10	−1.7/1.7	45/1577	0.02
		37.5	10/10	−2.2/1.5	20/1004	0.01
		18.7	9/10	−0.6/1.5	19/1004	0.01
		9.3	10/10	−0.4/1.5	140/1004	0.13
		9.3	10/10	0.4/2.3	369/1661	0.22
		4.6	10/10	0.6/2.3	1244/1661	0.74
		2.3	9/10	1.7/2.3	1605/1661	0.96
		1.1	10/10	0.8/2.3	1317/1661	0.79

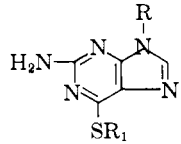
poured into 300 ml. of ice water and allowed to chill overnight. The precipitate was filtered, washed with water, and dried to give the crude product.

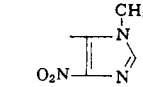
Method B.—A mixture of 20 g. of 2-amino-4-chloro-6-hydroxypyrimidine,[7] 3 molar equivalents of the appropriate amine (Table I), and 50 ml. of 2-ethoxyethanol was refluxed for 1 hr., except for cyclopentylamine, where 16 hr. was required for complete replacement. The hot solution was then poured into 300 ml. of ice water and allowed to chill overnight. The precipitate was filtered, washed with water, and dried to yield the crude product.

2-Amino-5-formamido-6-hydroxy-4-substituted Aminopyrimidines (VII) (Table II) **Method A.**—2-Amino-4-chloro-6-hydroxypyrimidine[7] (50 g.) was treated with the appropriate amine (see Table II) exactly as described in Method A for the preparation of the desired 2-amino-6-hydroxy-4-substituted aminopyrimidine (VI) except that the hot, reacted solution of 2-ethoxyethanol was poured into 600 ml. of water and then just cooled to room temperature by the addition of chopped ice. Glacial acetic acid (200 ml.) was added and the mixture stirred

TABLE XII

EVALUATION OF THE ANTITUMOR ACTIVITY OF 9-ALKYLTHIOGUANINE DERIVATIVES AGAINST SARCOMA 180



R	R_1	Dose, mg./kg.	Survivors	Wt. change (test/control)	Tumor wt. (test/control)	T/C
$(CH_2)_2CH_3$	H	15	3/6	−2.8/−0.6	325/878	toxic
		11	4/6	−3.3/−0.7	238/621	0.38
		7.5	6/6	−1.5/−0.7	285/1126	0.25
		7.5	6/6	−2.9/−1.6	285/856	0.33
		7.5	6/6	0.0/2.5	861/1100	0.78
		7.5	5/6	−3.9/−0.4	158/663	0.23
		7.5	6/6	−2.1/−0.1	325/651	0.49
		7.5	6/6	−1.8/−1.0	238/812	0.29
		7.5	4/6	−2.9/−0.7	287/621	0.46
		5.0	5/6	−1.7/−0.7	228/621	0.36
		3.3	4/6	−0.7/−0.7	393/621	0.63
$(CH_2)_3CH_3$		18.75	6/6	−0.9/1.9	317/610	0.51
		12.5	4/6	−0.2/−0.6	363/1276	0.28
		12.5	6/6	−0.2/1.9	408/610	0.66
		8.3	6/6	1.2/1.9	325/610	0.53
		5.5	6/6	1.8/1.9	583/610	0.95

manually as 40 g. of sodium nitrate, dissolved in 200 ml. of water, was added rather rapidly. The temperature of the mixture rose very slightly. The mixture was allowed to stand 2 hr. with occasional stirring, and the red-orange nitroso derivative was filtered and washed with water. It then was placed in 300 ml. of formamide and 100 ml. of 90% formic acid at 70° and was completely reduced by the addition of sodium hydrosulfite with stirring. The mixture was allowed to boil 15–20 min., 500–800 ml. of hot water and a generous portion of Norit was added, and boiling was continued for another 15–20 min. The boiling mixture was then filtered and the filtrate allowed to cool. The precipitate was filtered, washed with water, and dried at 50–60° to give the desired product.

Method B.—2-Amino-4-chloro-6-hydroxypyrimidine[7] (50 g.) was treated with the appropriate amine (see Table II) exactly as described in Method B for the preparation of VI. The reacted solution of 2-ethoxyethanol was poured into 600 ml. of water and then just cooled to room temperature by the addition of chopped ice. The nitrosation, reduction, and formylation was then carried out in a manner identical with that employed in Method A above.

9-Substituted Guanines (VIII) (Table III).—The appropriate 2-amino-5-formamido-6-hydroxy-4-substituted aminopyrimidine (VII) (25 g.) was covered with 100 ml. of formamide and 8 ml. of 90% formic acid and refluxed for 3–4 hr. The hot mixture was poured into 400 ml. of ice water, with stirring, and allowed to stand a few min. The precipitate was filtered, washed with water, dissolved in 400 ml. of dil. boiling hydrochloric acid solution, treated with Norit, and filtered. The filtrate was made basic by addition of 28% ammonium hydroxide, and the precipitate that formed was filtered after standing a few min., dissolved in 400 ml. of dilute boiling potassium hydroxide solution, treated with Norit, filtered, and the filtrate acidified with glacial acetic acid. The white crystals that formed were filtered hot and washed first with water and then with acetone. Upon drying at 100° an analytical product was obtained.

2-Amino-9-substituted-6-purinethiols (IX) (Table VI): **Method A.**—A mixture of 50 g. of the appropriate 9-substituted guanine analog (VIII), 150 g. of phosphorus pentasulfide and 650 ml. of pyridine was stirred and refluxed for 12 hr. and then allowed to cool to approximately 50–60°. The precipitate was filtered and washed with acetone. The crude material was dissolved in 1000 ml. of boiling, dilute potassium hydroxide solution with Norit added. After filtration, the filtrate was acidified with glacial acetic acid, and the precipitate that formed was filtered and washed with water. One more reprecipitation gave a near-white product which was washed with acetone and dried at 100°.

Method B.—The appropriate 9-substituted guanine (VIII) (30 g.) and 90 g. of phosphorus pentasulfide in 1500 ml. of pyridine were refluxed and stirred for 100 hr. (adding 20 g. of fresh phosphorus pentasulfide at the end of 50 and 80 hr.). The precipitate was filtered after the solution had cooled to 40–50° and was washed with acetone. The crude material was dissolved in 1000 ml. of boiling, dilute potassium hydroxide solution, treated with Norite, filtered, and the filtrate acidified with glacial acetic acid (pH 5-6). The precipitate was filtered and washed with water and then dissolved in 300 ml. of boiling, 1:6 hydrochloric acid, treated with Norit, filtered, and allowed to cool after the addition of 150 ml. of concd. hydrochloric acid. The crystals that formed were filtered and dissolved in 300 ml. of boiling dil. potassium hydroxide solution, the solution treated with Norit, filtered, and the filtrate adjusted to pH 5-6 with glacial acetic acid. The mixture was allowed to stand a few min., and the precipitate was filtered, washed with water and then acetone, and dried at 100°.

Method C.—The appropriate 9-substituted guanine (VIII) (20 g.) and 60 g. of phosphorus pentasulfide in 200 ml. of pyridine were stirred and refluxed for 7 hr. The dark solution was reduced to a partially gummy residue *in vacuo* on a steam-bath. The residue was covered with 300 ml. of water, heated on the steam-bath for 4 hr., and allowed to cool. The precipitate was filtered, washed with water, dissolved in 400 ml. of dil. cold potassium hydroxide, treated with Norit, and filtered. The filtrate was heated to boiling, again treated with Norit, and filtered. The filtrate was acidified with glacial acetic acid and the precipitate filtered hot and washed with water. One more reprecipitation gave the desired product.

2-Amino-9-ethyl-6-purinethiol (Table IV).—Twenty grams of 9-ethylguanine[2] and 60 g. of phosphorus pentasulfide in 500 ml. of pyridine were refluxed for 8 hr. The method of isolation was then carried out in a manner identical to that employed in Method C (above) for the preparation of IX.

6-Alkylthio-2-amino-9-substituted Purines (X) from the Appropriate 2-Amino-9-substituted 6-Purinethiols (IX) (Table V): **Method A.**—The appropriate 2-amino-9-substituted 6-purinethiol (IX) (5 g.) was dissolved in 50 ml. of water containing 4 g. of potassium hydroxide. One molar equivalent of the alkyl halide (shown in Table V), along with 10 ml. of dioxane, was then added to the stirred mixture. The mixture was heated at 45-55° for 3-4 hr. and allowed to cool. The precipitate was filtered, washed with water, air-dried, then finely pulverized, triturated with 70 ml. of petroleum ether (30-60°), and filtered. The crystals were dried at 50°.

Method B.—To a solution of 5 g. of the appropriate 9-alkyl-2-amino-6-purinethiols (IX) in 50 ml. of water containing 4 g. of potassium hydroxide, one molar equivalent of chloroacetic acid was added. The mixture was stirred at 45–55° for 3-4 hr., adjusted to pH 6 with glacial acetic acid, allowed to cool, and the pre-

cipitate was filtered, washed with water, and dried at 80° to yield a white product.

Method C.—The 2-amino-9-substituted 6-purinethiol (10 g.) (IX) was placed in 100 ml. of 14% aqueous ammonia. One molar equivalent of dimethyl sulfate was added. The mixture was stirred at room temperature for 3 hr. and allowed to chill overnight. The precipitate was filtered, washed with a small amount of cold water, and allowed to air dry to yield the crude product.

9-Alkyl-2-amino-6-methylthiopurines (V) from the Appropriate 4-Alkylamino-2,5-diamino-6-methylthiopyrimidine (IV) (Table Va).—The appropriate 4-alkylamino-2,5-diamino-6-methylthiopyrimidine (IV) (25 g.) and 250 ml. of a 1:1 mixture of ethyl orthoformate and acetic anhydride were refluxed for 2 hr. and then reduced to dryness *in vacuo* on a steam-bath. To the residue was added 150 ml. of water and then a saturated solution of potassium hydroxide until a precipitate began to form. The mixture was boiled 5 min. and cooled. The precipitate was filtered, dissolved in 150 ml. of boiling water, treated with Norit, and filtered. The filtrate was allowed to cool, and the precipitate that formed was filtered and dried at 60° to give the crude product.

4-Alkylamino-2-amino-6-chloropyrimidines (I) (Table VI).—Fifty grams of 2-amino-4,6-dichloropyrimidine[6] was placed in 300 ml. of absolute ethanol. Two molar equivalents of the primary amine (where 4-methylamino and 4-ethylamino derivatives were required, aqueous solutions of 40% methylamine in water and 70% ethylamine in water were used) was added. This mixture was refluxed for 1 hr., evaporated to dryness *in vacuo* on a steam-bath, and the crystalline residue was swirled in 300 ml. of water and filtered. Upon drying at 80° the desired product was obtained.

4-Alkylamino-2-amino-6-pyrimidinethiols (II) (Table VII): **Method A.**—Eighty grams of the appropriate 4-alkylamino-2-amino-6-chloropyrimidine (I) was added to a stirring mixture of 300 g. of sodium hydrosulfide in 300 ml. of ethylene glycol at 60°. The reaction temperature was raised to 140–150° for 30 min., the mixture was diluted with 2000 ml. of water, adjusted to pH 5-6 with glacial acetic acid, and allowed to cool. The crude product was filtered, washed with water, and dried at 80°. It was generally necessary to recrystallize the crude product from water before using it for further synthetic work.

Method B.—The 4-alkylamino-2-amino-6-chloropyrimidine (I) (80 g.) was treated exactly as described in Method A except that the acetic acid mixture was brought to a boil, treated with Norit, and filtered. The filtrate was adjusted to pH 8-9 with ammonium hydroxide and allowed to cool. The precipitate that formed was filtered, washed with water, and dried at 80° to yield a product which generally did not require further purification for additional synthetic work.

4-Alkylamino-6-alkylthio-2-aminopyrimidines (III) (Table VIII): **Method A.**—To a solution of 30 g. of the appropriate 4-alkylamino-2-amino-6-pyrimidinethiol (II) in 300 ml. of water containing 20 g. of potassium hydroxide, was added, dropwise, one molar equivalent of the proper alkyl halide (Table VIII) at 25°. The product precipitated immediately, and the reaction mixture was allowed to stir 1-2 hr. longer. The white precipitate was filtered, washed with water, and air-dried to yield the required product.

Method B.—To 20 g. of the appropriate 4-alkylamino-2-amino-6-pyrimidinethiol (II) and 20 g. of anhydrous potassium carbonate in 140 ml. of N,N-dimethylformamide, was added one molar equivalent of benzyl chloride. The mixture was stirred at 60° for 1 hr., then diluted with 600 ml. of water, and allowed to cool.

The precipitate was filtered, washed with water, and dried at 60° to give the benzylated product.

2,5-Diamino-4-methylamino-6-methylthiopyrimidine (IV, R, R′ = CH_3).—To a suspension of 20 g. of 2-amino-4-methylamino-6-methylthiopyrimidine (III, R, R′ = CH_3) in 250 ml. of water and 80 ml. of glacial acetic acid, 15 g. of sodium nitrite in 50 ml. of water was added dropwise, with stirring, at room temperature and allowed to stir for 1 hr. The purple nitroso derivative was filtered, washed with water, and then suspended in 300 ml. of water at 60–70°. Sodium hydrosulfite was added with stirring until complete decolorization was afforded. A small amount of gummy material was filtered from the solution, and the filtrate then was adjusted to pH 8–9 with 28% ammonium hydroxide. Upon cooling, the precipitate was filtered, washed with a small portion of cold water, and dried at 50° to give 15.3 g. of product. All attempts to obtain an analytical sample were to no avail due to the fact that in the drying process a small amount of oxidation produced a slightly pink coloration.

2,5-Diamino-4-ethylamino-6-methylthiopyrimidine (IV, R = C_2H_5, R′ = CH_3).—Twenty grams of 2-amino-4-ethylamino-6-methylthiopyrimidine (III, R = C_2H_5, R′ = CH_3) was nitrosated and reduced in the same manner as 2-amino-4-methyl-amino-6-methylthiopyrimidine above.

Potential Purine Antagonists. XXXII. The Synthesis and Antitumor Activity of Certain Compounds Related to 4-Aminopyrazolo[3,4-d]pyrimidine[1,2]

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A number of new derivatives of 4-aminopyrazolo[3,4-d]pyrimidine (4-APP) have been prepared and examined for antitumor activity against Adenocarcinoma 755. The structure–activity relationships of this group of compounds is discussed. Derivatives of 4-APP with a tetrahydrofuryl or tetrahydropyranyl ring at position 1 were especially active. These compounds can be considered analogs of 4-APP deoxyriboside.

4-Aminopyrazolo[3,4-d]pyrimidine[3] has been shown to prolong

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(3) R. K. Robins, *J. Am. Chem. Soc.*, **78**, 784 (1956).