(**16**) was converted to the dihydro-*s*-triazine by the three-component method of Modest.[11]

Reaction of *m*-fluorosulfonylphenyl isocyanate with **18**[12] in the presence of 1 equiv of triethylamine afforded **13**. The last compound, **12**, was synthesized from *m*-aminobenzenesulfonyl fluoride, cyanoguanidine, and acetone according to the general method of Modest.[11]

Experimental Section[13]

4,6-Diamino-1,2-dihydro-2,2-dimethyl-1-[*m*-(*m*-fluorosulfonylphenylureidomethyl)phenyl]-*s*-triazine Ethanesulfonate (13).—To a mixture of 117 mg (0.25 mmole) of **18**,[12] 0.2 ml of DMF, and 0.13 ml of 2 m*M* Et_3N in DMF stirred in an ice bath was added 75 mg (0.38 mmole) of *m*-fluorosulfonylphenyl isocyanate (Aldrich) in 0.10 ml of DMF. Within 5 min the clear solution began to deposit white crystals. After 15 min, the mixture was diluted with 1 ml of reagent Me_2CO, then stirred at ambient temperature for 40 min. The product was collected on a filter and washed with Me_2CO. Recrystallization from EtOH–petroleum ether (bp 30–60°) gave 105 mg (76%) of white crystals: mp 154–155°; λ_{max}^{EtOH} 249, 299 (weak) mμ. See Table III for additional data.

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(12) The synthesis of this compound in two steps from *m*-aminobenzonitrile has been previously described by B. R. Baker and G. J. Lourens, *J. Med. Chem.*, **11**, 26 (1968), paper CIX of this series.

(13) Melting points were taken in capillary tubes on a Mel-Temp block and are uncorrected. All analytical samples gave ir and uv spectra compatible with their assigned structures.

Lipid-Soluble Derivatives of 6-Mercaptopurine[1]

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Several S,9-dialkyl derivatives of 6-mercaptopurine designed for lipid solubility have been synthesized and evaluated against Adenocarcinoma 755 implanted both subcutaneously and intercerebrally and against leukemia L1210 implanted intraperitoneally and intracerebrally to assess their ability to cross the blood–brain barrier. One compound 6-(cyclopentylthio)-9-ethylpurine appears to be more effective than 6-mercaptopurine against the intracerebral diseases.

Many of the most potent anticancer agents that are in use today, including 6-mercaptopurine, are ineffective against leukemia L1210 implanted intracerebrally in mice.[2] Since we had previously found that certain 9-alkyl derivatives of 6-mercaptopurine[3] are highly active against Adenocarcinoma 755 implanted intraperitoneally in mice,[4] it seemed reasonable to synthesize and evaluate a series of S,9-disubstituted derivatives of 6-mercaptopurine, designed for lipid solubility, that might penetrate the blood–brain barrier[5] better than 6-mercaptopurine itself. To this end the anions of 9-ethylpurine-6(1H)-thione and 9-butylpurine-6(1H)-thione were alkylated in N,N-dimethylformamide in the usual manner[6] to give the desired S-alkyl derivatives **1–6** (see Experimental Section). The synthesis[3] and evaluation against Adenocarcinoma 755 implanted subcutaneously[4] of 9-ethyl-6-methylthiopurine was reported previously.

Results and Discussion

All of the S-alkyl compounds were effective in inhibiting the growth of Adenocarcinoma 755 implanted subcutaneously, although the octylthio compounds (**3** and **6**) were significantly less effective than the others (Table I). As judged by therapeutic index the 9-ethyl compounds (**1–3**) were more effective than the butyl compounds (**4–6**) (Table III). All the compounds prolonged the life of mice implanted intracerebrally with Ad755 cells, although the activity of the octylthio compounds and of 9-butyl-6-methylthiopurine was minimal. Again the 9-ethyl compounds appear to be more effective than 9-butyl compounds (Table II). None of the compounds, however, were more effective than 6-mercaptopurine (6-MP) (Table III), and only two, **1** and **2**, were as effective. These results indicate that 6-mercaptopurine itself can cross the blood–brain barrier in sufficient quantity to profoundly affect the growth of a sensitive tumor,[4] Ad755. Although it is likely that the S,9-dialkyl derivatives which are quite soluble in organic solvents, cross the "barrier" more easily than 6-mercaptopurine, most of them are less effective than 6-mercaptopurine against the intracerebral disease, presumably because they are inherently less effective in inhibiting the growth of Ad755, as can be seen from their therapeutic index against the subcutaneous tumor where entry into the brain is not involved (Table III).

In order to determine if the two highly active S,9-dialkyl derivatives **1** and **2** were active against less sensitive cancer cells implanted intracerebrally, they were evaluated against L1210 leukemia cells implanted both intraperitoneally and intracerebrally (Table IV). **1** was only slightly effective against the intraperitoneal disease and **2** was more effective than **1** but less effective than 6-MP, which in repeated runs has increased the lifespan of intraperitoneal-leukemic mice 70–80% on the average. On the other hand, 6-(cyclopentylthio)-9-ethylpurine (**2**) increased by 64–69% the life-

(1) This work was supported by funds from the C. F. Kettering Foundation and the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. PH43-64-51.

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Table I: Activity of Thiopurines against Adenocarcinoma 755 Implanted Subcutaneously in BDF_1 Mice

No.	Compd	Dose[a]	Host wt change T, C, g	Tumor wt Treated	Tumor wt Control	T/C, %
1	6-(Cyclopentylthio)-9-ethylpurine	500	−1.6, +2.8	0	1118	0
		200	−0.1, +1.9	0	1245	0
		100	−0.7, +1.9	0	1245	0
		50	−1.0, −1.9	0	1245	0
		25	+0.1, +1.9	179	1245	14
		15	−2.3, +2.6	0	1763	0
		10	+1.2, +2.6	58	1763	3
		7.5	−1.3, +2.6	84	1763	4
		5	−0.5, −2.6	298	1763	16
		3.8	+0.7, +0.3	198	661	29
		1.9	+1.9, +0.3	370	661	55
		0.9	+2.2, +0.3	810	661	>100
		0.5	+1.9, +0.3	507	661	76
2	9-Ethyl-6-(isopropylthio)purine	125	−3.5, +2.8	0	651	0
		62	−1.1, +2.8	0	651	0
		31	+0.6, +2.8	31	651	4
		16	+1.7, +2.8	277	651	42
3	9-Ethyl-6-(octylthio)purine	500	−0.2, +3.2	43	930	4
		300	+2.3, +2.9	163	954	17
		150	+2.7, +2.9	163	954	17
4	9-Butyl-6-(methylthio)purine	250	Toxic, subacute			
		187	+1.7, +2.9	16	954	1
		125	+3.0, +3.2	38	930	4
		125	+1.4, +2.9	47	954	4
		84	+0.5, −2.9	49	954	5
		53	+1.9, +2.9	52	954	5
		50	+1.6, +2.5	78	762	10
		40	+1.5, +2.5	109	762	14
		30	+2.0, +2.5	199	762	26
		20	+1.7, +2.5	159	762	20
		10	+2.3, +0.9	422	643	65
		7.5	+2.6, +0.9	768	643	>100
		5	−1.6, +0.9	577	643	89
5	9-Butyl-6-(cyclopentylthio)purine	500	−3.1, −2.8	17	1118	1
		200	+0.8, +1.9	38	1245	3
		100	+0.6, +1.9	59	1245	4
		50	+0.8, +1.9	169	1245	13
		40	+1.5, +1.9	477	1245	38
6	9-Butyl-6-(octylthio)purine	500	−1.2, +2.9	163	954	17
		375	+1.8, +2.8	793	1021	77
		250	+2.6, +2.8	998	1021	97
		187	+3.2, +2.8	1387	1021	>100
		93	+3.6, +2.8	947	1021	92

[a] Mg/kg/day ip, qd 1–11.

Table II: The Activity of Thiopurines against Adenocarcinoma 755 Implanted Intracerebrally

No.	Compd	Dose[a]	Lifespan, days Treated	Lifespan, days Control	% increase in lifespan[b]
	6-Mercaptopurine	30	>42.8	19.5	>119
		28	>44	12.8	>243
		28	43.1	18.7	>130
	9-Ethyl-6-(methylthio)-purine	60	32.1	19.5	64
1	6-(Cyclopentylthio)-9-ethylpurine	500	Toxic		
		375	26.1	12.8	103
		250	>37.6	12.8	>193
		187	35.5	12.8	177
		125	41.2	12.8	221
		62	43.6	12.8	>240
		500	38.4	18.7	>105
		250	49.3	18.7	>163
		125	47.4	18.7	>153
		62	39.5	18.7	110
		30	29.3	18.7	56
2	9-Ethyl-6-(isopropyl-thio)purine	125	44.7	12.8	>249
		93	31.4	12.8	145
		62	25.6	12.8	100
		46	30.8	12.8	140
		31	26.1	12.8	105
		16	22.4	12.8	175
3	9-Ethyl-6-octylthio)-purine	500	23.0	18.7	22
		250	>24.7	18.7	>32
		125	20.8	18.7	11
		62	20.4	18.7	9
		30	18.4	18.7	0
4	9-Butyl-6-(methylthio)-purine	250	Toxic		
		125	22.8	18.7	21
		62	23.1	18.7	23
		125	Toxic		
		62	20.7	11.0	17
		31	19.3	11.0	37
		15	16.3	14.0	16
		150	15.8	16.3	0
		100	19.1	16.3	17
5	9-Butyl-6-(cyclopentyl-thio)purine	500	34.8	18.7	86
		250	26.5	18.7	41
		125	23.1	18.7	23
		62	21.1	18.7	12
		30	18.7	18.7	0
6	9-Butyl-6-octylthio)-purine	250	16.3	14.0	16
		125	13.2	14.0	0
		62	14.0	14.0	0
		31	15.7	14.0	12

[a] Mg/kg/day ip, qd 1–11. [b] A > sign indicates survivors.

TABLE III

SUMMARY. ACTIVITY OF THIOPURINES AGAINST ADENOCARCINOMA 755 INPLANTED SUBCUTANEOUSLY AND INTRACEREBRALLY

Compd	Subcutaneous MED[a]	Subcutaneous TI[b]	Intracerebral OD[c]	Intracerebral % ILS[d]	Ratio OD/MED
6-Mercaptopurine	3	13	30	>243	10
2	30	>4	125	>249	4
1	7	>70	250	>240	36
5	65	3	500	86	8
	15	3[e]	≥60	64	≥4
4	58	4	62	23, 47	1
3	*Ca.* 420	1	250	32, 16	0.6
6	>500	≤1	250	16	<0.5

[a] Minimum effective dose. [b] Therapeutic index. [c] Optimal dose. [d] % increase in lifespan. [e] See ref 4.

Experimental Section

Biological Methods.—Compounds **1–6** were evaluated for activity against Adenocarcinoma 755 in BDF_1 hybrid mice by procedures previously reported.[4] The therapeutic indices of these compounds were calculated as previously described.[7] They were also evaluated against Ad755 in the brain. BDF_1 mice were inoculated intracerebrally with 0.03 ml of a 20% brei of Ad755 cells. The drugs were injected intraperitoneally qd 1–11 and their effectiveness was judged by the increase in lifespan of the treated mice compared to the lifespan of untreated controls. Surviving animals were observed for at least 45 days post treatment. Some of the compounds were also evaluated against leukemia L1210 implanted intraperitoneally and intracerebrally as previously described.[2,5]

9-Butyl-6-methylthio-9H-purine (4).—Methyl iodide (8 g) was added in seven portions over a period of 1.5 hr with constant stirring at room temperature to a mixture of 9-butyl-9H-purine-6(1H)-thione (10 g) in water (75 ml) containing 2 *N* NaOH (25 ml). After stirring for an additional 0.5 hr, the mixture was extracted with ether (three 100-ml portions) and the combined extracts were washed (H_2O, 85 ml) and dried ($MgSO_4$). The ether solution was concentrated under reduced pressure, and the residual oil was distilled *in vacuo* to give a low-melting solid. The yield and properties of **4** are summarized in Table V.

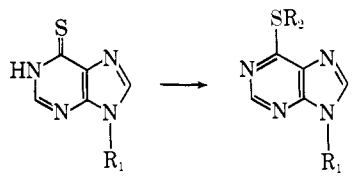
6-Alkylthio-9-alkyl-9H-purines.—The following is typical of the procedure used to prepare the other five 6-alkylthiopurines. A mixture of 9-ethyl-9H-purine-6(1H)-thione (7.0 g), bromocyclopentane (6.3 g), and anhydrous K_2CO_3 (5.6 g) in DMF (25

TABLE IV

ACTIVITY OF THIOPURINES AGAINST L1210 LEUKEMIA IMPLANTED INTRAPERITONEALLY AND INTRACEREBRALLY

	Dose, mg/kg/day	Schedule (ip)	ip L1210 (10^5 cells) Lifespan, days Treated	ip L1210 Control	ip % ILS	ic L1210 (10^4 cells) Lifespan, days Treated	ic L1210 Control	ic % ILS
9-Ethyl-6-(isopropylthio)purine	125	qd 1–30	11.9	9.5	25	10.7	8.5	25
	62	qd 1–30	10.2	9.5	7	9.4	8.5	10
	31	qd 1–30	9.6	9.5	1	9.3	8.5	9
	16	qd 1–30	9.1	9.5	0	8.5	8.5	0
6-(Cyclopentylthio)-9-ethylpurine	500	qd 1–30	9.6	9.5	1	8.4	8.5	0
	250	qd 1–30	12.1	9.5	27	14.0	8.5	64
	125	qd 1–30	10.8	9.5	13	11.7	8.5	37
	62	qd 1–30	9.1	9.5	0	10.1	8.5	18
	500	qd 1–15	11.9	8.2	45	12.4	8.5	45
	375	qd 1–15	11.6	8.2	41	14.4	8.5	69
	250	qd 1–15	11.7	8.2	42	12.6	8.5	48
	125	qd 1–15	10.2	8.2	24	10.5	8.5	23
	62	qd 1–15	9.1	8.2	10	10.6	8.5	24
	30	qd 1–15	8.6	8.2	4	10.1	8.5	18
	15	qd 1–15	7.9	8.2	0	>10.7	8.5	>25

TABLE V



No.	R_1	R_2	Yield, %	Bp (mm) or mp, °C	Formula	Carbon % Calcd	Carbon % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found	Sulfur, % Calcd	Sulfur, % Found	Ultraviolet spectra[a,b] λ_{max}, mμ ($\epsilon \times 10^{-3}$)
1	Et	Cyclopentyl[c]	89	42–44	$C_{12}H_{16}N_4S$	58.03	58.30	6.49	6.19	22.56	22.43	12.9	12.7	295 (19.4)
2	Et	*i*-Pr[d,e]	73	138–140 (0.05–0.06)	$C_{10}H_{14}N_4S$	54.03	54.37	6.35	6.45	25.21	25.11			294 (17.8)
3	Et	Octyl[c]	76	27–28	$C_{18}H_{34}N_4S$	61.61	61.82	8.27	8.06	19.16	18.99	11.0	10.8	295 (19.3)
4	Bu	Me[d]	90	135–148 (0.17–0.20)	$C_{10}H_{14}N_4S$	54.03	53.94	6.35	6.63	25.21	25.09	14.4	14.4	293(18.6)
5	Bu	Cyclopentyl[c]	80	52	$C_{14}H_{20}N_4S$	60.83	60.72	7.29	7.09	20.27	20.21	11.6	11.5	296 (21.0)
6	Bu	Octyl[d]	47	188–194 (0.28–0.35)	$C_{17}H_{28}N_4S$	63.70	63.93	8.80	8.60	17.48	17.25	10.0	10.1	293 (18.7)[f]

[a] These maxima were determined in a pH 7 phosphate buffer solution or when indicated in EtOH with a Cary Model 14 spectrophotometer. [b] Only the long-wavelength band is given. [c] Prepared from the alkyl bromide. [d] Prepared from the alkyl iodide. [e] The structure of **2** was confirmed by its pmr spectra in DMSO-d_6. [f] EtOH.

span of intracerebrally implanted animals, whose disease is affected only slightly, if at all, by 6-mercaptopurine.[2] These results tend to support the position that 6-(cyclopentylthio)-9-ethylpurine (**2**) is better able to cross the blood–brain barrier than the less lipid-soluble 6-mercaptopurine.[8] None of the other compounds (**3–6**) showed activity against intracerebral L1210 leukemia.

(8) Attempts to provide direct evidence for this statement by means of ^{35}S-labeled compounds were inconclusive.

ml), protected with a drying tube, was gradually heated with stirring to 70° and maintained at this temperature for 3 hr. The reaction mixture was then diluted with water (200 ml) and extracted with three 100-ml portions of petroleum ether (bp 30-60°). The combined extracts were washed (H_2O, two 100-ml portions), dried ($MgSO_4$), and evaporated to dryness under reduced pressure. The resulting residue solidified (scratching) and was recrystallized from the minimum amount of hot petroleum ether (bp 30-60°) to give the pure product. The residue containing **2** and **6** did not solidify and was distilled *in vacuo*. The yields and properties are summarized in Table V.

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Derivatives and Analogs of 6-Mercaptopurine Ribonucleotide[1]

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A number of derivatives of 6-mercaptopurine ribonucleotide have been prepared and evaluated for cytotoxicity in normal and 6-mercaptopurine-resistant cell lines.

In earlier papers we described the synthesis of 6-mercaptopurine ribonucleotide (**8**)[2] and a number of ester derivatives of it.[3,4] One of these derivatives, thioinosinyl-(5′→5′)-thioinosine, was found to inhibit the growth of human epidermoid carcinoma cells resistant to 6-mercaptopurine (HEp-2/MP).[5] Later the monophenyl ester of 6-mercaptopurine ribonucleotide was also found to inhibit this cell line.[6] In pursuit of this activity of phosphate esters, a number of other derivatives of 6-mercaptopurine ribonucleotide have been prepared and evaluated for their cytotoxicity.

9-(5-*O*-Trityl-β-D-ribofuransoyl)-9*H*-purine-6(1*H*)-thione[4] was acetylated with acetic anhydride in pyridine and the trityl group of the resultant 9-(2,3-di-*O*-acetyl-5-*O*-trityl-β-D-ribofuranosyl)-9*H*-purine-6(1*H*)-thione (**1**) was removed by treatment with aqueous acetic acid to give 9-(2,3-di-*O*-acetyl-β-D-ribofuranosyl)-9*H*-purine-6(1*H*)-thione (**2**) (Scheme I). Treatment of **2** with di-*o*-tolylphosphorochloridate, di-*p*-tolylphosphorochloridate, and di-3,5-xylylphosphorochloridate gave the corresponding phosphate esters (**3b–d**). The diphenyl ester (**3a**) was prepared by acetylation of the diphenyl ester of 6-mercaptopurine ribonucleotide (**4a**).[3] The di-*p*-nitrophenyl ester was prepared by the reaction of di-*p*-nitrophenyl phosphate with **2** using *N*,*N*-di-*p*-tolylcarbodiimide to effect the esterification. 9-(2,3-Di-*O*-acetyl-β-D-ribofuranosyl)-9*H*-purine-6(1*H*)-thione 5′-di-*p*-nitrophenyl phosphate (**3e**) was converted by basic hydrolysis to the mono-*p*-nitrophenyl ester (**6**) of 6-mercaptopurine ribonucleotide for comparison of its activity with that of the monophenyl ester.[6]

Since there is evidence that the 3′,5′-cyclic phosphate of adenosine can penetrate cells, intact,[7–9] and that it is enzymatically cleaved to the 5′-phosphate,[10] the 3′,5′-cyclic phosphate of 6-mercaptopurine ribonucleoside (**10**) was prepared by the reaction of its *N*,*N*′-dicyclohexylcarboxamidinium salt with dicyclohexylcarbodiimide in pyridine solution.[10]

The biologic activity of 6-methylthiopurine ribonucleoside has been shown to result from its enzymic conversion to the ribonucleotide (**9**) by adenosine kinase.[11] We synthesized **9** for comparison with the biosynthetic material and this synthesis by the methylation of 6-mercaptopurine ribonucleotide is described below.

Reaction of 9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-9*H*-purine-6(1*H*)-thione or 9-(2,3-di-*O*-acetyl-β-D-ribofuranosyl)-9*H*-purine-6(1*H*)-thione (**2**) with 5′-*O*-trityl-5-fluorouridine 3′-phosphate followed by the appropriate deblocking procedures gave 5-fluorouridylyl-(3′→5′)-thioinosine (**5**), an isomer of an ester previously prepared.[4]

Reaction of an analog of 6-mercaptopurine ribonucleoside, *cis*-3-(1,6-dihydro-6-thioxopurin-9-yl)cyclopentanemethanol (**11**),[12] with *p*-nitrophenylphosphorodichloridate gave the phosphate ester **12** which was converted to bis[*cis*-3-(1,6-dihydro-6-thioxopurin-9-yl)-cyclopentanemethyl] phosphate (**13**) by treatment with aqueous sodium hydroxide.

In order to compare the activity of some inosine phosphates (**7a** and **b**) with the corresponding thioinosine compounds, these latter compounds (**4a** and **b**) were converted to the S-(2-hydroxyethyl) derivatives which are hydrolyzed readily by aqueous base to **7a** and **7b**. This approach to the conversion of derivatives of 6-mercaptopurine to the corresponding derivatives of hypoxanthine was suggested by the observation of the

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