of X, m.p. 129–129.5°, and 2.2 g. of an insoluble, somewhat tan residue. Further recrystallization from heptane gave 2.6 g. (24.1%) of white solid, m.p. 131–131.5°. This compound exhibited at pH 1: λ_{max} 267.5 mμ, ϵ 12,900; at pH 11: λ_{max} 286 mμ, ϵ 17,200 and 267 mμ (inflection). The R_f values of this compound in the solvents A, B, C, and D[38] were 0.687, 0.295, 0.827, and 0.126, respectively. R_f values of 0.687, 0.297, 0.844, and 0.126 for solvents A, B, C, and D, respectively, were found for the same compound previously prepared by Cheng and Robins.[14]

Anal. Calcd. for $C_8H_{11}N_5$: C, 54.2; H, 6.2; N, 39.6. Found: C, 54.5; H, 6.3; N, 39.6.

The insoluble residue was crystallized from toluene and treated with charcoal, followed by repeated recrystallizations from benzene, to give 0.2 g. (1.9%) of white solid (XI), m.p. 194–195.5°. This compound exhibited at pH 1: λ_{max} 294 mμ, ϵ 13,800 and at pH 11: λ_{max} 298 mμ, ϵ 18,000. The R_f values for this compound were 0.472, 0.273, 0.787, and 0.063 in solvents A, B, C, and D, respectively.

Anal. Calcd. for $C_8H_{11}N_5$: C, 54.2; H, 6.2; N, 39.6. Found: C, 54.2; H, 6.3; N, 39.6.

(38) Solvent A: 1-butanol–water–1% aqueous ammonia; Solvent B: 1-butanol–glacial acetic acid–water (5:2:3); Solvent C: disodium hydrogen phosphate (59% in water) saturated with isoamyl alcohol; Solvent D: 1-butanol–formic acid–water (77:10:13).

The Preparation and Antitumor Activity of Certain Derivatives of 6-Mercaptopurine[1]

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A number of new 6-alkylthiopurines have been prepared and tested against Adenocarcinoma 755 and S-180 in experimental mice. Several derivatives possess a therapeutic index greatly superior to that of 6-mercaptopurine in both S-180 and Ad 755. The synthesis of several N-alkylpurine-6-sulfonamides is described. These derivatives exhibit significant inhibition of Ad 755 and L-1210. Certain 6-alkylsulfonylpurines are also active against Ad 755. The significance of these results is discussed briefly.

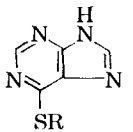
The antitumor activity of 6-mercaptopurine and various 6-alkylthiopurines has been studied in Sarcoma 180[2,3] and in Adenocar-

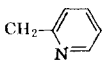
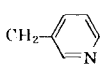
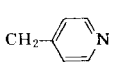
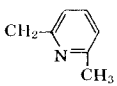
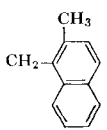
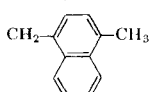
(1) This study was supported by Contract SA-43-ph-1928 with the Cancer Chemotherapy National Service Center of the National Cancer Institute of the National Institutes of Health.

(2) D. A. Clarke, F. S. Philips, S. S. Sternberg, C. C. Stock, G. B. Elion, and G. H. Hitchings, *Cancer Research*, **13**, 593 (1953).

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

TABLE I: ALKYLTHIOPURINES

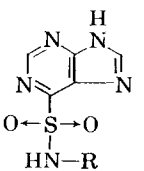


R	M.p.,[a] °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Prepn. method	Recrystn. solvent	Alkyl halide
$CH_2CON(C_2H_5)_2 \cdot H_2O$	80–81					24.6	24.4	A	EtOAc	Cl
$CH_2C_6H_3(CH_3)_2$-3,4	189–190	62.2	62.5	5.2	5.1	20.7	20.4	A	EtOAc	Cl
$CH_2C_6H_4OCH_3$-*p*	217–219	58.0	58.0	4.4	4.9	20.6	20.8	A	MeOH	Cl
$CH_2C_6H_4Cl$-*m*[b]	170–172	52.1	52.3	3.3	3.5	20.2	19.7	A	EtOAc	Cl
$CH_2C_6H_4Br$-*p*	200–202	44.8	45.0	2.8	3.0	17.4	16.0	A	. .	Br
	187–188	54.3	54.3	3.7	3.8	28.8	28.9	A	EtOAc-EtOH	Cl
	220–223	54.3	54.6	3.7	3.7	28.8	28.7	A	C_6H_6	Cl
	256–258	54.3	55.0	3.7	4.1	28.8	28.9	A	EtOH	Cl
	184–185	56.1	56.3	4.3	4.3	27.2	27.3	A	C_6H_6	Cl
	220–222	66.6	66.5	4.7	4.7	18.2	17.8	A	MeOH-EtOH	Cl
	243–245	66.6	66.9	4.7	4.5	18.2	18.6	A	EtOAc	Cl

$C(CH_3)_2CH_2CH_3$	155–156	54.1	54.4	6.3	6.3	25.2	25.2	B	EtOAc	
$CH_2CHOHCH_2OH$	>300	42.5	42.6	4.4	4.3	24.8	24.4	B	H_2O	
$CH_3CHC_6H_5$	178–179	60.5	60.8	4.7	4.7	21.9	22.2	B	EtOAc-C_7H_{16}	
$COOHCHCH_2COOH$	228–232 d.	40.3	40.1	3.0	2.9	20.8	20.5	B	H_2O	
$CH_3CH(CH_2)_3CH_3$	146–148	56.0	56.0	6.8	6.6	23.8	23.5	C	EtOAc	Br
$C_2H_5CH(CH_2)_2CH_3$	124–126	56.0	56.4	6.8	7.2	23.8	23.6	C	EtOAc-C_7H_{16}	Br
$CH_2C_6H_4NO_2$-*o*	203	50.2	50.0	3.1	3.2	24.4	24.6	C	H_2O	Cl

[a] See ref. 14. [b] Testing of this compound against S-180 has been reported (ref. 2) but directions for the synthesis have not as yet been published.

TABLE II



R	M.p.,[a] °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Yield, %	Recrystn. solvent	Ultraviolet abs. no. ethanol λmax, mμ	Ultraviolet abs. no. ethanol ε
n-Propyl	226	39.8	39.8	4.6	4.3	29.0	29.0	85	EtOH-H_2O	277	8,700
n-Butyl	217	42.2	42.6	5.5	5.1	27.3	27.3	50	EtOH-H_2O	278	9,700
Isobutyl	224	42.2	42.4	5.5	5.1	27.3	27.0	64	EtOH-H_2O	278	10,000
Allyl	222	40.2	40.3	3.8	3.9	29.3	29.2	80	EtOH-H_2O	278	10,200
Benzyl	200	49.8	49.7	3.8	3.9	24.2	24.2	49	EtOH	278	6,100
3-Methoxypropyl	204	39.8	40.1	4.8	4.9	25.8	25.5	69	H_2O	277	7,900
2-Ethoxyethyl	209	39.8	39.8	4.8	4.9	25.8	26.1	69	H_2O	278	9,700

cinoma 755.[4] It has been reported[4] previously that 6-benzylthiopurine and 6-methylthiopurine possess therapeutic indexes greater than that of 6-mercaptopurine against Adenocarcinoma 755. The present work included a continuation of an earlier report from our Laboratory of the synthesis of 6-alkylthiopurines[5] and includes an effort to compare the antitumor activity of these compounds with published reports for similar derivatives. The synthesis of the 6-alkylthiopurines listed in Table I was accomplished either from the appropriate alkyl halide and 6-mercaptopurine (Methods A and C) or from 6-chloropurine and the appropriate alkanethiol (Method B) essentially by published procedures.[5]

A number of N-alkyl-6-sulfonamides have been prepared from purine-6-sulfonyl fluoride[6] and the appropriate alkylamine in aqueous solution (see Table II).

Discussion of Antitumor Testing

The antitumor testing data listed in Tables IV and V were supplied by the Cancer Chemotherapy National Service Center. The testing procedures employed have been adequately described previously.[6a]

6-Mercaptopurine exhibits an approximate therapeutic index of 30 against Adenocarcinoma 755.[4] Table III reveals that two alkylthiopurines exhibit a therapeutic index equal to or greater than that of 6-mercaptopurine in this test system. Particularly striking is the activity of 6-(2-pyridylmethylthio)purine (NSC 45146). Of the compounds listed in Table III, which exhibit a therapeutic index of 16 or greater, only 6-(*p*-methoxybenzylthio)purine (NSC 47789) has been tested against any other tumor. Against Sarcoma 180, NSC 47789 shows good inhibition (see Table V). Since 6-benzylthiopurine previously has been shown to be inactive[7] against Sarcoma 180, activity upon the introduction of a *p*-methoxy group would seem to be rather significant. Certainly the 6-alkylthiopurines possessing a therapeutic index of 16 or greater, listed in Table III, should be subjected to further testing in various other tumor systems and their antitumor spectra compared with that of 6-mercaptopurine.

Table IV contains, in addition, the testing data against Adeno-

(4) H. E. Skipper, J. A. Montgomery, J. R. Thomson, and F. M. Schabel, Jr., *Cancer Research*, **19**, 425 (May 1959); *ibid.*, **19**, 287, part 2 (July 1959).

(5) H. C. Koppel, D. E. O'Brien, and R. K. Robins, *J. Org. Chem.*, **24**, 259 (1959).

(6) A. G. Beaman and R. K. Robins, *J. Am. Chem. Soc.*, **83**, 4038 (1961).

(6a) J. Leiter, A. R. Bourke, S. A. Schepartz, and I. Wodinsky, *Cancer Research*, **20**, 734 (1960).

(7) J. A. Montgomery, T. P. Johnston, A. Gallagher, C. R. Stringfellow, and F. M. Schabel, Jr., *J. Med. Pharm. Chem.*, **3**, 265 (1961).

TABLE III

COMPARISON OF THERAPEUTIC INDICES OF CERTAIN 6-ALKYLTHIOPURINES AGAINST ADENOCARCINOMA 755

NSC no.	Name	Therapeutic index[a]	Maximum degree of effectiveness T/C at MTD
45146	6-(2-Pyridylmethylthio)purine	128	0.00
49811	6-(4-Pyridylmethylthio)purine	32	0.02
39332	3-(6-Purinylthio)-1,2-propanediol	16	0.05
47789	6-(*p*-Methoxybenzylthio)purine	16	0.00
50708	N,N-Diethyl-2-(purin-6-ylthio)acetamide	>13	0.00
39333	6-(1,1-Dimethylpropylthio)purine	>8	0.03
47787	6-(3-Pyridylmethylthio)purine	8	0.02
50709	6-(*m*-Chlorobenzylthio)purine	8	0.00
47788	6-(6-Methyl-2-pyridylmethylthio)purine	8	0.00
48713	6-(3,4-Dimethylbenzylthio)purine	8	0.00
51462	6,6′-(Ethylenedithio)dipurine	8	0.00
39334	6-(*o*-Nitrobenzylthio)purine	8	0.00
48714	6-(2-Methyl-1-naphthylmethylthio)purine	7.5	0.00
36828	6-(α-Methylbenzylthio)purine	6.3	0.02
48715	6-(4-Methyl-1-naphthylmethylthio)purine	4	0.11
51463	6-(*p*-Bromobenzylthio)purine	4	0.01

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

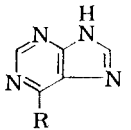
carcinoma 755 on purine-6-sulfonamide[6] and various related N-alkylpurine-6-sulfonamides. In general these derivatives possess a therapeutic index against Adenocarcinoma 755 inferior to that of the 6-alkylthiopurines. However, they represent a new group of compounds which possess significant antitumor activity and are worthy of further study. Purine-6-sulfonamide (NSC 55466) and N-ethylpurine-6-sulfonamide (NSC 56459) have also been tested against Leukemia 1210 (see Table V) and exhibit significant inhibition at several dosage levels. Several related 6-alkylsulfonylpurines have been prepared[8] and tested against Adenocarcinoma 755. 6-Methylsulfonylpurine (NSC 25646) and 6-ethylsulfonylpurine (NSC 34481) both significantly inhibit this tumor (see Table IV).

It is quite interesting that an oxidized sulfur atom in the form of a sulfone or sulfonamide at position 6 results in purine derivatives

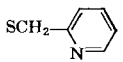
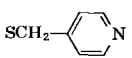
(8) C. W. Noell and R. K. Robins, *J. Am. Chem. Soc.*, **81**, 5997 (1959).

Table IV

Antitumor Activity of Various Derivatives of 6-Mercaptopurine against Adenocarcinoma 755



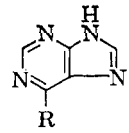
NSC No.	R	Dose, mg./kg.	Survivors	Wt. change (test/control)	Tumor wt. (test/control)	T/C
39332	$SCH_2CHOHCH_2OH$	600	2/10	−2.0/−0.9	0/1042	toxic
		300	9/10	−2.5/0.6	61/1141	0.05
		150	9/10	−2.6/−0.9	33/1042	0.03
		75	8/10	−2.1/−0.9	81/1042	0.07
		37.5	10/10	−2.2/−0.6	215/475	0.45
		18.75	9/10	−1.8/−0.6	131/475	0.27
		10	9/10	−0.8/−0.1	794/1163	0.68
		9.37	10/10	−1.3/−0.6	165/475	0.34
		5	10/10	−0.5/−0.1	745/1163	0.64
		2.5	10/10	−0.6/−0.1	500/1163	0.42
		1.25	9/10	−0.8/−0.1	772/1163	0.66
47789	$SCH_2C_6H_4OCH_3$-*p*	500	6/10	−3.1/0.7	8/1433	toxic
		250	7/10	−2.7/0.7	7/1433	0.00
		125	8/10	−2.9/0.7	19/1433	0.01
		62.5	9/10	−1.8/−0.1	11/1119	0.00
		31.2	9/10	−1.9/−0.1	121/1119	0.10
		15.6	10/10	−2.3/−0.1	155/1119	0.13
		7.8	10/10	−1.1/−0.1	660/1119	0.58
39334	$SCH_2C_6H_4NO_2$-*o*	250	9/10	−2.6/0.6	11/1141	0.00
		125	5/10	−2.2/−0.9	0/1042	toxic
		62.5	7/10	−2.7/−0.9	0/1042	0.00
		31.25	8/10	−2.1/−0.6	25/475	0.05
		15.62	8/10	−1.6/−0.6	38/475	0.08
		8	9/10	−1.7/−0.1	313/1163	0.26

NSC No.	R	Dose, mg./kg.	Survivors	Wt. change (test/control)	Tumor wt. (test/control)	T/C
		7.81	9/10	−2.5/−0.6	50/475	0.10
		4	9/10	−0.6/−0.1	578/1163	0.49
		2	9/10	−1.3/−0.1	556/1163	0.47
		1	7/10	−1.1/−0.1	921/1163	0.79
45146		100	9/10	−2.9/0.1	0/849	0.00
		50	9/10	−1.4/0.3	11/995	0.01
		25	7/10	−1.1/0.3	0/995	0.00
		12.5	10/10	−1.9/0.3	0/995	0.00
		6.25	9/10	−1.8/1.5	72/1837	0.03
		6	10/10	−1.4/1.2	104/1057	0.09
		3.12	8/10	−2.1/1.5	75/1837	0.04
		1.56	10/10	−0.9/1.5	180/1837	0.09
		0.78	10/10	−0.2/1.5	715/1837	0.38
49811		200	7/10	−3.6/−0.1	29/1119	0.02
		100	8/10	−2.2/−0.1	79/1119	0.07
		50	8/10	−1.4/−0.1	144/1119	0.12
		25	10/10	−2.5/−0.1	189/1119	0.16
		12.5	9/10	−1.0/−0.4	372/1265	0.29
		6.25	10/10	−0.3/−0.4	500/1265	0.39
		3.1	10/10	−0.1/−0.4	915/1265	0.72
25646	SO_2CH_3	30	1/10	−0.2/3.6	50/945	toxic
		15	10/10	2.0/5.0	413/2090	0.19
		7.5	10/10	2.5/3.6	471/945	0.49
		3.7	10/10	3.6/3.6	449/945	0.47
34481	$SO_2C_2H_5$	32	8/10	2.4/3.3	236/868	0.27
		16	9/10	0.8/2.9	324/1413	0.22
		8	10/10	2.3/3.3	384/868	0.44
		4	8/10	2.8/3.3	1159/868	1.33

NSC No.	R	Dose, mg./kg.	Survivors	Wt. change (test/control)	Tumor wt. (test/control)	T/C
55466	SO_2NH_2	25	9/10	−0.9/0.3	40/1046	0.03
		12.5	10/10	−0.8/0.3	157/1046	0.15
		6.2	10/10	−1.1/0.3	816/1046	0.78
		3.1	10/10	0.9/0.3	1103/1046	1.05
56459	$SO_2NHC_2H_5$	100	9/10	−2.5/−0.7	0/645	0.00
		75	9/10	−2.5/−0.2	4/412	0.00
		50	10/10	−1.9/−0.7	0/645	0.00
		25	10/10	−2.0/−0.2	31/412	0.07
		12.5	10/10	0.5/−0.7	234/645	0.36
		6.2	8/10	−1.1/−0.7	430/645	0.66
62390	$SO_2NH(CH_2)_2CH_3$	75	2/10	−2.9/0.0	60/1101	toxic
		50	10/10	−2.5/0.3	43/1185	0.03
		37	10/10	−2.5/0.0	44/1101	0.03
		18	10/10	−1.3/0.0	191/1101	0.17
		9	9/10	−1.0/0.0	579/1101	0.52
61745	$SO_2NH(CH_2)_3OCH_3$	150	3/10	−3.4/3.1	37/2394	toxic
		100	8/10	−1.5/0.6	0/817	0.00
		50	9/10	−1.9/3.1	133/2394	0.05
		25	10/10	−0.4/0.6	103/817	0.12
		12.5	10/10	−0.5/0.3	116/1309	0.08
61746	$SO_2NHCH_2CH(CH_3)_2$	100	6/10	−3.9/0.6	0/817	toxic
		50	9/10	−1.8/0.6	0/817	0.00
		25	10/10	−0.5/0.3	114/1309	0.08
		12.5	7/10	−1.3/0.3	325/1309	0.24

TABLE V

ANTITUMOR ACTIVITY OF SOME DERIVATIVES OF 6-MERCAPTOPURINE AGAINST SARCOMA 180 AND LEUKEMIA 1210



NSC No.	R	Dose, mg./kg.	Survivors	Wt. change (test/control)	Tumor wt. (test/control)	T/C
			Sarcoma 180			
47789	$SCH_2C_6H_4OCH_3$-*p*	375	4/6	−2.7/1.2	113/1064	0.10
		250	4/6	−1.9/1.4	88/1371	0.06
		166	6/6	−0.6/1.2	317/1064	0.29
		111	6/6	−0.7/1.2	517/1064	0.48
			Leukemia 1210			
55466	SO_2NH_2	75	6/6	−0.6/−0.5	13.7/8.3	1.65
		50	6/6	−0.8/−0.5	12.7/8.3	1.53
		33	6/6	0.5/−0.5	11.2/8.3	1.34
		22	6/6	−0.7/−0.5	10.3/8.3	1.24
56459	$SO_2NHC_2H_5$	150	6/6	0.0/1.0	12.0/8.5	1.41
		100	6/6	−0.7/3.1	12.7/8.6	1.47
		66	6/6	−0.6/1.0	10.5/8.5	1.23
		44	6/6	0.9/1.0	10.0/8.5	1.17

possessing antitumor action. Sodium purine-6-sulfinate[9] and purine-6-sulfonate[9] are not inhibitors of Sarcoma 180.[9] It would be of interest to study the activity of the purine-6-sulfonamides against a 6-mercaptopurine resistant tumor line to check for cross resistance. In at least one case the antitumor activity of a 6-substituted thiopurine has been attributed to *in vivo* dealkylation to give 6-mercaptopurine.[10] On the other hand, the rat and patients with leukemia have been shown[11] to methylate 6-mercaptopurine to 6-methylthiopurine which was isolated from the urine. It has been shown[12] that the rat can methylate 6-mercaptopurine and demethylate 6-methylthiopurine *in vivo*. Thus, the relationship of the mechanism of action of the 6-alkylthiopurines and 6-mercaptopurine is not clear although cross resistance of certain 6-alkylthiopurines with 6-mercaptopurine has been demonstrated.[4] Recently[13] evidence has been presented that

(9) I. Doerr, I. Wempen, D. A. Clarke, and J. J. Fox, *J. Org. Chem.*, **26**, 3401 (1961).

(10) G. B. Elion, S. Callahan, S. Bieber, G. H. Hitchings, and R. W. Rundles, *Cancer Chemotherapy Repts.*, **14**, 93 (1961).

(11) E. J. Sarcione and L. Stutzman, *Seventh Intern. Cancer Congr.*, 1958; Abstracts, p. 147.

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(13) M. R. Atkinson, J. F. Jackson, and R. K. Morton, *Nature*, **192**, 946 (1961).

6-mercaptopurine acts on tumors *via* interference with the biosynthesis of phosphopyridine nucleotide coenzymes. Further study of the purine-6-sulfonamides in other tumors and various biological systems will be necessary to determine the mechanism of action and usefulness of this new class of compounds.

Experimental[14]

Preparation of 6-Alkylthiopurines Listed in Table I. Method A.—This general method is illustrated by the preparation of 6-(*p*-methoxybenzylthio)purine and 6-(2-pyridylmethylthio)purine.

6-(*p*-Methoxybenzylthio)purine.—To 10 g. of 6-mercaptopurine,[6,15] dissolved in 150 ml. of concd. aqueous ammonia, was added 25 ml. of dioxane and then 10 g. of *p*-chloromethylanisole (Aldrich Chemical Co.). The mixture was stirred and heated for 1 hr. at 60°. At the end of this period the volume was doubled by the addition of water, and the mixture was cooled, filtered, and washed with water and methanol to yield 6.3 g. of crude product. Recrystallization was effected from methanol.

6-(2-Pyridylmethylthio)purine.—Ten grams of 6-mercaptopurine[6,15] was dissolved in 150 ml. of concentrated aqueous ammonia, and 10.7 g. of 2-picolyl chloride hydrochloride (Aldrich Chemical Co.) was added with stirring. The solution was stirred and heated at 60° for 1 hr. and the solution allowed to cool at room temperature overnight. The product (15.2 g.) was filtered, dried, and recrystallized from an ethyl acetate-ethanol mixture. The melting point of the product was 187–188°.

Method B.—This general method is illustrated by the preparation of **3-(6-purinylthio)-1,2-propanediol.**—Six grams of 6-chloropurine was added to a solution of 8 g. of 1-thioglycerol in 100 ml. of 5% potassium hydroxide. The solution was stirred and heated on the steam bath for 30 min., then acidified with dilute hydrochloric acid, and chilled. White crystals (4.2 g.) were obtained. Recrystallization was accomplished from water.

Method C.—This general method is illustrated by the preparation of **6-(*o*-nitrobenzylthio)purine.**—Ten grams of 6-mercaptopurine was dissolved in 100 ml. of 5% potassium hydroxide. To this solution was added 11.2 g. of *o*-nitrobenzyl chloride. The mixture was heated and stirred for 2 hr., and the resulting product was filtered and washed with water and methanol. For analysis the product was recrystallized from water. Recrystallization from ethanol gave a product with a melting point of 195–196°.

6,6′-(Ethylenedithio)dipurine.—Six grams of 6-chloropurine was added to a solution of 8 g. of 1,2-ethanedithiol in 100 ml. of 4% potassium hydroxide solution. The solution was stirred on the steam bath for 1 hr., acidified with dilute hydrochloric acid, cooled, and filtered. The yield of pale-yellow, crude product was 3.5 g. The compound was suspended in ethanol and boiled for a few minutes to remove some excess dithiol. For analysis the compound was recrystallized from acetic acid to give a product which melted at 305° dec.

Anal. Calcd. for $C_{12}H_{10}N_8S_2$: C, 43.6; H, 3.0; N, 33.9. Found: C, 43.4; H, 3.3; N, 33.5.

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

(15) G. B. Elion, E. Burgi, and G. H. Hitchings, *J. Am. Chem. Soc.*, **74**, 411 (1952).

Purine-6-alkylsulfonamides Listed in Table II.—The appropriate amine (0.0747 mole) (see Table II) in 50 ml. of water was cooled to 15° and stirred as 5 g. (0.0247 mole) of 6-sulfonylfluoropurine[6] was added in small portions so that the temperature of the mixture did not exceed 20°. This mixture was stirred for 15 min. and then acidified with glacial acetic acid. The precipitate that formed was filtered, washed with water, dried at 60°, and then recrystallized from the indicated solvent (Table II).

Potential Hypoglycemic Agents: 1,3,4-Oxadiazoles and Related Compounds

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A number of thiadiazole and oxadiazole derivatives were synthesized and evaluated for oral hypoglycemic activity. All of the compounds were tested by single dose administration in rats and/or dogs by the oral route. Most of the derivatives exhibited some degree of activity. 5-Cyclohexyl-2-(*p*-toluenesulfonamido)-1,3,4-oxadiazole was fairly potent in both rats and dogs, and on daily administration in dogs produced and maintained a hypoglycemia. Some toxicity data are presented.

Over the years many substances have been examined for hypoglycemic properties. The observation by Watanabe[1] that guanidine caused a drop in the sugar levels in animals stimulated a search for orally active antidiabetic agents. Janbon[2] in 1942 found that the antibacterial sulfonamide 2-(*p*-aminobenzenesulfonamido)-5-isopropyl-1,3,4-thiadiazole lowered blood sugar. Loubatieres[3] and others studied this phenomenon, and in 1955 this compound was applied in the treatment of diabetes.[4] At the same time a series of N-arylsulfonyl-N′-alkylureas was found to have utility in the treatment of diabetes and at present, three compounds are in extensive use.[5] These are N-*p*-aminobenzenesulfonyl-N′-*n*-butylurea (carbu-

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