(*E*)-(−)-*N*-[2-(Methylsulfinyl)-1-(hydroxymethyl)ethyl]-3-(1,2,3,4-tetrahydro-6-methyl-2,4-dioxo-5-pyrimidinyl)-2-propenamide Monohydrate (10c). To 5.4 g (18.0 mmol) of sulfide **9c** slurried in 114 ml of H_2O at 25 °C was added dropwise 3.91 g (18.3 mmol) of sodium metaperiodate in 57 ml of H_2O. After addition, the solution was stirred at room temperature for 2 h, then diluted with MeOH to 900 ml, cooled to 10 °C, and filtered and the solid discarded. The filtrate was then evaporated under vacuum and the residue chromatographed over silica gel Woelm (dry column grade, activity III) with absolute EtOH to give 3.5 g (62%) of **10c**. Recrystallization from EtOH gave an analytical sample: mp 172 °C with wetting at 140 °C; $[\alpha]^{25}D$ −72.77° (*c* 0.96, H_2O).

(*E*)-(±)-*N*-[2-(*n*-Decylsulfinyl)-1-(hydroxymethyl)-ethyl]-3-(1,2,3,4-tetrahydro-6-methyl-2,4-dioxo-5-pyrimidinyl)-2-propenamide (10i). To 3.0 g (7.04 mmol) of sulfide **9i** in 150 ml of H_2O was added 6.6 ml (77 mmol) of 30% H_2O_2 and the mixture stirred at room temperature. After 7 days, another 3.3 ml of 30% H_2O_2 was added. This was repeated after 6 more days and the mixture stirred 1 week longer and then filtered. Recrystallization from EtOH gave 2.2 g (71%) of **10i**, mp 228–232 °C dec with wetting at 145 °C.

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Supplementary Material Available: biological data on inactive target compounds (1 page). Ordering information is given on any current masthead page.

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Potential Antitumor Agents. Some Sulfur-Substituted Derivatives of α- and β-2′-Deoxythioguanosine

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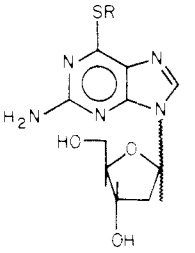
A series of ten S-substituted derivatives of the α and β anomers (**1a** and **1b**) of 2′-deoxy-6-thioguanosine has been prepared by S-alkylation of the parent nucleosides and/or by mercaptide displacement reactions on 6-chloro intermediates. Against L1210 murine leukemia all β anomers were active but potency was reduced relative to **1b**. Most *S*-alkyl α anomers were inactive in this test. Limited testing against P388 murine leukemia showed all α-anomer derivatives to be inactive but the β anomers were more effective than the parent. S-Substitution sharply reduced acute toxicity in both series. In vitro DNA and RNA synthesis inhibition data are also reported. The antitumor activity of these derivatives and of the 2′,5′-di-*O*-acetyl derivatives of **1a** and **1b** against lymphoid leukemia L1210 is reported. Some results with the lymphocytic leukemia P388 and an in vitro assay of the inhibition of nucleic acid synthesis are also given.

2′-Deoxythioguanosine (**1b**),[1] originally designed to by-pass some of the mechanisms of resistance to thioguanine (6-TG),[2a] has demonstrated antitumor activity[2] and is being considered as a candidate for clinical trials.[3] Its α anomer, **1a**,[1,4] is unique because it is the only nucleoside α anomer found to date to have significant in vivo antitumor activity.[2a,5] Laboratory and preclinical toxicology studies[6] show that **1a** is much less toxic than **1b** in mice, rats, dogs, and monkeys. LePage and his colleagues have found that both **1a** and **1b** are phosphorylated by extracts of many murine and human neoplasms, including neoplastic bone marrows. However, extracts of normal bone marrows, with one exception, did not phosphorylate **1a**,[7] therefore suggesting that this anomer has some selectivity for tumors. Tamaoki and LePage also have suggested that **1a** may be a unique tool for the study of DNA replication since it terminates chain elongation[8] when incorporated into DNA.

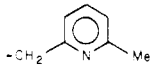
Because of these interesting properties of **1a** and **1b**, other investigators have prepared the related seleno compounds,[9a] the Se-substituted derivatives,[9b] and the 6-amino-2-methylthiopurin-9-yl deoxyribonucleosides.[9c] We have synthesized the series of S-substituted derivatives shown in Scheme I and Table I.

The specific S-substituents were chosen because they are able to impart desirable properties to the analogous purine ribonucleosides. *S*-Methyl-6-mercaptopurine ribose, for example, is believed to exert its antitumor action by

Table I. Properties of Some Derivatives of 1

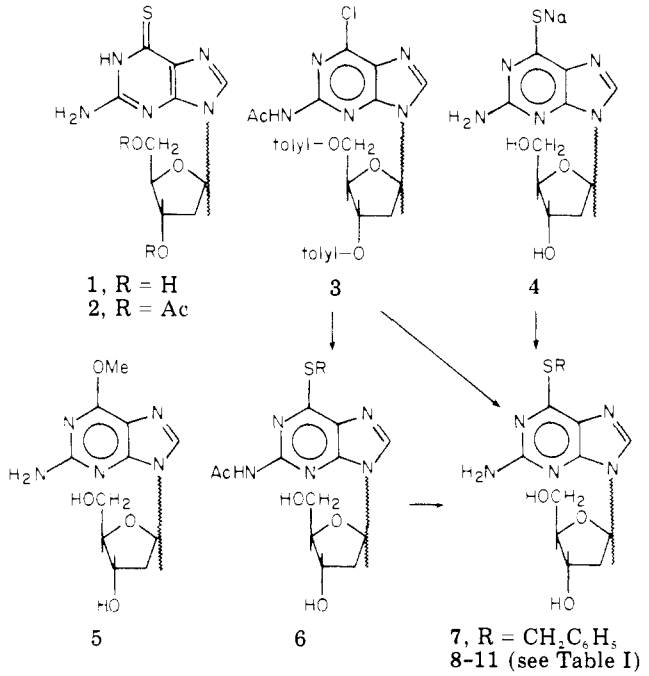


8-11 and others

No.	R	Prepn[a] method	Yield,[b] %	Mp,[b] °C	Solvent[c]	Chromatography[d]	Optical rotation,[e] $[\alpha]^{20}D$	Formula	Analyses[f]
6b	Me	A	40 (53)	184-185	A	0.20	−0.4	$C_{13}H_{17}N_5O_4S$	C, H, N
8b	Me	A	(68)	98-100 (98-100)	B	0.20	−20.9	$C_{11}H_{15}N_5O_3S\cdot0.5H_2O$	C, H, N
9a	$CH_2CH{=}CH_2$	B (A)	55 (79)	167.5-168.0	C	0.22	+100	$C_{13}H_{17}N_5O_3S$	C, H, N
9b	$CH_2CH{=}CH_2$	A (B)	45 (60)	75-80	D	0.29	−5.1	$C_{13}H_{17}N_5O_3S\cdot0.6MeOH$	C, H, N
10a		B	(90)	105-107	E	0.18	+77	$C_{17}H_{20}N_6O_3S\cdot0.25H_2O$	C, H, N
10b		B	84	127-128	E	0.25	−21.7	$C_{17}H_{20}N_6O_3S\cdot0.4EtOAc$	C, H, N
11a		B	94	158-159	F	0.12	+76	$C_{14}H_{16}N_8O_5S\cdot H_2O$	C, H, N
11b		B	36 (44)	150-151	G	0.29	−22.5	$C_{14}H_{16}N_8O_5S\cdot H_2O$	C, H, N
2a		Ac_2O	84	200-201	H	0.68		$C_{14}H_{17}N_5O_5S\cdot0.25H_2O$	C, H, N
2b		Ac_2O	16 (83)	215-216 (212-213)	H	0.67		$C_{14}H_{17}N_5O_5S$	C, H, N

[a] See discussion for methods A and B; 2a and 2b were prepared from 1a and 1b by treatment with acetic anhydride in pyridine. [b] Yield and melting point data are for analytical samples, except for values in parentheses which are for homogeneous products (by TLC). [c] Crystallization solvents used are A, EtOH-Et_2O (1:5); B, aqueous eluent from ion-exchange column; C, MeOH-toluene (1:3); D, methanol-water (5:95) eluent from ion-exchange column; E, EtOAc; F, 95% EtOH; G, H_2O; H, MeOH. [d] TLC were run on silica gel HF_{254} (E. Merck) with 10% MeOH in EtOAc for solvent except for 2a, 2b, and 11b, which were run with 20% MeOH in EtOAc. [e] The optical rotations were all run at 20 °C with *c* 0.25 in DMF except for 9a and 9b, which were run at 21 °C, and 8b, at 22 °C. [f] Analyses are all within 0.4% of the calculated values.

Scheme I[a]



[a] a denotes α anomers; b, β anomers.

a mechanism different from that of its parent.[10] The other substituents have all been associated with ribosyl nucleosides that possess significant activity against L1210 mouse leukemia.[5] The *S*-benzyl and *S*-methyl α anomers, **7a** and **8a**, had been prepared previously[1] but not in sufficient quantity for antitumor screening in vivo. Because formerly scarce intermediates are now readily available[4] **7a** and **8b** have been reprepared, and in vivo data are reported here.

The 3′,5′-di-*O*-acetyl derivatives (**2a** and **2b**) of **1a** and **1b** were prepared on the suggestion of LePage because they might escape in vivo cleavage by nucleoside phosphorylase, yet retain activity through slow deacetylation.

Chemistry. The S-substituted derivatives (7–11) of **1** were prepared by two methods. In method A, **3** was treated with the sodium mercaptide and excess mercaptan in methanol. At reflux temperature, a good yield of **7** was obtained using benzyl mercaptan. Treatment of **3b** with methyl mercaptan under the same conditions afforded by-product **5**[11] together with **8b**, although this procedure was successful in another series.[12] At room temperature, no **5** was formed. The chlorine atom of **3** was completely displaced by methyl mercaptide along with partial deacylation to give product **6b**, R = Me, which required further sodium methoxide treatment for complete deacylation to **8b**.

Method B was preferred. It entailed reaction of the sodium salt **4** with an alkyl halide. In general, the yields were good, and the reaction products required less purification than those from method A. Preparation methods and properties of the various S-substituted derivatives are summarized in Table I, together with data on the two 3′,5′-di-*O*-acetylated products, **2a** and **2b**. The ultraviolet spectra of **7–11** were like those of other similar derivatives[12] and have been omitted except for a representative sample in the Experimental Section.

Bioassays. All target compounds were tested for antitumor activity against lymphoid leukemia L1210 by

Table II. Biological Activity of S-Alkylated 2′-Deoxythioguanosine

Compd	In vivo antitumor activity[a,b] L1210 lymphoid leukemia[d,e] OD	L1210 T/C	P388 lymphocytic leukemia[f] OD	P388 T/C	Inhibn of nucleic acid synthesis,[c] ED_{50}, μM DNA	RNA
1b	5.0	219[g]	0.60	138	>100	50
	4.5 (9)	208				
1a	16	161	25	168	>100	>100
	160 (16)	174				
7b	20 (1)	172[h,i]	NT		NT	
7a	400 (9)	144[h]	NT		NT	
8b	400	128	NT		27	24
8a	400	I	400	I	>100	>100
9b	400	245[j]	200	181	5.5	3.0
9a	400	I	400	I	>100	>100
10b	600	153	400	I	64	31
10a	400	I	400	I	79	72
11b	12.5	173	6.25	161	25	11
11a	400	137	400	I	>100	>100
2b	20	156	20	174 (3)	NT	
2a	100	I	NT		NT	
6b, R = Me	400	I	NT		NT	

[a] Protocols and tumor systems are described in ref 13. [b] In a minimum of one additional experiment, these compounds were determined to have a T/C value not more than 15% lower than the value shown in this table. All compounds with active T/C values (see text for definition of activity) are confirmed active (at least one additional active test was performed). OD = optimum dose (mg/kg/dose). T/C = (treated animal average survival time/control animal average survival time) × 100%. I = inactive (T/C < 125). NT = not tested. [c] The procedure is described in ref 14. ED_{50} values for DNA and RNA are drug concentrations required to inhibit tritiated thymidine and uridine incorporation, respectively, into the isolated nucleic acids of cultured L1210 cells by 50%. [d] QD1-5 treatment schedule unless noted otherwise.[e] [e] Other treatment schedule denoted by a number in parentheses: i.e., (1) denotes schedule of one dose; (9) denotes QD1–9; and (16) denotes QD1-16. [f] QD1-9 treatment schedule, unless noted otherwise.[e] [g] Also 3/10 cures (three of ten test mice were cured). [h] A second test for confirmation has not been run. [i] Highest dose used was 400 mg/kg which gave T/C = 157%. [j] Confirmation experiment gave T/C = 179%.

standard National Cancer Institute protocols;[13] some also were tested in the lymphocytic leukemia P388 system. Results are reported in Table II. All T/C data have been satisfactorily duplicated in separate experiments unless otherwise noted. The results for **7b**[1] as well as similar results for **1a** and **1b** have been reported by others[5] but are included for comparison.

Data on inhibition of nucleic acid synthesis in cultured L1210 cells are also included in Table II; the test procedure is described elsewhere.[14] This assay was of interest because **1a** and **1b** are incorporated into DNA and are thereby thought to disrupt DNA metabolism.[8,15,16]

Discussion

In the L1210 antitumor test all β anomers increased the survival time of treated animals significantly. In the α anomer series only two compounds, the *S*-benzyl and *S*-nitroimidazolyl derivatives (**7a** and **11a**, respectively) showed significant activity. In both series, activity was associated with much higher dose levels than required by parent compounds **1a** and **1b**. In the P388 system activity was again found much more commonly among β anomers; of five β anomers tested against this tumor, four were active including the parent **1b**. Among the five α anomers tested, only the parent effected significant survival time increases. The amount of drug required for optimal survival time in this system was again markedly increased in almost every case.

Two compounds deserve special mention. *S*-Allyl β anomer **9b**, although requiring doses in the range of 200–400 mg/kg to give optimum survival time, nevertheless provided the greatest survival time of any of the compounds tested including the parent with no S-substituent. The *S*-nitroimidazolyl derivative **11b** is an exception to the general rule that S-alkylation reduces potency markedly. The optimum dose for **11b** in the L1210 system was 12.5 mg/kg, only two to three times that of **1b**. In the P388 test, the optimum dose of **11b** was 6.25 mg/kg, about ten times that required by **1b**. Nevertheless, this is still markedly less than the 400 mg/kg optimum dose required by most other active *S*-alkyl derivatives. It is of interest that **9b** and **11b** both provide longer survival times in the P388 system than does parent **1b**.

In the in vitro nucleic acid synthesis inhibition assay the parent β anomer **1b** was moderately inhibitory for RNA synthesis but ineffective as a DNA synthesis inhibitor at 100 μM. α anomer **1a** was ineffective as an inhibitor of either nucleic acid at 100 μM. S-Alkylation enhanced potency in the β-anomer group as all compounds were inhibitory for both DNA and RNA synthesis at levels well below 100 μM. On the other hand, in only one case (**10a**) did S-alkylation in the α-anomer series provide detectable effects in this test. *S*-Allyl derivative **9b** was notable for its low inhibitory levels and *S*-nitroimidazolyl derivative **11b** also displayed significantly low ED_{50} values. Although the mechanism of action of these compounds is unknown, the nucleic acid synthesis inhibition test selected the two *S*-alkyl derivatives that had unique properties in the in vivo tests.

Compound **2b**, the diacyl derivative of **1b**, retained significant antitumor activity in both the L1210 and P388 tests, thus suggesting that deacetylation occurs in vivo as anticipated. The corresponding α anomer **2a** was inactive in the L1210 system but the highest dose level used (100 mg/kg) may have been inadequate. Intermediate **6b**, the *N*-acetyl derivative of **8b**, was inactive in the L1210 test.

These results establish that S-substitution in 2′-deoxythioguanosine is compatible with retention of antitumor activity and, in two cases (**9b** and **11b**), superior efficacy results. While the mechanism of action of these derivatives is unknown, the in vitro nucleic acid synthesis inhibition studies support the view that nucleic acid metabolism is involved. Because of the widely varying character of S-substituents compatible with in vivo activity in this series, further manipulation of substituent structural parameters appears to offer a good opportunity for

developing improved therapeutic properties.

Experimental Section

Melting points were taken on a Fisher-Johns hot stage and were not corrected. Ultraviolet spectra were run in methanol solution containing some pH 7 buffer on a Cary 11; infrared spectra were run in Nujol on a Perkin-Elmer 137; and optical rotations were measured at the D line on a Perkin-Elmer 141 polarimeter. All evaporations were carried out in spin evaporators at a bath temperature of 45 °C under vacuum (either water aspirator and/or mechanical pump, as required), unless specified otherwise. Anhydrous Na_2SO_4 was used for drying solutions, unless otherwise specified.

Method A. 2-Amino-6-methylthio-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)-9*H*-purine (8b). A methanol solution (150 ml) of NaOMe (32 mmol) and MeSH (128 mmol) was stirred with 8.00 g (15.3 mmol) of **3b**[4] for 4 days at room temperature; it was then worked up and evaporated as in the literature procedure[12] for the 3′-deoxy analogue of **8b**. The residue was dissolved in 250 ml of MeOH containing NaOMe (15 mmol) and stirred for 56 h, after which TLC indicated that the conversion of **6b** to **8b** was completed. After neutralization (HOAc) and evaporation, the residue was passed through a 57.5 × 392 mm column of Dowex 1 (OAc) and eluted with water to afford 3.18 g (68%) of **8b**: UV max (MeOH) 220 nm (ε 18800), 245 (15000), 310 (12700). The properties are listed in Table I. In one run, the final treatment with NaOMe was omitted. The product isolated, after columning the residue through Dowex 1 (OAc), was **6b** (53% yield); the properties are given in Table I.

In another run, the reaction was performed at reflux for 3.5 h, without a final NaOMe treatment. The products isolated, after Dowex columning, were **8b** (21% yield) and **5** (12% yield): mp 140–141 °C (lit.[9b] 129–131 °C); $[\alpha]^{21}D$ -20.5 (*c* 0.25, DMF); UV max (MeOH) 248 nm (ε 9300), 280 (8800). Anal. ($C_{11}H_{25}N_5O_4 \cdot 0.5CH_3OH$) C, H, N.

Method B. 2-Amino-6-(6-methyl-2-pyridyl)methylthio-9-(2-deoxy-9-β-D-*erythro*-pentofuranosyl)-9*H*-purine (10b). To 0.56 g (2.0 mmol) of **1b** and 3 mmol of NaOMe in 30 ml of methanol was added 0.35 g (2.5 mmol) of 6-methyl-2-(chloromethyl)pyridine.[17] The solution was kept at 50 °C for 20 h, acidified with HOAc, and evaporated to dryness. The residue in 65 ml of methylene chloride was washed with water (225 and 125 ml) and evaporated. The residue was extracted with 300 ml of hot EtOAc, which was concentrated to about 10 ml to afford 0.71 g (84%) of **10b** as white crystals of analytical purity: UV max (MeOH) 245 nm (ε 14000), 311 (13200). See Table I for properties.

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Fluorinated Pyrimidine Nucleosides. 1. Synthesis of a Nitrogen Analogue of the Antitumor Agent 2,2′-Anhydro-1-β-D-arabinofuranosyl-5-fluorocytosine Hydrochloride

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The nitrogen-bridged compound 2,2′-anhydro-1-β-D-arabinofuranosyl-2,4-diamino-5-fluoropyrimidinium chloride (**2**), an analogue of the antitumor agent anhydro-ara-FC (1), has been synthesized. 5-Fluorocytidine was converted into 1-β-D-ribofuranosyl-2,4-diamino-5-fluoropyrimidinium chloride (**4**), but cyclization of **4** was not achieved due to a competing side reaction. The nitrogen bridge was therefore introduced by cyclization of 5-fluoroisocytidine (**10**) to give the 2,2′-imino-bridged compound **16**. The latter was converted into **2** by the standard procedure of thiation, S-methylation, and treatment with ammonia. Compound **2**, as well as a number of the synthetic intermediates, was tested for activity against S180 sarcoma in mice. None of the new compounds exhibited any antitumor activity.

2,2′-Anhydro-1-β-D-arabinofuranosyl-5-fluorocytosine hydrochloride (anhydro-ara-FC, 1, Figure 1) is a promising new antitumor agent originally synthesized by Fox and co-workers[1] and shown in clinical studies by Burchenal et al.[2] and Gee et al.[3] to be active against acute myeloblastic leukemia. Although the remission rate achieved with 1 was