Registry No. 1, 553-27-5; 2, 2045-19-4; 3, 29523-51-1; 4, 22964-38-1; 5, 55743-71-0; 6, 122567-47-9; 7, 122567-48-0; 8, 23721-18-8; 9, 24813-13-6; 10, 1669-15-4; 11, 122567-49-1; 12, 122567-50-4; 13, 24813-06-7; 14, 64977-17-9; 15, 1204-68-8; 16, 1204-57-5; 17, 1448-52-8; 18, 6636-74-4; 19, 945-68-6; 20, 13686-10-7; 21, 779-28-2; 22, 100858-18-2; 23, 5321-00-6; 24, 7334-82-9; 25, 24812-82-6; 26, 18226-17-0; methyl 3-aminophenyl sulfone, 35216-39-8; methyl phenyl sulfone, 3112-85-4; methyl 3-nitrophenyl sulfone, 2976-32-1; 3-nitroaniline, 99-09-2; ethylene oxide, 75-21-8; 4-aminothioanisole, 104-96-1; 2-chloroethanol, 107-07-3; 4-chloronitrobenzene, 100-00-5; diethanolamine, 111-42-2; *N,N*-bis(2-hydroxyethyl)aniline, 120-07-0; *N,N*-bis(2-hydroxyethyl)-4-(methylthio)aniline, 122567-51-5; 3-chloroperoxybenzoic acid, 937-14-4.

Synthesis and in Vivo Antitumor Activity of 2-Amino-9*H*-purine-6-sulfenamide, -sulfinamide, and -sulfonamide and Related Purine Ribonucleosides

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A number of 6-sulfenamide, 6-sulfinamide, and 6-sulfonamide derivatives of 2-aminopurine and certain related purine ribonucleosides have been synthesized and evaluated for antileukemic activity in mice. Amination of 6-mercaptopurine ribonucleoside (**7a**) and 6-thioguanosine (**7b**) with chloramine solution gave 9-β-D-ribofuranosylpurine-6-sulfenamide (**8a**) and 2-amino-9-β-D-ribofuranosylpurine-6-sulfenamide (sulfenosine, **8b**), respectively. Selective oxidation of **8a** and **8b** with 3-chloroperoxybenzoic acid (MCPBA) gave (*R,S*)-9-β-D-ribofuranosylpurine-6-sulfinamide (**9a**) and (*R,S*)-2-amino-9-β-D-ribofuranosylpurine-6-sulfinamide (sulfinosine, **9b**), respectively. However, oxidation of **8a** and **8b** with excess of MCPBA gave 9-β-D-ribofuranosylpurine-6-sulfonamide (**10a**) and 2-amino-9-β-D-ribofuranosylpurine-6-sulfonamide (sulfonosine, **10b**), respectively. Similarly, amination of 5′-deoxy-6-thioguanosine (**7c**) afforded the 6-sulfenamide derivative (**8c**), which on controlled oxidation gave (*R,S*)-2-amino-9-(5-deoxy-β-D-ribofuranosyl)purine-6-sulfinamide (**9c**) and the corresponding 6-sulfonamide derivative (**10c**). Treatment of 6-thioguanine (**12**) with aqueous chloramine solution gave 2-amino-9*H*-purine-6-sulfenamide (**13**). Oxidation of **13** with 1 molar equiv of MCPBA afforded (*R,S*)-2-amino-9*H*-purine-6-sulfinamide (**14**), whereas the use of 4 molar equiv of MCPBA furnished 2-amino-9*H*-purine-6-sulfonamide (**15**). The resolution of *R* and *S* diastereomers of sulfinosine (**9b**) was accomplished by HPLC techniques. The structures of (*R*)-**9b** and **10b** were assigned by single-crystal X-ray diffraction studies. (*R*)-**9b** exists in the crystal structure in four crystallographically independent conformations. Of the 18 compounds evaluated, 13 exhibited very significant anti-L1210 activity in mice. Sulfenosine (**8b**) at 22 mg/kg per day × 1 showed a T/C of 170, whereas sulfinosine (**9b**) at 173 mg/kg per day × 1 showed a T/C of 167 against L1210 leukemia. The 5′-deoxy analogue of sulfinosine (**9c**) at 104 mg/kg per day also showed a T/C of 172. A single treatment with **8b**, **9b**, and **9c** reduced body burdens of viable L1210 cells by more than 99.8%.

The development of sulfonamides is one of the most fascinating and informative chapters in medical science, highlighting the roles of skillful planning and serendipity in drug research.[1] The introduction of prontosil over 50 years ago as an antibacterial agent (discovered by Gerhard Domagk, for which he was awarded the Nobel Prize in 1939) marked the beginning of a tempestuous development of other sulfonamides, and from the sulfonamide era developed the age of effective chemotherapy for infectious diseases. Since the initial dramatic results obtained with sulfonamides in the treatment of streptococcal infections, studies with compounds containing the sulfonamide group have been extended to viruses. The compounds of particular interest are 2-amino-5-(2-sulfamoylphenyl)-1,3,4-thiadiazole (G413)[2] and sodium 5-sulfamoyl-2,4-dichlorobenzoate (M12325),[3] both of which are found to be effective in inhibiting the replication of a broad spectrum of viruses in vitro as well as in vivo at concentrations which do not exhibit any toxic effects on host cells.

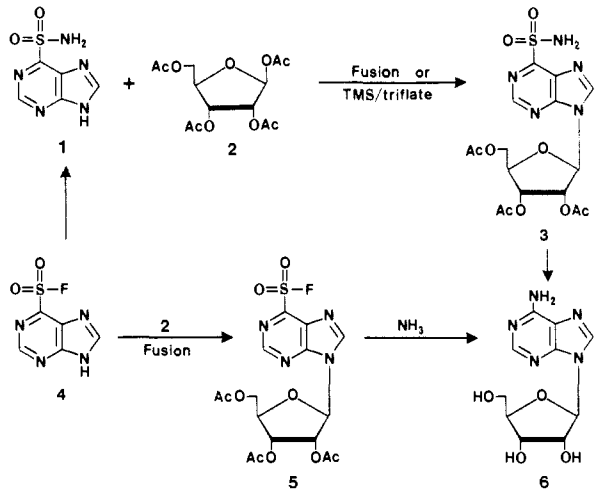
There is probably no class of compounds, as characterized by a single functional group, that exceeds sulfonamides in their influence on medical practice and treatment of human disease.[4] The sulfamoyl group has been extensively utilized as an activity-modifying substituent in many different classes of drugs. The purine derivatives and analogues have played a very magnificent role in cancer chemotherapy since the introduction of 9*H*-purine-6(1*H*)-thione (6-mercaptopurine, 6-MP) by Elion and Hitchings[5] in 1952, to treat lymphoblastic leukemia in children.[6] Medicinal chemists have continued to synthesize novel purine derivatives with the hope of obtaining greater potency and selective toxicity in compounds with a broader spectrum of antitumor activity. 9*H*-Purine-6-sulfonamide (1) and its 6-*N*-alkyl derivatives, first synthesized and reported from our laboratory,[7] exhibited significant antitumor activity against Adenocarcinoma 755 and L1210 leukemia in mice at several dosage levels.[8,9] 9*H*-Purine-6-sulfonamide (1) at 75 mg/kg per day × 5

† On leave from National Research Center, Dokki, Cairo, Egypt.

(1) Anand, N. In *Burger's Medicinal Chemistry*; 4th ed., Part II; Wolff, M. E., Ed.; Wiley-Interscience: New York, 1979; pp 1–40.
(2) Bonina, L.; Orzalesi, G.; Merendino, R.; Arena, A.; Mastroeni, P. *Antimicrob. Agents Chemother.* **1982**, *22*, 1067.
(3) Ohnishi, H.; Yamaguchi, K.; Shinada, S.; Himuro, S.; Suzuki, Y. *Antimicrob. Agents Chemother.* **1982**, *22*, 250.
(4) Allen, R. C. In *Diuretics Chemistry, Pharmacology, and Medicine*; Cragoe, E. J., Ed.; Wiley-Interscience: New York, 1983, pp 49–177.
(5) For a commentary, see: Chabner, B. A. *JNCI, J. Natl. Cancer Inst.* **1988**, *80*, 1512.
(6) Burchenal, J. H.; Murphy, M. L.; Ellison, R. R.; Sykes, M. P.; Tan, C. T. C.; Leone, L. A.; Karnofsky, D. A.; Craver, L. F.; Dargeon, H. W.; Rhoads, C. P. *Blood* **1953**, *8*, 965.
(7) Beaman, A. G.; Robins, R. K. *J. Am. Chem. Soc.* **1961**, *83*, 4038.
(8) Lewis, L. R.; Noell, C. W.; Beaman, A. G.; Robins, R. K. *J. Med. Pharm. Chem.* **1962**, *5*, 607.
(9) Robins, R. K. *J. Med. Chem.* **1964**, *7*, 186.

0022-2623/90/1833-0121$02.50/0

Scheme I



against L1210 leukemia showed a T/C of 165, whereas N^6-methylpurine-6-sulfonamide at 200 mg/kg per day × 5 showed a T/C of 182 against L1210 leukemia.[10] It is quite interesting that a subtle change to an oxidized sulfur atom in the form of sulfonamide or substituted sulfonamide at position 6 resulted in a new group of purine derivatives possessing significant antitumor properties.

The effectiveness of these purine bases against certain tumor lines has suggested that the nucleosides or nucleotides of these purine sulfonamides would be worthy of consideration in order to determine whether they exert a more selective effect against neoplastic cells than against normal cells or if they might be useful in patients whose disease has become resistant to 6-mercaptopurine or 6-thioguanine (**12**). Moreover, the observation in animal models that purine nucleotide biosynthesis[11] is accomplished primarily with nucleosides of purines and purine precursors rather than with the free bases[12] suggested that nucleosides of these sulfonamidopurines might be more active as anticancer agents. For example, when given by the oral route, 6-thioguanosine[13] (**7b**, which is approximately twice as soluble in aqueous solution as is 6-thioguanine) is more active than 6-thioguanine (**12**) against certain acute leukemias.[14] In view of these observations, we initiated an extensive program to synthesize and evaluate certain nucleoside derivatives of purine-6-sulfonamide and related compounds.

Results and Discussion

Chemistry. Although the most obvious approach to such a purine-6-sulfonamide nucleoside appeared to be through a sulfonyl halide derivative,[15] our attempts to convert the corresponding protected nucleoside to the target sulfamoyl purine nucleoside have met with little success. In the early glycosylation studies we elected to use the stable purine-6-sulfonyl fluoride[7] (**4**). Purine-6-sulfonyl fluoride (**4**) was prepared as reported previously[7] and fused at 120 °C with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**2**) in the absence of an acid catalyst (Scheme I). An intractable reaction mixture was obtained from which the desired 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-purine-6-sulfonyl fluoride (**5**) was isolated in 22% yield after silica gel column chromatography. However, attempted deacetylation of **5** with methanolic ammonia at low temperature resulted in the isolation of adenosine (**6**), the sulfonyl fluoride being a good leaving group.[7]

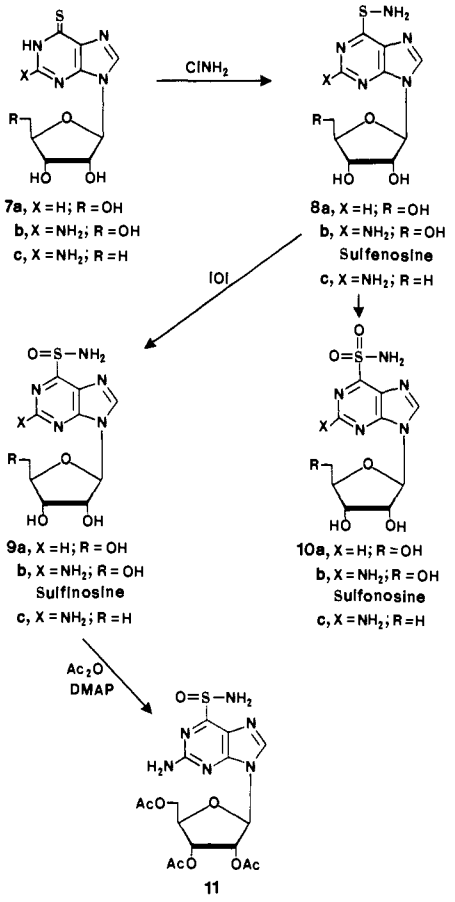
In an attempt to circumvent this undesired course of reaction, we decided to employ 9*H*-purine-6-sulfonamide (**1**) itself in the glycosylation studies. Treatment of **4** with anhydrous liquid ammonia as described by Beaman and Robins[7] gave **1** in 85% yield, which was silylated with hexamethyldisilazane in the presence of $(NH_4)_2SO_4$. Glycosylation of the trimethylsilyl derivative of **1** with **2** in anhydrous CH_3CN in the presence of 1.44 molar equiv of trimethylsilyl trifluoromethanesulfonate, according to the general procedure described by Vorbrüggen and coworkers,[16] gave crystalline 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine-6-sulfonamide (**3**) in a 46% yield. The synthesis of **3** was also accomplished via the acid-catalyzed [bis(*p*-nitrophenyl) phosphate] fusion[17] of **1** with **2**. However, the isolated yield of **3** by this latter procedure was only 22%. Again, attempted deacetylation of **3** with methanolic ammonia furnished adenosine (**6**) as the predominant product.

A literature survey revealed that the oxidation (by $KMnO_4$) of certain sulfenamides to sulfonamides has been described,[18-20] and that this approach has been successfully employed for the preparation of uracil-6-sulfonamide[21] from a stable sulfenamide derivative obtained from 2,4-dimethoxypyrimidine-6(1*H*)-thione and ammoniacal hypochlorite (i.e. chloramine) solution. This S-amination condition is very similar to that described by Carr and co-workers[22] for the preparation of benzothiazole-2-sulfenamide. Subsequently, this procedure has been used widely in the preparation of other substituted benzothiazole-2-sulfenamides[23,24] and pyrimidine-2-sulfenamides.[25] Thus, it seemed propitious for us to use this methodology for the preparation of the purine-6-sulfonamide ribonucleosides and, surprisingly enough, it was found to be remarkably successful.

Treatment of 9-β-D-ribofuranosylpurine-6(1*H*)-thione (6-mercaptopurine ribonucleoside, **7a**) with an aqueous chloramine solution (prepared from commercial sodium hypochlorite and ammonium hydroxide solution at 0 °C) at ambient temperature and purification of the reaction product by silica gel column chromatography gave a 50% yield of 9-β-D-ribofuranosylpurine-6-sulfenamide (**8a**) (Scheme II). When one considers the several reactions which may occur in a mixture of **7a**, hypochlorite, and ammonium hydroxide, it is rather surprising that any of the desired **8a** can be isolated. The free chlorine in the

(10) Robins, R. K.; Revankar, G. R. *Med. Res. Rev.* **1985**, *5*, 273.
(11) Balis, M. E.; Levin, D. K.; Brown, G. B.; Elion, G. B.; Nathan, H. C.; Hitchings, G. H. *Arch. Biochem. Biophys.* **1957**, *71*, 358.
(12) Greenberg, G. R. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1954**, *13*, 745.
(13) Fox, J. J.; Wempen, I.; Hampton, A.; Doerr, I. L. *J. Am. Chem. Soc.* **1958**, *80*, 1669.
(14) Krakoff, I. H.; Ellison, R. R.; Tan, C. T. C. *Cancer Res.* **1961**, *21*, 1015.
(15) Hanna, N. B.; Dimitrijevich, S. D.; Larson, S. B.; Robins, R. K.; Revankar, G. R. *J. Heterocycl. Chem.* **1988**, *25*, 1857.
(16) Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234.
(17) Sanghvi, Y. S.; Hanna, N. B.; Larson, S. B.; Fujitaki, J. M.; Willis, R. C.; Smith, R. A.; Robins, R. K.; Revankar, G. R. *J. Med. Chem.* **1988**, *31*, 330.
(18) Bann, B.; Krug, P.; Wheeler, D. E.; Taylor, W.; Gladding, G. British Patents 551205, 1943; 551206, 1943; 551207, 1943.
(19) Barber, J. British Patent 550446, 1943.
(20) Smith, G. E. P., Jr. U.S. Patent 2560021, 1951.
(21) Greenbaum, S. B. *J. Am. Chem. Soc.* **1954**, *76*, 6052.
(22) Carr, E. L.; Smith, G. E. P., Jr.; Alliger, G. *J. Org. Chem.* **1949**, *14*, 921.
(23) Korman, J. *J. Org. Chem.* **1958**, *23*, 1768.
(24) Schoenwald, R. D.; Eller, M. G.; Dixson, J. A.; Barfknecht, C. F. *J. Med. Chem.* **1984**, *27*, 810.
(25) Hurley, T. J.; Robinson, M. A. *J. Med. Chem.* **1965**, *8*, 888.

Scheme II



hypochlorite solution may react with excess ammonia to produce nitrogen and ammonium chloride. Also, the hypochlorite may react with **7a** to produce a disulfide[26] or the salt of a sulfonic acid.[22] Despite the fact that some of these side reactions are most certainly taking place, we have been able to isolate sulfenamides of high purity and in satisfactory yields.

Although potassium permanganate has generally been used as the oxidation reagent for the heterocyclic sulfenamide–sulfonamide conversion,[18-21,23,24] recently reported[27] peracid oxidation was found to be the method of choice. Even though oxidation of 4,6-dimethylpyrimidine-2-sulfenamide with 3-chloroperoxybenzoic acid (MCPBA) reportedly[28] failed to provide the desired sulfonamide, treatment of **8a** with 1 molar equiv of MCPBA in EtOH at 0 °C gave an oxidized product, which was isolated in 67% yield as crystalline material and identified as a diastereomeric mixture of (*R,S*)-9-β-D-ribofuranosylpurine-6-sulfinamide (**9a**). To the best of our knowledge, this is the first example of the isolation of a crystalline N-unsubstituted sulfinamide nucleoside derivative. However, treatment of **8a** with 4 molar equiv of MCPBA at room temperature gave the fully oxidized product 9-β-D-ribofuranosylpurine-6-sulfonamide (**10a**). Compounds **8a–10a** appear to be quite stable when dry and free from acid or alkali; however, upon exposure to aqueous acid or alkaline solution they tend to hydrolyze to inosine.

In order to stabilize the sulfenamide and the corresponding oxidized groups at the 6-position of purine ri-

Scheme III

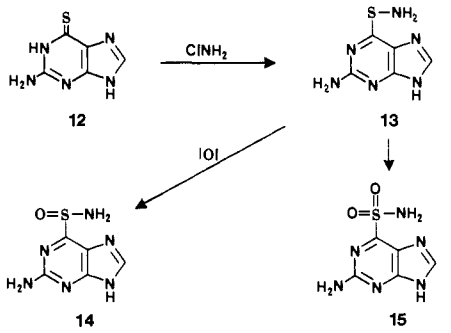


Table I. The NH_2 Proton Chemical Shifts in the ^1H NMR Spectra of Sulfenamide, Sulfinamide, and Sulfonamide Derivatives of Certain Purines and Purine Ribonucleosides

	chemical shifts (ppm) in Me_2SO-d_6		
compd	SNH_2	$SONH_2$	SO_2NH_2
8a	4.15		
9a		6.68	
10a			7.80
8b	3.91		
9b		6.98	
10b			7.52
8c	3.89		
9c		6.98	
10c			7.54
13	3.92		
14		6.59	
15			7.61

bonucleosides, we considered using 6-thioguanosine in the amination/oxidation reactions. The NH_2 group at the 2-position of the purine ring was expected to stabilize the modified 6-thio function. Thus, amination of 6-thioguanosine[29] (**7b**) with chloramine solution gave a 74% yield of 2-amino-9-β-D-ribofuranosylpurine-6-sulfenamide (sulfenosine, **8b**), which on subsequent oxidation with 1 molar equiv of MCPBA in ethanol at ambient temperature afforded (*R,S*)-2-amino-9-β-D-ribofuranosylpurine-6-sulfinamide (sulfinosine, **9b**) (Scheme II). When 4 molar equiv of MCPBA in ethanol was used to oxidize **8b**, 2-amino-9-β-D-ribofuranosylpurine-6-sulfonamide (sulfonosine, **10b**) was formed and isolated as crystalline material in over 86% yield. The structure of sulfonosine (**10b**) was confirmed by single-crystal X-ray diffraction analysis. Acetylation of sulfinosine (**9b**) with acetic anhydride in the presence of 4-(*N,N*-dimethylamino)pyridine (DMAP) gave a 75% yield of 2′,3′,5′-tri-*O*-acetylsulfinosine (**11**). As expected, compounds **8b**, **9b** and **10b** were found to be relatively more stable as compared to **8a**, **9a** and **10a**, respectively.

These amination and oxidation methods were also found to be equally successful with 6-thioguanine (Scheme III). Thus, treatment of 6-thioguanine[29] (**12**) with aqueous chloramine solution at 0 °C readily gave the desired 2-amino-9*H*-purine-6-sulfenamide (**13**). However, the isolated yield of the analytically pure **13** was only 34%. Oxidation of **13** with 1 molar equiv of MCPBA in ethanol afforded (*R,S*)-2-amino-9*H*-purine-6-sulfinamide (**14**), whereas use of 4 molar equiv of the oxidizing agent furnished the fully oxidized product 2-amino-9*H*-purine-6-sulfonamide (**15**).

In a similar manner, 2-amino-9-(5-deoxy-β-D-ribofuranosyl)purine-6(1*H*)-thione[30] (**7c**) was aminated with

(26) Sisler, H. H.; Kotia, N. K.; Highsmith, R. E. *J. Org. Chem.* **1970**, *35*, 1742.
(27) Larsen, R. D.; Roberts, F. E. *Synth. Commun.* **1986**, *16*, 899.
(28) Brown, D. J.; Hoskins, J. A. *J. Chem. Soc., Perkin Trans. 1* **1972**, 522.
(29) Commercially available in bulk quantity from Heinrich Mack Nachf, 7918 Illertissen, Bayern, Federal Republic of Germany.
(30) Reist, E. J.; Hart, P. A.; Goodman, L.; Baker, B. R. *J. Org. Chem.* **1961**, *26*, 1557.

Table II. Hydrolysis of Sulfinosine at 22 °C

medium	1 h	15 h	3 days	5 days	15 days
water	no change	<2% converted to Guo	<4% converted to Guo	<5% converted to Guo	most of it converted to Guo
1 N NaOH	converted to Guo				
1 N HCl	converted to Guo (56.5%), 6-TGuo (43.5%)				

Table III. Summary of Conformational Parameters of Compounds (*R*)-**9b** and **10b**

parameter	(*R*)-**9b**-A	(*R*)-**9b**-B	(*R*)-**9b**-C	(*R*)-**9b**-D	**10b**
χ (O1′-C1′-N9-C4), deg	63.6	-130.9	61.1	91.6	54.0
glycosyl	syn	anti	syn	high anti	syn
θ_0 (C1′-C2′-C3′-C4′), deg	-38.4	-22.9	-23.3	26.7	-35.5
θ_1 (C2′-C3′-C4′-O1′), deg	28.0	0.9	17.2	-39.0	25.1
θ_2 (C3′-C4′-O1′-C1′), deg	-3.2	22.8	-2.3	38.2	-3.6
θ_3 (C4′-O1′-C1′-C2′), deg	-23.0	-36.4	-14.2	-23.1	-19.5
θ_4 (O1′-C1′-C2′-C3′), deg	47.5	40.6	24.5	-3.4	34.5
P, deg	166.0	125.5	165.1	49.7	167.0
τ_m, deg	39.6	39.4	24.2	41.3	36.4
sugar pucker	$C_{2'}$-endo	$C_{1'}$-exo	$C_{2'}$-endo	$C_{4'}$-exo	$C_{2'}$-endo
ϕ_{oo}(O1′-C4′-C5′-O5′), deg	-73.6	49.2	-69.0	71.1	-71.1
ϕ_{co} (C3′-C4′-C5′-O5′), deg	44.0	178.5	53.2	-174.6	48.1
orientation	g^-g^+	g^+t	g^-g^+	g^+t	g^-g^+

chloramine solution (Scheme II). The reaction product was purified by silica gel column chromatography to give 2-amino-9-(5-deoxy-β-D-ribofuranosyl)purine-6-sulfenamide (**8c**) in over 87% yield. Controlled oxidation of **8c** with MCPBA gave the corresponding sulfinamide (**9c**) and sulfonamide (**10c**) derivatives in good yield.

The ^{1}H NMR spectral comparison of the NH_2 proton chemical shifts in Me_2SO-d_6 of sulfenamides, sulfinamides, and sulfonamides revealed an interesting pattern in this group of compounds (Table I). For sulfenamides, the SNH_2 chemical shift was found to be in the region δ 3.89–4.15 ppm. The oxidation of sulfenamides to sulfinamides resulted in the shift of the SONH_2 protons to lower field (6.59–6.98 ppm) and further oxidation of sulfinamides to sulfonamides causes the NH_2 group to shift still further (in the region δ 7.52–7.80 ppm). This effect is in correlation with the expected increased deshielding by the extra oxygen attached to sulfur in the sulfonamide.[31]

It has been well-established[31] that the sulfur atom of sulfinamides constitutes a chiral center. As a result, the sulfinamide derivatives prepared during this study exist as a mixture of *R* and *S* diastereomers. Since sulfinosine (**9b**) exhibited significant anticancer activity, the resolution of the *R* and *S* diastereomers was deemed desirable and was accomplished on a prepacked ODS column (C_{18}, semipreparative) (see the Experimental Section). The structure of the *R* diastereomer was established by single-crystal X-ray diffraction analysis.

The racemic mixture of sulfinosine was more water soluble (17.3 mg/mL) than 6-thioguanosine (0.81 mg/mL), whereas the *R* diastereomer (17.3 mg/mL) was more than 4 times as soluble as the *S* diastereomer (3.7 mg/mL) in water at 22 °C. Table II shows the rate of hydrolysis of sulfinosine in aqueous media.

Single-Crystal X-ray Diffraction Analysis of Compounds (*R*)-9b and 10b. The *R* diastereomer of sulfinosine (**9b**) exists in the crystal structure in four crystallographically independent conformations, which are illustrated in Figure 1; the conformation of sulfonosine (**10b**) is depicted in Figure 2. Molecules (*R*)-**9b**-A, (*R*)-**9b**-C, and **10b** [Figures 1 (conformations A and C) and 2, respectively] are in the syn conformation [χ_{CN} (O1′-C1′-N9-C4) = 63.6°, 61.1°, and 54.0°, respectively] with a stabilizing

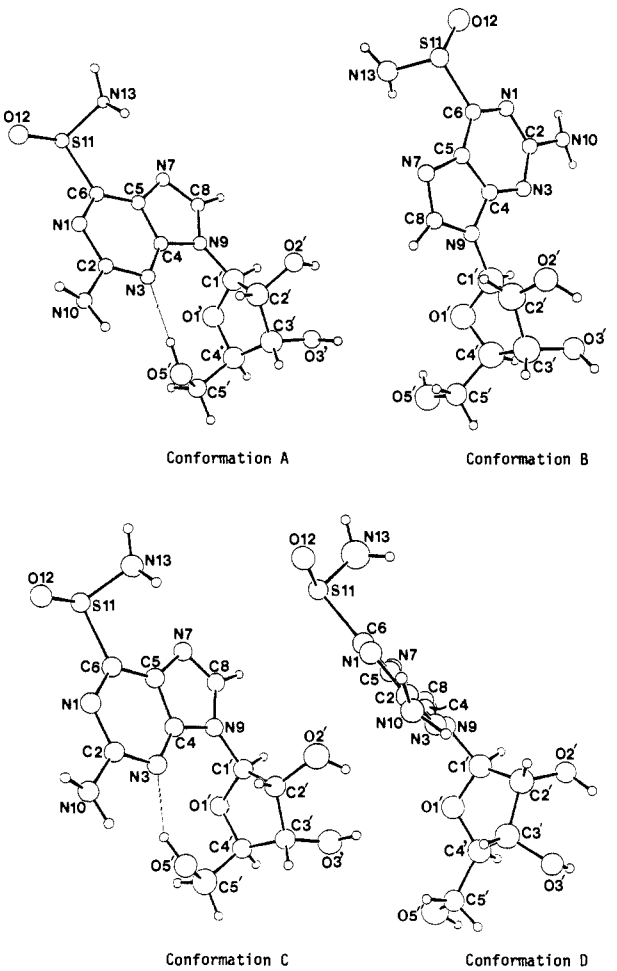


Figure 1. Perspective drawing of compound (*R*)-**9b**.

O5′-H···N3 intramolecular hydrogen bond, features that are similar to those found in the 8-substituted guanosines 8-chloro-,[32] 8-bromo-,[33] 8-methyl-,[34] and 7-methyl-8-oxo-

(31) Moriarty, R. M. *J. Org. Chem.* **1965**, *30*, 600.

(32) Birnbaum, G. I.; Lassota, P.; Shugar, D. *Biochemistry* **1984**, *23*, 5048.

(33) Tavale, S. S.; Sobell, H. M. *J. Mol. Biol.* **1970**, *48*, 109.

(34) Hamada, K.; Honda, I.; Fujii, S.; Fujiwara, T.; Tomita, K. *Acta Crystallogr.* **1985**, *C41*, 1486.

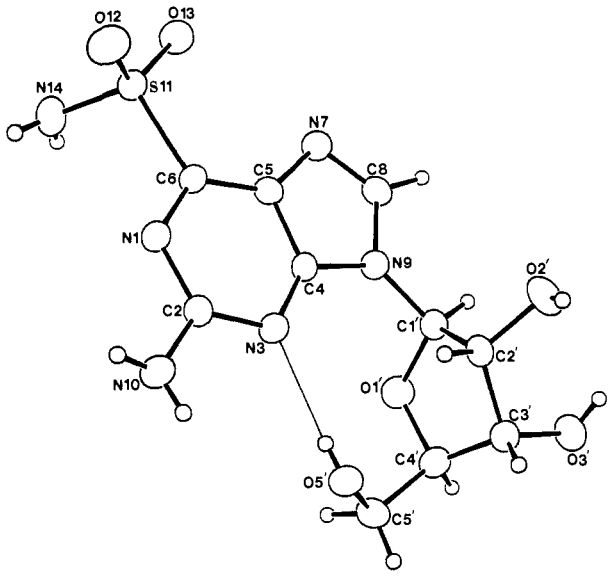


Figure 2. ORTEPII drawing of compound **10b**.

guanosines.[35] The ribose puckering in these syn conformations is $C_{2'}$-endo (pseudorotation angle[36] P = 166.0°, 165.1°, and 167.0° for **9b**-A, **9b**-C, and **10b**, respectively). However, conformer C has a considerably flatter furan ring as measured by the amplitude of pucker[36] (τ_m) than the other molecules. Conformational parameters are summarized in Table III. Conformers B and D of (*R*)-**9b** (Figure 1) are very distinct from each other as well as from A and C. B is in the anti conformation (χ = −130.9°), with sugar puckering corresponding to $C_{1'}$-exo (P = 125.5°) and a gauche–trans C5′–O5′ side chain; D is intermediate between syn and anti (χ = 91.6°) with a sugar pucker of $C_{4'}$-exo (P = 49.7°) and the side chain is also gauche–trans.

In all conformations of (*R*)-**9b** the sulfinamido groups are oriented similarly with respect to the purine rings. Thus, the average dihedral angle of the C6–S–N planes to the purine planes is 124 ± 6° and the oxygens are nearly coplanar with the purine planes and trans to the imidazole ring. On the other hand, the sulfonamido group in **10b** has an oxygen nearly coplanar with the purine plane but cis to the imidazole ring; the NH_2 and the other oxygen straddle the purine plane. In each of the four conformations of (*R*)-**9b** and in **10b**, the following hydrogen bonding features are observed. The C8 hydrogen appears to interact weakly [d(H8···O12) = 2.39–2.49 Å] with an oxygen attached to the sulfur atom of a related molecule. In each amino group, one proton is considerably more strongly interacting than the other proton. All hydroxyl groups of **10b** are involved in hydrogen bonding as both donors and acceptors. Due to the nature of the structural determination of (*R*)-**9b** (see Experimental Section), it is only possible to say that it is likely that all hydroxyl groups are involved in hydrogen-bonding interactions. The majority of the interactions between conformers involve A with B and C with D; in fact, there are no intermolecular contacts to suggest that conformer A interacts with D or that conformer B interacts with C. Further details will be published elsewhere.[37]

Antileukemic Activity. Eighteen compounds, derived from or otherwise related to 9*H*-purine-6-sulfonamide, were evaluated for antileukemic activity in mice. As indicated by the data presented in Table IV, the solubilities and anticancer activities of these compounds were greatly dissimilar. Solubility in water ranged from a nadir of 0.81 mg/mL for compound **7b** to a high of 48 mg/mL for compounds **8a**, **10a**, and **10c**. Two additional compounds (**11** and **13**), which were not soluble in water, were dissolved in Me_2SO. Administered qd (once daily) on day 1 at dosages determined by solubility, 13 of the 18 compounds exhibited biologically significant anti-L1210 activity; i.e., they produced a T/C ≥ 125. Four less active compounds (**4**, **9a**, **14**, and **15**) reduced body burdens of viable L1210 cells by 20–73%, and only one compound (**11**) lacked activity. In the present study, a diastereomeric mixture of sulfinosine [(*R*,*S*)-**9b**] was used due to problems encountered in separating the *R* and *S* diastereomers and because the mixture appeared more effective against L1210 leukemia than either *R* or *S* diastereomer alone. From data not included in Table IV, *R* and *S* diastereomers of **9b** produced T/C values of 156 and 125, respectively. Studies are presently being conducted to establish the relative importance of the *R* and *S* diastereomers to the overall performance of sulfinosine [(*R*,*S*)-**9b**].

Under the conditions of these studies, variations in solubility and antileukemic activity did not define any discernible structure dependence; thus, structural alterations in the base and sugar moieties of the compounds did not produce uniform changes in biologic characterization. Whether modifications such as introduction of an amino group at the 2-position of the purine ring or the substitution of a 5′-deoxy sugar improved or lessened solubility or anticancer activity appeared to depend on the molecule

Table IV. Responses of L1210 Inoculated Mice to a Single Treatment with Certain Sulfur-Containing Purines and Purine Nucleosides

compd	dosage,[a] mg/kg	postinoculation lifespan[b] (%T/C)	% viable L1210 cells killed by single treatment[c]
1	104	134	95.48
4	62	115	73.54
7a	173	150	98.36
7b	8.1	147	98.41
7c	37	169	99.82
8a	480	149	97.82
8b	22	170	99.84
8c	13	136	95.90
9a	62	114	70.87
9b	173	167	99.80
9c	104	172	99.87
10a	173 (480)	147	98.36
10b	62	128	92.40
10c	480	130	94.38
11	22D[d]	99	0
13	37D[d] (104)	159	99.04
14	22	113	67.94
15	22	103	20.78

[a] All solutions were delivered ip (0.01 mL/g mouse wt). Control mice were injected with a 0.9% solution of NaCl. The dosages presented in mg/kg are 10 times maximum solubility in mg/mL. Drugs that were lethally toxic at their maximum soluble dosage (indicated by numbers in parenthesis) were studied at lower dosages. [b] Treatment responses (six mice/treatment group) presented as %T/C were calculated according to the equation: mean life span of treated mice/mean life span of control mice by 100. The data presented were derived from six different studies in which the mean life spans of 10 control mice/study ranged from 6.40 ± 0.55 to 6.70 ± 0.48 days. A T/C ≥ 125 is considered biologically significant. [c] Estimations of residual leukemic cell populations and, hence, percentage cell kill were made using inoculum-response data indicating the relationship between inoculum size and resultant postinoculation life span. [d] D indicates solubility in Me_2SO; drugs not so indicated were soluble in water.

(35) Larson, S. B.; Cottam, H. B.; Robins, R. K. *Acta Crystallogr.* In press.
(36) Altona, C.; Sundaralingam, M. *J. Am. Chem. Soc.* **1972**, *94*, 8205.
(37) Larson, S. B.; Hanna, N. B.; Revankar, G. R.; Robins, R. K. *Acta Crystallogr.* In press.

subjected to such alterations. It is a fact, however, that a clear majority of the tested compounds exhibited biologically very significant anticancer activity and that a single treatment with several of the compounds reduced body burdens of viable L1210 cells by more than 99%. While major efforts along the lines of dosage ranging and scheduling trials will be required to optimize drug activity, the present findings suggest that this group of sulfur-containing compounds may yield several effective new anticancer agents. In particular, nucleoside (*R,S*)-**9b** has been selected for further animal studies.

Experimental Section

General Procedures. Melting points (uncorrected) were determined in a Thomas-Hoover capillary melting point apparatus. Elemental analyses were performed by Robertson Laboratory, Florham Park, NJ. Thin-layer chromatography (TLC) was performed on Merck pre-coated silica gel 60 F_{254} plates. Silica gel (E. Merck; 230–400 mesh) was used for flash column chromatography. All solvents used were reagent grade. Detection of nucleoside components in TLC was by UV light and with 10% H_2SO_4 in MeOH spray followed by heating. Evaporations were conducted under diminished pressure with the bath temperature below 30 °C. Infrared (IR, in KBr) spectra were recorded with a Perkin-Elmer 1420 spectrophotometer and ultraviolet (UV, sh = shoulder) spectra were recorded on a Beckman DU-50 spectrophotometer. Proton magnetic resonance (^{1}H NMR) spectra were recorded at 300 MHz with an IBM NR/300 spectrometer. The chemical shift values are expressed as δ values (parts per million) relative to tetramethylsilane as an internal standard (key: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). The presence of solvent as indicated by elemental analysis was verified by ^{1}H NMR spectroscopy.

9-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)purine-6-sulfonamide (3). Method A. A mixture of 9*H*-purine-6-sulfonamide[7] (1, 1.99 g, 10 mmol), hexamethyldisilazane (HMDS, 20 mL), and ammonium sulfate (0.1 g) was heated under reflux (150–155 °C, oil bath temperature) for 3 h with the exclusion of moisture. The excess HMDS was distilled off and the residual HMDS was coevaporated with anydrous toluene (2 × 50 mL). After drying the residual silylated sulfonamide for 1 h at 50 °C in vacuo, it was dissolved in dry acetonitrile (30 mL) and, with stirring at room temperature, 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**2**, 3.5 g, 11 mmol) was added, followed by trimethylsilyl trifluoromethanesulfonate (triflate, 2.78 mL, 14.4 mmol). After stirring for 1 h under anhydrous conditions, the reaction mixture was evaporated. The residue was dissolved in ethyl acetate (150 mL) and poured into an ice-cold aqueous solution of 5% sodium bicarbonate (150 mL). The organic layer was separated, dried (Na_2SO_4), and evaporated. The residue was purified on a flash silica gel column (3 × 20 cm), eluting successively with 200-mL portions of $CHCl_3$/MeOH (98:2, 96:4, 94:6, v/v). The homogeneous fractions were pooled and evaporated to dryness, and the residue was crystallized from CH_2Cl_2 to provide 2.1 g (46%) of **3**: mp 179–181 °C; IR ν_{max} 1030 (S=O), 1220, 1350 (O=S=O), 1730 (C=O), 3100–3500 (NH_2) cm^{-1}; UV λ_{max} (pH 1) 272 nm (ε 2500); (pH 7) 277 nm (ε 2200); (pH 11) 272 nm (ε 2200); ^{1}H NMR (Me_2SO-d_6) δ 2.0–2.13 (3 s, 9 H, 3 COCH_3), 4.21–4.42 (2 m, 3 H, C_4'H and C_5'CH_2), 5.70 (m, 1 H, C_3'H), 6.11 (t, 1 H, C_2'H), 6.44 (d, 1 H, $J_{1',2'}$ = 5.4 Hz, C_1'H), 7.92 (s, 2 H, SO_2NH_2), 9.10 (s, 1 H, C_2H), and 9.40 (s, 1 H, C_8H). Anal. ($C_{16}H_{19}N_5O_9S$, MW 457.41) C, H, N, S.

Method B. A finely ground mixture of 1 (0.4 g, 2 mmol) and **2** (0.7 g, 2.2 mmol) was fused with stirring at 150 °C in the presence of bis(*p*-nitrophenyl) phosphate (20 mg) under reduced pressure for 1 h. The cooled reaction mixture was dissolved in ethyl acetate (50 mL) and poured into an ice-cold aqueous solution of 5% $NaHCO_3$ (50 mL). The organic layer was separated, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue as described above and crystallization of the homogeneous product from CH_2Cl_2 gave 0.2 g (22%) of **3**, which was identical with **3** prepared by method A.

9-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)purine-6-sulfonyl Fluoride (5). A finely ground mixture of 9*H*-purine-6-sulfonyl fluoride[7] (4, 0.4 g, 2 mmol) and 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**2**, 0.71 g, 2.2 mmol) was heated with stirring at 120 °C under reduced pressure for 5 min. Chromatography of the resulting reaction mixture on a silica gel column (1.5 × 20 cm) using $CHCl_3$/MeOH (95:5, 9:1, v/v) as the eluent provided pure product, which on crystallization from CH_2Cl_2 gave 0.2 g (22%) of **5** as an amorphous solid: mp 115 °C; IR ν_{max} 1040 (S=O), 1220, 1370 (O=S=O), 1735 (C=O) cm^{-1}; UV λ_{max} (pH 1) 269 nm (ε 2200); (pH 7) 271 nm (ε 2400); (pH 11) 270 nm (ε 2300); ^{1}H NMR (Me_2SO-d_6) δ 1.96–2.08 (3 s, 9 H, 3 COCH_3), 4.23–4.41 (2 m, 3 H, C_4'H and C_5'CH_2), 5.61 (m, 1 H, C_3'H), 6.10 (t, 1 H, C_2'H), 6.32 (d, 1 H, $J_{1',2'}$ = 5.4 Hz, C_1'H), 8.79 (s, 1 H, C_2H), and 8.92 (s, 1 H, C_8H). Anal. ($C_{16}H_{17}FN_4O_9S$·H_2O, MW 478.4) C, H, N, S.

Attempted Deacetylation of 3 and 5. The protected nucleoside **3** (or **5**) (0.2 g) was combined with MeOH/NH_3 (10 mL, saturated at 0 °C) and the resulting solution was stirred at −5 °C for 5 h in a pressure bottle. The MeOH/NH_3 was evaporated and the residue was purified on a silica gel column (2 × 20 cm) using CH_2Cl_2/MeOH (8:2, v/v) as the eluent. The major product isolated from the homogeneous fractions was crystallized from water (95 mg, 80%) and identified as adenosine (**6**): mp 234–236 °C (mixed mp 235 °C). UV, ^{1}H NMR, and TLC (in four different solvent systems) were found to be similar in all respects to authentic adenosine.

9-β-D-Ribofuranosylpurine-6-sulfenamide (8a). Commercial 0.77 M sodium hypochlorite solution (5.25%, 15 mL) was cooled to 0 °C in an ice bath. Ammonium hydroxide (0.77 M, 40 mL) was similarly cooled in an ice bath and added with stirring to the bleach solution. The mixture was stirred at 0 °C for 15 min and then a cold (0 °C) solution of 9-β-D-ribofuranosylpurine-6-(1*H*)-thione (**7a**, 2.84 g, 10 mmol) in 2 N KOH (5 mL) was added. The flask was stoppered and stirred for 45 min until it had warmed to room temperature. The solvents were evaporated. The residue was dissolved in MeOH (50 mL) and adsorbed onto silica gel (5 g). The excess solvent was evaporated and the dry residue was loaded onto a silica gel column (3 × 40 cm) packed in CH_2Cl_2. The column was eluted with a mixture of CH_2Cl_2/MeOH (8:2, 7:3, v/v). The homogeneous fractions were pooled, the solvents were evaporated, and the residue was crystallized from aqueous MeOH to yield 1.5 g (50%) of **8a**: mp 100 °C; IR ν_{max} 3000–3450 (NH_2, OH) cm^{-1}; UV λ_{max} (pH 1) 301 nm (ε 11 100); (pH 7) 288 nm (ε 8700); (pH 11) 288 nm (ε 9500); ^{1}H NMR (Me_2SO-d_6) δ 3.63 (m, 2 H, C_5'CH_2), 3.97 (m, 1 H, C_4'H), 4.15 (s, 2 H, SNH_2), 4.17 (m, 1 H, C_3'H), 4.61 (m, 1 H, C_2'H), 5.16 (t, 1 H, C_5'OH), 5.27 (d, 1 H, C_3'OH), 5.55 (d, 1 H, C_2'OH), 6.00 (d, 1 H, $J_{1',2'}$ = 5.7 Hz, C_1'H), 8.70 (s, 1 H, C_2H), and 8.77 (s, 1 H, C_8H). Anal. ($C_{10}H_{13}N_5O_4S$, MW 299.3) C, H, N, S.

(*R,S*)-9-β-D-Ribofuranosylpurine-6-sulfinamide (9a). To a stirred and ice-cooled (0 °C) solution of **8a** (0.3 g, 1 mmol) in EtOH (30 mL) was added during 10 min a solution of commercial 3-chloroperoxybenzoic acid[38] (MCPBA, 80–85%, 0.21 g, 1 mmol) in EtOH (10 mL). After 45 min of stirring at 0 °C, the solvent was evaporated. The residue was dissolved in MeOH (30 mL) and adsorbed onto silica gel (5 g). The excess solvent was evaporated and the dry residue was loaded onto a flash silica gel column (2 × 40 cm) packed in CH_2Cl_2. The column was eluted with CH_2Cl_2/MeOH (8:2, 7:3, v/v). The homogeneous fractions were combined, the solvents were evaporated, and the residue was crystallized from EtOH to yield 0.21 g (67%) of **9a**: mp 80 °C; IR ν_{max} 1050, 1330 (S=O), 3000–3600 (NH_2, OH) cm^{-1}; UV λ_{max} (pH 1) 272 nm (ε 3600); (pH 7) 273 nm (ε 4100); (pH 11) 273 nm (ε 3200); ^{1}H NMR (Me_2SO-d_6) δ 3.65 (m, 2 H, C_5'CH_2), 3.98 (m, 1 H, C_4'H), 4.21 (m, 1 H, C_3'H), 4.62 (m, 1 H, C_2'H), 5.20 (t, 1 H, C_5'OH), 5.29 (d, 1 H, C_3'OH), 5.56 (d, 1 H, C_2'OH), 6.08 (d, 1 H, $J_{1',2'}$ = 5.4 Hz, C_1'H), 6.68 (s, 2 H, $SONH_2$), 9.00 (s, 1 H, C_2H), and 9.08 (s, 1 H, C_8H). Anal. ($C_{10}H_{13}N_5O_5S$·$^1/_2H_2O$, MW 324.3) C, H, N, S.

9-β-D-Ribofuranosylpurine-6-sulfonamide (10a). To a solution of **8a** (0.3 g, 1 mmol) in EtOH (35 mL) was added during 10 min a solution of MCPBA (0.86 g, 4 mmol) in EtOH (20 mL). The mixture was stirred at room temperature for 30 min and then evaporated to dryness. The residue was purified on a flash column (2 × 40 cm) as described for **9a** to give 0.11 g (33%) of the title

(38) Commercially available from Aldrich Chemical Company, Inc., Milwaukee, WI.

compound: mp 157 °C dec; IR ν_{max} 1060, 1080, 1340 (O=S=O), 3100–3600 (NH_2, OH) cm^{-1}; UV λ_{max} (pH 1) 275 nm (ϵ 14000); (pH 7) 275 nm (ϵ 12900); (pH 11) 272 nm (ϵ 17800); ^1H NMR (Me_2SO-d_6) δ 3.65 (m, 2 H, $C_{5'}CH_2$), 3.99 (m, 1 H, $C_{4'}H$), 4.21 (m, 1 H, $C_{3'}H$), 4.61 (m, 1 H, $C_{2'}H$), 5.11 (t, 1 H, $C_{5'}OH$), 5.30 (d, 1 H, $C_{3'}OH$), 5.63 (d, 1 H, $C_{2'}OH$), 6.10 (d, 1 H, $J_{1',2'}$ = 5.4 Hz, $C_{1'}H$), 7.80 (br s, 2 H, SO_2NH_2), 9.04 (s, 1 H, C_2H), and 9.10 (s, 1 H, C_8H). Anal. ($C_{10}H_{13}N_5O_6S \cdot C_2H_5OH \cdot {}^1/_2H_2O$) C, H, N, S.

2-Amino-9-β-D-ribofuranosylpurine-6-sulfenamide (Sulfenosine, 8b). In a similar manner to that described for **8a**, amination of 6-thioguanosine[29] (**7b**, 15 g, 50.1 mmol) with chloramine solution (generated from 76 mL of commercial sodium hypochlorite and 200 mL of 1.4 M ammonium hydroxide at 0 °C) gave 11.7 g (74%) of **8b**: mp 196–198 °C dec; IR ν_{max} 3000–3600 (NH_2, OH) cm^{-1}; UV λ_{max} (pH 1) 332 nm (ϵ 3000); (pH 7 and 11) 311 nm (ϵ 3500); ^1H NMR (Me_2SO-d_6) δ 3.61 (m, 2 H, $C_{5'}CH_2$), 3.90 (m, 1 H, $C_{4'}H$), 3.91 (s, 2 H, SNH_2), 4.10 (m, 1 H, $C_{3'}H$), 4.49 (m, 1 H, $C_{2'}H$), 5.11 (t, 1 H, $C_{5'}OH$), 5.18 (d, 1 H, $C_{3'}OH$), 5.46 (d, 1 H, $C_{2'}OH$), 5.80 (d, 1 H, $J_{1',2'}$ = 6.0 Hz, $C_{1'}H$), 6.50 (s, 2 H, NH_2), and 8.18 (s, 1 H, C_8H). Anal. ($C_{10}H_{14}N_6O_4S$, MW 314.32) C, H, N, S.

(*R*,*S*)-2-Amino-9-β-D-ribofuranosylpurine-6-sulfinamide (Sulfinosine, 9b). A mixture of **8b** (1.57 g, 5 mmol), ethanol (700 mL), and water (50 mL) was vigorously stirred and cooled in an ice bath. After the temperature of the suspension had reached below 10 °C, acetone was added to the ice bath to obtain a temperature of <0 °C. With continual stirring, a solution of MCPBA (80–85%, 1.1 g, 5.0 mmol) in EtOH (50 mL) was added dropwise over a period of 15 min. The reaction flask was stoppered; the mixture was allowed to stir and warm as the ice melted, and then it was stirred at ambient temperature for a total reaction time of 19 h. The reaction mixture was filtered (Whatman GF/A glass-microfiber filter) to remove a trace of undissolved solid and then the filtrate was evaporated at a temperature of <25 °C to near dryness. The product was washed from the evaporation flask with ethyl ether (75–100 mL), and the solid was collected by filtration, suspended in ethyl ether (50 mL), refiltered, and then dried under vacuum (0.1 mm) at ambient temperature to yield 1.3 g (85%) of sulfinosine: mp >100 °C dec (with prior sintering and darkening); IR ν_{max} 1040 (S=O), 3100–3600 (NH_2, OH) cm^{-1}; UV λ_{max} (pH 1) 333 nm (ϵ 2900); (pH 7) 326 nm (ϵ 10700); (pH 11) 325 nm (ϵ 8700); ^1H NMR (Me_2SO-d_6) δ 3.60 (m, 2 H, $C_{5'}CH_2$), 3.90 (m, 1 H, $C_{4'}H$), 4.11 (m, 1 H, $C_{3'}H$), 4.49 (m, 1 H, $C_{2'}H$), 5.09 (t, 1 H, $C_{5'}OH$), 5.21 (d, 1 H, $C_{3'}OH$), 5.52 (d, 1 H, $C_{2'}OH$), 5.85 (d, 1 H, $J_{1',2'}$ = 5.5 Hz, $C_{1'}H$), 6.49 (s, 2 H, NH_2), 6.98 (s, 2 H, $SONH_2$), and 8.45 (s, 1 H, C_8H). Anal. ($C_{10}H_{14}N_6O_5S \cdot 1^1/_2H_2O$, MW 357.35) C, H, N, S.

2-Amino-9-β-D-ribofuranosylpurine-6-sulfonamide (Sulfonosine, 10b). To a stirred suspension of sulfenosine (**8b**, 3.14 g, 10 mmol) in ethanol (600 mL) and water (60 mL) at room temperature was added portionwise during 1 h a solution of MCPBA (8.6 g, 40 mmol) in ethanol (60 mL). The reaction mixture became clear after 3 h. The stirring was continued for an additional 15 h at ambient temperature. The crystalline material that separated was collected by filtration to yield 2.0 g of **10b**. The fitlrate was evaporated to dryness. The residue was dissolved in MeOH (50 mL) and adsorbed onto silica gel (10 g). The excess solvent was evaporated and the dry residue was loaded onto a flash silica gel column (4 × 50 cm) packed in CH_2Cl_2. The column was eluted with CH_2Cl_2/MeOH (8:2, v/v). The homogeneous fractions were combined and the solvents were evaporated. Crystallization of the combined solids from aqueous methanol gave 3.0 g (86.7%) of sulfonosine: mp 210 °C dec; IR ν_{max} 1320 (O=S=O), 3000–3600 (NH_2, OH) cm^{-1}; UV λ_{max} (pH 1) 332 nm (ϵ 7700); (pH 7) 328 nm (ϵ 8600); (pH 11) 320 nm (ϵ 12700); ^1H NMR (Me_2SO-d_6) δ 3.60 (m, 2 H, $C_{5'}CH_2$), 3.90 (m, 1 H, $C_{4'}H$), 4.12 (m, 1 H, $C_{3'}H$), 4.50 (m, 1 H, $C_{2'}H$), 5.04 (t, 1 H, $C_{5'}OH$), 5.19 (d, 1 H, $C_{3'}OH$), 5.50 (d, 1 H, $C_{2'}OH$), 5.85 (d, 1 H, $J_{1',2'}$ = 5.8 Hz, $C_{1'}H$), 6.99 (s, 2 H, NH_2), 7.52 (s, 2 H, SO_2NH_2), and 8.48 (s, 1 H, C_8H). Anal. ($C_{10}H_{14}N_6O_6S$, MW 346.32) C, H, N, S.

(*R*,*S*)-2-Amino-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine-6-sulfinamide (11). A mixture of 4-(*N*,*N*-dimethylamino)pyridine (10 mg), acetic anhydride (1 mL), and anhydrous *N*,*N*-dimethylformamide (2 mL) was cooled to −15 °C. Dry, powdered sulfinosine (**9b**, 0.10 g, 0.3 mmol) was added and the mixture was stirred at −15 °C for 45 min with the exclusion of moisture. The reaction was quenched by the addition of MeOH (5 mL) and the resulting solution was stirred at −10 °C for 20 min. After evaporation of the solution to dryness, the resultant residue was triturated with ethyl ether (15 mL), the product was collected by filtration and crystallized from hexanes to yield 0.10 g (75%) of **11**: mp 115 °C dec; IR ν_{max} 1050, 1095 (S=O), 1745 (C=O), 3200–3500 (NH_2) cm^{-1}; UV λ_{max} (pH 1) 335 nm (ϵ 6100); (pH 7) 328 nm (ϵ 6700); (pH 11) 321 nm (ϵ 7000); ^1H NMR (Me_2SO-d_6) δ 2.03–2.13 (3 s, 9 H, 3 $COCH_3$), 4.27–4.42 (2 m, 3 H, $C_{4'}H$ and $C_{5'}CH_2$), 5.54 (m, 1 H, $C_{3'}H$), 5.92 (t, 1 H, $C_{2'}H$), 6.15 (d, 1 H, $J_{1',2'}$ = 6.0 Hz, $C_{1'}H$), 6.51 (s, 2 H, NH_2), 7.07 (s, 2 H, $SONH_2$), and 8.44 (s, 1 H, C_8H). Anal. ($C_{16}H_{20}N_6O_8S$, MW 456.43) C, H, N, S.

2-Amino-9-(5-deoxy-β-D-ribofuranosyl)purine-6-sulfenamide (8c). In a similar manner to that described for **8a**, 2-amino-9-(5-deoxy-β-D-ribofuranosyl)purine-6(1*H*)-thione[30] (**7c**, 0.56 g, 2 mmol) was aminated with a chloramine solution (prepared from 3.2 mL of commercial sodium hypochlorite and 15 mL of 0.77 M ammonium hydroxide solution at 0 °C). After 3 h of stirring (2 h at 0–22 °C and 1 h at 23 °C), the clear reaction mixture was evaporated to dryness. The residue was dissolved in MeOH (20 mL) and adsorbed onto silica gel (5 g), and the excess solvent was evaporated to dryness. The dry residue was loaded onto a silica gel column (1.5 × 20 cm) packed in CH_2Cl_2. The column was eluted with CH_2Cl_2/MeOH (85:15, 8:2, v/v); the homogeneous fractions were pooled and evaporated to dryness. Crystallization of the residue from MeOH gave 0.52 g (87%) of **8c**: mp 160–162 °C dec; IR ν_{max} 3100–3400 (NH_2, OH) cm^{-1}; UV λ_{max} (pH 1) 328 nm (ϵ 10800); (pH 7) 306 nm (ϵ 9500); (pH 11) 308 nm (ϵ 10300); ^1H NMR (Me_2SO-d_6) δ 1.28 (d, 3 H, 5′-CH_3), 3.89 (s, 2 H, SNH_2), 3.93 (m, 2 H, $C_{2',3'}H$), 4.56 (m, 1 H, $C_{4'}H$), 5.12 (d, 1 H, $C_{3'}OH$), 5.43 (d, 1 H, $C_{2'}OH$), 5.74 (d, 1 H, $J_{1',2'}$ = 5.2 Hz, $C_{1'}H$), 6.51 (s, 2 H, NH_2), and 8.12 (s, 1 H, C_8H). Anal. ($C_{10}H_{14}N_6O_3S$, MW 298.32) C, H, N, S.

(*R*,*S*)-2-Amino-9-(5-deoxy-β-D-ribofuranosyl)purine-6-sulfinamide (9c). A solution of MCPBA (0.11 g, 0.5 mmol) in EtOH (10 mL) was added dropwise to an ice-cooled and stirred solution of **8c** (0.15 g, 0.5 mmol) in EtOH (25 mL), during 15 min. The reaction mixture was stirred at 0 °C for 15 h and then evaporated to dryness. The residue was triturated with a mixture of EtOH (2 mL) and ethyl ether (30 mL). The precipitated crystalline product was collected by filtration and dried (over P_2O_5 at 0.1 mm) at 80 °C for 5 h to give 70 mg (45%) of **9c**: mp >100 °C dec; IR ν_{max} 1050 (S=O), 3100–3600 (NH_2, OH) cm^{-1}; UV λ_{max} (pH 1) 330 nm (ϵ 3600); (pH 7) 324 nm (ϵ 4400); (pH 11) 321 nm (ϵ 4300); ^1H NMR (Me_2SO-d_6) δ 1.30 (d, 3 H, 5′-CH_3), 3.95 (m, 2 H, $C_{2',3'}H$), 4.63 (m, 1 H, $C_{4'}H$), 5.20 (d, 1 H, $C_{3'}OH$), 5.53 (d, 1 H, $C_{2'}OH$), 5.80 (d, 1 H, $J_{1',2'}$ = 5.2 Hz, $C_{1'}H$), 6.51 (s, 2 H, NH_2), 6.98 (s, 2 H, $SONH_2$), and 8.40 (s, 1 H, C_8H). Anal. ($C_{10}H_{14}N_6O_4S$, MW 314.32) C, H, N, S.

2-Amino-9-(5-deoxy-β-D-ribofuranosyl)purine-6-sulfonamide (10c). Compound **8c** (0.30 g, 1 mmol) in EtOH (35 mL) was oxidized with MCPBA (0.86 g, 4 mmol) as described for **10b**. The reaction mixture was evaporated to dryness and the residue was triturated with a mixture of EtOH (2 mL) and ethyl ether (20 mL). After storing in the refrigerator (0–5 °C) overnight, the deposited crystalline product was collected by filtration, washed with ethyl ether (2 × 5 mL), and dried at 60 °C over P_2O_5 under vacuum for several hours to yield 0.17 g (52%) of **10c**: mp >90 °C dec; IR ν_{max} 1160, 1350 (O=S=O), 3100–3600 (NH_2, OH) cm^{-1}; UV λ_{max} (pH 1) 331 nm (ϵ 5400); (pH 7) 326 nm (ϵ 5500); (pH 11) 318 nm (ϵ 6500); ^1H NMR (Me_2SO-d_6) δ 1.30 (d, 3 H, 5′-CH_3), 3.95 (m, 2 H, $C_{2',3'}H$), 4.64 (m, 1 H, $C_{4'}H$), 5.23 (d, 1 H, $C_{3'}OH$), 5.55 (d, 1 H, $C_{2'}OH$), 5.80 (d, 1 H, $J_{1',2'}$ = 5.1 Hz, $C_{1'}H$), 6.99 (s, 2 H, NH_2), 7.54 (s, 2 H, SO_2NH_2), and 8.44 (s, 1 H, C_8H). Anal. ($C_{10}H_{14}N_6O_5S$, MW 330.32) C, H, N, S.

2-Amino-9*H*-purine-6-sulfenamide (13). Sodium hypochlorite (0.77 M, 5.25%, 34 mL, a freshly opened bottle of commercial bleach) was cooled to <0 °C in an ice bath. Ammonium hydroxide (0.77 M, 20 mL) was similarly cooled in an ice bath and then added rapidly to the bleach solution, and the flask was immediately stoppered. The mixture was stirred in the cold (−5 to 0 °C) for about 15 min and then a solution of 6-thioguanine[29] (**12**, 3.7 g, 22 mmol) in 2 N KOH (15 mL) was added quickly and rinsed into the chloramine mixture with a small amount of water.

The flask was immediately stoppered and stirred at 0 °C for 30 min. The reaction mixture was initially a clear, light yellow solution, but after 15 min a solid began separating. After allowing the reaction mixture to stand at 0 °C for an additional 1 h, the precipitated product was collected by filtration and washed with a small amount of cold water, followed by ethanol to yield 1.45 g (34.3%) of **13**. A small amount was crystallized from water for analytical purposes: mp >250 °C; IR ν_{max} 3200–3400 (NH, NH_2) cm^{-1}; UV λ_{max} (pH 1) 325 nm (ϵ 6400); (pH 7) 310 nm (ϵ 5900); (pH 11) 312 nm (ϵ 5900); ^1H NMR (Me_2SO-d_6) δ 3.92 (s, 2 H, SNH_2), 6.25 (br s, 2 H, NH_2), 7.90 (s, 1 H, C_8H), and 11.72 (br s, 1 H, N_8H). Anal. ($C_5H_6N_6S \cdot {}^1/_2H_2O$, MW 191.2) C, H, N, S.

(*R,S*)-2-Amino-9*H*-purine-6-sulfinamide (**14**). To a stirred and ice-cooled (0 °C) suspension of **13** (1.91 g, 10 mmol) in ethanol (500 mL) was added commercial MCPBA (80–85%, 2.1 g, 10 mmol) portionwise during 1 h. The stirring was continued for an additional 30 min. The reaction mixture was filtered and the filtrate was concentrated to about half the volume. Ethyl ether (250 mL) was added and the solution was allowed to stand in a refrigerator overnight. The precipitated solid was collected by filtration, washed with ethyl ether (2 × 25 mL), and air dried. Crystallization from aqueous ethanol gave 1.15 g (58%) of **14**: mp >250 °C; IR ν_{max} 1050, 1100 (S=O), 3100–3400 (NH, NH_2) cm^{-1}; UV λ_{max} (pH 1) 240 nm (sh) (ϵ 5100), 332 (4600); (pH 7) 326 nm (ϵ 4500); (pH 11) 283 nm (ϵ 2800), 326 (4200); ^1H NMR (Me_2SO-d_6) δ 6.57 (br s, 2 H, NH_2), 6.59 (br s, 2 H, $SONH_2$), 8.12 (s, 1 H, C_8H), and 12.50 (br s, 1 H, N_9H). Anal. ($C_5H_6N_6OS$, MW 198.21) C, H, N, S.

2-Amino-9*H*-purine-6-sulfonamide (**15**). To a suspension of **13** (0.53 g, 2.8 mmol) in ethanol (250 mL) was added MCPBA (80–85%, 2.35 g, 11 mmol) and the mixture was stirred for 1.5 h at room temperature. After filtration, the filtrate was evaporated to dryness. The residue was triturated with ethyl ether (2 × 25 mL) and then the solid was purified on a silica gel column (2.5 × 20 cm) using ethyl acetate/upper phase of EtOAc–H_2O–1-PrOH, 4:2:1 (90:10, v/v) as the eluent. The homogeneous fractions were pooled and concentrated to ~5 mL, and the product was precipitated by adding an ethanol/ethyl ether mixture (1:1) to give 0.16 g (28%) of pure **15**: mp >250 °C dec; IR ν_{max} 1120, 1150 (S=O), 1320 (O=S=O), 3100–3400 (NH, NH_2) cm^{-1}; UV λ_{max} (pH 1) 338 nm (ϵ 4200); (pH 7) 329 nm (ϵ 4000); (pH 11) 285 nm (ϵ 2800), 325 (4100); ^1H NMR (Me_2SO-d_6) δ 6.67 (br s, 2 H, NH_2), 7.61 (br s, 2 H, SO_2NH_2), 8.29 (s, 1 H, C_8H), and 12.75 (br s, 1 H, N_9H). Anal. ($C_5H_6N_6O_2S$, MW 214.21) C, H, N, S.

Resolution of *R* and *S* Diastereomers from a Racemic Mixture of Sulfinosine (9b). The resolution of the *R* and *S* diastereomers of **9b** was performed on a prepacked ODS (C_{18}, semipreparative) column (10 × 30 mm i.d., particle size S-5) using a Rabbit HP system of Rainin Instrument Co., Inc., Woburn, MA. The racemic mixture **9b** (5 mg) was dissolved in Milli-Q-purified water (0.2 mL), filtered, and then injected onto the equilibrated column. The column was eluted with a mixture of H_2O/CH_3CN (96:4, v/v). A flow rate of 2.5 mL/min was maintained throughout the separation at room temperature. An ISCO-V^4 variable-wavelength UV detector (ISCO Inc., Lincoln, NE) set at 274 nm was used. The retention time was 24 min. The *S* diastereomer was eluted first. The HPLC-pure fractions of *R* and *S* diastereomers were collected, freezed, and lyophilized. From 10 injections (50 mg), a total of 15 mg of *S* and 10 mg of *R* diastereomers of purity >99.5% was obtained. The *R* diastereomer was crystallized from MeOH for X-ray diffraction studies, whereas the *S* isomer did not crystallize in our hands. The spectroscopic properties (IR, UV, and ^1H NMR) of the racemates are essentially similar to that of **9b**.

R diastereomer of **9b**: mp 160 °C dec. Anal. ($C_{10}H_{14}N_6O_5S \cdot 2^1/_2H_2O$) C, H, N, S.

S diastereomer of **9b**: mp 130 °C dec. Anal. ($C_{10}H_{14}N_6O_5S \cdot 1^1/_2H_2O$) C, H, N, S.

X-ray Diffraction Analysis. Very thin, colorless, transparent, crystalline plates of (*R*)-**9b** were obtained from MeOH. Prismatic crystals of **10b** were obtained from water/ethanol (8:2) solution. Both compounds crystallize in the monoclinic space group $P2_1$. Cell parameters for (*R*)-**9b** are a = 7.044 (2) Å, b = 14.247 (3) Å, c = 29.82 (2) Å, and β = 92.59 (4)°; for **10b**, the parameters are a = 6.2899 (12) Å, b = 13.276 (3) Å, c = 8.4161 (14) Å, and β = 105.686 (16)°. There are four crystallographically independent molecules (Z = 8) in the former while there is only one in the latter (Z = 2). The crystal quality of (*R*)-**9b** was very poor. Although positions of all non-hydrogen atoms were determined with the program SHELXS86,[39] refinement of all such parameters resulted in unreasonable bond lengths. Therefore, the structure was constrained in the following ways: (1) each 2-aminopurine-6-sulfinamide moiety was generated by a best molecular fit of the same moiety from the previously refined structure of (*S*)-2-amino-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)purine-6-sulfinamide,[40] the 2′-deoxy-α-ribonucleoside analogue of **9b** but containing a sulfinamido group having the *S* configuration. This fragment was refined as a rigid group; (2) the furan ring C—C bonds were constrained to be 1.53 Å in length; (3) the C4′—C5′ bonds were constrained to 1.51 Å; (4) all hydroxyl C—O and the C1′—O1′ bonds were constrained to 1.41 Å; (5) the C4′—O1′ bonds were constrained to 1.44 Å; (6) all S=O bonds were constrained to be equal as were all S—N bonds; (7) the C—H hydrogens were placed in ideal positions; and (8) the initial positions of the hydroxyl hydrogens were assigned on the basis of possible hydrogen-bonding interactions as determined by interatomic distances of the oxygens to possible acceptor atoms. The hydroxyl groups were allowed to rotate about the C—O bond maintaining the idealized geometry. Under these conditions, the structure of (*R*)-**9b** was refined to R = 0.17 for 1384 reflections ($F \geq 4\sigma_F$) out of 3507 measured reflections. The final R for the refinement of **10b** was 0.039 for 1713 reflections having $F \geq 4\sigma_F$ (2034 total unique reflections). Refinement was accomplished with the program SHELX76.[41] ORTEPII[42] was used to produce Figures 1 and 2.

Therapeutic Determinations in Vivo. In vivo assessments of antileukemic activity and host toxicity were performed as described previously.[43] Briefly, BDF_1 female mice (~18 g) purchased from the Charles River Co. were inoculated ip on day 0 with 1 × 10^6 cells of murine leukemia L1210 and treated with compound *once* by ip bolus injection 24 h later. Drugs were solubilized immediately before use and delivered in uniform volumes of 0.01 mL/g mouse wt. This scheme allowed the delivery of all drugs at 10 times in mg/kg their solubility in mg/mL. Control mice were given equal volumes of a 0.9% solution of NaCl.

The end points by which responses to treatment were gauged were the incidence of drug- or leukemia-related deaths and the postinoculation life span of mice that died. Temporal patterns of death and observations at necropsy examination were the major criteria for assigning deaths to leukemia or drug toxicity. Inoculum response data, defining the relationship between life span and inoculum size, were used to estimate the body burdens of leukemia cells that survived treatment and, hence, the percentage of such cells that were killed.

Registry No. 1, 82499-01-2; **2**, 13035-61-5; **3**, 123002-33-5; **4**, 1513-63-9; **5**, 123002-34-6; **6**, 58-61-7; **7a**, 574-25-4; **7b**, 85-31-4; **7c**, 4680-63-1; **8a**, 123002-35-7; **8b**, 123002-38-0; **8c**, 123002-41-5; (*R*)-**9a**, 123002-36-8; (*S*)-**9a**, 123002-48-2; (*R*)-**9b**, 123002-46-0; (*S*)-**9b**, 123002-47-1; (*R*)-**9c**, 123002-42-6; (*S*)-**9c**, 123002-50-6; **10a**, 123002-37-9; **10b**, 123002-39-1; **10c**, 123026-03-9; (*R*)-**11**, 123002-40-4; (*S*)-**11**, 123002-49-3; **12**, 154-42-7; **13**, 123002-43-7; **14**, 123002-44-8; **15**, 123002-45-9.

(39) Sheldrick, G. M. SHELXS86. Program for crystal structure determination; University of Göttingen: Göttingen, Federal Republic of Germany, 1986.
(40) Revankar, G. R.; Hanna, N. B.; Ramasamy, K.; Larson, S. B.; Smee, D. F.; Finch, R. A.; Avery, T. L.; Robins, R. K. *J. Chem. Soc., Perkin Trans. 1* In press.
(41) Sheldrick, G. M. SHELX76. Program for crystal structure determination; University of Cambridge; Cambridge, England, 1976.
(42) Johnson, C. K. ORTEPII. A Fortran Thermal-Ellipsoid Plot Program for Crystal Structure Illustrations; Oak Ridge National Laboratory (ORNL-5138): Oak Ridge, TN, March 1976; Third Revision.
(43) Kuehl, M.; Brixner, D. I.; Broom, A. D.; Avery, T. L.; Blakley, R. L. *Cancer Res.* **1988**, *48*, 1481.