purified by silica gel chromatography with EtOAc as the eluant. The appropriate fractions were combined and evaporated to give a glassy residue (36.5 g, 83.4%): ^{1}H NMR ($CDCl_3$) δ 7.74 (s, 1, H-6), 6.28 (d, 1, $J_{1',2'}$ = 4.5 Hz, H-1'), 5.49 (dd, 1, $J_{2',3'}$ = 1.5 H_z, H-2'), 5.08 (m, 1, H-3'), 4.34–4.12 (m, 3, H-4', H-5', H-5''), 2.14, 2.03, 1.98 (3 s, 9, $COCH_3$), 0.24 (s, 9, $Si(CH_3)_3$).

1-β-D-Arabinofuranosyl-5-ethynylcytosine (4). Anhydrous K_2CO_3 (500 mg) was added to a solution of **3** (3.56 g) in MeOH (400 mL) and the reaction mixture was stirred at room temperature for 5 h. The solution was concentrated by evaporation to approximately 100 mL and placed on a column (4 × 120 cm) of Amberlite C6-50 (H^+) irrigated in H_2O–MeOH (1:1) and eluted with H_2O–MeOH (1:1, v/v). After evaporation of the solvents and crystallization of the residue from methanol, 14.54 g (64.6%) of **4** was obtained, mp, 265–270 °C dec. The filtrate after separation of the crystalline **4** was evaporated and the residue chromatographed on silica gel, eluting with EtOAc–MeOH (9:1), to give 0.7 g of a byproduct, 5-acetyl-1-β-D-arabinofuranosylcytosine: mp 254 °C dec; ^{1}H NMR (DMSO-d_6) δ 8.66 (s, 1, H-6), 8.3, 7.88 (2 s, 2, NH_2), 6.08 (d, 1, $J_{1',2'}$ = 4.3 Hz, H-1'), 5.54, 5.42 (2 d, 2, J = 6 and 4.5 Hz, CHO*H*, exch), 5.16 (t, 1, J = 5.1 Hz, CH_2O*H*, exch), 2.32 (s, 3, $COCH_3$). Anal. ($C_{11}H_{15}N_3O_6$) C, H, N.

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Registry No. 1, 58227-71-7; 2, 110098-05-0; 3, 110098-06-1; 4, 74954-66-8; β-D-arabinofuranosylcytosine hydrochloride, 69-74-9; β-D-arabinofuranosylcytosine tetraacetate, 6742-08-1; (trimethylsilyl)acetylene, 1066-54-2; 5-acetyl-1-(β-D-arabinofuranosyl)cytosine, 110098-07-2; kinase, 9031-44-1; dCyd deaminase, 37259-56-6.

1,2-Bis(sulfonyl)hydrazines. 3. Effects of Structural Modification on Antineoplastic Activity

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A series of 1,2-bis(sulfonyl)hydrazines was synthesized and evaluated for antineoplastic activity against the L1210 leukemia and the B16 melanoma. The most active agent to emerge from this study, 1,2-bis(methylsulfonyl)-1-methylhydrazine, produced a maximum % T/C for mice bearing the L1210 leukemia or the B16 melanoma of 340% and 278%, respectively. Two *N*-chloroethyl analogues, conceived as bifunctional alkylating agents, were also synthesized and evaluated for antineoplastic activity against the L1210 leukemia and the B16 melanoma. Although such a modification resulted in retention of antineoplastic activity against both tumor cell lines, it did not result in enhanced antineoplastic activity.

1,2-Bis(sulfonyl)-1-methylhydrazines have activity against a variety of experimental tumor systems.[1-3] Base-catalyzed decomposition of the parent molecule to generate the putative methylating species **1** has been hypothesized to be responsible for the observed antineoplastic activity of this class of agents.[1] In an earlier report,[3] we

$$\underset{\mathbf{1}}{RSO_2N{=}NCH_3}$$

demonstrated a correspondence between the ability of some 1,2-bis(sulfonyl)-1-methylhydrazines to alkylate a model nucleophile, 4-(4-nitrobenzyl)pyridine, and antitumor activity against the L1210 leukemia. However, while the capacity of these agents to generate a reactive species appears to be a necessary condition for antineoplastic activity against the L1210 leukemia, the inherent capability to generate a reactive species does not guarantee antitumor efficacy. Thus, 1,2-bis[(4-chlorophenyl)sulfonyl]-1-methylhydrazine, which was found to be capable of alkylating 4-(4-nitrobenzyl)pyridine with great facility under the experimental conditions employed, was found to be inactive against the L1210 leukemia. This result suggests that parameters other than alkylating ability are important for the anticancer activity displayed by these agents in this tumor system. To gain a further understanding of the relationship between structure and the antineoplastic activity of agents of this class, we have synthesized a relatively large number of 1,2-bis(sulfonyl)-1-methylhydrazines

Scheme I

$$R^1SO_2NHN(CH_2CH_2Cl)SO_2R^2 \xrightarrow{B:} \underset{\mathbf{2}}{R^1SO_2N{=}NCH_2CH_2Cl} \xrightarrow{Nu^1H} R^1SO_2H + N_2 + Nu^1CH_2CH_2Cl \xrightarrow{Nu^2H} Nu^1CH_2CH_2Nu^2$$

and have measured their antineoplastic activity against the L1210 leukemia and/or the B16 melanoma in mice.

In tests against the transplanted L1210 leukemia in mice, 5-[3,3-bis(2-chloroethyl)-1-triazenyl]-1*H*-imidazole-4-carboxamide (BIC), the chloroethyl analogue of the clinically useful anticancer agent, 5-(3,3-dimethyl-1-triazenyl)-1*H*-imidazole-4-carboxamide (DTIC),[4,5] has been reported to be considerably superior to DTIC and to other imidazole and benzenoid triazenes lacking a chloroethyl group.[6,7] The results of other studies[8] indicate that BIC, which undergoes metabolic dealkylation to the (chloroethyl)triazene MCIC, owes its high activity to the formation of a chloroethylating species. Similarly, the most active of the *N*-nitrosoureas against experimental tumors are the *N*-(2-chloroethyl)-*N*-nitrosoureas.[9,10] For example, *N*-(2-chloroethyl)-*N*-nitrosourea is considerably more ac-

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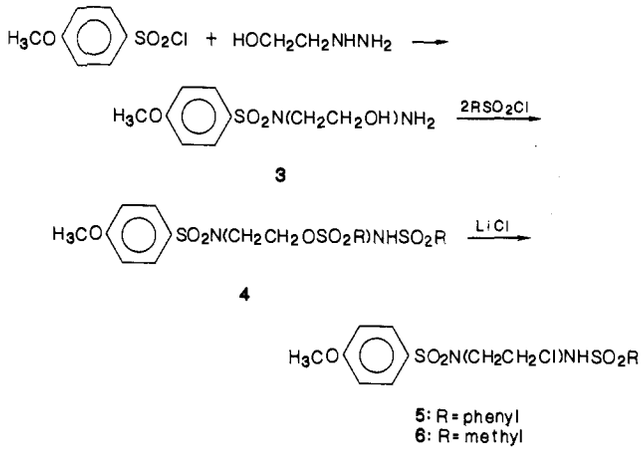
Scheme II



tive than *N*-methyl-*N*-nitrosourea as an anticancer agent against the L1210 leukemia.[11] Decomposition studies[12,13] of the (chloroethyl)nitrosoureas showed that these compounds were capable of generating species (e.g., 2-chloroethanediazohydroxide) that can attach a chloroethyl group to biological macromolecules by reaction at nucleophilic centers. Studies, such as those of Ludlum et al.,[14] Kohn,[15] and Lown et al.,[16] indicate that (chloroethyl)nitrosoureas react with DNA and that the attached chloroethyl group can then react with another nucleophilic center to crosslink DNA. These findings provide a rationale for the development of other chloroethylating agents. Thus, replacement of the *N*-methyl group in the 1,2-bis(sulfonyl)-1-methylhydrazines by chloroethyl could result in compounds capable of generating the putative chloroethylating species (**2**) upon base-catalyzed elimination (Scheme I). Two prototypical *N*-chloroethyl analogues were synthesized, and their activities were compared with those of the corresponding *N*-methyl analogues.

Chemistry

1,2-Bis(sulfonyl)-1-methylhydrazines (Table I) were synthesized by using or adapting methodology described earlier.[1-3] Compounds in which R^1 and R^2 are identical were prepared by reacting the appropriate sulfonyl chloride with methylhydrazine in a 2:1 molar ratio in pyridine. The remaining compounds were synthesized by reacting the appropriate 1-methyl-1-sulfonylhydrazide with the appropriate sulfonyl chloride in a 1:1 molar ratio in pyridine. The 1-methyl-1-sulfonylhydrazides were prepared by using or adapting procedures previously described.[2,17-19] The 1,2-bis(sulfonyl)-1-(2-chloroethyl)hydrazines were prepared as shown in Scheme II. The reaction of (2-hydroxyethyl)hydrazine with 4-methoxybenzenesulfonyl chloride in tetrahydrofuran gave 1-(2-hydroxyethyl)-1-[(4-methoxyphenyl)sulfonyl]hydrazine (**3**). Compound **3**, upon treatment with an excess of the appropriate sulfonyl chloride in pyridine, gave **4**, which on reaction with lithium chloride in acetone, gave the desired 1,2-bis(sulfonyl)-1-(2-chloroethyl)hydrazine.

Biological Results and Discussion

The tumor-inhibitory properties of compounds **5–71** were determined by measuring their effects on the survival time of mice bearing either the L1210 leukemia or the B16 melanoma; the results are summarized in Tables II and III. While all of the 1,2-bis(arylsulfonyl)-1-methylhydrazines tested displayed significant activity against the B16 melanoma and most were active against the L1210 leukemia, a few compounds, namely **9**, **25**, **33**, **36**, **41**, **42**, and **50**, were inactive against the L1210 leukemia. Replacement of either one or both of the arenesulfonyl moieties by benzylsulfonyl produced compounds with activity against the B16 melanoma and, with the exception of compound **63**, were also active against the L1210 leukemia. Some of the most active compounds against the B16 melanoma to emerge from this group were those in which the benzylsulfonyl moiety was attached to N-1. While the few styryl analogues (compounds **40**, **53**, and **66**) tested against the B16 melanoma did not appear to display anticancer activity significantly different from that of the benzenesulfonyl analogues, replacement of the benzenesulfonyl moiety attached to N-2 in compounds **14**, **24**, **33**, **45**, and **58** by methanesulfonyl resulted in compounds with slightly enhanced antineoplastic activity against the B16 melanoma. Thus, compounds **22**, **31**, **38**, **51**, and **64** produced % T/C values in mice bearing the B16 melanoma of 207, 204, 194, 225, and 203%, respectively. Of these, the most active member tested against the L1210 leukemia was compound **31** which produced a % T/C value for tumor-bearing mice of 274%. A few ethanesulfonyl derivatives were also tested against the B16 melanoma and were, in general, less active than the corresponding methanesulfonyl analogues. Furthermore, a methanesulfonyl analogue tested against B16 melanoma cells in culture (**22**; $ID_{50} = 1.6 \times 10^{-4}$ M) was approximately three times more toxic to these cells than the corresponding ethanesulfonyl analogue (**23**; $ID_{50} = 5.1 \times 10^{-4}$ M). The slightly enhanced antineoplastic activity observed in the case of 1-(arylsulfonyl)-1-methyl-2-(methylsulfonyl)-hydrazines led to the synthesis and evaluation of compounds in which the methanesulfonyl group is attached to N-1. Of the 2-(arylsulfonyl)-1-methyl-1-(methylsulfonyl)hydrazines tested, the most active members examined against the B16 melanoma and the L1210 leukemia were compounds **67** and **68**, respectively. The most active 1,2-bis(sulfonyl)-1-methylhydrazine examined thus far has been compound **71**, which produced % T/C values against the L1210 leukemia and the B16 melanoma of 340% and 278%, respectively.

It is difficult to derive meaningful structure–activity correlations from the data obtained, and more extensive structural modifications will be attempted in the future to probe this question. However, several generalizations are possible from the results obtained.

$Ar^1SO_2N(CH_3)NHSO_2Ar^2$ (I) $\quad ArSO_2N(CH_3)NHSO_2CH_3$ (II)

$CH_3SO_2N(CH_3)NHSO_2Ar$ (III)

The order of activity obtained, i.e., **71** > III > II > I suggests the importance of the following factors: (a) an optimal rate of breakdown of the parent molecule to generate the putative alkylating species 1;[3] (b) optimum

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Table I. Physical Constants for 1,2-Bis(sulfonyl)-1-methylhydrazines

$R^1SO_2N(CH_3)NHSO_2R^2$

compd	R^1	R^2	method	% yield	recryst solvent	mp, °C	formula	anal.
7[a]	phenyl	phenyl	I	36	gla. AcOH	172–173	$C_{13}H_{14}N_2O_4S_2$	C, H, N, S
8	phenyl	4-tolyl	II	43	EtOH	153–155	$C_{14}H_{16}N_2O_4S_2$	C, H, N
9	phenyl	4-chlorophenyl	II	13	$CHCl_3$–CCl_4	144–145	$C_{13}H_{13}ClN_2O_4S_2$	C, H, N
10	phenyl	4-bromophenyl	II	46	$CHCl_3$–CCl_4	145–147	$C_{13}H_{13}BrN_2O_4S_2$	C, H, N
11	phenyl	4-methoxyphenyl	II	39	$CHCl_3$–CCl_4	141–142	$C_{14}H_{16}N_2O_5S_2$	C, H, N
12	phenyl	2-naphthyl	II	37	EtOH	175–177	$C_{17}H_{16}N_2O_4S_2$	C, H, N
13	phenyl	benzyl	II	55	$CHCl_3$–CCl_4	135–137	$C_{14}H_{16}N_2O_4S_2$	C, H, N
14[a]	4-tolyl	phenyl	II	41	$CHCl_3$–CCl_4	171–173	$C_{14}H_{16}N_2O_4S_2$	C, H, N
15[a]	4-tolyl	4-tolyl	I	28	gla. AcOH	152–154	$C_{15}H_{18}N_2O_4S_2$	C, H, N
16[a]	4-tolyl	4-methoxyphenyl	II	35	$CHCl_3$–CCl_4	159–160	$C_{15}H_{18}N_2O_5S_2$	C, H, N
17[a]	4-tolyl	4-chlorophenyl	II	45	$CHCl_3$–CCl_4	176–178	$C_{14}H_{15}ClN_2O_4S_2$	C, H, N
18	4-tolyl	4-bromophenyl	II	62	EtOAc–pet. ether	182–184	$C_{14}H_{15}BrN_2O_4S_2$	C, H, N
19	4-tolyl	2-naphthyl	II	44	gla. AcOH	192–194	$C_{18}H_{18}N_2O_4S_2$	C, H, N
20	4-tolyl	4-nitrophenyl	II	48	$CHCl_3$–CCl_4	209–211	$C_{14}H_{15}N_3O_6S_2$	C, H, N
21[a]	4-tolyl	benzyl	V	62	$CHCl_3$–CCl_4	185–187	$C_{15}H_{18}N_2O_4S_2$	C, H, N
22[a]	4-tolyl	methyl	IV	50	$CHCl_3$–CCl_4	144–145	$C_9H_{14}N_2O_4S_2$	C, H, N
23[a]	4-tolyl	ethyl	IV	21	$CHCl_3$–CCl_4	135–136	$C_{10}H_{16}N_2O_4S_2$	C, H, N
24	4-methoxyphenyl	phenyl	II	77	$CHCl_3$–CCl_4	143–144	$C_{14}H_{16}N_2O_5S_2$	C, H, N
25[a]	4-methoxyphenyl	4-tolyl	II	16	$CHCl_3$–CCl_4	192–193	$C_{15}H_{18}N_2O_5S_2$	C, H, N
26[a]	4-methoxyphenyl	4-methoxyphenyl	I	37	gla. AcOH	195–197	$C_{15}H_{18}N_2O_6S_2$	C, H, N
27	4-methoxyphenyl	4-bromophenyl	V	43	$CHCl_3$–CCl_4	149–152	$C_{14}H_{15}BrN_2O_5S_2$	C, H, N
28	4-methoxyphenyl	2-nitrophenyl	V	16	$CHCl_3$–CCl_4	171–172	$C_{14}H_{15}N_3O_7S_2$	C, H, N
29	4-methoxyphenyl	2-naphthyl	V	57	$CHCl_3$–CCl_4	187–189	$C_{18}H_{18}N_2O_5S_2$	C, H, N
30	4-methoxyphenyl	benzyl	V	37	$CHCl_3$–CCl_4	166–167	$C_{15}H_{18}N_2O_5S_2$	C, H, N
31	4-methoxyphenyl	methyl	IV	29	$CHCl_3$–CCl_4	126–128	$C_9H_{14}N_2O_5S_2$	C, H, N
32	4-methoxyphenyl	ethyl	IV	21	$CHCl_3$–CCl_4	110–112	$C_{10}H_{16}N_2O_5S_2$	C, H, N
33	4-chlorophenyl	phenyl	II	45	EtOAc–pet. ether	192–194	$C_{13}H_{13}ClN_2O_4S_2$	C, H, N
34[a]	4-chlorophenyl	4-tolyl	II	70	$CHCl_3$–CCl_4	174–176	$C_{14}H_{15}ClN_2O_4S_2$	C, H, N
35	4-chlorophenyl	4-methoxyphenyl	II	36	EtOAc–pet. ether	193–195	$C_{14}H_{15}ClN_2O_5S_2$	C, H, N
36[a]	4-chlorophenyl	4-chlorophenyl	I	13	gla. AcOH	202–204	$C_{13}H_{12}Cl_2N_2O_4S_2$	C, H, N
37	4-chlorophenyl	2-naphthyl	II	59	gla. AcOH	205–207	$C_{17}H_{15}ClN_2O_4S_2$	C, H, N
38	4-chlorophenyl	methyl	IV	32	$CHCl_3$–CCl_4	176–178	$C_8H_{11}ClN_2O_4S_2$	C, H, N
39	4-chlorophenyl	ethyl	IV	41	$CHCl_3$–CCl_4	144–146	$C_9H_{13}ClN_2O_4S_2$	C, H, N
40	4-chlorophenyl	styryl	V	29	$CHCl_3$–CCl_4	171–172	$C_{15}H_{15}ClN_2O_4S_2$	C, H, N
41	2-naphthyl	phenyl	V	26	$CHCl_3$–CCl_4	187–188	$C_{17}H_{16}N_2O_4S_2$	C, H, N
42	2-naphthyl	4-tolyl	II	43	gla. AcOH	179–180	$C_{18}H_{18}N_2O_4S_2$	C, H, N
43[a]	2-naphthyl	2-naphthyl	I	37	gla. AcOH	194–195	$C_{21}H_{18}N_2O_4S_2$	C, H, N
44	2-naphthyl	methyl	V	52	$CHCl_3$–CCl_4	187–188	$C_{12}H_{14}N_2O_4S_2$	C, H, N
45	4-bromophenyl	phenyl	II	56	$CHCl_3$–EtOAc	200–202	$C_{13}H_{13}BrN_2O_4S_2$	C, H, N
46	4-bromophenyl	4-tolyl	II	45	EtOAc	185–187	$C_{14}H_{15}BrN_2O_4S_2$	C, H, N
47	4-bromophenyl	4-methoxyphenyl	II	36	$CHCl_3$–EtOAc	203–205	$C_{14}H_{15}BrN_2O_5S_2$	C, H, N
48	4-bromophenyl	4-chlorophenyl	II	48	EtOAc	209–210	$C_{13}H_{12}BrClN_2O_4S_2$	C, H, N
49	4-bromophenyl	4-bromophenyl	III	29	EtOAc	215–216	$C_{13}H_{12}Br_2N_2O_4S_2$	C, H, N
50	4-bromophenyl	2-naphthyl	II	47	EtOAc	205–209	$C_{17}H_{15}BrN_2O_4S_2$	C, H, N
51	4-bromophenyl	methyl	V	42	$CHCl_3$–CCl_4	183–184	$C_8H_{11}BrN_2O_4S_2$	C, H, N
52	4-bromophenyl	ethyl	V	6	$CHCl_3$–CCl_4	152–153	$C_9H_{13}BrN_2O_4S_2$	C, H, N
53	4-bromophenyl	styryl	II	22	$CHCl_3$	163–164	$C_{15}H_{15}BrN_2O_4S_2$	C, H, N
54	4-acetamidophenyl	4-bromophenyl	II	29	EtOAc–pet. ether	134–136	$C_{15}H_{16}BrN_3O_5S_2$	C, H, N
55	4-iodophenyl	4-tolyl	V	47	$CHCl_3$–CCl_4	196–197	$C_{14}H_{15}IN_2O_4S_2$	C, H, N
56	4-iodophenyl	methyl	V	26	$CHCl_3$–CCl_4	180–182	$C_8H_{11}IN_2O_4S_2$	C, H, N
57	4-iodophenyl	ethyl	V	17	$CHCl_3$–CCl_4	166–167	$C_9H_{13}IN_2O_4S_2$	C, H, N
58	benzyl	phenyl	II	29	$CHCl_3$–EtOAc	185–187	$C_{14}H_{16}N_2O_4S_2$	C, H, N
59	benzyl	4-tolyl	II	42	EtOAc–pet. ether	158–159	$C_{15}H_{18}N_2O_4S_2$	C, H, N
60	benzyl	4-methoxyphenyl	II	54	$CHCl_3$–CCl_4	165–166	$C_{15}H_{18}N_2O_5S_2$	C, H, N
61	benzyl	4-chlorophenyl	II	24	$CHCl_3$–CCl_4	195–196	$C_{14}H_{15}ClN_2O_4S_2$	C, H, N
62	benzyl	4-bromophenyl	V	33	$CHCl_3$–CCl_4	201–203	$C_{14}H_{15}BrN_2O_4S_2$	C, H, N
63	benzyl	2-naphthyl	II	48	$CHCl_3$–CCl_4	174–177	$C_{18}H_{18}N_2O_4S_2$	C, H, N
64	benzyl	methyl	IV	29	$CHCl_3$–CCl_4	166–168	$C_9H_{14}N_2O_4S_2$	C, H, N
65	benzyl	benzyl	III	36	EtOAc	208–210	$C_{15}H_{18}N_2O_4S_2$	C, H, N
66	styryl	styryl	V	51	$CHCl_3$–CCl_4	181–182	$C_{17}H_{18}N_2O_4S_2$	C, H, N
67	methyl	4-tolyl	IV	41	$CHCl_3$–pet. ether	130–132	$C_9H_{14}N_2O_4S_2$	C, H, N
68	methyl	4-methoxyphenyl	V	26	$CHCl_3$–CCl_4	152–155	$C_9H_{14}N_2O_5S_2$	C, H, N
69	methyl	4-chlorophenyl	V	28	$CHCl_3$–CCl_4	171–172	$C_8H_{11}ClN_2O_4S_2$	C, H, N
70	methyl	4-bromophenyl	V	29	$CHCl_3$–CCl_4	180–182	$C_8H_{11}BrN_2O_4S_2$	C, H, N
71	methyl	methyl	IV	34	Ethanol	177–178	$C_3H_{10}N_2O_4S_2$	C, H, N

[a] Reported earlier.[1-3]

reactivity and selectivity of the alkylating species generated; and (c) optimum distribution properties.

Compound 71 should be more water soluble than the arylsulfonyl analogues, and this could result in more favorable pharmacodynamic properties. Furthermore, the alkylating species generated by compound 71 (1; R = CH_3) should react more slowly and, hence, more selectively than those generated by I and III (1; R = Ar). However, the slight lowering of antineoplastic activity observed when the methanesulfonyl moiety in II was replaced by ethanesulfonyl suggests that the alkylating species generated should have an optimal reactivity rather than a slow one.

Table II. Effects of 1,2-Bis(sulfonyl)hydrazines on the Survival Time of Mice Bearing the L1210 Leukemia

compd	optimum effective daily dose, mg/kg[a]	av Δ wt, %[b]	max % T/C[c]
5	10	+4.8	136
6	10	−10.9	214[e]
7[d]	50	−4.8	147
8	50	+10.7	153
9	50	+14.6	122
11	50	+4.5	136
14[d]	50	+2.0	162
15[d]	50	+3.7	147
16[d]	100	+7.8	162
17[d]	50	+3.7	188
18	50	+5.6	169
19	75	+9.3	134
21[d]	50	+10.8	174
22[d]	30	−7.9	209
23	30	−2.6	162
24	100	−3.9	142
25[d]	150	+9.8	113
26[d]	50	+10.9	149
27	100	+3.4	134
30	50	+1.5	153
31	20	−6.4	274
32	50	−8.7	149
33	50	+6.8	115
34[d]	100	+5.5	141
35	150	−4.3	130
36[d]	150	+1.3	124
37	100	+9.0	109
38	20	+5.3	167
41	100	+1.8	106
42	75	+8.6	120
43[d]	150	−3.3	156
46	100	+0.8	127
47	100	+7.8	165
49	150	+1.7	183
50	100	+18.3	123
58	50	−3.1	185
59	100	+0.3	126
61	50	+10.2	128
63	50	+10.3	115
64	20	+6.7	165
67	40	−12.3	186
68	60	−13.7	221
69	60	−9.4	214
70	40	+6.3	191
71	25	−15.3	340

[a] Administered once daily for 6 consecutive days, beginning 24 h after tumor transplantation, with five animals being used per group. [b] Average change in body weight from onset to termination of therapy. [c] % T/C = average survival time of treated/control animals × 100. [d] Reported earlier.[1-3] [e] One 50-day survivor.

A slow rate of breakdown of the parent molecule to a reactive species also appears to have beneficial effects on activity, as evidenced by the observation that compounds of the general structure III were comparable in activity to II. The overall superiority of compound **71** may be the result of all of the above factors existing in the same molecule.

Replacement of the *N*-methyl group in compounds **24** and **31** by 2-chloroethyl resulted in the retention of antineoplastic activity against both the L1210 leukemia and the B16 melanoma. However, unlike the nitrosourea type compounds, this kind of modification did not result in enhanced activity against the two tumor cell lines. However, more extensive structural modifications of this kind will be attempted and the results reported in a future publication.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton magnetic resonance spectra were recorded on a Varian T-60A or EM-390 spectrometer with Me_4Si as an internal standard. The spectral measurements were as expected; therefore, only representative data are included. Elemental analyses were performed by the Baron Consulting Co. (Orange, CT) and the data were within ±0.4% of the theoretical values for the 1,2-bis(sulfo-

Table III. Effects of 1,2-Bis(sulfonyl)hydrazines on the Survival Time of Mice Bearing the B16 Melanoma

compd	optimum effective daily dose, mg/kg[a]	av Δ wt, %[b]	max % T/C[c]
5	12.5	−2.8	138
6	10	+3.8	184
7	100	−2.3	175
8	50	+0.8	178
9	100	−2.9	148
10	50	−1.6	187
11	50	−5.9	191
12	50	+2.5	181
13	100	+2.2	186
14	150	+8.5	168
15[d]	150	−2.7	165
16	100	+9.1	200
17	50	+2.9	171
18	150	−5.1	161
20	100	+1.4	192
21[d]	50	−2.4	172
22[d]	10	−1.9	207
23[d]	50	−1.1	174
24	100	+4.7	151
25	100	−14.0	151
26	100	−2.4	191
27	100	−0.1	205
28	150	+1.5	158
29	100	−0.1	163
30	50	+2.1	160
31	20	−7.5	204
33	50	+2.3	146
34	50	−0.4	162
35	50	+1.0	189
36	50	+4.8	163
37	50	−4.0	153
38	20	−1.4	194
39	10	−0.1	164
40	50	+1.1	143
41	50	+5.1	163
43	100	+4.6	164
44	20	+1.4	193
45	100	+4.5	160
47	100	+1.3	167
48	200	+2.5	145
49	50	−3.8	160
50	200	+3.7	146
51	20	+4.2	225
52	30	+4.5	190
53	100	+0.7	178
54	150	−5.7	164
55	50	+1.4	176
56	40	+4.0	195
57	30	+5.2	177
58	50	−1.5	208
59	50	+2.7	206
60	150	+0.2	182
61	50	+1.4	184
62	50	+4.7	163
63	50	+2.5	179
64	30	+1.9	203
65	150	−17.1	152
66	50	+2.0	171
67	60	−8.6	256
68	60	−11.9	233
69	60	−8.7	219
70	100	−11.4	235
71	50	−7.9	278

[a] Administered once daily for six consecutive days, beginning 24 h after tumor transplantation, with five animals being used per group. [b] Average change in body weight from onset to termination of therapy. [c] % T/C = average survival time of treated/control animals × 100. [d] Reported earlier.[2]

nyl)hydrazines reported. Pertinent physical data for the compounds synthesized are listed in Table I.

Antitumor Activity. The L1210 leukemia and the B16 melanoma were maintained and transplanted as reported earlier.[1,2] Compounds were administered over a wide range of dosage levels (10–150 mg/kg per day) by intraperitoneal injection, beginning 24 h after tumor implantation and continuing once daily for 6 consecutive days. The test compounds were injected as fine suspensions, prepared by homogenization in 2 to 3 drops of 20% aqueous Tween 80 and made to volume with isotonic saline. All animals were distributed into groups of five mice of comparable weight and maintained throughout the course of the experiment on laboratory chow pellets and water ad libitum. Control tumor-bearing animals, given injections of comparable volumes of vehicle, were included in each experiment. Mice were weighed during the course of the experiments, and the percent change in body weight from onset to termination of therapy was used as an indication of drug toxicity. Determination of the sensitivity of neoplasms to these agents was based on the prolongation of survival time afforded by the drug treatments.

Determination of Cytotoxicity. The cytotoxicities of compounds **22** and **23** were determined by measuring their effects on the colony-forming ability of B16 melanoma cells; the experimental details have been described earlier.[2]

Synthesis. Synthetic methods I–V are representative for compounds reported in Table I.

Methods I and II. These methods have been reported earlier.[1,3]

Method III. The appropriate arenesulfonyl chloride (0.02 mol) was added in portions to an ice-cold stirred solution of methylhydrazine (0.5 g, 0.01 mol) in pyridine (4 mL) while maintaining the temperature between 0 and 10 °C. After an additional 3 h, the reaction mixture was poured into ice and concentrated HCl (25 mL, 1:1, v/v). The solid that separated was filtered immediately, heated with glacial acetic acid (3 mL) to 60 °C, and cooled. The precipitate obtained was filtered, washed with cold water, and dried. Recrystallization from an appropriate solvent gave the desired product.

1,2-Bis[(4-bromophenyl)sulfonyl]-1-methylhydrazine (49): ^{1}H NMR (acetone-d_6, 90 MHz) δ 8.4 (br s, 1 H, NH), 7.6–8.0 (m, 8 H, Ar), 2.9 (s, 3 H, NCH_3).

1,2-Bis(benzylsulfonyl)-1-methylhydrazine (65): ^{1}H NMR (acetone-d_6, 60 MHz) δ 7.1–7.8 (m, 11 H, Ar and NH), 4.6 (s, 4 H, 2 CH_2), 3.3 (s, 3 H, NCH_3).

Method IV. The appropriate sulfonyl chloride (0.01 mol) was added in portions to a cold stirred suspension of the appropriate 1-methyl-1-arylsulfonyl)hydrazine (0.01 mol) in pyridine (2 mL) while the temperature was maintained between 5 and 15 °C. The reaction mixture was allowed to stand in the freezer overnight and then poured into a mixture of ice and concentrated HCl (25 mL, 1:1, v/v). The solid that separated was filtered immediately, washed with water, pressed dry, and recrystallized from an appropriate solvent.

2-(Ethylsulfonyl)-1-[(4-methoxyphenyl)sulfonyl]-1-methylhydrazine (32): ^{1}H NMR ($CDCl_3$, 60 MHz) δ 7.7 and 7.0 (2 d, 4 H, Ar), 5.5 (br s, 1 H, NH), 3.9 (s, 3 H, OCH_3), 3.3 (q, 2 H, CH_2), 3.1 (s, 3 H, NCH_3), 1.4 (t, 3 H, CH_3).

Method V. In method V, which is a modification of method IV, the solid that separated after pouring the reaction mixture into ice and concentrated HCl was filtered immediately, boiled or heated with glacial acetic acid, and cooled. The precipitate obtained was filtered, washed with cold water, and dried. The compound was recrystallized from an appropriate solvent.

1-Methyl-2-(methylsulfonyl)-1-[(4-iodophenyl)sulfonyl]hydrazine (56): ^{1}H NMR (acetone-d_6, 90 MHz) δ 7.9 and 7.5 (2 d, 4 H, Ar), 7.8 (br s, 1 H, NH), 3.0 (s, 3 H, NCH_3).

1-(Benzylsulfonyl)-2-[(4-chlorophenyl)sulfonyl]-1-methylhydrazine (61): ^{1}H NMR (acetone-d_6, 90 MHz) δ 8.9 (br s, 1 H, NH), 8.0 and 7.7 (2 d, 4 H, aromatic H ortho and para to Cl), 7.2–7.6 (m, 5 H, aromatic H ortho, meta, and para to CH_2), 4.5 (s, 2 H, CH_2), 2.9 (s, 3 H, NCH_3).

1-(2-Hydroxyethyl)-1-(4-methoxyphenyl)hydrazine. To an ice-cold stirred solution of 4-methoxybenzenesulfonyl chloride (10.3 g, 0.05 mol) was added (2-hydroxyethyl)hydrazine (7.4 g, 0.1 mol) while the temperature was maintained between 0 and 5 °C. After an additional 3 h, the solvent was removed on a rotary evaporator, and the residue was triturated with cold water (300 mL). The crude compound that precipitated out was filtered, dried, and recrystallized from ethyl acetate (8.6 g, 70%, mp 84–86 °C): ^{1}H NMR ($CDCl_3$, 60 MHz) δ 7.8 and 7.0 (2 d, 4 H, Ar), 3.9 (s and t, 5 H, OCH_3 and CH_2O) and 3.2 (br s and t, 5 H, NH_2, OH, and NCH_2).

1-[(4-Methoxyphenyl)sulfonyl]-2-(phenylsulfonyl)-1-[2-[(phenylsulfonyl)oxy]ethyl]hydrazine. 1-(2-Hydroxyethyl)-1-(4-methoxyphenyl)hydrazine (4.9 g, 0.02 mol) and benzenesulfonyl chloride (7.1 g, 0.04 mol) were reacted in pyridine, and the product was isolated as described in method V. The compound was recrystallized from ethanol (2.9 g, 27%, mp 123–124 °C): ^{1}H NMR (acetone-d_6, 90 MHz) δ 8.6 (br s, 1 H, NH), 7.3–8.1 (m, 12 H, Ar), 7.0 (d, 2 H, aromatic H ortho to OCH_3), 4.2 (t, 2 H, CH_2O), 3.9 (s, 3 H, OCH_3) and 3.5 (t, 2 H, CH_2N).

1-[(4-Methoxyphenyl)sulfonyl]-1-[2-[(methylsulfonyl)oxy]ethyl]-2-(methylsulfonyl)hydrazine. This compound was prepared by a procedure analogous to that used for synthesizing 1-[(4-methoxyphenyl)sulfonyl]-2-(phenylsulfonyl)-1-[2-[(phenylsulfonyl)oxy]ethyl]hydrazine. The compound was recrystallized from methanol: yield 36%; mp 173–175 °C; ^{1}H NMR (acetone-d_6, 90 MHz) δ 8.2 (br, 1 H, NH), 7.9 and 7.1 (2 d, 4 H, Ar), 4.5 (t, 2 H, CH_2O), 3.9 (s, 3 H, OCH_3), 3.6 (t, 2 H, CH_2N), 3.0–3.2 (2 s, 6 H, 2 CH_3).

1-(2-Chloroethyl)-1-[(4-methoxyphenyl)sulfonyl]-2-(methylsulfonyl)hydrazine (6). A mixture of 1-[(4-methoxyphenyl)sulfonyl]-1-[2-[(methylsulfonyl)oxy]ethyl]-2-(methylsulfonyl)hydrazine (2.0 g, 0.005 mol), lithium chloride (0.4 g, 0.009 mol), and acetone (10 mL) was heated under reflux for 24 h. The reaction mixture was cooled to room temperature, filtered, and evaporated to dryness on a rotary evaporator. After the residue was triturated with chloroform (25 mL), Norit A (0.5 g) was added and the mixture was filtered. To the filtrate was added petroleum ether until turbidity appeared. Upon cooling in the refrigerator overnight, the compound separated. Recrystallization from chloroform–carbon tetrachloride afforded the analytical product (1.1 g, 65%, mp 134–136 °C): ^{1}H NMR ($CDCl_3$, 90 MHz) δ 7.9 and 7.1 (2 d, 4 H, Ar), 6.5 (br s, 1 H, NH), 3.9 (s, 3 H, OCH_3), 3.4–4.1 (m, 4 H, CH_2CH_2), 3.1 (s, 3 H, CH_3).

1-(2-Chloroethyl)-1-[(4-methoxyphenyl)sulfonyl]-2-(phenylsulfonyl)hydrazine (5). This compound was prepared by a procedure analogous to that employed for synthesizing compound **6**: yield 69%; mp 147–150 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 7.8 (d, 2 H, aromatic protons meta to OCH_3), 7.3–7.7 (m, 5 H, phenyl H), 6.9 (d, 2 H, aromatic protons ortho to OCH_3), 3.9 (s, 3 H, OCH_3), 3.6–3.8 (m, 4 H, CH_2CH_2).

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