B) R_f 0.76; TLC (solvent C) R_f 0.52; mp 185-188 °C; IR (Neat) 3500, 1720, 1670, 1650, 1620 cm^{-1}; NMR (acetone-d_6) δ 7.26 (m, 1 H), 6.0-6.24 (m, 2 H), 4.99 (d, J = 1.9 Hz, 2 H), 4.1-4.7 (br m, 2 H), 3.84 (m, 2 H), 3.30 (s, 3 H), 2.40-2.86 (m, 14 H), 1.61 (s, 3 H), 0.98 (m, 3 H). Anal. of the trifluoroacetate ($C_{28}H_{37}F_4NO_8{\cdot}H_2O$) C, H, N. The ^{14}C-labeled dexamethasone 21-(γ-aminobutyrate) was obtained from the t-Boc derivative as above with 6 mg of starting material: yield 75%; specific activity 34 μCi/mmol.

Biochemistry. Brain Uptake Studies. Each labeled test compound was injected as a solution in 0.5 mL of saline for compound **7** or in 25% propylene glycol in water for compounds **1**, **5**, and **6** subcutaneously (sc) into young adult male BALB-c mice (18-24 g body weight). After 5 min (or later), animals were sacrificed, and the brain and liver were removed, weighed, and homogenized, respectively, in 8 and 10 mL of "brain protein solvent"[25] (1%, w/v, sodium dodecyl sulfate in 6 M urea and 19 mM EDTA, pH 7.4, 0.03 M phosphate). Aliquots (0.5 mL) of the homogenates were mixed with 10 mL of Aquasol 2 (New England Nuclear Corp.) and counted in a Beckman liquid scintillation counter. The total uptake of each compound per gram of brain and liver tissue was calculated. The proportion of uptake into brain as compared to liver (100%) of the same animal was designated as the "Brain Penetration Index" (BPI), expressed as a percentage typically at 5 min after injection. The TLC methods used to identify ^{14}C-labeled material are described in the legend for Table I.

Pharmacology. General Locomotor Activity Tests. The compounds were dissolved in 25% propylene glycol in water and injected ip into male BALB-c mice (18-24 g) and rats (200 g). Dose-response measurements were obtained for six animals per dose or time point; animals were monitored singly for 60 min with a Stoelting electronic activity monitor (EAM) apparatus as previously described[15] to assess general motor activity of the animals. The dose at which a compound reduced such spontaneous motor activity by 50% in comparison to the control (vehicle-injected and uninjected) animals was used as a measure of pharmacological activity.

Anticonvulsant Activity in Mice. The compounds were injected ip at 1, 6, and 24 h before the administration of bicuculline (0.3 mg/kg sc). The latency to the onset of generalized tonic-clonic epileptic seizures[26,27] and the protection against lethality[28] of bicuculline were measured and evaluated as a percent of the data for vehicle-injected controls (Table V).

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Registry No. 1, 75319-75-4; 2, 57294-38-9; 2 (^{14}C labeled), 89210-65-1; 3, 89231-63-0; 3 (^{14}C labeled), 89231-64-1; 5, 89210-66-2; 5 (^{14}C labeled), 89210-67-3; 6, 89210-68-4; 6·HCl, 89210-69-5; 6 (^{14}C labeled), 89210-70-8; 6 (N-acetyl derivative), 89210-71-9; 7, 89231-65-2; 7 (^{14}C labeled), 89231-66-3; 8, 89210-72-0; 8 (^{14}C labeled), 89210-73-1; 9, 89210-74-2; 9 (^{14}C labeled), 89210-75-3; 10, 89231-67-4; 11, 89231-68-5; 11 (^{14}C labeled), 89231-69-6; γ-aminobutyric acid, 56-12-2; 2-[(*tert*-butoxycarbonyl)oximino]-2-phenylacetonitrile, 58632-95-4; cholesterol, 57-88-5; linolenyl alcohol, 506-44-5; dexamethasone, 50-02-2; [U-^{14}C]GABA, 29315-46-6; [U-^{14}C]GABA butyl ester, 89210-76-4.

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2-Chloroethyl (Methylsulfonyl)methanesulfonate and Related (Methylsulfonyl)methanesulfonates. Antineoplastic Activity in Vivo

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2-Haloethyl and ethyl (methylsulfonyl)methanesulfonates were prepared via sulfene intermediates. 2-Chloroethyl (methylsulfonyl)methanesulfonate is highly active against P388 leukemia in vivo; the majority of leukemic mice treated with this compound at 50 mg/kg per day, qd 1-5, survived more than 30 days and about 37% survived for more than 60 days. 2-Fluoroethyl (methylsulfonyl)methanesulfonate is also highly effective against P388 cells in vivo, but it is more toxic. Other (methylsulfonyl)methanesulfonate esters are more active than the analogous methanesulfonates and chloromethanesulfonates.

The most active of the N-nitrosoureas against experimental neoplasma are the N-(2-chloroethyl)-N-nitrosoureas (**1**, X = Cl; Chart I) and the N-(2-fluoroethyl)-N-nitrosoureas (**1**, X = F).[1-4] Similarly, the most active triazenylimidazoles or triazenylbenzenes against murine L1210 leukemia are 3-(2-chloroethyl)-1-triazenyl derivatives (**2**); i.e., the most active triazenes have at least one 2-chloroethyl group attached to the terminal nitrogen atom.[5,6] Studies of the decomposition of N-(2-chloroethyl)-N-nitrosoureas (**1**, X = Cl) in aqueous media[7-16]

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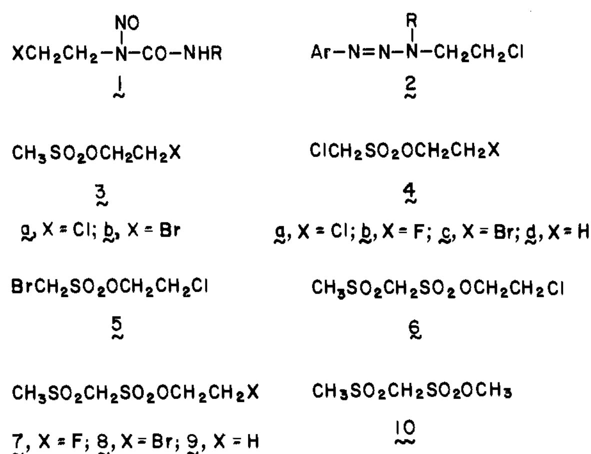
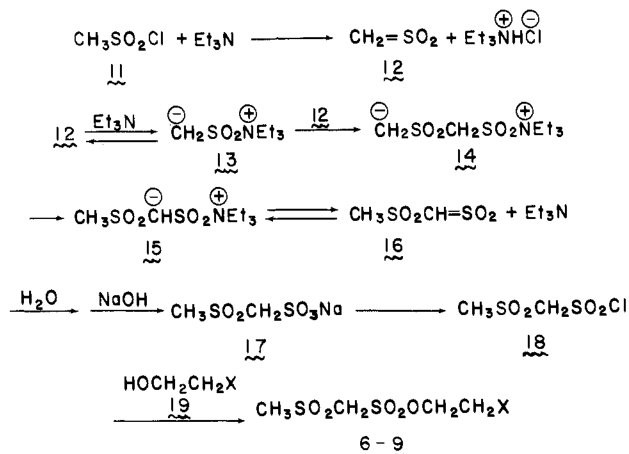
Chart I



Scheme I



indicate that at least one of the major modes of decomposition generates chloroethylating species [e.g., 2-chloroethyl diazohydroxide or diazotate, (2-chloroethyl)-diazonium ion, or (2-chloroethyl)carbonium ion] that may react at nucleophilic centers of biological macromolecules. Further studies of the mechanism of action of *N*-(2-chloroethyl)-*N*-nitrosoureas indicate that interaction of such derivatives and DNA results in chloroethylation of DNA by the reactive species.[17-24] Chloroethyl groups may become attached at various positions of the heterocyclic groups[22,24-26] or at the phosphate groups.[27] The attached chloroethyl groups may then react further, interstrand or intrastrand cross-linking of DNA being one of the subsequent reactions.[18-20,23-26] It has been postulated that 2-hydroxyethylation of DNA occurs via nitrosooxazolidines[28] or 1,2,3-oxadiazoline intermediates.[13,14,22,24,29] Studies of triazenes indicate that 3-(2-chloroethyl)-1-triazenyl derivatives (**2**, R = H) generate or function as 2-chloroethylating agents[30] and suggest that 3-alkyl-3-(2-chloroethyl)-1-triazenyl derivatives (**2**, R = alkyl) also become chloroethylating agents after dealkylation by microsomal oxidases.[6,31] The high antineoplastic activity of *N*-(2-chloroethyl)-*N*-nitrosoureas and (2-chloroethyl)triazenes, together with the studies implicating 2-chloroethylation as the principal mechanism of action, suggested that other types of compounds that may function in vivo as chloroethylating agents be investigated.

Because the leaving-group potential of sulfonate groups can be varied, 2-haloethyl sulfonates constitute another type of haloethylating structure that might produce useful activity in vivo. Recently, this possibility was discussed, and a variety of 2-chloroethyl arenesulfonates, alkenesulfonates, and substituted methanesulfonates was prepared and evaualted.[32] This study demonstrated that the activity of the 2-chloroethyl sulfonate structure against murine P388 leukemia could be significantly enhanced over the marginal activity of 2-chloroethyl methanesulfonate (**3a**). Thus, in simultaneous tests, 2-chloroethyl chloromethanesulfonate (**4a**) increased the survival time of treated mice by 118%, whereas the methanesulfonate (**3a**) increased survival time by only 33%. The bromomethanesulfonate (**5**) and the analogous cyanomethanesulfonate also significantly increased survival time in the P388 leukemia test.[32] The methanesulfonates (**3**) and a few related 2-haloethyl sulfonates were among various sulfonates and poly(methylene)bis(sulfonate)s that had been prepared by Ross and Davis[33] before the superior effectiveness of 2-haloethylating agents had been demonstrated. Although **3a** has antitumor activity and has received considerable study, it is not a useful anticancer agent. The increased antineoplastic activity of the chloromethanesulfonate (**4a**) indicated that varying the sulfonate moiety may uncover 2-haloethyl sulfonates having markedly improved anticancer activity. Now, further investigation of 2-haloethyl sulfonates has shown that 2-chloroethyl (methylsulfonyl)methanesulfonate (**6**, NSC 338947) has exceptional antineoplastic activity and that the methylsulfonyl group appears to enhance the antileukemic activity of methanesulfonates.

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Chemistry. The synthesis of the (methylsulfonyl)methanesulfonates (**6–10**) was based on sulfene intermediates[34-40] (**12** and **16**; Scheme I). The trimethylamine adduct analogous to **15** has been isolated and characterized by Opitz and Bücher.[38] Representation (Scheme I) of the formation of the (methylsulfonyl)sulfene[37] (**16**) and its triethylamine adduct (**15**) is adapted from the scheme of Grossert and Bharadwaj.[41] The solution containing **16** and (or) **15** was treated with an equivalent amount of water and, after removal of triethylamine hydrochloride by filtration, with aqueous base in order to isolate sodium (methylsulfonyl)methanesulfonate[42,43] (**17**). Sulfonate **17** was converted to the sulfonyl chloride (**18**), and the latter compound was treated with ethanol or a 2-haloethanol (**19**) to form **6–9** or with methanol to obtain **10**. The conditions employed in the final step (triethylamine in ethyl acetate) undoubtedly regenerate the (methylsulfonyl)sulfenes (**15** and **16**), and the sulfonate esters (**6–10**) must then be formed from these intermediates. The preparation of **6–10** directly from the original reaction mixture (**11** and triethylamine) may be feasible, but the isolation of the sodium sulfonate (**17**) permits the accumulation of a common intermediate and removes other products[39,41] that may result from sulfene formation. (However, dimerization[41] may occur after regeneration of **16** in the final step.)

The mass spectra of compounds **6–10** include strong peaks corresponding to $(CH_3SO)^{+\cdot}$, $(CH_3SO_2)^{+\cdot}$, $(CH_3SO_2CH_2)^{+\cdot}$, $(CH_3SO_2CH_2SO_2)^{+\cdot}$, and $(CH_3SO_2CH_2SO_2O + 2H)^{+\cdot}$. The spectra of compounds **6–9** also include prominent peaks arising from $(M + H)^{+\cdot}$, $(M - X)^{+\cdot}$, and $(M - CH_2X)^{+\cdot}$. The chemical shift of the methylene group ($SO_2CH_2SO_3$) is δ 4.69 in the proton NMR spectra of **6–8** and 4.60 in the spectra of **9** and **10**. The chemical shift of the methyl group (CH_3SO_2) is δ 3.25 in **6–10**. In the IR spectra of **6–10**, strong bands (3–5) resulting from sulfone and sulfonate stretching frequencies appear in the regions 1390–1300 and 1190–1120 cm^{-1}.

Antineoplastic Evaluation. Compounds **6–10** were administered intraperitoneally on days 1–5 after intraperitoneal inoculation of mice with 10^6 P388 leukemia cells.[44] In the initial tests (Table I, lines 1–3) of the 2-chloroethyl derivative (**6**), the median survival time of mice treated with 50 mg/kg per day was greatly prolonged; four of the six treated animals survived for more than 30 days, and two of the six survived until the experiment was terminated after 60 days. In this test and in subsequent tests (Table I) at this dose, the weight-change difference on day 5 indicated some acute toxic effects, but long-term survival of all of the treated mice and survival of some for 30 or 60 days were confirmed and indicated recovery from acute toxicity. In one of the tests at this dose, all six of the treated mice survived until the experiment was terminated after 60 days, and spleen weights at autopsy were within the normal range (57–103 mg). In seven separate tests at 50 mg/kg per day, 28 of 41 (68%) of the treated mice survived for more than 30 days, and in six of these tests that were observed for 60 days, 13 of 35 (37%) of the treated mice survived. In these tests the median life spans of the groups of untreated control mice were in the range of 10.5–13 days. In five tests at 33 mg/kg per day involving a total of 29 mice, the median survival times were 21.5–25.7 days (T/C = 179–214%). The 2-fluoroethyl derivative (**7**) was also highly effective against P388 cells, but it appears to be more toxic. In two tests, the weight-change differences on day 5 showed acute toxicity at 25 mg/kg per day, but the median survival times of the mice that survived the acute toxic effects were 277 and 286% of control medians. Half of the treated animals (5/10) that recovered from acute toxicity at this dose survived for more than 30 days, but only one survived for 60 days. At 50 mg/kg per day, **7** was palpably toxic, although two of the treated animals survived until the end of the test after 60 days.

The 2-bromoethyl (**8**) and ethyl (**9**) derivatives were much less active than **6** and **7** in standard tests against P388, but they significantly increased survival times of treated mice (Table I). The limited data from two tests of these compounds suggest that **8** is more effective than **9** in killing P388 cells, but further testing at intermediate doses would be required to compare the activity of these two compounds. The methyl derivative (**10**) demonstrated only borderline activity, comparable to that observed[32] in similar tests of 2-chloroethyl methanesulfonate (**3a**).

Discussion

In contrast to these results of tests of **6**, there were no long-term survivors after treatment (qd 1–9) of P388 leukemia with the analogous 2-chloroethyl chloromethanesulfonate (**4a**), although large increases in survival time (T/C > 200%) were observed.[32] As stated, the analogous methanesulfonate[33] (**3a**) caused only very modest increases in survival time (T/C = 130–134%).[32] Also, no significant increases in survival time were observed in standard tests of 2-fluoroethyl chloromethanesulfonate[32] (**4b**), 2-bromomethyl chloromethanesulfonate (**4c**, Table I), or ethyl chloromethanesulfonate[32] (**4d**) or 2-bromoethyl methanesulfonate (**3b**, Table I) against P388 leukemia, whereas the analogous (methylsulfonyl)methanesulfonates **7–9** caused the significant increases summarized in Table I. Thus, the (methylsulfonyl)methanesulfonates **6–9**, as a group, appear to be more effective antineoplastic agents than the corresponding chloromethanesulfonates or methanesulfonates, and **6** is the most active 2-haloethyl sulfonate tested, thus far, against P388 leukemia.

Like *N*-(2-chloroethyl)-*N*-nitrosoureas (**1**), 2-chloroethyl sulfonates are expected to function as chloroethylating agents. However, it is reasonable to anticipate differences that might be advantageous. 2-Chloroethyl sulfonates will generate different byproducts, and they may have different transport properties and may alkylate different sites on DNA or other biological macromolecules. Obviously, the isocyanates, oxadiazolines, or oxazolidines that form from nitrosoureas as byproducts or intermediates will not be products of the reactions of sulfonates in vivo. Toxicity to bone marrow caused by nitrosoureas was thought initially to be associated with carbamoylation by isocyanates formed from the nitrosoureas, but further studies indicate that carbamoylating activity and bone-marrow toxicity do not correlate.[45-47] However, it is believed at present that

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isocyanates interfere with DNA repair,[23,47,48] that this effect may be disadvantageous,[23] and that alkylating activity by nitrosoureas is irrelevant to inhibition of DNA repair.[48] Whatever toxic effects may be *specifically* caused by isocyanates will not be manifested by chloroethyl sulfonates.

Experimental Section

General Methods. Melting temperatures were determined in capillary tubes heated in a Mel-Temp apparatus. Infrared spectra were recorded with a Nicolet 10MXE spectrometer from samples in KBr disks. Mass spectral data were taken from low-resolution, electron-impact spectra determined at 70 eV with a Varian/MAT Model 311A spectrometer; M = molecular ion ($M^{+\cdot}$). Other MS peaks are assigned to fragments [e.g., (M minus a fragment)$^{+\cdot}$ or (fragment)$^{+\cdot}$] that are represented for simplicity as uncharged species. Nuclear magnetic resonance spectra were determined with a Varian Model XL-100-15 spectrometer operating at 100.1 MHz for proton NMR spectra and at 25.2 MHz for carbon-13 spectra; the internal reference was $(CH_3)_4Si$, and the solvent was $CDCl_3$. Thin-layer chromatography was performed by applying solutions of **6**–**10** in ethyl acetate to plates of silica gel.[49] Specimens of the sulfonate esters were protected from atmospheric moisture and were stored in a freezer.

2-Chloroethyl (Methylsulfonyl)methanesulfonate (6). A solution, protected from atmospheric moisture, of 21 g (109 mmol) of (methylsulfonyl)methanesulfonyl chloride (**18**) in 130 mL of dry ethyl acetate was chilled in an ice bath. A mixture of 9.7 g (120 mmol) of 2-chloroethanol and 14.0 g (138 mmol) of triethylamine was added dropwise (during 0.5 h) to the well-stirred methanesulfonyl chloride solution. The reaction mixture was stirred for 3 h in an ice bath and then stored in a refrigerator overnight. The triethylamine hydrochloride was separated by filtration and washed with ethyl acetate. The filtrate (plus washings) was washed three times with saturated NaCl solution, dried ($MgSO_4$), and concentrated to a waxy solid: weight 22.5 g. The crude product was mixed well with hot benzene (300 mL), the hot mixture was filtered, and the residue was extracted with a second portion (100 mL) of hot benzene. The two filtrates were combined, and the benzene solution was diluted with hexane. The resulting precipitate was collected by filtration, washed with hexane, and dried in vacuo: weight 19.5 g; mp 56–58 °C. The crude product was dissolved in hot benzene (22 mL/g), and the warm (50 °C) solution was diluted with an equal volume of hexane. After considerable crystallization had occurred, warm hexane (2 additional volumes/volume of benzene) was added with stirring. The mixture was allowed to cool, chilled at -20 °C (2 h), and filtered. The crystalline material was separated by filtration, washed with hexane, and dried in vacuo: yield 66%; mp 58–60 °C. This product contained a small amount of a nitrogen-containing, chloroform-soluble impurity.[50] A mixture of this material and chloroform (3.75 mL/g) was stirred under a nitrogen atmosphere for 40 min and then filtered. The undissolved material was washed with chloroform and dried, mp 59.5–62 °C. This material was treated in the same way with chloroform (2.4 mL/g) for 50 min: yield 45%;[51] mp 60.5–62 °C; TLC 1 spot (developed with 1:1 hexane–ethyl acetate, detection with iodine vapor); MS (direct-probe temperature 20 °C), *m/e* 237 (M + H), 201 (M − Cl) 200 (M − HCl), 187 (M − CH_2Cl), 175 ($CH_3SO_2CH_2SO_3$ + 2H), 157 ($CH_3SO_2CH_2SO_2$), 142 ($ClCH_2CH_2OSO_2$ − H), 127 ($ClCH_2CH_2OSO$), 109, 96, 94, 93 ($CH_3SO_2CH_2$), 80, 79 (CH_3SO_2), 65, 63 (CH_3SO and $ClCH_2CH_2$), 62 (CH_2=CHCl); IR (medium and strong bands) 3040, 3025, 2990 (s), 2930, 2935 (sh), 1465, 1430, 1415, 1390, 1370 (s), 1320 (s), 1240, 1200, 1185 (s), 1175 (s), 1165 (s), 1160 (sh), 1125, 1070, 990 (s), 955 (s), 920 (s), 870 (s), 790 (s), 765, 755, 665, 600, 530 (s), 505, 465 (s), 420 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.25 (s, CH_3), 3.79 (pseudotriplet, CH_2Cl), 4.65 (pseudotriplet, OCH_2), 4.68 (s, SCH_2S); ^{13}C NMR ($CDCl_3$) δ 40.95, 42.30, 68.78, 72.34. Anal. ($C_4H_9ClO_5S_2$) C, H.

2-Fluoroethyl (Methylsulfonyl)methanesulfonate (7). By the procedure described for the preparation of **6**, crude **7** was obtained, as a viscous oil, from 5 g (26 mmol) of **18**, 1.8 g (28.6 mmol) of 2-fluoroethanol, 3.3 g (33 mmol) of triethylamine, and 30 mL of ethyl acetate. A solution of the crude product (4.9 g) in ethyl acetate was filtered, and the filtrate was diluted slowly with hexane. The oil that initially separated was induced to crystallize, and the mixture was chilled in an ice bath. The precipitate was collected by filtration, washed with hexane, and dried in vacuo over P_2O_5: yield 3.79 g (65%); mp 50–52 °C dec; TLC 1 spot (developed with 1:1 hexane–ethyl acetate, detection with iodine vapor); MS (direct-probe temperature 20 °C), *m/e* 221 (M + H), 201 (M − F), 200 (M − HF), 187 (M − CH_2F), 175 ($CH_3SO_2CH_2SO_3$ + 2H), 157 ($CH_3SO_2CH_2SO_2$), 142, 126, 122, 111, 109, 96, 95, 94, 93 ($CH_3SO_2CH_2$), 80, 79 (CH_3SO_2), 65, 63 (CH_3SO), 46 (CH_2=CHF); IR (medium and strong bands) 3030, 3020, 3000 (s), 2975, 2935 (s), 1450, 1420, 1385 (s), 1365 (s), 1330 (s), 1300 (s), 1265, 1245, 1190 (s), 1150, 1140 (s), 1060 (s), 1015 (s), 980, 930 (s), 875 (s), 810 (s), 785, 715, 595, 535, 505 (s), 470 (s), 445 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.25 (s, CH_3), 4.69 (s, SCH_2S), 4.40–5.05 (m, CH_2CH_2F, AA′BB′X system). Anal. ($C_4H_9FO_5S_2$) C, H.

2-Bromoethyl (Methylsulfonyl)methanesulfonate (8). The bromoethyl ester (**8**) was prepared from **18** and 2-bromoethanol by the procedure described for the preparation of **6**. The crude yellow solid was triturated with chloroform, and the resulting white solid was dried in vacuo: yield 50%; mp 63–65 °C; TLC 1 spot (developed with 2:1 hexane–ethyl acetate, detection with iodine vapor or 4-nitrobenzylpyridine spray); MS (direct-probe temperature 20 °C), *m/e* 281 (M + H), 201 (M − Br), 187 (M − CH_2Br), 175 ($CH_3SO_2CH_2SO_3$ + 2H), 157 ($CH_3SO_2CH_2SO_2$), 123, 121, 106 (CH_2=CHBr), 94, 93 ($CH_3SO_2CH_2$), 80, 79 (CH_3SO_2), 63 (CH_3SO); IR (medium and strong bands) 3040, 3025, 2990 (s), 2930, 2935 (sh), 1460, 1425, 1415, 1390, 1370 (s), 1320 (s), 1280, 1240, 1190 (s), 1170 (sh), 1165 (s), 1125 (s), 1060, 970 (s), 945 (s), 900 (s), 870 (s), 785 (s), 765, 755, 700, 600, 570, 525 (s), 505, 465 (s), 400 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.25 (s, CH_3), 3.61 (t, CH_2Br), 4.69 (s, SCH_2S), 4.70 (t, OCH_2). Anal. ($C_4H_9BrO_5S_2$) C, H.

Ethyl (Methylsulfonyl)methanesulfonate (9). Crude **9** was obtained as a yellow oil from **18** and ethanol and was crystallized twice from methylene chloride–hexane: yield 44%; mp 51.5–53 °C; TLC 1 spot (developed with 2:1 hexane–ethyl acetate, detection with iodine vapor); MS (direct-probe temperature 20 °C), *m/e* 203 (M + H), 201 (M − H), 187 (M − CH_3), 175 ($CH_3SO_2CH_2SO_3$ + 2H), 157 ($CH_3SO_2CH_2SO_2$), 144, 124, 109 (SO_2OEt), 96, 95, 94, 93 ($CH_3SO_2CH_2$), 80, 79 (CH_3SO_2), 65, 63 (CH_3SO); IR (medium and strong bands) 3035 (sh), 2995 (s), 2935 (s), 1380 (s), 1365 (s), 1325 (s), 1315 (sh), 1300 (sh), 1255 (sh), 1240 (s), 1230 (sh), 1185 (s), 1150 (s), 1125, 1055 (s), 995 (s), 975, 930 (s), 865, 795 (s), 615, 585, 525, 510 (s), 470 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.47 (t, CH_3CH_2), 3.24 (s, CH_3SO_2), 4.51 (q, CH_2CH_3), 4.60 (s, SCH_2S). Anal. ($C_4H_{10}O_5S_2$) C, H.

Methyl (Methylsulfonyl)methanesulfonate (10). The sulfonyl chloride (**18**) was treated with methanol according to the procedure described for **6**. The reaction mixture was stored in a refrigerator overnight. The supernatant solution was decanted from an amorphous precipitate, and the residue was triturated with three portions of ethyl acetate. The four ethyl acetate solutions were combined, and the resulting solution was washed with NaCl solution, dried ($MgSO_4$) and concentrated to dryness in vacuo: yield 37%; mp 101–104 °C (lit.[52] mp 94–98 °C); MS (direct-probe temperature 180 °C), *m/e* 189 (M + H), 175 ($CH_3SO_2CH_2SO_3$ + 2H), 173 (M − CH_3), 157 ($CH_3SO_2CH_2SO_2$), 143, 124, 110, 109, 94, 93 ($CH_3SO_2CH_2$), 80, 79 (CH_3SO_2), 65, 63 (CH_3SO); IR (medium and strong bands) 3040, 3015, 2995 (s), 2935, 1450, 1415, 1385 (sh), 1380 (s), 1365, 1310 (s), 1307 (s), 1240 (s), 1190 (s), 1160 (s), 1125, 1120, 1045, 980 (s), 820, 800 (s), 760,

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(50) Microanalytical data indicated that the nitrogen content of this specimen was about 0.3–0.4%.

(51) Compound **6** is less soluble in chloroform than the impurity, but considerable **6** was lost in the chloroform filtrates.

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Table I. (Methylsulfonyl)methanesulfonates vs. P388 Leukemia in Vivo[a,b]

compd	expt no.	treated mice	dose, mg/kg per day, qd 1-5[c]	mortality by day 5, deaths/total	wt change diff on day 5: T − C, g	median survival time,[d] days: control mice	median survival time,[d] days: nonsurviving (<60 days) treated mice	ratio of median survival times for nonsurvivors:[e] T/C, %	treated mice: 30-day survivors: no./total	treated mice: 60-day survivors:[f] no./total
2-chloroethyl (methylsulfonyl)methanesulfonate (6)	1	F	200	5/6	−5.0	11.2		t		
			100	1/6	−4.0	11.2	17.0	151		
			50	0/6	−3.4	11.2	31.5	281	4/6	2/6
	2	M	150	5/5		11.2		t		
			100	1/5	−4.1	11.2	22.5	200		
			75	0/5	−4.2	11.2	17.5	156		
			50	0/5	−3.4	11.2	27.0	241	2/5	0/5
			33	0/5	−2.5	11.2	23.5	209		
	3	M	33	0/5	−2.8	11.1	22.0	198		
			22	0/5	−1.3	11.1	18.5	166		
			15	0/5	−0.9	11.1	16.0	144		
	4	M	50	0/6	−3.0	10.5			6/6	6/6
			33	0/6	−2.6	10.5	21.5	205	1/6	0/6
			22	0/6	−1.2	10.5	19.0	180		
	5	F	50	0/6	−2.2	12.0	27.0	225	3/6	1/6
			33	0/6	−1.5	12.0	25.7	214		
			22	0/6	−1.3	12.0	19.4	161		
	6	M	50	0/6	−3.1	13.0	43.5	335	5/6	2/6
			33	0/6	−2.1	13.0	23.3	179		
			22	0/6	−1.4	13.0	20.8	160		
	7	M	50	0/6	−3.0	10.7		*g*	4/6	*h*
			33	0/6	−2.4	10.7	22.3	208		
			22	0/6	−2.2	10.7	18.0	168		
	8	M	200	6/6		11.0		t		
			100	2/6[i]	−6.0	11.0	6.0	55t	1/6	1/6
			50	0/6	−1.6	11.0	30.0	273	4/6	2/6
2-fluoroethyl (methylsulfonyl)methanesulfonate (7)	1	F	100	6/6		11.2		t		
			50	6/6		11.2		t		
			25	2/6	−4.3	11.2	31.0[j]	277[j]	2/6	0/6
	2	M	50	1/6[i]	−4.8	10.5	*k*		3/6	2/6
			25	0/6	−5.6	10.5	30.0	286	3/6	1/6
			12	0/6	−3.7	10.5	19.8	188		
			6	0/6	−1.8	10.5	15.0	142		
2-bromoethyl (methylsulfonyl)methanesulfonate (8)	1	M	200	5/6	−5.4	10.5		t		
			100	0/6	−2.9	10.5	23.5	224	1/6	0/6
			50	0/6	−2.1	10.5	16.7	159		
			25	0/6	−0.8	10.5	14.3	136		
	2	M	100	2/6[l]	−4.7	13.0	7.0	54t	1/6	0/6
			50	0/6	−1.8	13.0	18.0	138		
			25	0/6	−1.5	13.0	16.0	123		
			12	0/6	+0.3	13.0	12.8	98		
ethyl (methylsulfonyl)methanesulfonate (9)	1	F	200	0/6	−5.0	11.2	6.9	t		
			100	0/6	−3.4	11.2	18.0	160		
			50	0/6	−1.4	11.2	13.3	118		
	2	M	150	0/6	−5.4	10.5	11.0	104		
			100	0/6	−4.3	10.5	17.9	170		
			50	0/6	−1.8	10.5	14.0	133		

methyl (methylsulfonyl)methanesulfonate (10)	1	M	25	0/6	−0.6	10.5	12.4	118
			25	6/6		10.7		t
			12	0/6	−4.1	10.7	14.0	130
			6	0/5	0.0	10.7	14.5	135
	2	M	25	4/6	−2.8	10.7		t
			12	1/6	−2.8	10.7	13.7	128
			6	0/6	−0.8	10.7	13.4	125
2-bromoethyl chloromethanesulfonate (4c)[m]	1	F	200	5/6		11.1		t
			100	0/6	−1.5	11.1	12.7	114
			50	0/6	−0.5	11.1	12.3	110
2-bromoethyl methanesulfonate (3b)[n]	1	F	200	6/6		11.1		t
			100	2/6	−3.0	11.1	11.8	106
			50	0/6	−2.0	11.1	12.3	110
			25	0/6	−0.7	11.1	12.0	108

[a] Tests of these compounds against P388 leukemia were performed in accordance with the protocols outlined in ref 44, except for the calculation of median survival times of the groups of control animals and of those treated groups in which there were no 30-day survivors; see footnote *d*. [b] C = control groups of animals; T = treated groups. [c] All compounds were administered intraperitoneally within about 5 min of the preparation of solutions or suspensions; see Experimental Section. [d] Median survival times of the untreated control groups and of the treated mice in those tests in which there were no 30-day survivors were calculated by considering the mortality data as grouped data. This method has been employed by the National Cancer Institute since about 1973. Median survival times for tests in which there were 30- or 60-day survivors were calculated, as described in ref 44 (protocol 11), by considering the survival-time data as ungrouped data. [e] t = toxic. [f] Experiments were terminated on day 60. [g] One death on day 6, one death on day 27, and four 30-day survivors. [h] Experiment terminated after 30 days. [i] Mortality was 3/6 by day 6. [j] Based on the four of six that survived beyond day 5. [k] Day 32 was the day of death of the one animal that survived more than 6, but less than 60 days. [l] Mortality was 5/6 by day 7. [m] Included for comparison with compound **8**. Data for the chloromethanesulfonate analogues of **6**, **7**, and **9** are tabulated in ref 32. [n] Administered as a 5-min unstable compound (footnote *c*). Previously, compound **3b** had been administered as a stable compound.[32]

695, 610, 580, 520, 505, 475, 450 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.25 (s, CH_3SO_2), 4.10 (s, OCH_3), 4.59 (s, SCH_2S). Anal. ($C_3H_8O_5S_2$) C, H.

Sodium (Methylsulfonyl)methanesulfonate (17). A solution of 132 g (1.3 mol) of dry triethylamine in 350 mL of dry acetonitrile was protected with a tube of drying agent and a nitrogen atmosphere and was cooled to −30 to −40 °C. Methanesulfonyl chloride (100 g, 0.87 mol) was added slowly (during 30–40 min) to the stirred solution. The reaction mixture was stirred for 1 h, water (7.9 mL, 0.5 equiv based on 11) was added, and the resulting mixture was stirred for 15 min and then filtered to remove triethylamine hydrochloride. The filtrate was concentrated in vacuo to an oil, cold 2 N sodium hydroxide (437 mL) was added, and the resulting mixture was stirred for 2 h in an ice bath and then stored in a refrigerator overnight. A crystalline precipitate was collected by filtration, washed with a small amount of ice–water, and dried in vacuo over P_2O_5: yield 59 g (60%); mp 242–244 °C dec (lit.[43] mp 239–241 °C); IR (strong bands) 1330, 1305, 1240, 1210, 1155, 1055, 870, 780, 620, 530, 505, 470.

(Methylsulfonyl)methanesulfonyl Chloride (18). Phosphorus pentachloride (79.3 g, 0.381 mol) and sodium (methylsulfonyl)methanesulfate (**17**; 70 g, 0.359 mol) were stirred with 150 mL of phosphorus oxychloride. As the mixture was warmed to 70 °C in an oil bath, hydrogen chloride was slowly evolved, and the slurry thinned enough to be stirred with a magnetic stirrer. The mixture was heated for 18 h in an oil bath at 80–90 °C, cooled, and filtered, and the residue was washed with dry chloroform. The chloroform caused the product to precipitate in the filtrate. The precipitate was collected, washed with a small amount of chloroform, and dried over sodium hydroxide pellets: yield 28.5 g (41%); mp 109–111 °C; MS (cf. ref 53 and 54) (direct-probe temperature, 20 °C), *m/e* 193 (M + H), 192 (M), 177 (M − CH_3), 157 ($CH_3SO_2CH_2SO_3$), 143, 141, 113 (CH_2SO_2Cl[53]), 98 (CH_3SOCl[54]), 94, 93 ($CH_3SO_2CH_2$), 79 (CH_3SO_2), 78, 64, 63 (CH_3SO); IR (strong and medium bands) 3045, 3025, 2995 (s), 2930 (s), 1405, 1390 (s), 1380 (s), 1360, 1335 (s), 1325 (sh), 1315 (s), 1225, 1175 (s), 1160 (s), 1110 (s), 980 (s), 965, 860 (s), 760 (s), 695, 595 (s), 515 (s), 495 (s), 460 (s) cm^{-1}.

Two additional crops were obtained. One was obtained by washing the chloroform-washed residue with ethyl acetate, evaporating the solvent, and crystallizing the residue from ethyl acetate and hexane: weight 3.9 g (6%); mp 108–110 °C. Another crop was obtained from the original filtrate after it had been chilled in a refrigerator overnight: yield 9.0 g (13%); mp 107–110 °C. The total amount of **18** that was suitable for conversion to the esters **6–10** was 41 g (60%).

2-Bromoethyl Chloromethanesulfonate (4c). Compound **4c** was prepared from chloromethanesulfonyl chloride and 2-bromoethanol by the general procedure described previously:[32] yield 40%; bp 81–83 °C (0.01–0.02 mm); MS (direct-probe temperature, 20 °C), *m/e* 237 (M + H), 187 (M − CH_2Cl), 143 (M − CH_2Br), 107 ($ClCH_2SO_3$), 106 (CH_2=CHBr); IR 1370 (s), 1175 (s) (SO_2O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.60 (t, CH_2Br), 4.66 (t, OCH_2), 4.68 (s, $ClCH_2SO_2$). Anal. ($C_3H_6BrClO_3S$) C, H.

Tests against P338 Leukemia. Tests (Table I) vs. P388 leukemia were performed in accordance with the protocols of the National Cancer Institute.[44] Mice (CDF_1) were inoculated intraperitoneally on day 0 with 10^6 P388 leukemia cells. Treatment of groups of six (occasionally, five) of these mice was begun on the following day (day 1). A group of 30 of the leukemia-inoculated mice served as an untreated control group. On day 0, mice in both the treated and the control groups weighed 19–22 g. The difference between the average change in weight of the treated mice and the average change in weight of the control group was recorded on day 5. The day of death of each of the treated and untreated mice was determined by daily observations. Median survival times of the groups were calculated as explained in footnote *d* of Table I. All of the compounds were administered intraperitoneally within 5 min of the preparation of suspensions. Compounds **4c**, **7**, and **9** were administered in suspension in sterile

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saline (0.85% NaCl in distilled water), compounds **3b**, **8**, and **10** were administered in saline plus Tween 80, and compound **6** was administered in saline plus Tween 80 in most experiments (experiments 4–8, Table I) and, also, in suspension in saline.

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Registry No. **3b**, 4239-10-5; **4c**, 88343-71-9; **6**, 88343-72-0; **7**, 88343-73-1; **8**, 88343-74-2; **9**, 88343-75-3; **10**, 61801-29-4; **17**, 35329-86-3; **18**, 22317-89-1; 2-chloroethanol, 107-07-3; 2-fluoroethanol, 371-62-0; 2-bromoethanol, 540-51-2; methanesulfonyl chloride, 124-63-0.

Synthesis and Antiviral Evaluation of Carbocyclic Analogues of Ribofuranosides of 2-Amino-6-substituted-purines and of 2-Amino-6-substituted-8-azapurines

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Carbocyclic analogues of ribofuranosides of 2-amino-6-substituted-purines and of 2-amino-6-substituted-8-azapurines were prepared from the 2-amino-6-chloropurine ribofuranoside analogue (**2**) and the 2-amino-6-chloro-8-azapurine ribofuranoside analogue (**9**), respectively. Analogues of purine ribofuranosides with the chloro, amino, methylamino, or methylthio group at position 6, the thioguanosine analogue, and the previously reported guanosine analogue were evaluated in vitro against herpes simplex virus, type 1 (HSV-1). 8-Azapurine ribofuranoside analogues with the chloro, amino, or methylthio group at position 6 and the previously reported 8-azaguanosine analogue were also evaluated against HSV-1. The carbocyclic analogue (**6**) of 2,6-diaminopurine ribofuranoside is highly active against HSV-1 and, also, against vaccinia virus. The 2-amino-6-chloropurine, 2-amino-6-(methylamino)purine, and the 2,6-diamino-8-azapurine derivatives also demonstrated significant activity against HSV-1.

Carbocyclic analogues of 6-substituted-purine ribofuranosides, including the racemic analogue (C-Ado) of adenosine, constituted the first group of carbocyclic analogues of nucleosides.[1-3] The adenosine analogue was subsequently isolated as the antibiotic aristeromycin (1′*R*,2′*S*,3′*R*,4′*R* enantiomer, nucleoside numbering).[4,5] The identity of C-Ado and aristeromycin was reported[5] and was confirmed in more detail[6] after a later synthesis and resolution were claimed.[7] Other ribofuranoside analogues synthesized in the early stages of this work were the carbocyclic analogues of guanosine,[8] 8-azaguanosine,[8] and 8-azapurine ribofuranosides.[9] Initial biochemical studies showed that C-Ado may function either as a substrate for or as an inhibitor of enzymes involved in the biosynthesis de novo or in interconversions of purine nucleotides,[10,11] and tests of the 8-azaadenosine analogue in vivo showed that it is active against P388 leukemia in mice.[12] Bennett et al.[13] reported in 1975 that several members of the initial group of carbocyclic analogues of 6-substituted-purine ribofuranosides have antiviral activity. Subsequently, it was shown that carbocyclic analogues of cytidine and arabinofuranosylcytosine (*ara*-C),[14-16] arabinofuranosyladenine (*ara*-A),[17] 3-deazaadenosine,[18] and 5-substituted-2′-deoxyuridines[19] also have antiviral activity. In addition to the guanosine (**3**) and 8-azaguanosine (**4**) analogues,[8] we had also prepared carbocyclic analogues of ribofuranosides of other 2-aminopurines and 2-amino-8-azapurines (1,2,3-triazolo[4,5-*d*]pyrimidines); we now describe the preparation, antiviral evaluation, and antineoplastic testing of these carbocyclic analogues.

Chemistry. The synthesis of the pyrimidine precursor (**1**) of both the 2-aminopurine and 2-amino-8-azapurine analogues was described earlier.[8] Previously, the acid-catalyzed reaction of triethyl orthoformate with pyrimidine **1** in dimethylformamide and the use of the total crude product of this reaction to produce the guanosine analogue (**3**) were reported.[8] In addition to forming the purine ring, interaction of **1** and triethyl orthoformate should produce

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