2-Amino-6-[[3-(trifluoromethyl)phenyl]thio]-4(3*H*)-quinazolinone (2b). In 320 mL of bis(2-methoxyethyl) ether, 20.0 g (0.0594 mol) of 6-[[3-(trifluoromethyl)phenyl]thio]-2,4-quinazolinediamine and 200 mL of 2 N hydrochloric acid were heated under reflux for 6 h. The chilled mixture was made basic by addition of 5 N ammonium hydroxide. The white solid precipitate was collected, washed with water, and dried in a vacuum oven at 50 °C to give 18.7 g (92.7%) of the desired product.

2-Amino-6-[[3-(trifluoromethyl)phenyl]thio]-4-quinazolinethiol (3b). A mixture of 18.7 g (0.0555 mol) of 2-amino-6-[[3-(trifluoromethyl)phenyl]thio]-4(3*H*)-quinazolinone and 50.0 g (0.225 mol) of phosphorus pentasulfide in 200 mL of pyridine was heated at 80 °C for 22 h. The two-phase mixture (dark solution and yellow solid) was poured into 2500 mL of stirred hot water. After being boiled for 2 h, the mixture was filtered hot to collect 18.5 g of yellow-brown solid. This crude product was dissolved in about 500 mL of hot anhydrous ethanol, and water was added to the cloud point. The chilled dark mixture was filtered through several thicknesses of paper to remove a gummy brown precipitate. Water was again added to the warmed filtrate to the cloud point, and a reddish-orange precipitate was removed. The yellow filtrate was poured into 1800 mL of water, and the bright yellow precipitate was collected and dried, yielding 13.7 g of the desired thiol compound.

4-(Methylthio)-6-[[3-(trifluoromethyl)phenyl]thio]-2-quinazolinamine (4b). A mixture of 11.0 g (0.0312 mol) of 2-amino-6-[[3-(trifluoromethyl)phenyl]thio]-4-quinazolinethiol and 3.4 mL (5.2 g, 0.0367 mol) of iodomethane in 50 mL of *N*,*N*-dimethylformamide was stirred at room temperature for 1 h. The resulting amber solution was poured into 600 mL of ice water. The suspension was made weakly acidic (pH 6.5–7.0) by addition of 10% sodium hydroxide. After the mixture was allowed to stand for 1 h, the yellow precipitate was collected and recrystallized from anhydrous ethanol to give 6.1 g of the desired product as tan crystals, which darken slowly with exposure to light.

4-Hydrazino-6-[[3-(trifluoromethyl)phenyl]thio]-2-quinazolinamine (5b). To a solution of 2.0 g (0.0057 mol) of 2-amino-6-[[3-(trifluoromethyl)phenyl]thio]-4-quinazolinethiol in 40 mL of pyridine was added 1.6 mL (0.05 mol) of anhydrous hydrazine. The mixture was stirred at room temperature overnight and poured into 300 mL of iced water. The precipitate that formed was collected and recrystallized from acetonitrile to afford 1.45 g of product.

N^4-Hydroxy-6-[[3-(trifluoromethyl)phenyl]thio]-2,4-quinazolinediamine (6d). A mixture of 2.0 g (0.005 25 mol) of 4-(methylthio)-6-[[3-(trifluoromethyl)phenyl]thio]-2-quinazolinamine and 0.37 g (0.005 32 mol) of hydroxylamine hydrochloride in 10 mL of pyridine was stirred at room temperature for 27 h. The reaction mixture was poured into 300 mL of ice water, and the cream colored precipitate was collected and air-dried to give 1.7 g of the title compound.

N^4-Methoxy-6-[[3-(trifluoromethyl)phenyl]thio]-2,4-quinazolinediamine (6e). A mixture of 1.0 g (0.002 72 mol) of 4-(methylthio)-6-[[3-(trifluoromethyl)phenyl]thio]-2-quinazolinamine and 1.0 g (0.012 mol) of methoxyamine hydrochloride in 7 mL of pyridine was warmed at 40–45 °C for 6 h. The reaction mixture was poured into 150 mL of cold water and the yellow gum that formed recrystallized twice from anhydrous ethanol and once from methanol to obtain 0.3 g of the title compound containing methanol (1:1). This product was combined with 0.4 g of the title compound containing methanol (1:1) obtained similarly from 1.5 g (0.004 08 mol) of 4-(methylthio)-6-[[3-(trifluoromethyl)-phenyl]thio]-2-quinazolinamine and heated at 100 °C under high vacuum for 24 h. The solvent-free product (0.6 g) was obtained as white needles.

4-(1-Methylhydrazino)-6-[[3-(trifluoromethyl)phenyl]-thio]-2-quinazolinamine (6f). A mixture of 3.6 g (0.0098 mol) of 4-(methylthio)-6-[[3-(trifluoromethyl)phenyl]thio]-2-quinazolinamine in 20 mL of pyridine and 3.0 mL of methylhydrazine was warmed at 50 °C for 20 h. The cooled reaction mixture was poured into 400 mL of water, and the yellow precipitate was collected and recrystallized twice from ethyl acetate to give 0.6 g of the title compound.

N^2,N^4-Dihydroxy-6-[[3-(trifluoromethyl)phenyl]thio]-2,4-quinazolinediamine (7b). A mixture of 1.2 g (0.003 56 mol) of 6-[[3-(trifluoromethyl)phenyl]thio]-2,4-quinazolinediamine and 1.5 g (0.0216 mol) of hydroxylamine hydrochloride in 10 mL of pyridine was stirred and warmed at 50 °C for 24 h. After standing at room temperature (ca. 23 °C) for an additional 48 h, the reaction mixture was poured into 250 mL of cold water to precipitate a white solid. Recrystallization from ethanol/water, followed by trituration with cold ethanol, yielded 0.8 g of the title compound as a white powder, which darkens on exposure to light.

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Registry No. **1a**, 51123-83-2; **1b**, 51123-99-0; **2a**, 52979-11-0; **2b**, 109890-44-0; **3a**, 52979-00-7; **3b**, 109890-45-1; **4a**, 109890-46-2; **4b**, 109890-47-3; **5a**, 109890-48-4; **5b**, 109890-49-5; **6a**, 109890-50-8; **6b**, 109890-51-9; **6c**, 109890-52-0; **6d**, 109890-53-1; **6e**, 109890-54-2; **6f**, 109890-55-3; **7a**, 109890-43-9; **7b**, 109890-56-4; **8**, 109890-57-5.

Acetylenic Nucleosides. 4.[1] 1-β-D-Arabinofuranosyl-5-ethynylcytosine. Improved Synthesis and Evaluation of Biochemical and Antiviral Properties[2]

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5-Ethynyl-1-β-D-arabinofuranosylcytosine (EAC) was prepared from 1-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)cytosine by iodination followed by coupling with (trimethylsilyl)acetylene and deblocking. At 50 μM, EAC was found to inhibit the in vitro replication of herpes simplex virus type 1 and type 2 by >99%. EAC also showed activity against a strain of HSV-1 resistant to (*E*)-5-(2-bromovinyl)-2′-deoxyuridine which has an alteration of the virus-induced thymidine kinase (TK). At 100 μM, EAC did not inhibit the in vitro growth of leukemia L1210 and HeLa cells. EAC was resistant to the action of dCR-CR deaminase, its rate of deamination being approximately 2% that of dCR. The compound was a poor substrate for dCR kinase, but it was phosphorylated by HSV-1- and HSV-2-induced TKs at 50% and 30%, respectively, the rate of thymidine.

The 5-ethynyl derivative of araC (**4**) was previously synthesized[3] in our laboratory as a potential anticancer and/or antiviral agent. The original synthetic method entailed difficult separation of the α- and β-anomers of **4** and was not, therefore, suitable for a "scale-up" preparation

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(1) For part 3 of this series, see: Sharma, R. A.; Kavai, I.; Hughes, R. G., Jr.; Bobek, M. *J. Med. Chem.* **1984**, *27*, 410.

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Scheme I

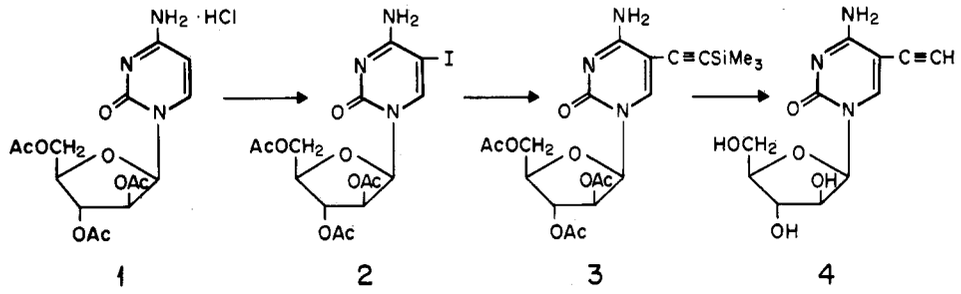

Table I. Inhibition of HSV Replication by EAC (4) in Strains Sensitive and Resistant to Acyclovir (ACV), 5(*E*)-(Bromovinyl)-2′-deoxyuridine (BVdU), and Phosphonoformic Acid (PFA)[a]

	PFU, % of control				
	EAC				
virus strain	50 μM	100 μM	ACV, 50 μM	BVdU, 30 μM	PFA, 50 μM
HSV-1 kinase mutants[12]					
SCS (parental)	0.38	0.12	0.2	0.4	
S1 (ACV)	70	59	18	3.7	
B3 (BVdU)	0.04	0.06	0.3	52	
Tr7 (ACV)	4.7	0.12	10	0.8	
DNA polymerase mutants[13]					
KOS (parental)	0.06	0.06	3		2.9
PFA^r 1a (PFA)	0.54	0.04	37		37
PFA^r 3b (PFA)	0.36	0.04	63		24
PFA^r 5a (PFA)	0.0	0.10	21		63
HSV-2					
333	0.28				

[a] The viral assays were performed by the yield reduction method as described in ref 11. The compounds used to develop resistant mutants are indicated in parentheses. The isolation and characteristics of the kinase and DNA polymerase mutants has been described previously.[12,13]

to provide a sufficient amount for biological evaluation. Utilizing the method of Robins and Barr,[4,5] we attempted to couple (trimethylsilyl)acetylene to 5-iodotetraacetylarabinofuranosylcytosine in Et_3N at 50 °C in the presence of catalytic amounts of $(Ph_3P)_2PdCl_2$ and CuI; however, no significant amount of the ethynylated product was detected in the reaction mixture. A similar attempt to utilize an N,O-toluoylated cytidine derivative in the coupling reaction was recently reported[6] without experimental details. Our supposition that the presence of the *N*-acetyl group was interfering with the reaction was confirmed by the facile ethynylation of O-acetylated 5-iodoarabinofuranosylcytosine.

The starting material, 1-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)cytosine (1) (Scheme I), for the synthesis of the title compound was prepared from the corresponding tetraacetate by selective N-deacetylation[7] with $ZnBr_2$ in methanol at room temperature or by selective O-acetylation of arabinofuranosylcytosine as described by Beranek and Drasar.[8] Because of its simplicity and good yield, direct acetylation[8] is the preferable method for synthesis of **1**. Whereas iodination[9] of the crude (tri-*O*-acetylarabinofuranosyl)cytosine resulted in an incomplete reaction and several byproducts, iodination of purified **1** in a mixture of iodic acid, iodine, CCl_4, acetic acid, and water at 40 °C gave 5-iodo-1-(2,3,5-tri-*O*-acetylarabinofuranosyl)cytosine (**2**) in good yield (80%). Iodination of free arabinosylcytosine, utilizing similar conditions, has been reported[10] to give 5-iodoarabinofuranosylcytosine in low (25%) yield. Reaction of **2** with (trimethylsilyl)-acetylene in the presence of CuI–$PdCl_2$–Ph_3P gave **3** after chromatographic purification on silica gel. Treatment of **3** with a catalytic amount of anhydrous K_2CO_0 in MeOH at 20 °C afforded 5-ethynylarabinofuranosylcytosine (**4**). After separation of crystalline **4**, TLC examination of the filtrate showed the presence of a minor byproduct (about 5%) which was identified as 5-acetyl-1-β-D-arabinofuranosylcytosine. While this byproduct was apparently the result of hydration of the ethynyl group, the mechanism of this reaction is not clear since **4** is not readily hydrated in aqueous solution.

Antiviral Activity. The stocks of HSV-1, HSV-2, and HSV-1 mutants resistant to acyclovir (ACV), 5(*E*)-(2-bromovinyl)-2′-deoxyuridine (BVdU), and phosphonoformic acid (PFA) were maintained as previously described.[11]

To establish the antiviral activity of 5-ethynyl-araC (EAC, compound **4**), the virus yield reduction assay was

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Table II. Rates of Phosphorylation of Nucleoside Analogues Relative to dThd and dCyd by Kinases from Human and Viral Sources[a]

	relative velocity, %				
	human			viral	
compd	Cyto dThdK	Mito dThdK	Cyto dCydK	HSV-1 (KOS) dThdK	HSV-2 (333) dThdK
dThd	100	100	6	100	100
dCyd	5	100	100	97	119
araC	1	22	361	3	10
EAC	0	62	10	50	30

[a] This assay was performed according to the methods of Doberson and Greer.[14] Cytosolic (Cyto) and mitochondrial (Mito) dThd kinases were isolated from the peripheral blast cells of leukemic patients. HSV-1 and HSV-2 dThd kinases were extracted from kinase-deficient HeLa (BU-25) cells infected with strain HSV-1 (KOS) or HSV-2. These enzymes were affinity purified as described previously.[15] The dCyd kinase enzyme was purified from human leukemia cells as described previously.[16]

performed in parallel with ACV, BVdU, and PFA as previously described.[11] Briefly, HeLa BU cells were seeded into 25-cm^2 flasks. The following day the growth media were removed, and the respective virus was added at a multiplicity of infection of 3–5 plaque-forming units per cell. After a 1-h adsorption period, the virus was removed and growth medium was added with or without drug. The cells were incubated at 37 °C for 24 h and were stored at −70 °C until titration.

As shown in Table I, EAC exhibited potent antiviral activity against the HSV-1 parental strains (SCS, KOS) and the HSV-2 strain (333). This compound was also effective against the HSV-1 mutant B3 (BVdU), which has an altered thymidine kinase. However, the strain of HSV-1, S1 which is resistant to ACV, was cross-resistant to EAC. Compound 4 was also active against the three PFA-resistant strains of HSV-1. These virus strains have an altered DNA polymerase with no apparent alteration of thymidine kinase. At 100 μM, a very effective dose for antiviral activity, EAC exhibited no growth inhibition of L1210 or HeLa cells in vitro. The selectivity of this compound is likely due to its phosphorylation by viral thymidine kinase, since it was not effective against the thymidine kinase negative mutant. At this time the mechanism of action is not clear. 5-Acetyl-1-β-D-arabinofuranosylcytosine did not show antiviral activity and at 100 μM was not inhibitory to L1210 cells in vitro.

Thymidine Kinase (TK) Studies. The phosphorylating activities of HSV-1- and HSV-2-induced thymidine kinases for thymidine (dThd), 2′-deoxycytidine (dCyd), 1-β-D-arabinofuranosylcytosine (araC), and 4 are shown in Table II. Compound 4 was selectively phosphorylated by HSV-1- and HSV-2-induced TKs, but it was a poor substrate for human dCyd kinase, in contrast to effective phosphorylation of araC by this enzyme. EAC behaved as a competitive inhibitor of HSV-1- and HSV-2-induced dThd kinases, the K_i values being 8.39 ± 3.23 and 28.20 ± 12.73, respectively.

Deamination. Substitution of the 5-position of araC with the ethynyl groups lowered its rate of deamination to approximately 2% of that of dCR (Table III).

Table III. Kinetics of Deamination of dCyd Analogues by dCyd Deaminase (Ref 17)[a]

compd	K_m,[b] μM	rel velocity
dCyd	38	1.0
araC	160	0.85
EAC	800	0.02

[a] The enzyme used in this study was purified from human acute myeloblastic leukemia cells. [b] K_m values are means of one to three duplicate trials; the relative velocity represents the V_{max} for the analogue relative to the V_{max} for dCR (V_{max} dCR = 1.0).

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian XL-100 spectrometer using Me_4Si as an internal standard. Silica gel TLC was performed on 60F-254 precoated sheets (E. Merck) and column chromatography was conducted on silica gel (60–250 mesh; J. T. Baker No. 3405). Elemental analyses were performed by Galbraith Laboratory, Knoxville, TN, and were within ±0.4% of the calculated values. Analytical HPLC was performed on a Waters C_{18} μ-Bondapak column in water–methanol (99:1).

1-(2,3,5-Tri-*O*-acetyl-β-D-arabinofuranosyl)cytosine Hydrochloride (1). A mixture of a arabinofuranosylcytosine hydrochloride (79.3 g, 0.283 mol), pyridine (500 mL), and acetic anhydride (320 mL, 3.39 mol) was stirred at 45 °C for 16–18 h. The reaction mixture was evaporated to a syrup, which was coevaporated with xylene (3 × 200 mL). The oily residue was dissolved in methanol (300 mL) and pyridine (30 mL) to hydrolyze the remaining acetic anhydride. The solution was evaporated to a syrupy residue, which was coevaporated with xylene and dissolved in CH_2Cl_2 (1200 mL). The solution was successively washed with water (200 mL), $NaHCO_3$ solution (2 × 150 mL), and water (2 × 100 mL). Evaporation of CH_2Cl_2 gave crystalline arabinofuranosylcytosine tetraacetate (129 g). This product (128 g) was dissolved in $CHCl_3$ (320 mL) and methanol (300 mL), and to this solution was added anhydrous $ZnBr_2$ (16 g). The reaction solution was kept at room temperature overnight and evaporated. The residue, which was homogeneous by TLC (EtOAc), was dissolved in 1,2-dichloroethane (600 mL) and the solvent was evaporated. The syrupy *O*-acetylated arabinofuranosylcytosine was converted to a hydrochloride by dissolving it in a mixture of CH_2Cl_2 (200 mL), anhydrous ether (140 mL), and HCl (gaseous) (12.6 g). Toluene (200 mL) was added to this solution, and the solvents were evaporated to an oil (181 g), which was dissolved in a mixture of acetic acid (200 mL), $CHCl_3$ (400 mL), and acetyl chloride (100 mL). After 6 h at room temperature, the reaction mixture was evaporated to dryness. The residue was coevaporated with xylene and crystallized from ethanol–2-propanol. Crystalline 1 was filtered and washed with acetone: yield 68.1 g (55%); mp 186–187 °C dec (lit.[8] mp 171–174 °C). Concentration of the combined filtrate and washings gave 8 g of 1: total yield 61.3%; ^{1}H NMR (DMSO-d_6–$CDCl_3$, 1:2, v/v) δ 10.32, 9.07 (2 s, 2, NH_2), 7.84 (d, 1, $J_{5,6}$ = 8 Hz, H-6), 6.52 (d, 1, H-5), 6.24 (d, 1, $J_{1',2'}$ = 4.0 Hz, H-1′), 5.40 (dd, 1, $J_{2',3'}$ = 1.5 Hz, H-2′), 5.13 (m, 1, H-3′), 4.15–4.50 (m, 3, H-4′, H-5′, H-5″), 2.15, 2.12, 2.06 (3 s, 9, OCOCH_3).

1-(2,3,5-Tri-*O*-acetyl-β-D-arabinofuranosyl)-5-iodocytosine (2). Compound 1 (51 g, 0.126 mol) was dissolved in a stirred mixture of acetic acid (450 mL), CCl_4 (450 mL), and iodine (19.3 g, 0.076 mol). The mixture was warmed to 40 °C and a solution of HIO_3 (19.3 g, 0.109 mol) in water (50 mL) was added. The reaction mixture was stirred at 40 °C for 4 h and evaporated. The residue was coevaporated with xylene (3 × 200 mL), dissolved in CH_2Cl_2 (1000 mL), filtered, washed with aqueous $NaHCO_3$, and dried (Na_2SO_4). Evaporation of the solvent gave crude 2, which was purified by silica gel chromatography with $CHCl_3$–2-propanol (25:1) as the eluant. The appropriate fractions were combined and evaporated to give 50 g (80.2%) of 2: mp 171–172 °C; ^{1}H NMR ($CDCl_3$) δ 7.84 (s, 1, H-6), 6.33 (d, 1, $J_{1',2'}$ = 4.0 Hz, H-1′) 5.46 (dd, 1, $J_{2',3'}$ = 1.5 Hz, H-2′), 5.10 (m, 1, H-3′), 4.36–4.20 (m, 3, H-4′, H-5′), 2.15, 2.11, 2.02 (3 s, 9, CH_3CO).

1-(2,3,5-Tri-*O*-acetyl-β-D-arabinofuranosyl)-5-[2-(trimethylsilyl)ethynyl]cytosine (3). To a stirred solution of 2 (50 g, 0.101 mol) in dry CH_2Cl_2 (800 mL) and dry Et_3N (800 mL) were added CuI (5.24 g, 0.027 mol), $(Ph_3P)_2PdCl_2$ (5.80 g, 0.0082 mol), and (trimethylsilyl)acetylene (17.2 mL, 0.12 mol). The vessel was flushed with argon and sealed and the mixture stirred at room temperature for 4 h. The mixture was evaporated to dryness, coevaporated with xylene (200 mL), dissolved in CH_2Cl_2 (1200 mL), and filtered through a Celite pad, which was then washed with CH_2Cl_2 (200 mL). The filtrate was extracted with 2% aqueous EDTA monosodium salt (2 × 150 mL) and water (50 mL), dried (Na_2SO_4), and evaporated to dryness. The residue was

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 Hz, 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.

Acknowledgment. This investigation was supported in part by Grants CA24538 and CA13038 awarded by the National Cancer Institute and by Grant CH29 from the American Cancer Society.

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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