

- Barczynska, *Arch. Immunol. Ther. Exp.*, **17**, 698-701 (1969).
 (11) M. Wilimowsky, K. Orzechowska, J. Prandota, and J. Barczynska, *Arch. Immunol. Ther. Exp.*, **17**, 833-835 (1969).
 (12) M. J. Michelson and E. V. Zeimel, *Int. Ser. Monogr. Pure Appl. Biol.*, **38**, 81 (1973).
 (13) L. Gyermek and K. Nador, *J. Pharm. Pharmacol.*, **9**, 209-229 (1957).
 (14) M. Rehavi, B. Yaavetz, Y. Kloog, S. Maayani, and M. Sokolovsky, *Biochem. Pharmacol.*, **27**, 1117-1124 (1978).
 (15) G. Lambrecht, *Experientia*, **32**, 365-367 (1976).
 (16) G. Lambrecht and E. Mutschler, *Arzneim.-Forsch.*, **24**, 1725-1729 (1974).
 (17) G. A. Neville, R. Deslauriers, B. J. Blackburn, and I. C. P. Smith, *J. Med. Chem.*, **14**, 717-721 (1971).

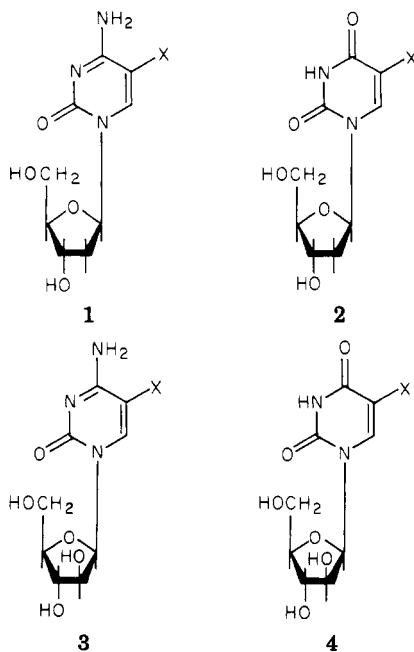
Nucleosides. 110. Synthesis and Antiherpes Virus Activity of Some 2'-Fluoro-2'-deoxyarabinofuranosylpyrimidine Nucleosides¹

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A series of 5-substituted 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)cytosines **7a-d** and their corresponding uracils **9a-d,f** were prepared by condensation of 3-O-acetyl-5-O-benzoyl-2-deoxy-2-fluoro-D-arabinosyl bromide (**5**) with appropriately trimethylsilylated pyrimidines followed by saponification of the protected nucleosides **6** or **8**. 1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodocytosine (**7e**) was obtained by iodination of **7a**. Iodination of **8a** followed by removal of the protecting acyl-protecting groups afforded the 5-iodo nucleoside **9e**. Several of these 2'-fluoro-substituted nucleosides completely obviated replication of herpes simplex virus type 1 (HSV-1) in monolayers of Vero cells at concentrations of 10-100 μg/mL. The 5-iodocytosine analogue **7e** was the most effective, showing 99.5% suppression of viral replication even at concentrations of 0.1 μg/mL. The cytotoxicity of **7e** to L5178Y or P815 cells in culture was minimal. A comparison of the efficacy of **7e** against HSV-1 with other known nucleoside antiviral agents indicates that further in vitro and in vivo evaluation of **7e** is warranted.

Studies by Cooper² and Schildkraut et al.³ showed that 5-bromo- and/or 5-iodo-2'-deoxycytidine (**1**, X = Br or I) inhibit the replication of herpes simplex virus (HSV) as effectively as their corresponding deoxyuridine analogues **2**. Their studies also showed that these deoxycytidine analogues are significantly less toxic to uninfected cells than are 5-iodo- (or 5-bromo-) 2'-deoxyuridine (**2**) apparently as a result of a virus-induced pyrimidine nucleoside kinase which converts the 5-halogenated deoxycytidines to their 5-halogenated deoxycytidylates and thence to the corresponding deoxyuridylates.



series a, X = H; b, X = F; c, X = Cl; d, X = Br; e, X = I; f, X = CH₃.

1-β-D-Arabinofuranosylcytosine (*ara*-C, **3a**), a potent anticancer drug,⁴ also inhibits the multiplication of several

DNA viruses in cell culture.⁵ Therapeutic trials of *ara*-C in herpes infections in animal models were not encouraging because its therapeutic to toxic ratio approached unity.⁶ Although 1-β-D-arabinofuranosyluracil (*ara*-U, **4a**) is devoid of antiviral or anticancer activity, the 5-halogeno analogues (**4**, X = Cl, Br, I) show antiviral activity in cell culture⁷ and in vivo.⁸ Gentry et al.⁹ demonstrated that *ara*-T (**4f**) also is active against HSV types 1 and 2 as well as against equine herpes virus. More recently they¹⁰ showed that 5-Me-*ara*-C (**3f**) is also active against herpes virus infected cells in which deoxycytidine deaminase is present, indicating that this nucleoside serves as an intracellular donor of *ara*-T that is phosphorylated to the nucleotide which then inhibits viral replication. (5-Me-*ara*-C is devoid of anticancer activity.¹¹) The 5-halogeno-*ara*-C derivatives (**3**, X = F, Cl, Br, I) have also shown antiherpes virus activity in culture and were also active against experimental herpes keratitis in rabbits.¹²

It is apparent from the above-mentioned data that the nature of the substituent at C-5 of the pyrimidine nucleosides **1-4** is an important factor in the determination of biological activity. Moreover, since activity is noted for both 2'-deoxyribo- as well as 2'-deoxyarabinopyrimidine nucleosides, the C-2' substituent also plays a role in the determination of biological activity. This report describes the syntheses and preliminary evaluation of a series of 5-substituted 1-(2-deoxy-2-fluoroarabinofuranosyl)pyrimidines (**7** and **9**) as part of our program in the design and syntheses of nucleosides of potential value as anticancer and/or antiviral agents.

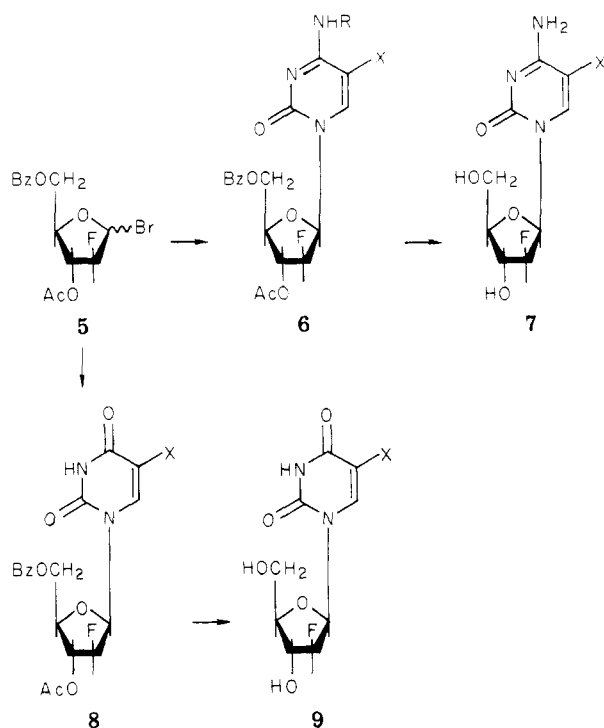
We had previously developed¹³ a practical synthesis of 3-O-acetyl-5-O-benzoyl-2-deoxy-2-fluoro-D-arabinofuranosyl bromide (**5**), a key intermediate in the syntheses of the desired nucleosides. Thus, condensation of halogenose **5** with trimethylsilylated cytosines afforded the blocked nucleosides **6** which were deprotected by saponification to the 2'-F-*ara*-C type nucleosides **7a-d**. The 5-iodo analogue **7e** was obtained by iodination of **7a**. The uracil nucleoside analogues **9a-d,f** were obtained by condensation of **5** with the corresponding trimethyl-

Table I. Capacity of 2'-Fluoro-2'-deoxyarabinosylcytosines and -uracils to Suppress HSV-1 Replication in Monolayers of Vero Cells

		antiviral act. ^a in $\mu\text{g/mL}$					cytotoxicity, ID ₅₀ in $\mu\text{g/mL}$ ^b	
	X	0.01	0.1	1.0	10	100	L5178Y	P815
Cytosine Nucleosides ^c								
7a ^d	H	—	+	+	+++	++++	0.05	0.05
7b	F	—	+	++	+++	ND ^e	0.5	0.4
7c	Cl	—	—	—	+++	ND	1.4	~1.0
7d	Br	—	+	++	+++++	ND	~10	>10
7e	I	+	++	++++	+++++	+++++	48	14
Uracil Nucleosides								
9a	H	—	—	++	++	ND	>10	>10
9b	F	—	++	++++	+++++	ND	1.0	0.7
9c	Cl	—	—	—	++++	ND	1.4	3.4
9d	Br	—	—	++	++++	ND	0.9	1.6
9e	I	—	+	+++	++++	ND	0.9	0.8

^a Percent reduction of HSV-1 titer: >90% = +; >99% = ++; >99.9% = +++; >99.99% = ++++; complete obviation of HSV-1 replication = +++++. (—) = <90% reduction of HSV-1 titer. ^b Concentration required for 50% inhibition of growth of cells in vitro after 96 h of incubation at 37 °C. ^c All pyrimidine nucleosides listed in this table and others discussed elsewhere are of the 1- β -D configuration and are in the neutral form except for compounds 7a and 7e which are in the form of their hydrochloride salts. ^d J. A. Wright, D. P. Wilson, and J. J. Fox, *J. Med. Chem.*, **13**, 269 (1970). ^e ND = not done.

silylated uracils and subsequent removal of the blocking groups. Iodination of 6a followed by saponification afforded the 5-iodo analogue 9e.



series a, X = H; b, X = F; c, X = Cl; d, X = Br; e, X = I; f, X = CH₃; R = H or acetyl

The capacity of these 2'-fluoroarabinosyl nucleosides 7 and 9 to suppress replication of herpes simplex virus type 1 (HSV-1) in monolayers of Vero cells is shown in Table I. Five of these nucleosides (7d,e and 9b,d,e) completely obviated replication of HSV-1 at concentrations of 100 $\mu\text{g/mL}$. At drug levels of 10 $\mu\text{g/mL}$, 2'-F-ara-5-IC (compound 7e) was equally effective while the 5-bromo analogue 7d was a close second. Even at levels of 0.1 $\mu\text{g/mL}$ compound 7e showed >99.5% suppression of viral replication in this system. By comparison, ara-A (9- β -D-arabinofuranosyladenine), an antiherpes drug with clinical efficacy,¹⁴ has, in our hands, only approached these levels of viral suppression at doses 1000–10 000-fold higher.

Of greater interest is the demonstration that the cytotoxicity of the cytosine nucleosides 7d,e against L5178Y and P815 cells was minimal at best. This inverse relationship (high antiviral activity associated with minimal cytotoxicity) seems to be characteristic of the 2'-fluoroarabinosylcytosine nucleosides in Table I. This relationship does not hold for the corresponding uracil series (compounds 9). Thus, though several of the 2'-fluoroarabinosyluracils (9b,d,e) exhibit significant inhibition of viral replication, they also show appreciable cytotoxicity against cells in culture.

The data in Table II attest to the importance of the 2'-fluoro substituent for the anti-HSV-1 activity exhibited by the 1- β -D-arabinofuranosyl nucleosides. Thus, 2'-fluoro-ara-5-iodocytosine (7e) is much more effective than 2'-deoxy-5-iodocytidine (IdC, 1e) or arabinosyl-5-iodocytosine (3e) which indicates that the 2'-fluoro substituent confers better antiviral activity to these 5-iodocytosine nucleosides than does a 2'-hydroxyl or a 2'-hydrogen substituent. A similar conclusion may be reached from a comparison of the 5-iodouracil nucleosides 9e, 2e, and 4e. Even in the thymine series, 2'-fluoroarabinosylthymine (9f) is clearly more effective against HSV-1 than is arabinosylthymine (4f).

Further in vitro and in vivo studies on HSV-1 and other herpes virus systems are underway in order to evaluate the possible clinical efficacy of 1-(2-fluoro-2-deoxy- β -D-arabinofuranosyl)-5-iodocytosine (7e).

Experimental Section

General. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and by Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting points were determined on a Thomas-Hoover capillary apparatus and were corrected. Melting points, crystallization solvents, and analytical data are listed in Table III.

1-(3-O-Acetyl-5-O-benzoyl-2-deoxy-2-fluoro- β -D-arabinofuranosyl)-5-fluorocytosine (6b). To a stirred solution of 5¹³ (3.6 g, 0.01 mol) in CH₂Cl₂ (50 mL) was added crude 5-fluorotris(trimethylsilyl)cytosine (prepared from 3.78 g, 0.03 mol, of 5-fluorocytosine) in CH₂Cl₂ (25 mL), and the mixture was stirred for 5 days at room temperature. MeOH (7 mL) was added and the suspension was filtered through a Celite pad which was thoroughly washed with CH₂Cl₂. The combined filtrate and washings were evaporated to dryness in vacuo, and the residue was crystallized from EtOH to give 2.0 g of 6b.

Compounds 6a,c,d (see Table III) were also obtained in a similar manner using the trimethylsilyl derivatives prepared from N⁴-

Table II. Comparison of Antiherpes Virus Activity of Certain 2'-Fluoro Nucleosides with Their Corresponding Nonfluorinated Arabino and/or 2'-Deoxyribo Analogues

nucleoside	antiviral act. ^a in $\mu\text{g/mL}$					cytotoxicity, ID_{50} in $\mu\text{g/mL}^b$	
	0.01	0.1	1.0	10	100	L5178Y	P815
ara-C	—	—	+	++++	++++	0.02	0.02
2'-F-ara-C (7a)	—	+	+	+++	++++	0.05	0.05
ara-IC (3e)	—	—	+	++++	ND	0.2	0.08
IdC (1e)	—	—	+	+++	ND	>100	>100
2'-F-ara-IC (7e)	+	++	++++	+++++	+++++	48	14
ara-IU (4e)	—	—	—	+	++++	30	16
IdU (2e)	—	—	—	+	+++++	4.2	0.9
2'-F-ara-IU (9e)	—	+	+++	++++	ND	0.9	0.8
ara-T (4f)	—	—	+	+++++	+++++	>100	13
2'-F-ara-T (9f)	—	+	+++	+++++	ND	1.6	1.9

^{a,b} See corresponding footnotes in Table I.**Table III^a**

compd	mp, °C	crystn solvent	formula
6a	198-201	EtOH	$\text{C}_{20}\text{H}_{20}\text{FN}_3\text{O}_7$
6b	237-239 dec	EtOH	$\text{C}_{18}\text{H}_{17}\text{F}_2\text{N}_3\text{O}_6$
6c	233	EtOH	$\text{C}_{18}\text{H}_{17}\text{ClFN}_3\text{O}_6$
6d	206	EtOH	$\text{C}_{18}\text{H}_{17}\text{BrFN}_3\text{O}_6$
8a	179-180	EtOH	$\text{C}_{18}\text{H}_{17}\text{FN}_3\text{O}_7$
8b	177-179	EtOH	$\text{C}_{18}\text{H}_{16}\text{F}_2\text{N}_3\text{O}_7$
8f	169-170	EtOH	$\text{C}_{17}\text{H}_{17}\text{FN}_3\text{O}_6^b$
7a	240-242	EtOH	$\text{C}_9\text{H}_{12}\text{FN}_3\text{O}_4$
7b	188-189 dec	EtOH	$\text{C}_9\text{H}_{11}\text{F}_2\text{N}_3\text{O}_4^c$
7c	205-206	EtOH	$\text{C}_9\text{H}_{11}\text{ClFN}_3\text{O}_4$
7d	201-102	EtOH	$\text{C}_9\text{H}_{11}\text{BrFN}_3\text{O}_4$
7e	177-181 dec	MeOH	$\text{C}_9\text{H}_{11}\text{FIN}_3\text{O}_4 \cdot \text{HCl}$
9a	162	i-PrOH-Et ₂ O	$\text{C}_9\text{H}_{11}\text{FN}_3\text{O}_5$
9b	167-168	EtOH	$\text{C}_9\text{H}_{10}\text{F}_2\text{N}_3\text{O}_5$
9c	195-196	H ₂ O	$\text{C}_9\text{H}_{10}\text{ClFN}_3\text{O}_5$
9d	214-216	H ₂ O	$\text{C}_9\text{H}_{10}\text{BrFN}_3\text{O}_5$
9e	216-217	EtOH	$\text{C}_9\text{H}_{10}\text{FIN}_3\text{O}_5$
9f	185-185.5	H ₂ O	$\text{C}_{10}\text{H}_{13}\text{FN}_3\text{O}_5$

^a All compounds in Table III gave satisfactory C, H, F, and N analyses. ^b Deacetylation occurred during work-up; confirmed by NMR. ^c The HCl salt of 7b was also obtained: mp 203-206 °C dec.

acetylcytosine, 5-chlorocytosine, and 5-bromocytosine, respectively.

1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-5-fluorocytosine (7b). Compound 6b (1.1 g) was dissolved in saturated NH_3 -MeOH (30 mL). After 16 h, the solvent was removed in vacuo and the residue was triturated with acetone. Crystalline 7b (460 mg) was filtered. The filtrate was evaporated in vacuo and the residue was triturated with ~7 mL of HCl-MeOH. The HCl salt of 7b (100 mg) was obtained as colorless crystals.

Similarly, treatment of 6a,c,d with NH_3 -MeOH afforded the corresponding free nucleosides 7a,c,d (see Table III).

1-(3-O-Acetyl-5-O-benzoyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)uracil (8a). A mixture of 5 (11.5 g) and crude 2,4-bis[(trimethylsilyl)oxy]pyrimidine (prepared from 5 g of uracil) in 150 mL of CH_2Cl_2 was stirred for 5 days at room temperature. MeOH (5 mL) was added to the mixture and the suspension was filtered through a Celite pad. The filtrate was evaporated in vacuo and the residue was triturated with Et₂O to give crude 8a (5.8 g) which was recrystallized from EtOH. Pure 8a (4.2 g) was obtained as colorless leaflets.

Compound 8f was also obtained in a similar manner (see Table III).

Conversion of 6a to 8a. A solution of 6a (200 mg) in 80% AcOH (20 mL) was heated under reflux for 1.5 h. The mixture was evaporated in vacuo and the residue was dissolved in a small amount of EtOH. To the solution was added Et₂O, and the precipitate was filtered and recrystallized from EtOH to afford 80 mg of compound identical with 8a obtained previously by an alternate route.

Conversion of 6b to 8b. A mixture of 6b (650 mg) in 80% AcOH (50 mL) was heated under reflux for 48 h. After removal

of the solvent in vacuo the residue was chromatographed over a column of silica gel G 60 (22 × 2 cm) using CHCl_3 -MeOH (30:1 v/v) as the eluant. The crystalline product (300 mg) obtained was identical with 8b obtained by condensation of 5 and 2,4-bis[(trimethylsilyl)oxy]-5-fluoropyrimidine (see below).

1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-5-fluorouracil (9b). **Method A.** Compound 8b (170 mg) was dissolved in saturated NH_3 -MeOH (10 mL) and the mixture left standing for 16 h. The solvent was removed by evaporation in vacuo, and the residue crystallized from EtOH to give 66 mg of 9b.

Similarly, compounds 9a,f were obtained from 8a,f, respectively (see Table III).

Method B. To a solution of 5¹³ (3.5 g, 0.01 mol) in CH_2Cl_2 (10 mL) was added 2,4-bis[(trimethylsilyl)oxy]-5-fluoropyrimidine (prepared from 2.6 g, 0.02 mol, of 5-fluorouracil) in CH_2Cl_2 (50 mL), and the mixture was stirred for 5 days at room temperature. MeOH (3 mL) was added and the suspension was filtered through a Celite pad which was thoroughly washed with CH_2Cl_2 . TLC (10:1 v/v CHCl_3 -MeOH) showed that the filtrate contained one major component contaminated with some partially deacylated products. The major component (8b) was isolated by chromatography on a silica gel G 60 (22 × 2.5 cm) column with 50:1 (v/v) CHCl_3 -MeOH as the solvent. Appropriate fractions (checked by TLC) were collected and evaporated in vacuo to a syrup which was dissolved in saturated NH_3 -MeOH (50 mL). After 2 days at room temperature, the solvent was removed by evaporation and the residue triturated with CHCl_3 . The insoluble material was crystallized from EtOH to give 265 mg of 9b which was identical with an authentic sample prepared by hydrolytic deamination of 6b to 8b followed by deacylation.

In a similar manner, 9c and 9d were prepared by condensation of 5 with the corresponding silylated 5-halogenouracils (see Table III).

1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodocytosine Hydrochloride (7e). A mixture of 7a (HCl salt, 610 mg), AcOH (2.2 mL), HIO_3 (196 mg), I_2 (327 mg), CCl_4 (1.5 mL), and H_2O (0.75 mL) was stirred at 40-50 °C for 2.5 h and then at room temperature overnight. H_2O (6 mL) was added and the yellow precipitate (650 mg; mp 115-125 °C dec) filtered. Anal. Calcd for $\text{C}_9\text{H}_{11}\text{FIN}_3\text{O}_4 \cdot \text{HCl} \cdot 0.5\text{H}_2\text{O}$: C, 22.45; H, 2.80; F, 3.95; I, 39.60; N, 8.73 (C, H, F, I, N).

The above product (610 mg) was dissolved in H_2O (100 mL) and the red-brown solution passed through a column of Amberlite IR-45 (OH^- , 20 mL). The column was washed with H_2O (200 mL). The combined eluates and washings were evaporated in vacuo, and the colorless residue was dissolved in HCl-MeOH (10 mL). Compound 7e (HCl salt, 190 mg) deposited as colorless crystals (see Table III).

1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodouracil (9e). To a mixture of 8a (400 mg) and I_2 (130 mg) in AcOH (5 mL) was added fuming HNO_3 (sp gr 1.5) dropwise with stirring until the color of I_2 disappeared. After evaporation in vacuo, the residue was triturated with H_2O and the insoluble product (515 mg) was collected by filtration.

The crude product (200 mg) was dissolved in saturated NH_3 -MeOH (50 mL). After 2 days, the solvent was removed by

evaporation and the residue dissolved in a small amount of EtOH. To the solution was added Et₂O and the product was collected by filtration and recrystallized from EtOH to give 86 mg of **9e** (see Table III).

5-Iodo-2'-deoxycytidine (IdC) and 5-iodo-2'-deoxyuridine (IdU) were commercial samples obtained from Sigma Chemical Co., St. Louis, Mo. *ara*-IC was synthesized according to Honjo et al.¹⁵ *ara*-IU (**4e**) was prepared according to Hunter.¹⁶

Antiviral Assay. Vero cell monolayers were infected with approximately 1 plaque-forming unit (PFU) per cell of herpes simplex virus type 1 (HSV-1) strain 2931 and incubated for 2 h. Maintenance media containing the various concentrations of drugs were used to overlay the monolayers. Supernatant fluids were collected 24 h later and titered on Vero cell monolayers as described previously.¹⁷ Percent inhibition over controls was calculated.

Cell Culture Studies (by Dr. J. H. Burchenal). The technique of Fischer¹⁸ was employed with modifications.¹⁹ Mouse cell lines L5178Y and P815 were incubated in McCoy's medium with 15% fetal calf serum. The initial inoculum was 40 000–60 000 leukemic cells/mL. For growth inhibition studies, 0.1 mL of a 50-fold concentration of the nucleoside in question was added to 5 mL of the cell-containing media. The tubes were set up in triplicate, loosely capped, and allowed to incubate in 5% CO₂ at 37 °C for 96 h. Growth to ~10⁶ cells/mL occurred in the control tubes. The contents of each tube was counted on a Coulter counter and the percentage of inhibition of growth was calculated.

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References and Notes

- (1) This investigation was supported by funds from the National Cancer Institute, National Institutes of Health, U.S. Public Health Service Grant No. CA-08748, CA-18601 and CA-18856.
- (2) G. M. Cooper, *Proc. Natl. Acad. Sci. U.S.A.*, **70**, 3788 (1973).
- (3) I. Schildkraut, G. M. Cooper, and S. Greer, *Mol. Pharmacol.*, **11**, 153 (1975); S. Greer and I. Schildkraut, *Ann. N.Y. Acad. Sci.*, **255**, 359 (1975), and references cited therein.
- (4) R. W. Talley, R. M. O'Bryan, W. G. Tucker, and R. V. Loo, *Cancer*, **20**, 809 (1967).
- (5) D. A. Buthala, *Proc. Soc. Exp. Biol. Med.*, **115**, 69 (1964); L. A. Feldman and E. Rapp, *ibid.*, **122**, 243 (1966).
- (6) See C. B. Lauter, E. J. Bailey, and M. Lerner, *Antimicrob. Agents Chemother.*, **6**, 598 (1974), and references cited therein.
- (7) J. deRudder and M. Privat de Garilhe, *Antimicrob. Agents Chemother.*, **578** (1965); H. E. Renis, C. A. Hollowell, and G. E. Underwood, *J. Med. Chem.*, **10**, 777 (1967).
- (8) G. E. Underwood, C. A. Wisner, and S. D. Weed, *Arch. Ophthalmol.*, **72**, 505 (1964).
- (9) G. A. Gentry and J. F. Aswell, *Virology*, **65**, 294 (1975); J. F. Aswell and G. A. Gentry, *Proc. Am. Soc. Microbiol.*, **240** (1975).
- (10) J. F. Aswell and G. A. Gentry, *Ann. N.Y. Acad. Sci.*, **284**, 342 (1977).
- (11) I. L. Doerr, J. F. Codington, and J. J. Fox, *J. Med. Chem.*, **10**, 247 (1967).
- (12) H. E. Renis, G. E. Underwood, and J. H. Hunter, *Antimicrob. Agents Chemother.*, **675** (1967); J. J. Fox, N. Miller, and I. Wempen, *J. Med. Chem.*, **9**, 101 (1966).
- (13) U. Reichman, K. A. Watanabe, and J. J. Fox, *Carbohydr. Res.*, **42**, 233 (1975).
- (14) L. T. Ch'ien, N. J. Cannon, L. J. Charamella, W. E. Diskmukes, R. J. Whitley, R. A. Buchanan, and C. A. Alford, *J. Infect. Dis.*, **128**, 658 (1973).
- (15) M. Honjo, Y. Furukawa, M. Nishikawa, K. Kamiya, and Y. Yoshioka, *Chem. Pharm. Bull.*, **15**, 1076 (1967).
- (16) J. H. Hunter, U.S. Patent 3 155 646 [*Chem. Abstr.*, **62**, P2821a (1965)].
- (17) C. Lopez and A. Giner-Sorolla, *Ann. N.Y. Acad. Sci.*, **284**, 351 (1977).
- (18) G. A. Fischer, *Ann. N.Y. Acad. Sci.*, **76**, 673 (1958).
- (19) J. H. Burchenal, K. Ciovacco, K. Kalaher, T. O'Toole, R. Kiefner, M. D. Dowling, C. K. Chu, K. A. Watanabe, I. Wempen, and J. J. Fox, *Cancer Res.*, **36**, 1520 (1976).

Preparation of the Enantiomeric Forms of 9-(5-Deoxy- α -threo-pent-4-enofuranosyl)adenine and 9-(3,5-Dideoxy- β -D-glycero-pent-4-enofuranosyl)adenine and in Vitro Antileukemic Screening

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The preparation and use of 5-deoxy-5-iodo-1,2-*O*-isopropylidene- α -D-xylofuranose and 5-deoxy-5-iodo-1,2-*O*-isopropylidene- α -D-arabinofuranose in the synthesis of the L and D forms of 9-(5-deoxy- α -threo-pent-4-enofuranosyl)adenine, respectively, are described. The preparation of 9-(3,5-dideoxy- β -D-glycero-pent-4-enofuranosyl)adenine (**19**) was accomplished from either 3,5-dideoxy-5-iodo-1,2-*O*-isopropylidene- α -D-erythro-pentofuranose or 3,5-dideoxy-5-iodo-1,2-*O*-isopropylidene- β -L-threo-pentofuranose. In each case, acetolysis was performed to obtain the acetates which were condensed with 6-(benzamidochloromercuri)purine by the titanium tetrachloride method. Treatment with 1,5-diazabicyclo[5.4.0]undec-5-ene and removal of the blocking groups produced the desired nucleosides. Only **19** showed inhibitory activity toward leukemia L1210 in vitro.

The nucleoside antibiotic decoyinine (angustmycin A) was reported to have antibacterial and antitumor activity.¹ The structure of decoyinine was shown to be 9-(6-deoxy- β -D-erythro-hex-5-enulofuranosyl)adenine.² The closely related compound which lacked the anomeric hydroxymethyl group, 9-(5-deoxy- β -D-erythro-pent-4-enofuranosyl)adenine, was shown to inhibit *Streptococcus faecalis* with the same potency as decoyinine.³ In order to further explore the biological effects of 4',5' unsaturation

in nucleosides and to possibly improve upon the range and extent of biological activity, this laboratory set out to prepare a number of compounds in this series.

Previous reports from this laboratory have described the synthesis of several 4',5'-unsaturated nucleosides.^{4,5} Originally the synthesis of such unsaturated nucleosides was undertaken starting from a preformed nucleoside.^{4,6} It became evident in time that synthesis by this route created a number of problems, among which were cyclonucleoside