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(22) No intermolecular stacking takes place in this concentration range; the uv spectrum of an equimolecular solution of the reference compounds **5** + **6** and **5** + **7** is superimposable with the summation curves of the spectra of the individual components. In the concentration range available, the solutions obey Beer's law.
(23) The value of H is very inferior (% H = 10 in the 300–380-nm range) in the interaction model of thymine, implying that quinoline–thymine interactions exist even though they are much less important than those between the quinoline and purine bases.
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(27) For the interaction model of thymine, the value of the maximum hypochromic effect is not attained.

Nucleosides. 102. Synthesis of Some 3′-Deoxy-3′-Substituted Arabinofuranosylpyrimidine Nucleosides[1]

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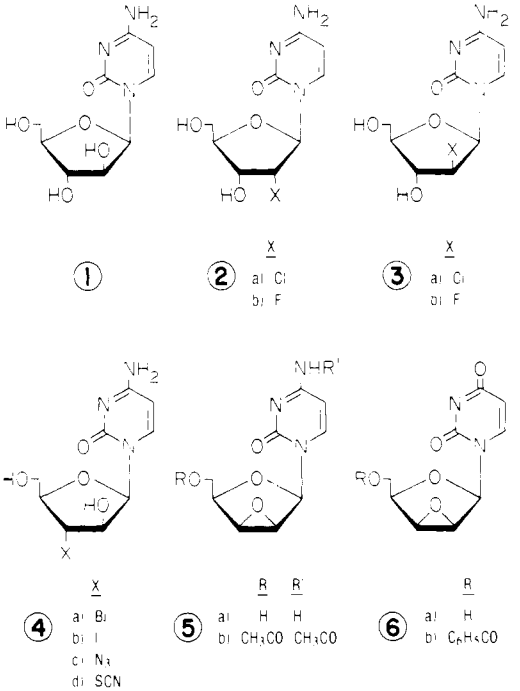
The synthesis of some 3′-deoxy-3′-substituted arabinofuranosylcytosine (**4a–d**) and uracil (**7a–d**, **8a–d**, X = Br, I, N_3, SCN) nucleosides was accomplished by treatment of the requisite 2′,3′-anhydrolyxofuranosylpyrimidine nucleoside (**5**, **6a,b**) with the appropriate ammonium salt in refluxing ethanol. Cleavage of the oxirane ring provided the desired 3′-deoxy-3′-substituted pyrimidine nucleosides (**4a–d**, **7a–d**, and **8a–d**). In vitro screening of compounds **4a–d**, and **7a–d**, with L5178Y cells in culture showed no significant inhibitory properties.

The nucleoside 1-β-D-arabinofuranosylcytosine (**1**, *ara*-C) is probably the most efficacious drug currently available for the treatment of acute myeoblastic leukemia.[2] Previous reports from this laboratory[3] have described the synthesis of 2′-deoxy-2′-halogeno analogues of cytidine and *ara*-C (compounds **2** and **3**, respectively). Some of these have shown significant activity against leukemic cells in culture.[3b,4] The mechanism(s) of this inhibition, however, has not been ascertained. Nucleosides **2** and **3** may act as analogues of 2′-deoxycytidine or as analogues of *ara*-C, or they may be converted in situ to *ara*-C. Chemically, the conversion of nucleoside types **2** and **3** to *ara*-C is readily accomplished by treatment with base.[3a,5]

Extension of our studies to the synthesis of 3′-deoxy-3′-substituted arabinofuranosylcytosines (**4**) became of interest as a method of examining the role of the 3′ position as a function of "*ara*-C-like" activity. The simplest method for synthesis of this type of compound seemed to be by cleavage of 2′,3′-anhydrolyxofuranosylcytosine (**5a**).[6] It has been demonstrated previously[7] that nucleophilic attack on 2′,3′-anhydrolyxofuranosyl nucleosides occurs predominantly, if not exclusively, at the 3′ position. A number of methods of cleaving epoxides were investigated using the 2′,3′-anhydrolyxofuranosyluracils **6a** and **6b**. It was found that treatment of such epoxides with ammonium salts proved to be the simplest method. These salts provide a mildly acidic reaction medium which leads to relatively rapid cleavage and allows facile isolation of the products. Thus the 2′,3′-epoxy nucleosides **5a** and **6** were refluxed



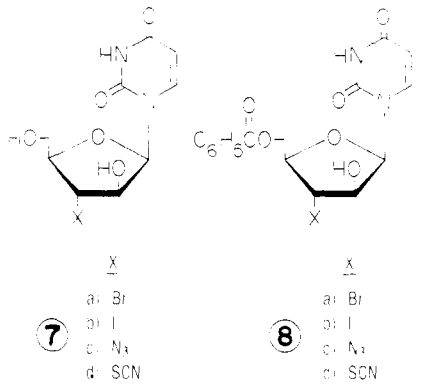
in ethanol in the presence of the appropriate ammonium salt until the evolution of ammonia ceased and TLC examination of the reaction mixture showed the absence of

Table I. 3'-Deoxy-3'-Substituted Arabinofuranosylpyrimidine Nucleosides

Compd	X	Mp, °C (solvent)	$[\alpha]^{27}D$, deg (solvent, c)	NH_4X/epoxide mole ratio	Yield,[a] % (g)	Analyses[b]	ID_{50},[c] %
7a	Br	185-185.5 (EtOH)	+44.4 (H_2O, 1.0)	1.12:1	61 (0.293)	C, H, N, Br[d]	6[c]
7b	I	204-205 (EtOH)	+33.8 (DMF, 1.03)	1.02:1	69 (0.565)	*e*	0[c]
7c	N_3	178-179.5 (EtOH)	+81.7 (H_2O, 1.2)	1.7:1	80 (0.450)	C, H, N[d]	0[c]
7d	SCN	185-189 (*i*-PrOH-H_2O)	+21 (MeOH, 2.24)	1.03:1	85 (2.3)	C, H, N, S	5[c]
8a	Br	227 dec (EtOH-H_2O)	+21.1 (DMF, 1.22)	6:1	66 (0.9)	C, H, N, Br	
8b	I	210-212 dec, lib I_2 (EtOH)	+15.7 (DMF, 1.08)	1.7:1	58 (0.9)	*f*	
8c	N_3	150-153 (MeOH)	+41.1 (DMF, 1.16)	10:1	86 (1.0)	C, H, N	
8d	SCN	178-179 (EtOH)	+1.05 (DMF, 1.2)	15:1	70 (2.2)	C, H, N, S	
4a	Br	181-183 (H_2O-MeOH-EtOH)		1.06:1	67 (0.207)	C, H, N, Br	10.0
4b	I	199 (*i*-PrOH)	+9.8 (DMF, 0.26)	1.2:1	57 (0.202)	C, H, N, I	1.0
4c	N_3	216 (browning 200) (MeOH)	+96.3 (H_2O, 0.50)	2:1	76 (0.136)	C, H, N	0.5
4d	SCN	170-173 (*i*-PrOH)	+29 (H_2O, 1.4)	1.3:1	85 (0.326)	C, H	34[c]

[a] Refers to material obtained from initial crystallization which, in general, was of analytical purity. Additional material could be obtained from the mother liquor. [b] Analyses are within ±0.3% of calculated values. References are given for previously reported compounds. [c] Given in μg/ml with L5178Y cells in culture. Percentages refer to inhibition at highest concentration tested, 10 μg/ml. For a description of test procedures, see ref 13. [d] See ref 11. [e] See ref 7b. [f] See ref 12.

starting material. The product (**4**, **7**, or **8**, X = Br, I, N_3, or SCN) was isolated either by direct crystallization or by a simple extractive procedure. The structures of some of these products (**7a–c**, **8b**) were established by their identity with previously reported compounds as shown in Table I. The structures of the new compounds (**4a–d**, **7d**, and **8a,c,d**) are indicated by analogy with the known route of



epoxide cleavage as shown above and by the overall similarities of their NMR spectra to those of the known nucleosides (see Table II). Although the formation of small amounts of the corrresponding 2'-deoxy-2'-substituted xylofuranosyl nucleosides cannot be precluded, TLC examination of the mother liquors of crystallization exhibited only single spots corresponding to the arabinofuranosyl nucleosides.

In vitro screening of compounds **4a–d** and **7a–d** against L5178Y cells in culture showed no significant inhibition. Compound **4c**, which had the highest activity in this system, possessed an ID_{50} = 0.5 μg/ml.[8] It must be concluded, therefore, that the 3'-hydroxyl group in the "down" arabino configuration, while necessary for enzymatic deamination,[3b,9] is also necessary for inhibition of this leukemic cell line.

Experimental Section

General. Melting points were determined on a Thomas-Hoover Unimelt apparatus. NMR spectra were obtained on a JEOL-PFT-100 spectrometer (see Table II). Optical rotations were measured on a modified Beckman DU spectrophotometer. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and Spang Microanalytical Laboratory, Ann Arbor, Mich.

1-(2,3-Anhydro-β-D-lyxofuranosyl)cytosine (5a). 2,2'-Anhydro-3'-(*O*-methanesulfonyl)arabinofuranosylcytosine methanesulfonate (2.0 g)[10] was dissolved in water (20 ml) and potassium carbonate was added (1.0 g). After 2 h, more potassium carbonate was added (0.5 g) and the solution was stirred at room temperature for 16 h. Excess Amberlite IRC-50 (H^+) was added, and after stirring for 2 h the solution was filtered. The filtrate was concentrated and placed on a Dowex-50 (H^+) column. After washing the column thoroughly, the nucleosides was eluted with 1 N NH_4OH. Evaporation provided 0.9 g of an amorphous foam. TLC examination of this foam showed two uv-absorbing spots (major, R_f = 0.46; minor, R_f = 0.20, 90% EtOH). Only the major component charred after sulfuric acid spray and exhibited a positive test for epoxides with methyl red spray: uv λ_{max} (H_2O) 269 nm, (pH 1) 277 nm. A portion of this material was dissolved in methanol and a few drops of ~5% HCl in MeOH was added. The solution was evaporated and ether was evaporated from the residue. Crystallization from ethanol provided the hydrochloride salt: mp 167–168 °C (lit.[6] mp 167–168 °C); NMR, see Table II.

Compound **5a** was further characterized as 1-(5-*O*-acetyl-2,3-anhydro-β-D-lyxofuranosyl)-N^4-acetylcytosine (**5b**).

1-(5-*O*-Acetyl-2,3-anhydro-β-D-lyxofuranosyl)-N^4-acetylcytosine (5b). 5a (87 mg) was dissolved in pyridine (1 ml) and acetic anhydride (3 ml) was added. After 14 h at room temperature, methanol was added and the reaction mixture was evaporated. The residue was coevaporated with methanol and then with 2-propanol. Crystallization from methanol provided an analytical sample of **5b** (68 mg): mp 231–235 °C; uv λ_{max} (MeOH) 297, 246 nm; uv λ_{min} (MeOH) 271, 224 nm; uv λ_{max} (MeOH) (H^+) 313, 241 nm.

Preparation of 1-(3-Deoxy-3-substituted β-D-arabinofuranosyl)pyrimidine Nucleosides 4a–d, 7a–d, and 8a–d. The appropriate ammonium salt and the requisite epoxide (see Table I for proportions) were refluxed in ethanol (6–16 h) until evolution of ammonia ceased and TLC indicated a single spot, corresponding to product. The reaction mixture was evaporated to dryness and (except for **8a,b,d**) the products were isolated by direct crystallization from the appropriate solvent. In **8a,b,d**, the residue left after evaporation of ethanol was partitioned between water and an appropriate solvent (**8a,d**, CH_2Cl_2; **8b**, EtOAc). The organic phase was separated, dried over Na_2SO_4, and evaporated to dryness. The residues were crystallized from the solvent shown in Table I.

Acknowledgment. The authors are indebted to Mr. Marvin J. Olsen for recording the NMR spectra.

Table II. NMR Parameters[e]

Compd	$C_{1'}$-H	$C_{2'}$-H	$C_{3'}$-H	$C_{4'}$-H	$C_{5',5''}$-H	C_5-H, C_6-H	Other
7a	6.14 (d, $J_{1',2'}$ = 6.1)	4.55 (q[c])	*a*	*a*	3.65–3.71 (m)	5.59 (d), 7.71 (d, $J_{5,6}$ = 8.2)	6.23 (d, 1 H, $J_{3',OH}$ = 5.8[d]), 5.27 (t, $J_{5',OH}$ = 5.5[d]), 4.0–4.25 (m, H-3', H-4'), 11.29 (s, 1 H, NH[d])
7b	6.09 (d, $J_{1',2'}$ = 6.7)	4.59 (q[c])	*a*	*a*	3.68–3.74 (m)	5.57 (d), 7.78 (d, $J_{5,6}$ = 8.2)	6.16 (d, $J_{2',OH}$ = 6.1[d]), 5.26 (t, $J_{5',OH}$ = 5.4[d]), 3.92–4.19 (m, H-3', H-4'), 11.24 (s, 1 H, NH[d])
7c	6.03 (d, $J_{1',2'}$ = 6.1)	4.34 (q[c])	3.99 (t)	*a*	*a*	5.59 (d), 7.71 (d, $J_{5,6}$ = 8.0)	6.11 (d, $J_{2',OH}$ = 5.2[d]), 5.25 (t, $J_{5',OH}$ ~ 4[d]), 3.33–3.73 (m, 3 H, H-4', H-5', H-5''), 11.14 (s, 1 H, NH[d])
7d	6.09 (d, $J_{1',2'}$ = 6.4)	4.45 (q[c])	*a*	*a*	*a*	5.61 (d), 7.75 (d, $J_{5,6}$ = 8.2)	6.36 (d, $J_{2',OH}$ = 6.8[d]), 5.31 (t, $J_{5',OH}$ = 5.5[d]), 3.50–3.96 (m, H-3', H-4', H-5', H-5''), 11.3 (s, 1 H, NH[d])
8a	6.23 (d, $J_{1',2'}$ = 5.5)	*a*	*a*	*a*	*a*	5.45 (dd[b]), 8.1 (d, $J_{5,6}$ = 7.9, $J_{5,NH}$ = 2)	7.46–8.0 (5 H, benzoyl), 6.37 (d, $J_{2',OH}$ = 5.2[d]), 4.47–4.73 (m, H-2', H-3', H-4', H-5', H-5''), 11.38 (s, 1 H, NH[d])
8b	6.20 (d, $J_{1',2'}$ = 6.1)	*a*	4.21 (t, $J_{2',3'}$ = 7.8)	*a*	*a*	5.42 (dd[b]), 8.01 (d, $J_{5,6}$ = 6.1, $J_{5,NH}$ = 2.1)	7.44–8.08 (5 H, benzoyl), 6.26 (d, $J_{2',OH}$ = 5.5[d]), 4.45–4.74 (m, H-2', H-4', H-5', H-5''), 11.35 (s, 1 H, NH[d])
8c ($CDCl_3$)	6.16 (d, $J_{1',2'}$ = 3.4)	*a*	*a*	*a*	4.20 (s)	5.31 (d), 8.1 (d, $J_{5,6}$ = 7.9)	7.39–8.12 (5 H, benzoyl), 5.39 (d, $J_{2',OH}$ ~6[d]), 4.62–4.82 (m, H-2', H-3', H-4'), 11.1 (s, 1 H, NH[d])
8d	6.15 (d, $J_{1',2'}$ = 6.1)	4.55 (unresolved m)	3.91 (dd, $J_{2',3'}$ = 7.0, $J_{3',4'}$ = 9.0)	4.24–4.37 (m)	4.45–4.81 (m)	5.44 (d), 8.02 (d, $J_{5,6}$ = 7.9)	7.46–8.08 (5 H, benzoyl), 6.46 (d, $J_{2',OH}$ = 5.2[d]), 4.45–4.69 (m, H-2'), 11.38 (s, 1 H, NH[d])
4a	6.20 (d, $J_{1',2'}$ = 5.1)	4.46 (unresolved m[c])	*a*	*a*	3.65 (b s)	5.70 (d), 7.63 (d, $J_{5,6}$ = 7.4)	7.16 (b s, 2H), 6.08 (d, $J_{2',OH}$ = 5.2[d]), 5.21 (b s, 1 H[d]), 4.13–4.25 (m, H-3', H-4')
4b	6.19 (d, $J_{1',2'}$ = 5.8)	4.51 (unresolved m[c])	*a*	*a*	3.67 (b s)	5.69 (d), 7.69 (d, $J_{5,6}$ = 7.3)	7.13 (b s, 2 H[d]), 5.98 (b d, 1 H[d]), 5.19 (b s, 1 H[d]), 3.95–4.10 (m, H-3', H-4')
4c	6.06 (d, $J_{1',2'}$ = 5.5)	4.26 (q[c])	3.99 (t, $J_{2',3'}$ = 5.7)	*a*	3.66 (b s)	5.69 (d), 7.62 (d, $J_{5,6}$ = 7.3)	7.14 (b s, 2 H[d]), 5.93 (d, 1 H, $J_{2',OH}$ = 5.5[d]), 5.20 (b t, $J_{5',OH}$ = 4.9[d]), 3.62–3.79 (H-5', H-5'' over H-4')
4d	6.12 (d, $J_{1',2'}$ = 5.8)	4.43 (unresolved m[c])	*a*	*a*	3.72 (b s)	5.74 (d), 7.70 (d, $J_{5,6}$ = 7.3)	7.33 (b s, 2 H[d]), 5.21 (b s, 1 H[d]), 3.51–3.95 (m, H-3', H-4')
5a	6.09 (s)	3.96 (d, $J_{2',3'}$ = 3.1)	4.05 (d)	3.94–4.09 (under H-2',3')	3.59 (d, $J_{5',5''}$ = 6)	5.77 (d), 7.57 (d, $J_{5,6}$ = 7.6)	7.30 (s, 2 H[d]), 5.01 (b s, 1 H[d])
5a HCl	6.07 (s)	*a*	*a*	*a*	3.61 (d, $J_{5',5''}$ = 6)	6.23 (d), 7.88 (d, $J_{5,6}$ = 7.8)	9.98 (s, 1 H[d]), 8.90 (s, 1 H[d]), 4.02–4.17 (H-2', H-3', H-4')
5b ($CDCl_3$)	6.27 (s)	3.89 (d, $J_{2',3'}$ = 3)	4.16 (d)	*a*	*a*	7.46 (d), 7.95 (d, $J_{5,6}$ = 7.6)	9.37 (s, 1 H[d]), 4.24–4.65 (m, H-4', H-5', H-5''), 2.27 (s, 3 H), 2.13 (s, 3 H)
5b	6.16 (s)	4.08 (d, $J_{2',3'}$ = 3)	4.18 (d)	4.33 (s)	4.33 (s)	7.24 (d), 8.00 (d, $J_{5,6}$ = 7.6)	10.92 (s, 1 H[d]), 2.11 (s, 3 H), 2.06 (s, 3 H)

[a] See under Other. [b] Collapses to doublet upon addition of D_2O. [c] Appears as a triplet upon addition of D_2O. [d] Disappears upon addition of D_2O. Me_2SO-d_6 was used as solvent except where indicated. [e] *J* values in hertz. s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad, dd = double doublet.

References and Notes

(1) This investigation was supported in part by funds from the National Institutes of Health, U.S. Public Health Service (Grants CA-18601, 17085, and 08748), and by a Fellowship (to D.H.H.) from the Westchester Division of the American Cancer Society.
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Analogues of 8-Azainosine

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A convenient synthesis of 8-azapurine ribonucleosides substituted at the 6 position with thio, alkylthio, alkoxy, amino, and alkylamino groups is described. The reaction of 6-(methylthio)-8-azapurine (1) with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride in the presence of Linde AW-500 molecular sieve gave a 2:1 mixture of **2** and **3**, respectively. This mixture was rearranged by heating with molecular sieve in refluxing toluene to give a 6:1 mixture of **2** and **3**. Treatment of **2** or **3** with the appropriate nucleophiles at room temperature gave 6-substituted 8-azapurine ribonucleosides (7-substituted 2- or 3-β-D-ribofuranosyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines) **4**–**13**. The thione **11** rearranges to *N*-β-D-ribofuranosyl[1,2,3]thiadiazolo[5,4-*d*]pyrimidin-7-amine (**14**) in the solid state or in solution. All of these compounds were cytotoxic to H.Ep. No. 2 cells in culture except the parent base, 8-aza-6-(methylthio)purine (**1**) and the 8-isomers (**3**, **12**, and **13**). Three of these compounds—8-azaadenosine (**4**), 8-aza-6-(methylthio)purine ribonucleoside (**5**), and 8-aza-6-(methoxy)purine ribonucleoside (**7**)—showed borderline activity in the leukemia L1210 system. The thiadiazolopyrimidine (**14**) showed activity at three dose levels.

The moderate anticancer activity of 8-azahypoxanthine against adenocarcinoma 755[1] is markedly enhanced by conversion of the azapurine to its ribonucleoside, 8-azainosine (3,6-dihydro-3-β-D-ribofuranosyl-7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-one),[2] which is active not only against Ca 755 but also against leukemia L1210 and a strain of L1210 resistant to 6-mercaptopurine and 8-azahypoxanthine.[3] 8-Azaadenosine (3-β-D-ribofuranosyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-amine) and 6-(methylthio)purine ribonucleoside, substrates for adenosine kinase,[4] have also shown antileukemic activity in test systems resistant to the parent heterocycles.[5,6] These results prompted us to prepare a number of 8-azapurine ribonucleosides substituted with thio, alkylthio, alkoxy, and alkylamino groups at the 6 position in an effort to find other potentially useful anticancer agents.

8-Aza-6-(methylthio)purine [7-(methylthio)-1,2,3-triazolo[4,5-*d*]pyrimidine, **1**] was prepared in 75% yield by the procedure of Weiss et al.[7] by nitrosation of 4,5-diamino-6-(methylthio)pyrimidine.[8] The reaction of **1** with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride[9] in refluxing benzene containing Linde AW-500 molecular sieve gave after 21 h an 89% yield of a 2:1 mixture of 7-(methylthio)-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,3-triazolo[4,5-*d*]pyrimidine and the 2-substituted isomer (**2** and **3**, respectively) as determined by ^{1}H NMR. A higher ratio of **2** to **3** (4:1) was formed in an earlier reaction, suggesting that **3** might rearrange to **2** with an increase in temperature or reaction time. The rearrangement of **3** to **2** was confirmed by refluxing a solution of **2** and **3** (2:1) in toluene containing molecular sieve for 4 days to give a 6:1 mixture of **2** and **3**. Additional details concerning this molecular sieve catalyzed rearrangement are described in a previous communication.[10] The mixture of **2** and **3** was separated by silica gel column chromatography to give a 61% overall yield of **2**, a 12% yield of **3**, and a 13% yield of a mixture of **2** and **3**. The high combined overall yield (86%) from **1** is proof that the final 6:1 ratio is a result of rearrangement rather than preferential decomposition of **3** from the initial 2:1 mixture. The structures of **2** and **3** were established by treatment with ammonia to give the known adenosine analogues, 3- and 2-β-D-ribofuranosyl-1,2,3-triazolo[4,5-*d*]pyrimidin-7-amines[11,12] (**4** and **12**, respectively). Compounds **4** and **12** were identical (TLC, uv, and NMR) to the authentic samples. Further evidence for the β configuration of **3** is the small ^{1}H NMR coupling constant[13] ($J_{1',2'}$) of 2.8 Hz and the observation that only one anomer of **3** was formed, since, in the rare cases in which the formation of cis nucleosides from 2-acyloxy-1-halofuranoses has been observed, the trans nucleoside always predominates.

The 7-methylthio group of **2** and **3** was readily replaced at room temperature with a variety of nucleophiles to give the corresponding 7-substituted nucleosides **4**–**13**. During