(3) K. J. Pedersen, *J. Am. Chem. Soc.*, **60**, 595 (1938).
(4) S. Kaneoko, *J. Biochem. (Tokyo)*, **28**, 1 (1938).
(5) F. H. Westheimer and W. A. Jones, *J. Am. Chem. Soc.*, **63**, 3283 (1941).
(6) K. J. Pedersen, *Acta Chem. Scand.*, **8**, 710 (1954).
(7) R. W. Hay, *Aust. J. Chem.*, **18**, 337 (1965).
(8) J. P. Guthrie, *J. Am. Chem. Soc.*, **94**, 7024 (1972).
(9) I. M. Klotz and V. H. Stryker, *J. Am. Chem. Soc.*, **90**, 2717 (1968).
(10) I. M. Klotz, G. P. Royer, and I. S. Scarpa, *Proc. Natl. Acad. Sci. U.S.A.*, **68**, 263 (1971).
(11) I. S. Scarpa, H. C. Kiefer, and I. M. Klotz, *Intra-Sci. Chem. Rep.*, **8**, 45 (1974).
(12) W. J. Spetnagel and I. M. Klotz, *J. Polym. Sci.*, in press.
(13) J. Hine, M. S. Cholod, and J. H. Jensen, *J. Am. Chem. Soc.*, **93**, 2321 (1971).
(14) J. Hine, M. S. Cholod, and R. A. King, *J. Am. Chem. Soc.*, **96**, 835 (1974).
(15) J. Suh, I. S. Scarpa, and I. M. Klotz, *J. Am. Chem. Soc.*, in press.
(16) E. Gelles and R. W. Hay, *J. Chem. Soc.*, 3673 (1958).
(17) G. W. Kosichi and S. N. Lipovac, *Can. J. Chem.*, **42**, 403 (1964).
(18) A. Kornberg and W. E. Pricer, Jr., *J. Biol. Chem.*, **193**, 481 (1951).
(19) R. W. Von Korff in "Methods in Enzymology", Vol. XIII, J. M. Lowenstein, Ed., Academic Press, New York, N.Y., 1969, p 521.
(20) L. K. M. Lam and D. E. Schmidt, Jr., *Can. J. Chem.*, 51, 1959 (1973).
(21) F. H. Westheimer, *Proc. Chem. Soc. London*, 253 (1963).
(22) E. H. Fischer, A. B. Kent, E. R. Snyder, and E. G. Krebs, *J. Am. Chem. Soc.*, **80**, 2906 (1958).
(23) B. L. Horecker, S. Pontremoli, C. Ricci, and T. Cheng, *Proc. Natl. Acad. Sci. U.S.A.*, **47**, 1949 (1961).
(24) C. S. Tasi, *Can. J. Chem.*, 45, 873 (1967).
(25) I. M. Klotz, G. P. Royer, and A. R. Sloniewsky, *Biochemistry*, **8**, 4752 (1969).
(26) F. H. Westheimer, *Proc. Robert A. Welch Found. Conf. Chem. Res.*, 15, 7–50 (1972).

Nucleic Acid Related Compounds. 22. Transformation of Ribonucleoside 2′,3′-O-Ortho Esters into Halo, Deoxy, and Epoxy Sugar Nucleosides Using Acyl Halides. Mechanism and Structure of Products[1,2]

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Abstract: Treatment of 2′,3′-*O*-methoxyethylideneadenosine (**2**) with pivalic acid chloride in refluxing pyridine gave an unresolved mixture of 6-*N*-pivalamido-9-(3-chloro-3-deoxy-2-*O*-acetyl-5-*O*-pivalyl-β-D-xylofuranosyl)purine (**4a**) and its 2′-chloroarabino isomer (**3a**) as the major product. In addition, 6-*N*-pivalamido-9-(3-chloro-3-deoxy-2-*O*-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-D-xylofuranosyl)purine (**4b**) and its 2′-chloroarabino isomer (**3b**) were produced by acylation reactions involving a 2′,3′-*O*-ketene acetal (**11**) which is in equilibrium with the initially formed 2′,3′-acetoxonium ion intermediate (**10**). The structure of the complex **4**,**4**-dimethyl-3-pivaloxypent-2-enoate (DMPP) group was deduced by NMR and mass spectroscopy and verified by synthesis of ethyl DMPP (**9**) from ethyl orthoacetate and pivalyl chloride/sodium iodide. Treatment of **2** with pivalyl chloride and excess sodium iodide in refluxing pyridine gave the corresponding 3′-iodoxylo and 2′-iodoarabino DMPP-blocked nucleosides (**4c** and **3c**) in good combined yield accompanied by unsaturated products. The absence of the corresponding acetyl iodo derivatives was rationalized on the basis of greater acylating activity of pivalyl iodide (generated in situ) in the postulated mechanistic sequence involving ketene acetal intermediates. A pivalylketene acetal derivative (**14**) was isolated and found to be converted to **3c** and **4c** under the reaction conditions. Treatment of **3a**,**4a** with tri-*n*-butyltin hydride or of **3c** and **4c** under catalytic hydrogenolysis conditions gave 2′-deoxyadenosine (**7**) and 3′-deoxyadenosine (cordycepin) (**8**), respectively, after deblocking. The ribo epoxide, 9-(2,3-anhydro-β-D-ribofuranosyl)adenine (**6**), was formed upon treatment of **3a–c** and **4a–c** with methanolic sodium methoxide. This proved the 2′,3′-trans orientation of halo and acyloxy substituents and provides convenient access to the synthetically useful **6**. Spectroscopic identification of products, the acyloxonium ion mediated mechanism and comparison of the route with previously reported procedures are discussed.

Syntheses of purine nucleosides containing modified sugar moieties have usually employed coupling of a suitably blocked (and stereochemically selected) carbohydrate derivative with a derivatized base.[4] Intramolecular base participation via purine-X[8]-cyclonucleosides (X = nucleophilic hetero atom) has also been applied.[5] Preparation of an appropriately substituted sugar derivative followed by elaboration of the desired heterocyclic base has been used in recent approaches to C-nucleosides[6] as well as in convenient syntheses of β-D-arabinopyrimidine nucleosides and other "natural" N-nucleosides.[7] However, cyclonucleoside chemistry analogous to that in the purine-8 series[5] is precluded, for example, in the pyrazolopyrimidine antibiotic formycin[8] (whose structure contains a formal exchange of C-8 and N-9 relative to adenosine). Although coupling procedures have provided structure proofs of pyrrolopyrimidine antibiotics,[9] these total syntheses are somewhat lengthy and uninviting for parallel routes to various modified sugar structures, and most published studies have concentrated on base changes.[10] The situation is similar with respect to the ring-elaborated C-nucleosides. Anomeric stereochemistry is an additional problem involved with coupling procedures.

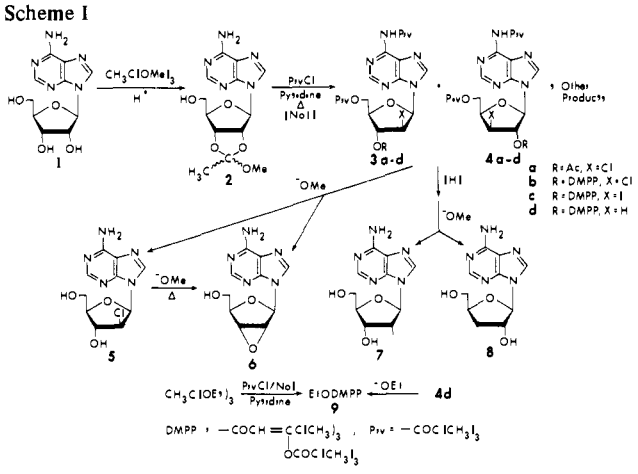
We were interested in developing generally applicable transformations of intact nucleosides into functionalized sugar products which were not dependent on any specific base structure or mode of attachment. Such an approach beginning with antibiotics obtained in quantity by fermentation has obvious advantages. The elegant pioneering work of Winstein and Meerwein on acyloxonium ion intermediacy and structure has been reviewed recently.[11] Examples of such intermediates involved in synthetic approaches[12] (and vide infra) or during neighboring group participation reactions[13] of carbohydrates and nucleosides have been reported. Preliminary accounts of our approach have been outlined.[14]

Adenosine (**1**) was conveniently converted into 2′,3′-*O*-methoxyethylideneadenosine (**2**) by modification of reported procedures.[15] Boron trifluoride etherate[12] or antimony pentachloride in the presence of added nucleophilic species invariably resulted in the formation of significant quantities of 2′(3′)-*O*-acetyladenosine after workup. Pyridine hydrohalides

gave incomplete conversion of **2** to products, and acetyl halides in hot pyridine gave dark intractable mixtures. Pivalic acid chloride (α,α,α-trimethylacetyl chloride) has no α hydrogens, and thus degradation to ketene and subsequent side reactions are precluded.

Treatment of **2** with pivalyl chloride in refluxing pyridine for 2 h resulted in disappearance of starting material and formation of a readily identified mixture of 6-*N*-pivalamido-9-(3-chloro-3-deoxy-2-*O*-acetyl-5-*O*-pivalyl-β-D-xylofuranosyl)purine (**4a**) and its 2′-chloroarabino isomer (**3a**) (see Scheme I) in ~60% combined yield. Acylation of the adenine

Scheme I



chromophore was indicated by a 12-nm bathochromic shift in the uv maxima of **3a,4a**. Two pivalyl groups (nine proton singlets) and an acetyl methyl singlet were observed in the NMR spectrum of this mixture. Integration of the anomeric proton signals of the crude acetate mixture indicated an ~8:1 ratio of **4a**:**3a**. Combustion analyses and mass spectra were in accord with the assigned structures. A minor fraction (~10%) of much higher chromatographic mobility (organic solvent systems) had molecular ions at *m/e* 663 (^{35}Cl). The NMR spectrum of this fraction (**3b,4b**) had peaks corresponding to four *tert*-butyl groups, but no resonance corresponding to an acetyl function. The uv spectrum of the mixture was analogous to that of **3a,4a** (max at 272 nm). Pivalylation of 0–5′ and N-6 occurs readily at room temperature. The two remaining *tert*-butyl groups result from formal bis-pivalylation of the acetyl moiety of **3a,4a** (vide infra).

Treatment of **3a,4a** or **3b,4b** with methanolic sodium methoxide at room temperature gave a minor quantity[16] of 9-(2-chloro-2-deoxy-β-D-arabinofuranosyl)adenine (**5**) plus 9-(2,3-anhydro-β-D-ribofuranosyl)adenine (**6**). More extended or higher temperature treatment of **5** gave **6** plus intramolecular degradation products via transitory $N^3 \rightarrow 3'$-cyclonucleoside formation.[16] Deblocking of the mixture of **3** and **4** with methanolic ammonia at 0 °C gave **5** and 9-(3-chloro-3-deoxy-β-D-xylofuranosyl)adenine, respectively.

Smooth dechlorination of **3a,4a** was effected using tri-*n*-butyltin hydride with azobisisobutyronitrile (AIBN) as initiator.[17] Deblocking of intermediates followed by separation of isomers on the Dekker anion exchange column[18] gave 2′-deoxyadenosine (**7**) and 3′-deoxyadenosine (**8**) (ratio ~1:7 by uv) in 62% crystalline yield.

Treatment of **2** with excess sodium iodide and pivalyl chloride (in situ generation of pivalyl iodide) in pyridine at reflux for 5–10 min resulted in disappearance of starting material. The major product fraction contained 6-*N*-pivalamido-9-(3-iodo-3-deoxy-2-*O*-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-5-*O*-pivalyl-β-D-xylofuranosyl)purine (**4c**) and its 2′-iodoarabino isomer (**3c**). The 3′,4′-unsaturated product derived from **4c** by loss of hydrogen iodide and the furan derivative resulting from further elimination were also formed in varying quantities depending on reaction times.[19] These compounds were separated by carbon column chromatography and fractional crystallization. The absence of 2′(3′)-*O*-acetyl products and the reduction in reaction time from 2 h to 6 min are presumably due to the enhanced acylating power of the acyl iodide and the greater nucleophilicity of iodide (vide infra).

Treatment of **3c** and **4c** with methanolic sodium methoxide gave the ribo epoxide (**6**). Formation of **6** confirmed the trans orientation of 2′ and 3′ halogen (up) and oxygen (down) substituents in intermediates **3a–c** and **4a–c**. Application of this procedure to the synthesis of adenosine epoxides and derived products has been investigated.[2b,16,20,21b] Hydrogenolysis of **3c** and **4c** over palladium on carbon proceeded quantitatively to give **3d** and **4d**, respectively. Deblocking of **3d** and **4d** gave **7** and **8** in a combined yield of 55% overall from adenosine.

Formal bis-pivalylation of the 2′(3′)-*O*-acetyl moiety could give either the C-diacylate structure i or the conjugated O-acylated enol pivalate ii. The α proton of the C-diacylate i would be expected to be in dynamic tautomeric equilibrium (with the enol form strongly favored in such a hindered system). The vinyl proton of ii, in contrast, should be immobile.

$$\mathrm{ROCOCH[COC(CH_3)_3]_2}$$

i

$$\mathrm{ROCOCH{=}C[OCOC(CH_3)_3]C(CH_3)_3}$$

ii

The NMR spectrum of **3d** was determined in $CDCl_3$, $CDCl_3/C_2D_5OD$, and $C_2D_5OD/D_2O/CD_3CO_2D$ (with warming and after standing for 24 h). No change in intensity nor apparent bandwidth of the sharp singlet at δ ~5.75 was observed. This precludes structure i and is compatible with ii, the 4,4-dimethyl-3-pivaloxypent-2-enoate (DMPP) function. The consistency of this sharp singlet (see Table **I**) suggests stereoselective formation of one geometric isomer (presumably hydrogen and *tert*-butyl cis) in all cases. This sterically hindered enol ester is remarkably stable. Treatment of intermediates containing this group under various conditions failed to effect selective cleavage of the enol-ester bond. Acids resulted in cleavage of the 6-*N*-pivalyl amide linkage and mineral acids also effected more drastic changes including glycosyl bond cleavage. Basic treatment effected amide cleavage, followed by removal of the intact DMPP grouping with accompanying formation of epoxide occurring in certain cases. The double bond of the DMPP function of **3c** and **4c** also remains unaffected during hydrogenolysis of the carbon-iodine bond to give **3d** and **4d**. This presumably results from steric hindrance to approach of the catalyst surface and/or resistance to compression from sp^2 to sp^3 geometry.

The splitting patterns for the 2′ or 3′ methylene protons of the deoxy derivatives **3d** and **4d** are almost identical. This suggests that compound **3d** must adopt the S-type conformation whereas **4d** must favor the N-type.[22] The deoxy protons designated "double primed" in Table I are oriented trans to the base. This assignment is in agreement with the coupling constants and also their upfield shift.[23]

Mass spectral fragmentations of these compounds are compatible with structure ii (see Figure 1 and Table II) and formed the basis of the initial assignments. As in the case of acetyl nucleosides,[24] sugar fragment (S) and its daughter ions are of high abundance. The presence of the chlorine isotope pattern provides a probe for sugar-backbone fragments. All compounds bearing a pivalyl group lose the *tert*-butyl residue to give an M − 57 ion. A characteristic ion (c) at M − 141 occurs in all compounds containing the DMPP substituent. This could arise from the molecular ion by loss of 84 amu (see Scheme II, path B) to give ion b, followed by loss of *tert*-butyl (57 amu) to give c (path C). Alternatively, M could lose *tert*-butyl (path A), followed by loss of 84 amu (path C′) to give c.

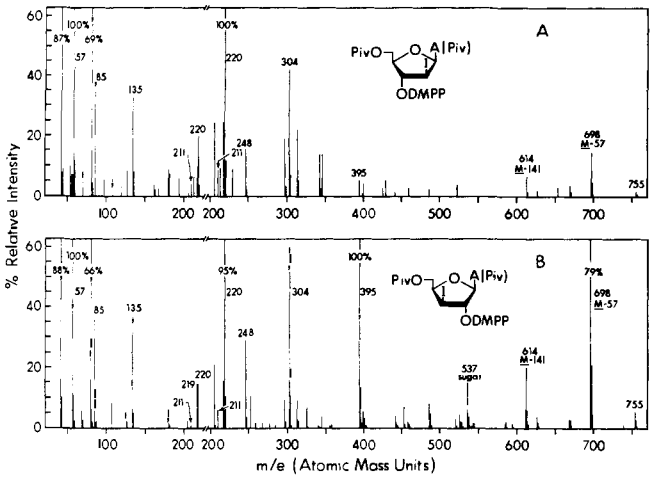
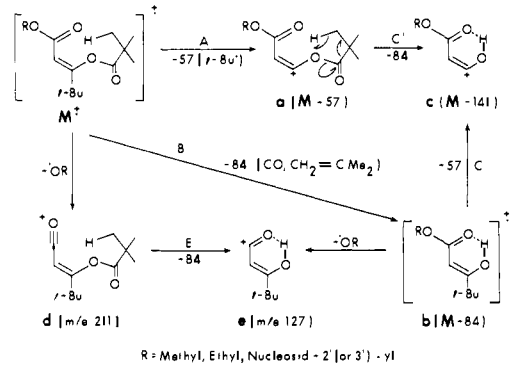


Figure 1. Mass spectra of **3c** (A) and **4c** (B).

Scheme II



Formation of c from a and b is indicated by metastable peaks at *m/e* 66.5 and 77, respectively, in the spectrum of ethyl DMPP (**9**). One possibility for the formation of b is a concerted loss of carbon monoxide and isobutylene from M. Presumably path C′ involves the same process, and the observed metastable peak at *m/e* 66.5 is in agreement with the elimination of two fragments simultaneously as illustrated in Scheme II. An analogous concerted fragmentation evolving carbon dioxide and ethylene has been postulated previously.[25] The DMPP moiety also gives rise to characteristic low-intensity ions at *m/e* 211 and 127. Accurate mass measurements (calcd 211.1334, found 211.1341 and calcd. 127.0759, found 127.0762) support formulation of these ions as d and e. A double peak at nominal mass 127 was observed in the iodo compounds (^{127}I) at high resolution. Sugar ion S undergoes similar fragmentations (S − 84) and [S − (84 + 57)]. An intense peak [mass spectral base peak for **4c**, *m/e* 395 (Figure 1B), and **4d**, *m/e* 269] is derived from the molecular ion by loss of [57 + 84 + base(Piv) + H]. The origin of this ion from ions a (*m/e* 698) and c (*m/e* 614) is indicated by metastable peaks at *m/e* 223.5 and 254 in the spectrum of **4c**. Peaks at *m/e* 304, 248, 220, and 219 are of high intensity and contain the heterocyclic base. Corresponding ions in the tubercidin[26] and guanosine[21] series had analogous peaks at 1 amu lower and 16 amu higher, respectively. The accurate mass of the *m/e* 304 peak (calcd for $C_{15}H_{22}N_5O_2$: 304.1772, found 304.1772) in the mass spectrum of **4d** indicates that one pivalyl group has been transferred to the base. Thermal migration of *N*-alkyl groups has been noted previously.[27] The high resolution spectrum of **3b,4b** had two peaks of nominal mass 304 in a ratio of 8:2. The higher intensity peak corresponds most closely to the above fragment and the accurate mass determination of the lower intensity ion (*m/e* 304.0666) agrees with (S − 141) (calcd for $C_{13}H_{17}{}^{35}ClO_6$:

Table I. ^{1}H NMR Spectral Data of Blocked Products[a]

Compd	H_1'	$H_2'(2'')$	$H_3'(3'')$	H_4'	H_5', H_5''	H_2	H_8	6-N*H*–	Enol–pivalyl(9) and $O^{5'}$-pivalyl(9)	C=C-*t*-Bu(9)	N^6-Pivalyl(9)	–C*H*=C
4a[b]	6.31 (d)[c]	5.63 (dd)[c]	4.48 (m)	4.65 (m)	4.48 (m)	8.76	8.41	8.56	1.23[d]	*d*	1.40	*d*
4b[b]	6.33 (d)[e]	5.57 (dd)[e]	4.47 (m)	4.65 (m)	4.47 (m)	8.76	8.41	8.53	1.23 1.25	1.16	1.41	5.76
4c	6.24 (d)[f]	5.81 (t)[f]	4.56–3.90 (m)	4.56–3.90 (m)	4.56–3.90 (m)	8.73	8.52	8.50	1.25	1.15	1.40	5.75
3c	5.95 (d)[g]	4.87 (dd)[g]	5.62 (t)[g]	4.61–4.17 (m)	4.61–4.17 (m)	8.76	8.31	8.60	1.26 1.34	1.18	1.41	5.75
4d	6.04 (d)[h]	5.69 (m)	2.74 (ddd)[h] 2.23 (ddd)[i]	4.54 (m)	4.33 (m)	8.76	8.09	8.53	1.20 1.29	1.15	1.40	5.74
3d	6.47 (dd)[j]	2.91 (ddd)[j] 2.66 (ddd)[k]	5.40 (m)	4.35 (br s)	4.35 (br s)	8.78	8.18	8.50	1.23 1.35	1.18	1.42	5.74

[a] δ (ppm) from Me_4Si internal standard in $CDCl_3$ at 100 MHz. Peaks are singlets unless indicated otherwise. First-order coupling constants (Hz) were determined by spin–spin decoupling in several cases. [b] Only the major isomer (**4a** or **4b**) was spectroscopically visible in these purified samples of **3a,4a** or **3b,4b**. [c] $J_{1'-2'}$ = 2 Hz, $J_{2'-3'}$ = 1.5 Hz. [d] No DMPP function present, δ 2.18 (s, 3, 2′-*O*-acetyl). [e] $J_{1'-2'}$ = 2 Hz, $J_{2'-3'}$ = 1.5 Hz. [f] $J_{1'-2'}$ = 2.5 Hz, $J_{2'-3'}$ = 1.5 Hz. [g] $J_{1'-2'}$ = 4.5 Hz, $J_{2'-3'}$ = 2 Hz, $J_{3'-4'}$ = 3 Hz. [h] $J_{1'-2'}$ = 1.5 Hz, $J_{3'-4'}$ = 6 Hz, $J_{3'-5''}$ = 10 Hz, $J_{3'-5''}$ = −14 Hz. [i] $J_{1'-2'}$ = 8 Hz, $J_{2'-3'}$ = 6 Hz, $J_{2'-2''}$ = −14 Hz. [k] $J_{2''-1'}$ = 6 Hz, $J_{2''-3'}$ = 2 Hz.

Table II. Characteristic Mass Spectral Ions of Blocked Nucleosides and Model Esters[a]

Compd	*m/e* (relative intensity)									Relative intensity				
	M	M − X[b]	a	b	M − 85	c	M − (X[b] + PivOH)	S	S − 84	S − (84 + 57)	M − (84 + 57 + BPiv + H)	BPiv + Piv + H (*m/e* 304)	BPiv + 30 (*m/e* 248)	BPiv + 2H (*m/e* 220)	BPiv + H (*m/e* 219)	d (*m/e* 211)	e (*m/e* 127)
3a,4a	495 (4.4)	460 (18)	438 (3)	411 (6.7)	410 (11)		358 (28)	277 (56)	193 (4.5)			4.3	100	83	27		
3b,4b	663 (3.6)	628 (3.7)	606 (50)	579 (3)	578 (2.9)	522 (38)	526 (5.2)	445 (13)	361 (5.9)	304 (67)	303 (75)	67	24	100	7.7	12	3.3
3c[c]	755 (1.8)	628 (2.2)	698 (15)	671 (1.8)	670 (4)	614 (6.9)	526 (0.9)	537 (2)	453 (1.1)	396 (0.9)	395 (5.6)	42	15	100	24.5	8.5	8.5
4c[d]	755 (5.4)	628 (3.6)	698 (75)	671 (2.8)	670 (2.8)	614 (20)	526 (4.6)	537 (15)	453 (6.8)	396 (14)	395 (100)	61	29	95	16	7.1	2.2
3d[e]	629 (2.6)		572 (12)	545 (1.4)	544 (2.6)	488 (5.5)		411 (11)	327 (1.7)	270 (0.7)	269 (4.3)	97	6.9	100	16	1.1	5.4
4d[f]	629 (2.3)		572 (19)	545 (1.1)	544 (1)	488 (4.7)		411 (19)	327 (10)	270 (14)	269 (100)	26	12	33	37	3.2	4.7
9[g]	256 (0.8)		199 (5.8)	172 (14)		115 (81)										2.9	3.7
g, *h*	242 (0.2)		185 (1.2)	158 (11)		101 (57)										0.6	1.7

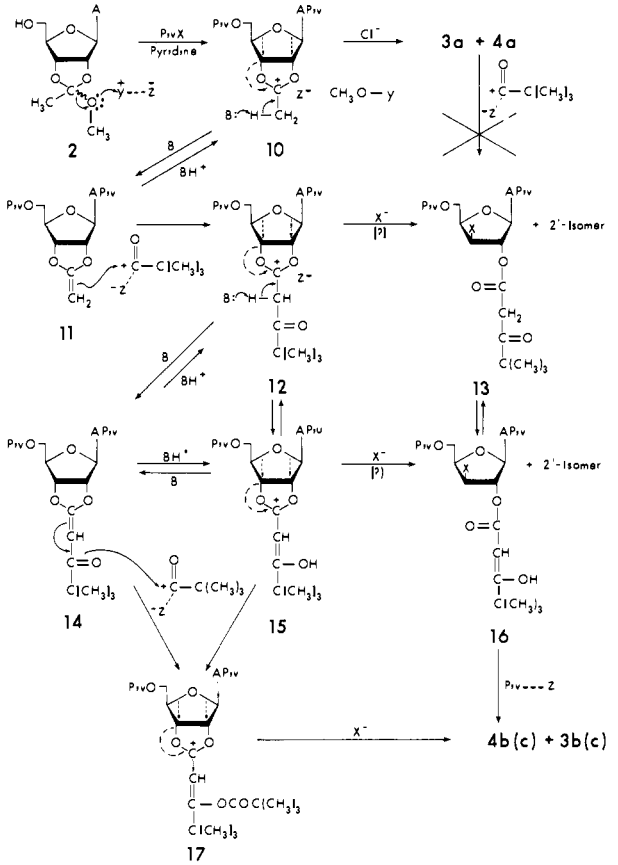
[a] See discussion and Scheme II for structures of ions. [b] X = ^{35}Cl or ^{127}I. [c] *m/e* 528 (4.2), 298 (19). [d] *m/e* 298 (9.6). [e] *m/e* 300 (5.9). [f] *m/e* 300 (2.1). [g] Mass spectral base peak *m/e* 57 (100). [h] Methyl 4,4-dimethyl-3-pivaloxypent-2-enoate.

304.0666). The peaks at *m/e* 248 [base(Piv) + 30], 220 [base(Piv) + 2H], and 219 [base(Piv) + H] are analogous to fragmentations (base + 30), (base + 2H), and (base + H) in the unsubstituted adenine nucleoside series.[24] Two mass spectral range scans were required with the high molecular weight compounds as seen in Figure 1.

Treatment of ethyl orthoacetate in pyridine with pivalyl chloride and sodium iodide resulted in an immediate exothermic reaction. A low yield of ethyl 4,4-dimethyl-3-pivaloxypent-2-enoate (**9**) was obtained by distillation of the partially polymerized mixture. The blocked 3′-deoxynucleoside (**4d**) was treated with ethanolic sodium ethoxide and the same ester (**9**) was isolated. The two samples of **9** were shown to be identical (including geometric stereochemistry) by melting point, mixed melting point, uv, ir, NMR, and mass spectroscopic comparison.

A plausible mechanistic outline in harmony with the observed results is presented in Scheme III. Acylation of the

Scheme III. Mechanism for Conversion of **2** to Observed Products



5′-OH and 6-NH_2 groups of **2** provides 2 equiv of HX. Attack of an electrophilic species Y^+-Z^- (Y^+ is a proton or acylium species $(CH_3)_3CCO^+$, Z^- is halide or pyridinium with halide as accompanying counterion) on the methoxyl oxygen of **2** followed by carbon–oxygen bond cleavage would lead to the 2′,3′-acetoxonium ion species **10** plus Y-OCH_3 (methanol or methyl pivalate, which would also result from acylation of methanol). Nucleophilic attack at C-2′ or C-3′ (as indicated by dashed arrows) of the 1,3-dioxolenium ion species **10** by chloride would give **3a** and **4a,** respectively. This pathway is seen to predominate when X = Cl, but is not observed when X = I. Abstraction of a proton from the acetoxonium methyl group of **10** in the refluxing pyridine solution would give ketene acetal intermediate **11**. Protonation of **11** (in equilibrium with pyridinium hydrohalide) would give reversal to **10,** whereas C-acylation of **11** would produce the pivalylacetoxonium ion **12**. Analogous deprotonation-protonation would establish an

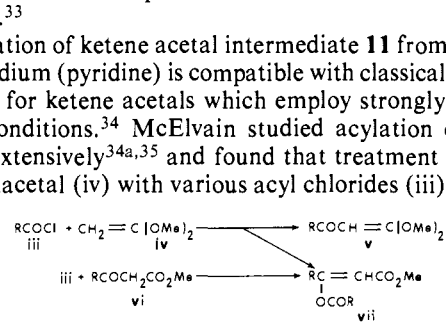
equilibrium between **12** and the pivalylketene acetal intermediate **14**. These species (**12** and **14**) could potentially be in equilibrium with enol acyloxonium ion species **15**. O-Acylation of **14** or **15** would give the 2-(3,3-dimethyl-2-pivaloxybut-1-enyl)-1,3-dioxolenium cation **17**. Nucleophilic attack at C-2′ and C-3′ of **17** by halide as indicated by dashed arrows would produce the observed 2′(3′)-halo-2′(3′)-deoxy-3′(2′)-DMPP products **3b** and **4b** (Cl) or **3c** and **4c** (I), respectively.

Alternative routes to the DMPP products could involve nucleophilic attack by halide at C-3′ and C-2′ of intermediate acylacetoxonium ions **12** or **15** (as indicated by dashed arrows) followed by O-pivalylation of the pivalylacetate moiety to produce **4b(c)** plus **3b(c)**. However, the potentially alternative route involving a "Claisen-type" C-pivalylation of the chloro-substituted acetate products **3a,4a** (or an iodo analogue of **4a**) was not observed. The mixture of **3a** and **4a** was isolated, purified, and subjected to the original reaction conditions (also additional experiments employed addition of 2 equiv of alcohol to provide pyridine hydrochloride comparable with reaction with **2**, and excess sodium iodide). Only trace amounts of faster migrating spots were detected (TLC) after 2 h at reflux, and the essentially unchanged mixture of **3a** and **4a** was reisolated. The DMPP function was oxidatively removed[19] from **4c** and the resulting 3′-iodo-2′-hydroxy product was acetylated. This iodo analogue of **4a** was heated at reflux for more than 10 min (and again with addition of alcohol) with excess sodium iodide/pivalyl chloride/pyridine. Only minor faster spots (TLC) were observed, and the presence of **3c** or **4c** could not be detected chromatographically or spectroscopically.

Conversion of orthoesters into acyloxonium ion species has ample precedent. In 1871, ethyl orthoformate was observed to give products compatible with this mechanistic intermediacy upon treatment with acetyl chloride.[28] Winstein[29] investigated acetoxonium ions formed by neighboring group participation as well as direct generation, and Meerwein[30] isolated and explored 1,3-dioxolan-2-ylium salts. Other related examples have been noted[31] and Paulsen has investigated acyloxonium ion formation, migration, and fluxional equilibration in aliphatic, alicyclic, and carbohydrate systems.[32]

Winstein[29c,d] observed rapid deuterium exchange at the methyl group of cyclohexan-1,2-acetoxonium ion in deuterioacetic acid solution which indicated the presence of a ketene acetal intermediate. Recent NMR evidence for ketene acetal–acyloxonium ion equilibria in deuterated solvent has been reported.[33]

Formation of ketene acetal intermediate **11** from **10** in the basic medium (pyridine) is compatible with classical synthetic methods for ketene acetals which employ strongly basic reaction conditions.[34] McElvain studied acylation of ketene acetals extensively[34a,35] and found that treatment of ketene dimethylacetal (iv) with various acyl chlorides (iii) gave two

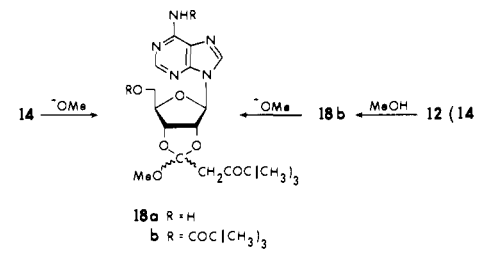


main products v and vii. With pivalyl chloride (iii, R = $C(CH_3)_3$), v was the predominant product[35] presumably owing to steric bulk. Thus, the pivalylketene acetal **14** (Scheme III) could be expected to be formed and might be isolable under conditions of incomplete reaction. It was demonstrated by McElvain[36] and earlier by Claisen[37] that acylacetic esters (vi) readily undergo O-acylation to the corresponding enol ester (vii) in the presence of a proton acceptor. Therefore, products analogous to vi would not be expected to survive in pyridine solutions containing acyl halides.

A solution of **2** and pivalyl chloride in pyridine was stirred for 66 h at 50 °C (rather than 2 h at reflux). A 36% yield of **14** was isolated in addition to **3a,4a** (21%), **3b,4b** (10%), and 4% of $N^6,O^{5'}$-dipivalyl-2′,3′-*O*-methoxyethylideneadenosine (acylated starting material). At lower temperatures reaction was sluggish, and at higher temperatures increased formation of **3a,4a** occurred. Purified **14** was subjected to the original reaction conditions. Only **3b,4b** was detected in addition to unreacted **14** (which could always be detected in the original reaction using **2**). Treatment of **14** with pivalyl chloride/sodium iodide/pyridine at reflux for 6 min produced **3c** and **4c** plus unsaturated compounds analogously to reaction of **2**.

Treatment of the purified $N^6,O^{5'}$-dipivalyl derivative of **2** under identical reaction conditions gave analogous results. This suggests that acetoxonium ion intermediate **10** may be generated by attack of an acylium-pyridine complex. However, trace quantities of moisture sufficient to provide adequate initial hydrogen halide concentrations may have been present. Nucleophilic attack at C-2′ or C-3′ of **10** to produce **3a,4a** is observed to occur at a comparatively low overall rate in the reaction with acid chloride. This step is irreversible, however, since the isolated mixture of **3a,4a** is stable under these reaction conditions (and in the presence of 2 equiv of hydrohalide produced by addition of alcohol). "Claisen-type" C-pivalylation of **3a,4a** to give **13** is also thereby excluded as a route to the DMPP-substituted final products **3b,4b**.

C-acylation of **11** to produce **12** competes successfully with chloride attack on **10** to give **3a,4a**, especially at 50 °C (vide supra). Deprotonation of **12** to give the α,β-unsaturated ketone **14** would be expected to be highly favorable, and protonation of **14** would presumably be impeded. Indirect evidence favoring this interpretation was obtained. Treatment of **14** with methanolic sodium methoxide gave 2′,3′-*O*-methoxy(4,4-dimethyl-3-oxopentylidene)adenosine (**18a**). This product had



been isolated previously from the original reaction mixture after treatment with methanol, followed by deblocking. Quenching of the original reaction mixture with ethanol followed by deblocking gave the ethyl orthoester analogue of **18a**. Addition of alcohol to the cooled original reaction mixture produced the blocked orthoester **18b** slowly (~24 h was required for complete conversion (TLC) of **14** → **18b** at room temperature). This suggests capture of alcohol by a low equilibrium concentration of acyloxonium ion intermediate **12**, and/or a slow Michael addition of alcohol to the α,β-unsaturated ketone system of **14** in the pyridine solution. Such an addition (**14** → **18a**) was complete in a few hours in methanolic sodium methoxide at room temperature.

The predictable unfavorability of generating the β-ketoacyloxonium ion **12** was demonstrated by two experiments. Treatment of **18a** or **18b** under the original reaction conditions (or in the presence of excess sodium iodide) resulted in partial conversion to **3b,4b** or **3c,4c**, but a considerable quantity of **18b** remained untransformed. In contrast, **14** was rapidly and completely converted to **3c** and **4c** using the standard reaction conditions (vide supra). The second experiment involved qualitative comparison of acid hydrolysis (intermediate oxonium ion formation) stabilities of **18a** and **2**. Compound **2** was completely hydrolyzed to the 2′(3′)-acetate in acetic acid solution within 12 min whereas **18a** was unchanged after 2 h (5 mg of compound in 1 ml of dioxane treated with 0.6 ml of 80% acetic acid in methanol at room temperature). Compound **2** had a half-life of <2 min (5 mg in 1 ml of 0.01 N HCl + 0.5

ml of methanol) whereas **18a** had a half-life of ~37 min under identical conditions.

O-Acylation of **14** provides a "trapped" species (**17**) which cannot be stabilized readily by deprotonation. Nucleophilic attack at C-3′ and C-2′ occurs to give **4b** and **3b**. Even with the bulky *tert*-butyl acyl halide, this O-acylation occurs readily. At 50 °C, C-acylation, deprotonation, and O-acylation (**11** → **12** → **14** → **17**) is favored relative to protonation–nucleophilic attack (**11** → **10** → **3a** + **4a**) on the ketene acetal intermediate **11** as indicated by the ~1:2 ratio of (**3b,4b**):(**3a,4a**) compared with the ~1:6 ratio observed at reflux (vide supra).

No acetyl products corresponding to **3a** and **4a** were observed in reactions involving excess sodium iodide. Acyl iodides are known to be much stronger acylating agents than the corresponding chlorides.[38] If rapid equilibrium deprotonation of initial acetoxonium ion **10** occurs, facile acylation of the ketene acetal **11** could result in exclusive formation of the C-acylated species **12**. Further O-acylation of the equilibrium deprotonated species **14** would also be enhanced leading to **17**. Iodide would be expected to be a more powerful nucleophile than the more basic (proton affinity) chloride in this pyridine hydrohalide system, leading more rapidly to **3c** and **4c**. Thus, completion of this reaction in ~5 min at reflux and absence of acetyl products are compatible with Scheme III.

Several procedures for generating halogen-substituted sugars and nucleosides have been reported recently which are based on acyloxonium ion mechanisms. Hanessian has reported transformations of benzylidene sugars[39] into halogen- and benzoate-substituted derivatives using *N*-bromosuccinimide. This procedure presumably involves initial free radical attack, followed by heterolysis to a benzoxonium ion intermediate.[39,40] However, no applications to purine nucleosides have been noted, and reactions in the pyrimidine series resulted in pyrimidine ring as well as sugar-2′ bromination.[41] Newman and co-workers[42] have described acyloxonium ion mediated conversions of diols into the *trans* acetoxy chloride products predictable by the Winstein mechanism.[29] Application of their trimethylsilyl chloride route[42c] to a uridine orthoester gave the $O^2 \rightarrow 2'$-cyclonucleoside.[43] However, preliminary experiments suggest that their trityl chloride procedure[42b] gives poor conversions with compound **2**,[44a] and no halohydrins could be detected (TLC) upon treatment of the guanosine analogue of **2** with trimethylsilyl chloride.[44b] Culbertson[45] has studied analogous substitution of a furanose sugar using a mixed orthoester amide group.[46] Moffatt and co-workers have studied the "abnormal Mattocks[47] reaction" of α-acyloxyisobutyryl chlorides with diols which also gives *trans* halohydrin acetates via acyloxonium ion intermediacy.[48a,49] An analogous reaction employing acetylsalicylyl chloride with diols gives acetoxy chlorides.[50] Although the Russian authors[50] favored an "S_Ni mechanism or a tight ion-pair," the results are compatible with the usual acetoxonium ion and S_N2-type attack. Pedersen has very recently explored bromo-sugar syntheses involving acyloxonium ion species.[51]

Of the methods noted, only the "abnormal Mattocks reaction" has been demonstrated to have versatility and utility[48,49] comparable with the presently described procedure.[14,16,19-21,26] The former reaction works smoothly with tubercidin[48c,49] and is convenient for epoxide formation in that series.[26] However, insolubility, side product formation, and glycosyl bond cleavage present problems with adenosine.[48b,e] The presently described highly organic soluble DMPP function allows convenient selective deblocking[19] of the secondary alcohol, which was employed to synthesize the first 1′,2′-unsaturated nucleoside.[52] We had initially[14] explored the possibility of direct generation of acetoxonium ions from **2** (and acylated derivatives) using boron trifluoride[12,29b,30] or antimony pentachloride,[32] but abandoned this route upon observation of major quantities of the 3′(2′)-acetates of adenosine produced by simple hydrolysis of the orthoacetate function (vide supra). Moffatt and co-workers have since applied this approach giving ~35% yields of halogen-substituted adenosine derivatives plus an unspecified quantity of 2′(3′)-*O*-acetyladenosine as one of "two major spots."[48d] This may be compared with the ~70% yields of halogenated-sugar products in the present procedures.

The antibiotic cordycepin (3′-deoxyadenosine) has been widely investigated[53] and remains a biochemical of current interest in the study of RNA synthesis.[54] Moffatt and co-workers encountered difficulties in attempted catalytic hydrogenolyses of chloro-sugar nucleosides and prepared the analogous bromo compounds for this purpose.[48b] However, hydrogenolysis of their 3′-bromo-2′-*O*-acetyl derivative led to essentially equivalent amounts of cordycepin and 2′,3′-dideoxyadenosine.[55]

The present study describes the smooth dechlorination of **3a,4a** to blocked derivatives of **7** and **8** using free radical conditions. Quantitative hydrogenolysis of the iodo intermediate **4c** followed by deblocking gave cordycepin (**8**) in 90% crystalline yield with no observable nucleoside by-products. Preparation and reactions of the ribo epoxide **6** in good yield by this procedure have been described.[16,20] The successful application of this approach to the defined preparation of each of the three possible endocyclic unsaturated-sugar adenine nucleosides[19] and unsaturated, deoxy, and stereochemically inverted derivatives of tubercidin[26] are described separately. Extension of these studies with inosine[21b] and guanosine[21] will be reported.

Experimental Section

General Procedures. Melting points were determined on a Reichert microstage apparatus and are uncorrected. Nuclear magnetic resonance spectra (^{1}H NMR) were recorded on Varian A-60 and HA-100 instruments with Me_4Si as internal reference. Ultraviolet (uv) spectra were recorded on Cary 14 or 15 spectrophotometers. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter using a 10-cm, 1-ml microcell. Mass spectra were obtained by the Mass Spectroscopy Laboratory of this department on AEI MS-2, MS-9, or MS-12 instruments via direct probe sample introduction at 70 eV and 150 to 230 °C. Elemental analyses were determined by the microanalytical laboratory of this department or by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y. Thin-layer chromatography (TLC) was performed on Eastman Chromatogram sheets (silica gel No. 13181, indicator No. 6060) in the solvent systems indicated. Developed chromatograms were evaluated under uv (2537 Å) light. Evaporations were carried out using a Büchler rotating evaporator with a dry ice cooled Dewar condensor under aspirator or oil pump vacuum, at 40 °C or less. Hydrogenations were effected using a Parr shaking apparatus at room temperature, under the specified hydrogen pressure with Matheson Coleman and Bell 5 or 10% palladium on carbon as catalyst.

Silica column chromatography was performed on Mallinckrodt SilicAR CC-7, J. T. Baker No. 3405, or Woelm (0.063–0.1 mm) silica gel. Unless specified, "silica" refers to the Mallinckrodt CC-7 adsorbent. Carbon chromatography was effected on Barnebey-Cheney AU-4 carbon which was refluxed with 1 N HCl for several hours, washed with water, and refluxed with 1 N NaOH. The carbon was then washed with water until the filtrate was neutral, followed by methanol, chloroform, and methylene chloride, and allowed to air dry. "Ether" refers to Mallinckrodt diethyl ether in all cases. Pyridine was refluxed over and then distilled from calcium hydride and stored over Linde 4A molecular sieves (dried at 200 °C). Sodium iodide was dried in the presence of phosphorous pentoxide at room temperature under high vacuum for at least 24 h. Pivalyl chloride was distilled before use.

"Diffusion crystallization"[56] was effected using ether/pentane for blocked intermediates and an alcohol/ether for unblocked products. A concentrated solution of the nucleoside (warming was necessary with unblocked products) in the first mentioned solvent contained in a beaker or small wide-mouth Erlenmeyer flask was allowed to stand in a closed desiccator containing a large volume of the second solvent, in which the material is insoluble. Crystallization was allowed to

proceed at room temperature for 2 to 5 days, and the crystals were then collected, without cooling. In no case was it necessary to collect more than two crops, with the first crop generally giving ~90% of the material obtained.

Adenosine was purchased from Raylo Chemicals Ltd. and Terochem Laboratories Ltd., Edmonton, Alberta.

2′,3′-*O*-Methoxyethylideneadenosine (2). To a suspension of 3 g (0.011 mol) of **1** in 75 ml of dry dioxane were added 4.12 g (0.034 mol) of trimethyl orthoacetate and 4.87 g (0.03 mol) of trichloroacetic acid. After heating the mixture at 50 °C for 20 min, an essentially clear solution resulted. The reaction mixture was neutralized with 120 ml of 5% aqueous $NaHCO_3$ solution, and most of the dioxane was evaporated. The aqueous solution was extracted with $CHCl_3$, and the combined organic phase was dried over Na_2SO_4, filtered, and evaporated to give a colorless solid foam (3.57 g, 98%). This material could be used without further purification in subsequent reactions. Purification of 1 g of this foam, which contained traces of **1** as well as a faster migrating (TLC) spot was achieved by column chromatography on Woelm silica (2.3 × 15 cm; 24 g) packed in $CHCl_3$ containing 1% of saturated NH_3/MeOH solution. The column was eluted with $CHCl_3$ containing increasing amounts of saturated NH_3/MeOH. The appropriately pooled (TLC) fractions contained 0.87 g (87%) of pure **2**. This material was dissolved in 20 ml of MeOH containing 0.5% saturated NH_3/MeOH, filtered, and allowed to stand in a desiccator containing Et_2O. After 3 days the resulting crystals were filtered and dried for 18 h at 60 °C (0.1 mm Hg) over $CaCl_2$ to give 0.155 g of colorless needles of **2**, mp 219–221 °C; uv (MeOH) max 258 nm (ϵ 14 700). The NMR spectrum indicated that this product consisted mainly of the exo isomer with about 14% of the endo isomer. A second crop of 0.065 g contained more of the endo isomer: NMR (Me_2SO-d_6) (exo isomer) δ 1.53 (s, 3, C-CH_3), 3.36 (s, 3, OCH_3), 3.57 (m, 2, $H_{5'}$, $H_{5''}$), 4.32 (m, 1, $H_{4'}$), 4.93–5.50 (complex, 3, $H_{2'}$, $H_{3'}$, 5′-OH), 6.29 (d, $J_{1'-2'} \sim 3.8$ Hz, 1, $H_{1'}$), 7.33 (s, 2, 6-NH_2), 8.20 (s, 1, H_2), 8.39 (s, 1, H_8); (endo isomer) δ 1.65 (s, 3, C-CH_3), 3.20 (s, 3, OCH_3) 6.20 (d, $J_{1'-2'} \sim 3.8$ Hz, 1, $H_{1'}$). Anal. ($C_{13}H_{17}N_5O_5$) C, H, N.

Reaction of 2 with Pivalyl Chloride/Pyridine at Reflux. To a solution of 2.9 g (0.009 mol) of **2** in 60 ml of dry pyridine was added 12 ml (0.1 mol) of pivalyl chloride dropwise with stirring and exclusion of moisture. The solution was then slowly (1 h) heated to reflux and refluxed for 1 h. The resulting yellow solution was allowed to cool to room temperature, and 20 ml of MeOH was added dropwise with stirring. This solution was evaporated until precipitation of solid began. Dry Et_2O (100 ml) was added and the mixture filtered. The filtrate was washed with 2 × 100 ml of 10% $NaHCO_3$, 2 × 100 ml of H_2O, dried over Na_2SO_4, filtered, and evaporated to give 4.6 g of a yellow solid foam.

A 2.7-g portion of crude product was applied to a silica column (2.3 × 45 cm, 70 g) packed in Et_2O. The column was eluted using 100-ml portions of Et_2O–$CHCl_3$ mixtures. The beginning portion was Et_2O–$CHCl_3$ 90:10, and the $CHCl_3$ concentration was raised by 10% increments to Et_2O–$CHCl_3$ 10:90. An additional 1000 ml of $CHCl_3$ was followed by EtOAc. Fractions (25 ml) 7–17 contained 0.37 g (11%) of **3b,4b** and fractions 65–92 contained 1.53 g (59%) of **3a,4a**. Samples of both fractions for analysis were obtained by dissolving the amorphous products in Et_2O, adding Skellysolve B, and cooling the mixture at −80 °C. After centrifugation, the supernatent liquid was decanted, and the semicrystalline products were dried at 0.1 mm Hg at room temperature. The purified **3a,4a** fraction (only **4a** now visible by NMR, see Table I) melted at ~80 °C had uv (MeOH) max 272 nm (ϵ 17 000); mass spectrum calcd for M^+ 495.1885, found *m/e* 495.1905. Anal. ($C_{22}H_{30}ClN_5O_6$) C, H, N.

Purified fraction **3b,4b** (only **4b** now visible by NMR, see Table I) melted at ~90 °C and had uv (MeOH) max 272 nm (ϵ 17 800); mass spectrum calcd for M^+ 663.3035, found *m/e* 663.3017. Anal. ($C_{32}H_{46}ClN_5O_8$) C, H. Calcd: N, 10.50. Found: N, 10.06. This reaction has been successfully scaled up tenfold.[2b]

9-(3-Chloro-3-deoxy-β-D-xylofuranosyl)adenine and 9-(2-Chloro-2-deoxy-β-D-arabinofuranosyl)adenine (5). The above procedure for the preparation of **3,4** was followed to the end of the first paragraph. A 2-g portion of the yellow solid foam was dissolved in 100 ml of MeOH presaturated with ammonia at −5 °C and allowed to stand at 0 °C for 24 h. The ammonia was evaporated at 0 °C, and 20 g of silica was added to the solution. The methanolic mixture was evaporated to dryness, and the impregnated powder was added to a column (4.3 × 80 cm, 400 g) of silica gel. The products were eluted with $CHCl_3$–MeOH (95:5). The first product to be eluted was 9-(3-chloro-3-deoxy-β-D-xylofuranosyl)adenine slightly contaminated, in the first fractions, with small amounts of epoxide **6**. Evaporation of the pure fractions gave 0.4 g of the chloroxylo compound as a white powder. A sample for analysis was recrystallized by diffusion (95% EtOH/Et_2O) and had mp 195–196 °C [α]^{24}D −32° (*c* 0.14, MeOH); [lit.[48b] mp 194–196 °C; [α]^{23}D −31.6° (*c* 0.14, MeOH)]; mass spectrum see ref 2b. Anal. ($C_{10}H_{12}ClN_5O_3$) C, H, Cl, N.

Further development of the above column with the same solvent system gave fractions containing both chloro isomers followed by fractions which were pooled and evaporated to give 0.027 g of pure **5**. A sample for analysis was recrystallized by diffusion (95% EtOH/Et_2O) and had mp 243–245 °C; [α]^{24}D, −8° (*c* 0.25, Me_2SO); [lit.[48b] mp 245–247 °C, [α]^{23}D, −10.5° (*c* 0.25, Me_2SO)]; mass spectrum see ref 2b. Anal. ($C_{10}H_{12}ClN_5O_3$) C, H, Cl, N.

9-(2,3-Anhydro-β-D-ribofuranosyl)adenine (6) and 9-(2-Chloro-2-deoxy-β-D-arabinofuranosyl)adenine (5). An impurity which corresponded to **5** was detected (TLC) in crude preparations of **6** before the described ion exchange column chromatographic purification.[16] This was verified by treating 2 g of yellow solid foam (crude **3** + **4**) in 50 ml of MeOH with 2 g of NaOMe for 22 h at room temperature. The solution containing **5** and **6** was evaporated, the residue dissolved in 50 ml of H_2O, and the resulting solution neutralized to pH 7.5 with 5 N AcOH. This solution was heated for 70 min at reflux to convert **6** to 5-amino-1-(3-amino-3-deoxy-β-D-xylofuranosyl)imidazole-4-carboxamidine-N^5 → 3′-cyclonucleoside hydroformate.[16] The cooled aqueous solution was extracted with Et_2O and $CHCl_3$, and the organic washes were discarded. The aqueous phase was then extracted continuously with EtOAc for 16 h. A solid which separated early in the evaporation of the EtOAc extract was filtered and discarded. The resulting filtrate was evaporated to dryness, and the residue was triturated with absolute EtOH. The colorless needles which formed were recrystallized from EtOH to give 58 mg of **5**, mp 248–250 °C. This product had spectroscopic properties identical with the above preparation of **5**. Anal. C, H, N.

Conversion of 5 to 6. To a solution of 15 mg (0.053 mmol) of **5** in 10 ml of MeOH was added 100 mg (1.85 mmol) of NaOMe in 10 ml of MeOH, and the reaction mixture was stirred for 11 days at room temperature. Only a trace of **5** remained (TLC), and the solution was evaporated. The oily residue was dissolved in H_2O, neutralized with 5 *N* AcOH, cooled, and the precipitate was filtered. This product was identical with **6** as judged by TLC, uv, and mass spectroscopy (M^+ 249).

Reaction of 2 with Sodium Iodide/Pivalyl Chloride/Pyridine at Reflux. To a solution of 646 mg (0.002 mol) of unpurified **2** in 40 ml of pyridine was added 6 g (0.04 mol) of NaI. The vigorously stirred solution was heated to reflux, and 2.4 ml (0.02 mol) of pivalyl chloride was added. The reaction was stirred at reflux for 4 min, allowed to cool for 20 min, and 10 ml of MeOH was added. The red solution was stirred for ~3 h and poured into 100 ml of H_2O containing 5 g of $NaHCO_3$ and 0.5 g of $Na_2S_2O_3$. The resulting yellow solution was extracted with Et_2O. The organic phase was washed with H_2O, and the washes were back extracted as indicated by TLC. The combined organic phase was evaporated to give a gum which upon successive coevaporations using toluene and 98% EtOH gave 1.38 g of a yellow-brown solid foam. This material was dissolved in EtOAc and applied to a carbon column (2.2 × 28 cm, 40 g) packed in EtOAc. The column was eluted with 1600 ml of EtOAc, followed by 500 ml of EtOAc–$CHCl_3$ (1:1). Fractions comprising 200 ml to 1300 ml of eluate yielded 932 mg of a mixture of **4c** and the corresponding 3′,4′-unsaturated derivative.[19] Fractions from 1300 ml to 1600 ml yielded 57 mg of a mixture of **4c** and **3c**. Fractions from 1600 ml to 2000 ml yielded 217 mg of **3c**. Rechromatography of the 57 mg of **4c** and **3c** on a small carbon column (1.0 × 17 cm, 4 g) using 140 ml of EtOAc followed by 60 ml of EtOAc–$CHCl_3$ 1:1 gave: from 40 ml to 140 ml, 21 mg of **4c**, and from 140 ml to 200 ml, 29 mg of **3c**. An analytical sample of **3c** (total yield 246 mg, 16%) was obtained by percolation of this material in $CHCl_3$ through a small silica column followed by crystallization from Et_2O/pentane which gave a solid: mp 95–97 °C; uv (MeOH) max 272; 213 nm (ϵ 18 600; 29 100) min 243 nm (ϵ 9700); NMR (see Table I); mass spectrum calcd for M^+ 755.2391, found *m/e* 755.2417 (and see Table II). Anal. ($C_{32}H_{46}IN_5O_8$) C, H, I, N.

The mixture of **4c** and the 3′-ene (953 mg) was dissolved in 5 ml of Et_2O and crystallized with diffusion of pentane to give 628 mg (42%) of pure **4c**. The mother liquors, containing 319 mg of material, were dissolved in Et_2O and applied to a column of silica (1.6 × 42 cm,

40 g), packed in and eluted with Et_2O. Fractions from 95 to 125 ml contained 95 mg of 3′-ene (8%), and from 125 to 255 ml, 174 mg of a mixture of **4c** and 3′-ene was obtained. "Diffusion crystallization" of this mixture (Et_2O/pentane) gave 116 mg of pure **4c** for a total crystalline yield of 744 mg (49%): mp 168–170 °C; uv (MeOH) max 271; 212 nm (ϵ 19 000; 32 700) min 243 nm (ϵ 11 000); NMR (see Table I); mass spectrum calcd for M^+ 755.2391, found *m/e* 755.2424 (and see Table II). Anal. ($C_{32}H_{46}IN_5O_8$) C, H, I, N.

Conversion of 3c and 4c into 6. Treatment of **3c** and/or **4c** with NaOMe/MeOH (as described[16] for the conversion of **3a,b + 4a,b → 6**) gave smooth conversion to the epoxide **6** (TLC, mass spectra) as the only detected product.

6-*N*-Pivalamido-9-(3-deoxy-5-*O*-pivalyl-2-*O*-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-D-*erythro*-pentofuranosyl)purine (4d). To 755 mg (0.001 mol) of **4c,** 420 mg of $NaHCO_3$, and 250 mg of 5% Pd/C were added 10 ml of H_2O and 50 ml of 95% EtOH. The mixture was then hydrogenated at 50 psi for 2 h. The reaction mixture was filtered through a Celite pad, and the catalyst was washed with 95% EtOH and then $CHCl_3$. After evaporation of the combined colorless filtrate, the residue was partitioned between Et_2O and H_2O. The organic layer was evaporated to give 629 mg (quantitative yield) of **4d** as a white solid foam. A crystalline sample of **4d** was obtained with difficulty from EtOH/water: mp 92.5–93.5 °C; uv (MeOH) max 271; 212 nm (ϵ 18 500; 33 100), shoulder 257 nm (ϵ 12 800), min 242 nm (ϵ 9700); NMR δ 3.30 (s, 1, H_2O) (and see Table I); mass spectrum (see Table II). Anal. ($C_{32}H_{47}N_5O_8 \cdot {}^1/_2\ H_2O$) C, H, N.

3′-Deoxyadenosine (Cordycepin) (8). Method A. A 629-mg (0.001 mol) sample of **4d** (the solid foam from a 0.001 mol reduction of **4c** as described above) was dissolved in 100 ml of MeOH–Et_3N–H_2O (45:10:45) and stirred at room temperature for 2 days. Evaporation of the solution to dryness and crystallization of the residue from MeOH (with Et_2O diffusion) gave (in two crops) 225 mg (90%) of crystalline **8**: mp 227–230 °C; $[\alpha]^{26}D$ −46.2° (*c* 0.49, H_2O); [lit.[48b] mp 225–226 °C; $[\alpha]^{23}D$ −45.8° (*c* 0.6, H_2O)]; mass and NMR spectra see ref 2a. Anal. ($C_{10}H_{13}N_5O_3$) C, H, N.

Method B. A 629-mg (0.001 mol) sample of **4d** was dissolved in 100 ml of absolute EtOH containing ~170 mg of sodium (already dissolved). After 18 h the solution was neutralized with HOAc and evaporated to dryness. The white residue was partitioned between pentane and H_2O. The aqueous layer was evaporated to a small volume and applied to a column of Dowex 1-X2(OH^-) resin (1.3 × 40 cm) packed in H_2O and eluted with 50 ml of H_2O, followed by 350 ml of 30% MeOH in H_2O. The fractions comprising 100 to 400 ml gave 251 mg (quantitative) of **8**. "Diffusion crystallization" (MeOH/Et_2O) of this material gave 214 mg (85%) of **8**.

6-*N*-Pivalamido-9-(2-deoxy-5-*O*-pivalyl-3-*O*-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-D-*erythro*-pentofuranosyl)purine (3d). A 755-mg (0.001 mol) sample of **3c** was hydrogenated and worked up identically with the reaction of **4c → 4d** described above. After evaporation of the colorless filtrate, the residue was partitioned between $CHCl_3$ and H_2O. Evaporation of the organic layer gave a white solid foam which was dissolved in 10 ml of Et_2O. Rapid crystallization of 395 mg of **3d** occurred. After filtration, the volume of the mother liquors was reduced to 5 ml and an additional 74 mg of **3d** separated for a total yield of 469 mg (75%): mp 127–129 °C; uv (MeOH) max 271; 212 nm (ϵ 19 700; 35 800), shoulder 257 nm (ϵ 13 800), min 242 nm (ϵ 10 000); NMR (see Table I); mass spectrum (see Table II). Anal. ($C_{32}H_{47}N_5O_8$) C, H, N.

2′-Deoxyadenosine (7). To 315 mg (0.0005 mol) of **3d** was added 200 ml of MeOH–Et_3N–H_2O (45:10:45). After stirring for 2 days at room temperature, the reaction was evaporated to a gum which was crystallized from 1 ml of MeOH (with Et_2O diffusion) to give 109 mg (87%) of **7**: mp 192–193 °C; $[\alpha]^{26}D$ −28.0° (*c* 1, H_2O); [lit.[57] mp 188–190 °C, $[\alpha]^{21}D$ −26° (*c* 1, H_2O)]; mass and NMR spectra see ref 2a. Anal. ($C_{10}H_{13}N_5O_3$) C, H, N.

Dechlorination/Deblocking of 3a and 4a to Give 7 and 8. To 1 g (0.002 mol) of the **3a,4a** amorphous glass dissolved in 50 ml of benzene was added 60 mg of α,α′-azobisisobutyronitrile and 1.5 ml of tri-*n*-butyltin hydride. After heating for 1 h at reflux, the mixture was evaporated and the residue was triturated with pentane. The pentane supernatent was discarded, the residue was dissolved in 60 ml of MeOH, and deblocked by stirring with 0.6 g (0.011 mol) of NaOMe for 20 h at room temperature. The mixture was evaporated, and an aqueous solution of the residue was applied to a column (3.2 × 43 cm) of Dowex 1-X2(OH^-) resin packed in H_2O. Elution was begun using 5.1 l. of H_2O, followed by 1560 ml of 23% MeOH. Fractions (50 ml) 54–90 contained 0.05 g (10%) of **7** and fractions 101–144 contained 0.37 g (72%) of **8** (by uv). Evaporation of the second combined fractions to a volume of ~15 ml resulted in separation of 0.30 g (58%) of colorless crystals of **8,** mp 225–228 °C. The first combined fractions were evaporated and the residue crystallized from MeOH/Et_2O to give 17 mg (3.5%) of **7,** mp 191–193 °C. These samples of **7** and **8** were identical with those prepared above.

Reaction of 2 with Pivalyl Chloride/Pyridine at 50 °C. To a solution of 3.23 g (0.01 mol) of **2** in 100 ml of pyridine heated in an oil bath at 50 °C was added 12 ml (0.1 mol) of pivalyl chloride. After stirring at 50 °C for 66 h the reaction was poured into 300 ml of saturated aqueous $NaHCO_3$ and extracted with Et_2O. The organic layer was washed with H_2O, and the washes were back-extracted. The combined organic phase was evaporated to a yellow gum which was coevaporated using toluene and 98% EtOH to give a solid foam. Addition of 50 ml of Et_2O resulted in the separation of 1.17 g (22%) of 6-*N*-pivalamido-9-(2,3-*O*-[4,4-dimethyl-3-oxo-pent-1-enylidene]-5-*O*-pivalyl-β-D-ribofuranosyl)purine (**14**): mp 130–131 °C; uv (MeOH) max 268; 210 nm (ϵ 37 200; 26 200) min 228 nm (ϵ 6200); the NMR spectrum showed **14** to be a mixture of geometric isomers in the ratio of ~7:3, NMR ($CDCl_3$) δ 1.11 (s, 9, C=COPiv), 1.15 (s, 9, 5′-OPiv), 1.38 (s, 9, 6-NPiv), 4.25 (m, 2, $H_{5'}$, $H_{5''}$), 4.43 (m, 1, $H_{4'}$), 5.27 (s, 1, C=CH), 5.59 (d of d, $J_{3'-4'}$ = 4 Hz, $J_{3'-2'}$ = 7 Hz, 1, $H_{3'}$), 5.74 (m, 1, $H_{3'}$ of minor isomer), 6.11 (m, 1, $H_{2'}$ of minor isomer), 6.18 (d of d, $J_{2'-3'}$ = 7 Hz, $J_{2'-1'}$ = 2 Hz, 1, $H_{2'}$), 6.39 (m, 1, $H_{1'}$ of minor isomer), 6.50 (d, $J_{1'-2'}$ = 2 Hz, 1, $H_{1'}$), 8.26 (s, 1, H_8), 8.50 (s, 1, H_8 of minor isomer), 8.57 (s, 2, 6-NH_2), 8.64 (s, 1, H_2), 8.67 (s, 1, H_2 of minor isomer). Anal. ($C_{27}H_{37}N_5O_7$) C, H, N.

The mother liquors from the crystallization of **14** were evaporated to give 5.55 g of a yellow solid foam. A 1.0-g sample of this material was dissolved in Et_2O and applied to a silica column (2.0 × 44 cm, 50 g) packed in Et_2O and eluted with: 300 ml of Et_2O; 700 ml of 2.5% MeOH in Et_2O; and 500 ml of 5% MeOH in Et_2O. From the fractions comprising 200 to 350 ml were obtained 123 mg (10%) of **3b,4b;** from 550 to 650 ml, 33 mg (4%) of pivalylated starting material; from 650 to 850 ml, 188 mg (21%) of **3a,4a,** contaminated with some pivalylated starting material; and from 1150 to 1500 ml 142 mg (14%) of **14** for a total yield of 36% of **14**.

Reaction of 14 with Sodium Iodide/Pivalyl Chloride/Pyridine at Reflux. A 1.09 g (0.002 mol) sample of **14** was treated with 6 g (0.04 mol) of NaI and 2.4 ml (0.02 mol) of pivalyl chloride in 40 ml of pyridine at reflux and the reaction mixture purified identically as described above for the analogous reaction of 0.002 mol of **2.** The product yields obtained were: **3c,** 152 mg (15%), **4c,** 754 mg (50%); the 3′-ene[19] derived from **4c,** 235 mg (15%).

Reaction of 4c with Warm 80% Acetic Acid. A 378-mg (0.0005 mol) sample of **4c** was dissolved in 10 ml of 80% HOAc and the solution stirred in an oil bath at 80 °C for 24 h. The solution was then evaporated to dryness and the dark residue triturated with Et_2O and filtered. The filtrate was evaporated to give 300 mg of a brown solid foam, uv max (MeOH) 259 nm; NMR ($CDCl_3$) δ 1.15 (s, 9, C=C-*t*-Bu), 1.25 (s, 18, 5′-OPiv and C=COPiv), 3.85–4.53 (m, 4, $H_{3'}$–$H_{5''}$), 5.76 (s, 1, CH=C), 5.81 (m, 1, $H_{2'}$), 6.05 (m, 3, $H_{1'}$, 6-NH_2), 8.33 (s, 2, H_2 and H_8).

Treatment of 3a,4a with Pivalyl Chloride/Pyridine at Reflux. To a solution of 0.2 g (0.0004 mol) of **3a,4a** in 5 ml of pyridine was added 0.033 ml (0.0008 mol) of MeOH and 0.5 ml (0.004 mol) of pivalyl chloride. The solution was refluxed for 2 h, allowed to cool, and 5 ml of MeOH added. The crude product (0.23 g) was isolated by extraction as described above for the preparation of **14.** TLC (silica, Et_2O), NMR, and mass spectral analysis showed only unreacted **3a,4a.**

Treatment of 3a,4a with Pivalyl Chloride/Sodium Iodide/Pyridine at Reflux. To a solution of 0.2 g (0.0004 mol) of **3a, 4a,** and 1.2 g (0.008 mol) of NaI in 5 ml of pyridine heated at reflux were added 0.033 ml (0.0008 mol) of MeOH and 0.5 ml (0.004 mol) of pivalyl chloride. The solution was refluxed for 5 min, allowed to cool, and 5 ml of MeOH added. The product (0.2 g) was isolated by extraction as described above for the preparation of **3c** and **4c.** TLC (silica, Et_2O), NMR, and mass spectral analysis showed only unreacted **3a,4a.** Analogous results were observed using 6-*N*-pivalamido-9-(3-iodo-3-deoxy-2-*O*-acetyl-5-*O*-pivalyl-β-D-xylofuranosyl)purine (the iodo analogue of **4a**) at reflux for 10 min.

Isolation of 2′,3′-*O*-Methoxy(4,4-dimethyl-3-oxopentylidene) adenosine (18a). A 10-g sample of the nonpolar material obtained from the final ether extracts of large scale preparations of **6**[16] was dissolved in 10 ml of 3% MeOH in $CHCl_3$ and applied to a 600-g column of J.

T. Baker silica. The column was packed in and eluted with the same solvent mixture at a fast flow rate. Fractions 1500–3200 ml contained 1.31 g of an unidentified mixture; 3200–3700 ml, 3.97 g of **18a** (mainly one diastereomer); 3700–3900 ml, 1.50 g of **18a** (mixture of diastereomers); and 3900–5100 ml, 3.33 g of **18a** (mainly the more polar diastereomer). The 3.97 g fraction was crystallized from Et_2O to give 1.96 g of the pure less polar diastereomer: mp 162–164 °C; uv (MeOH) max 259 nm; NMR ($CDCl_3$) δ 1.22 (s, 9, *t*-Bu), 3.30 (s, 2, $-CH_2-$), 3.38 (s, 3, $-OCH_3$), 4.02 (m, 2, $H_{5'}$, $H_{5''}$), 4.63 (m, 1, $H_{4'}$), 5.52 (m, 2, $H_{2'}$, $H_{3'}$), 6.42 (m, 3, $H_{1'}$, 6-NH_2), 8.06 (s, 1, H_2), 8.45 (s, 1, H_8). Anal. ($C_{18}H_{25}N_5O_6$) C, H, N.

The 3.33-g fraction was crystallized from acetone to give 1.95 g of the pure more polar isomer: mp 184–185 °C; uv (MeOH) max 259 nm; NMR ($CDCl_3$) δ 1.15 (s, 9, *t*-Bu), 3.24 (s, 2, $-CH_2-$), 3.55 (s, 3, $-OCH_3$), 3.98 (m, 2, $H_{5'}$, $H_{5''}$), 4.66 (m, 1, $H_{4'}$), 5.50 (m, 2, $H_{2'}$, $H_{3'}$), 6.39 (d, $J_{1',2'}$ = 2 Hz, 1, $H_{1'}$), 6.51 (s, 2, 6-NH_2), 8.03 (s, 1, H_2), 8.44 (s, 1, H_8). Anal. C, H, N.

The mother liquors from the crystallization of both isomers and the material from the overlapping fractions were combined and evaporated. The residue was dissolved in $CHCl_3$ and precipitated by dropwise addition to pentane to give after filtration 3.0 g of a 2:1 mixture (by NMR) of the more nonpolar to polar diastereomers of **18a**.

Reaction of 18a with Pivalyl Chloride/Pyridine at Reflux. A. To 1.02 g (0.0025 mol) of **18a** (mixed isomers) in 50 ml of pyridine was added 3.0 ml (0.025 mol) of pivalyl chloride and the solution heated at reflux for 2 h. After cooling, the mixture was poured into 100 ml of 10% $NaHCO_3$, stirred for 5 min, and extracted with Et_2O. The organic layer was washed with H_2O and evaporated. The residue was coevaporated using toluene and 98% EtOH to give 1.5 g of a solid foam. Crystallization of this material from Et_2O gave 355 mg (26%) of **14**. Purification of the mother liquors was effected on a silica column (2.2 × 32 cm, 51 g) packed in and eluted with Et_2O. Fractions comprising 200 to 400 ml contained 200 mg (12%) of **3b,4b**. Fractions from 400 to 580 ml contained 50 mg of a mixture of **3b,4b** and pivalylated starting material (**18b**), and from 580 to 1100 ml contained 470 mg (33%) of **18b**, identified by comparison of NMR and mass spectra with **18a** and by conversion to **18a** on treatment with sodium methoxide.

B. A 0.12-g (0.0003 mol) sample of **18a** in 7.5 ml of pyridine was treated with 0.35 g (0.003 mol) of pivalyl chloride for 5 h at reflux. After cooling, 2 ml of MeOH was added and the solution stirred overnight. Isolation of products was effected as described in part A and gave 170 mg of a solid foam. TLC (silica, Et_2O) indicated this material to be a mixture of **3b,4b** and **18b** in a ratio of ~1:3.

Reaction of 18a with Pivalyl Chloride/Sodium Iodide/Pyridine at Reflux. To 0.1 g (0.00025 mol) of **18a** and 0.75 g (0.005 mol) of NaI in 10 ml of refluxing pyridine was added 0.3 ml (0.0025 mol) of pivalyl chloride. Heating was continued for 6 min, the reaction allowed to cool, and 5 ml of MeOH added. After stirring overnight the products (188 mg) were isolated by extraction as in the preparation of **3c** and **4c**. TLC (silica, Et_2O) indicated this material to a mixture of ~50% of **18b** and ~50% (combined) of **3c**, **4c**, and 3′-ene.[19]

Reaction of 14 with Sodium Methoxide in Methanol. To 193 mg (0.00035 mol) of **14** dissolved in 5 ml of MeOH was added 200 mg of NaOMe and the mixture stirred overnight (complete by TLC after ~4 h at room temperature). The mixture was evaporated, dissolved in H_2O, and this solution was extracted with CH_2Cl_2. Evaporation of the organic layer gave a gum which was triturated with Et_2O and filtered. The solid obtained (40 mg) was found to be identical with **18a** by TLC (silica, 3% MeOH in Et_2O) and NMR spectral comparison.

Ethyl 4,4-Dimethyl-3-pivaloxypent-2-enoate (9). Method A. To 49 g (0.33 mol) of NaI in 250 ml of pyridine was added 39 ml (0.33 mol) of pivalyl chloride, followed by the dropwise addition of 20 ml (0.11 mol) of triethyl orthoacetate over 15 min. The reaction was stirred for 1 h, and 50 ml of MeOH was added. After standing for 2 days at room temperature, the reaction was poured into 500 ml of H_2O containing 30 g of $NaHCO_3$ and 5 g of $Na_2S_2O_3$. This mixture was extracted with pentane, and the pentane layer was washed with H_2O, dried, and distilled. A 3.03-g (11%) fraction of **9** was collected at 82–84 °C (0.1 mm Hg). A pure sample was obtained by crystallization of the solidified distillate from pentane to give crystals of **9**: mp 36–37 °C; uv (MeOH) max 216 nm (ϵ 12 800); NMR ($CDCl_3$) δ 1.13 (s, 9, C≡C-*t*-Bu), 1.24 (t, J = 7.2 Hz, 3, OCH_2CH_3), 1.34 (s, 9, C≡COPiv), 4.07 (q, J = 7.2 Hz, 2, OCH_2CH_3), 5.62 (s, 1, CH=C); ir (neat) cm^{-1} 1760 (C≡C-O*C*O*C*[CH_3]$_3$); 1722 (EtO*C*O*C*=C); 1645, 842 (C=C). Anal. ($C_{14}H_{24}O_4$) C, H.

Method B. Evaporation of the pentane layer from the preparation of **8** (method B) gave 232 mg of an oil which was crystallized from pentane to give a first crop of 122 mg (50%) of **9**, mp 35–36 °C. The ir, uv, NMR, and mass spectra of **9** prepared by the two methods were identical.

Methyl 4,4-dimethyl-3-pivaloxypent-2-enoate was obtained by method B from a methanolic sodium methoxide deblocking of **4d** → **8**. This oily product was examined by NMR and mass spectroscopy (see Table II).

References and Notes

(1) (a) Generous financial support from the National Research Council of Canada (A5890), the National Cancer Institute of Canada, and The University of Alberta is gratefully acknowledged. (b) For the previous paper in this series see: M. J. Robins, M. MacCoss, S. R. Naik, and G. Ramani, *J. Am. Chem. Soc.*, in press.
(2) Abstracted in part from the Ph.D. dissertations of (a) R. A. Jones, The University of Alberta, Spring 1974; and (b) Y. Fouron, The University of Alberta, Spring 1975.
(3) Postdoctoral Fellow, The University of Alberta, 1969–1971.
(4) For comprehensive reviews see: (a) J. A. Montgomery and H. J. Thomas, *Adv. Carbohydr. Chem.*, **17**, 301 (1962); (b) A. M. Michelson, "The Chemistry of Nucleosides and Nucleotides", Academic Press, London, 1963; (c) C. A. Dekker and L. Goodman in "The Carbohydrates Chemistry and Biochemistry", 2d ed, Vol. IIA, W. Pigman and D. Horton, Ed., Academic Press, New York, N.Y., 1970, pp 1–68; (d) L. Goodman in "Basic Principles in Nucleic Acid Chemistry", Vol. I, P.O.P. Ts'o, Ed., Academic Press, New York, N.Y., 1974, pp 93–208.
(5) M. Ikehara, *Acc. Chem. Res.*, **2**, 47 (1969).
(6) Reference 4d, pp 117–122.
(7) Reference 4d, pp 113–117.
(8) R. J. Suhadolnik, "Nucleoside Antibiotics", Wiley-Interscience, New York, N.Y., 1970, Chapter 9.
(9) R. L. Tolman, R. K. Robins, and L. B. Townsend, *J. Am. Chem. Soc.*, **90**, 524 (1968); *ibid.*, **91**, 2102 (1969).
(10) See: K. H. Schram and L. B. Townsend, *J. Chem. Soc., Perkin Trans. 1*, 1253 (1975), and references therein.
(11) C. U. Pittman, Jr., S. P. McManus, and J. W. Larsen, *Chem. Rev.*, **72**, 357 (1972).
(12) J. R. McCarthy, Jr., R. K. Robins, and M. J. Robins, *J. Am. Chem. Soc.*, **90**, 4993 (1968).
(13) L. Goodman, *Adv. Carbohydr. Chem.*, **22**, 109 (1967).
(14) R. Mengel and M. J. Robins, 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March–April 1971, Abstract CARB-002; M. J. Robins, R. Mengel, and R. A. Jones, *J. Am. Chem. Soc.*, **95**, 4074 (1973).
(15) (a) H. P. M. Fromageot, B. E. Griffin, C. B. Reese, and J. E. Sulston, *Tetrahedron*, **23**, 2315 (1967); (b) F. Eckstein and F. Cramer, *Chem. Ber.*, **98**, 995 (1965).
(16) M. J. Robins, Y. Fouron, and R. Mengel, *J. Org. Chem.*, **39**, 1564 (1974).
(17) H. G. Kuivila, *Synthesis*, 499 (1970); J. Farkaš and F. Šorm, *Collect. Czech. Chem. Commun.*, **32**, 2663 (1967).
(18) C. A. Dekker, *J. Am. Chem. Soc.*, **87**, 4027 (1965).
(19) M. J. Robins, R. A. Jones, and R. Mengel, following paper in this issue.
(20) R. Mengel and H. Wiedner, *Chem. Ber.*, **109**, 433, 1395 (1976).
(21) (a) R. Mengel and W. Muhs, *Nucleic Acids Res.*, Spec. Publ. **No.** 1, s41 (1975); (b) R. Mengel et al., to be published.
(22) C. Altona and M. Sundaralingam, *J. Am. Chem. Soc.*, **95**, 2333 (1973).
(23) K. N. Slessor and A. S. Tracey, *Carbohydr. Res.*, **27**, 407 (1973).
(24) J. A. McCloskey in "Basic Principles in Nucleic Acid Chemistry", Vol. I, P.O.P. Ts'o, Ed., Academic Press, New York, N.Y., 1974, pp 209–309.
(25) J. H. Bowie, S.-O. Lawesson, G. Schroll, and D. H. Williams, *J. Am. Chem. Soc.*, **87**, 5742 (1965).
(26) (a) M. J. Robins, R. A. Jones, and R. Mengel, submitted for publication; (b) M. J. Robins, Y. Fouron, and W. H. Muhs, submitted for publication.
(27) H. J. Veith and M. Hesse, *Helv. Chim. Acta*, **52**, 2004 (1969).
(28) A. Ladenburg, *Ber. Dtsch. Chem. Ges.*, **4**, 726 (1871) (see footnote on p 728).
(29) See for example: (a) S. Winstein and R. E. Buckles, *J. Am. Chem. Soc.*, **65**, 613 (1943); (b) R. Boschan and S. Winstein, *ibid.*, **78**, 4921 (1956); (c) R. M. Roberts, J. Corse, R. Boschan, D. Seymour, and S. Winstein, *ibid.*, **80**, 1247 (1958); (d) C. B. Anderson, E. C. Freidrich, and S. Winstein, *Tetrahedron Lett.*, 2037 (1963), previous papers, and references therein.
(30) See for example: (a) H. Meerwein, *Angew. Chem.*, **67**, 374 (1955); H. Meerwein in Houben-Weyl "Methoden Der Organischen Chemie", Band VI/3, Georg Thieme Verlag, Stuttgart, 1965, pp 295–365; (b) H. Meerwein, K. Bodenbenner, P. Borner, F. Kunert, and K. Wunderlich, *Justus Liebigs Ann. Chem.*, **632**, 38 (1960), and references therein.
(31) (a) H. Baganz and L. Domaschke, *Chem. Ber.*, **91**, 653 (1958); (b) B. T. Golding, D. R. Hall, and S. Sakrikar, *J. Chem. Soc., Perkin Trans. 1*, 1214 (1973).
(32) See for example: H. Paulsen and H. Behre, *Chem. Ber.*, **104**, 1264, 1281, 1299 (1971), references therein, and subsequent papers.
(33) L. R. Schroeder, *J. Chem. Soc. B*, 1789 (1970).
(34) (a) S. M. McElvain, *Chem. Rev.*, 45, 453 (1949); (b) D. Borrmann in Houben-Weyl "Methoden Der Organishen Chemie", Band VII/4, Georg Thieme Verlag, Stuttgart, 1968, pp 340–391.
(35) S. M. McElvain and G. R. McKay, Jr., *J. Am. Chem. Soc.*, **78**, 6086 (1956).
(36) S. M. McElvain and D. Kundiger, *J. Am. Chem. Soc.*, **64**, 254 (1942).
(37) L. Claisen and E. Haase, *Ber. Dtsch. Chem. Ges.*, **33**, 1242 (1900).

(38) A. Kivinen in "The Chemistry of Acyl Halides", S. Patai, Ed., Interscience, London, 1972, p 221.
(39) (a) S. Hanessian, *Carbohydr. Res.*, **2**, 86 (1966); (b) S. Hanessian and N. R. Plessas, *J. Org. Chem.*, **34**, 1035, 1045, 1053 (1969).
(40) E. N. Marvel and M. J. Joncich, *J. Am. Chem. Soc.*, **73**, 973 (1951); A. Rieche, E. Schmitz, W. Schade, and E. Beyer, *Chem. Ber.*, **94**, 2926 (1961).
(41) M. M. Ponpipom and S. Hanessian, *Carbohydr. Res.*, **17**, 248 (1971); M. M. Ponpipom and S. Hanessian, *Can. J. Chem.*, **50**, 246, 253 (1972).
(42) (a) M. S. Newman and C. H. Chen, *J. Am. Chem. Soc.*, **94**, 2149 (1972); M. S. Newman and C. H. Chen, *J. Org. Chem.*, **38**, 1173 (1973); (b) M. S. Newman and C. H. Chen, *J. Am. Chem. Soc.*, **95**, 278 (1973); (c) M. S. Newman and D. R. Olson, *J. Org. Chem.*, **38**, 4203 (1973).
(43) M. W. Logue, *Carbohydr. Res.*, **40**, C9 (1975).
(44) (a) Dr. Y. Fouron, (b) Dr. R. Mengel, unpublished data.
(45) T. P. Culbertson, *J. Org. Chem.*, **38**, 3624 (1973).
(46) S. Hanessian and E. Moralioglu, *Tetrahedron Lett.*, 813 (1971); *Can. J. Chem.*, **50**, 233 (1972).
(47) A. R. Mattocks, *J. Chem. Soc.*, 1918, 4840 (1964).
(48) (a) S. Greenberg and J. G. Moffatt, *J. Am. Chem. Soc.*, **95**, 4016 (1973); (b) A. F. Russell, S. Greenberg, and J. G. Moffatt, *ibid.*, **95**, 4025 (1973); (c) T. C. Jain, A. F. Russell, and J. G. Moffatt, *J. Org. Chem.*, **38**, 3179 (1973); (d) T. C. Jain, I. D. Jenkins, A. F. Russell, J. P. H. Verheyden, and J. G. Moffatt, *ibid.*, **39**, 30 (1974); (e) F. W. Lichtenthaler, K. Kitahara, and K. Strobel, *Synthesis*, 860 (1974).
(49) M. J. Robins, J. R. McCarthy, Jr., R. A. Jones, and R. Mengel, *Can. J. Chem.*, **51**, 1313 (1973).
(50) A. A. Akhrem, V. A. Zharkov, G. V. Zaitseva, and I. A. Mikhailopulo, *Tetrahedron Lett.*, 1475 (1973).
(51) K. Bock, C. Pedersen, and P. Rasmussen, *Acta Chem. Scand., Ser. B*, **29**, 389 (1975), and related studies.
(52) M. J. Robins and R. A. Jones, *J. Org. Chem.*, **39**, 113 (1974).
(53) R. J. Suhadolnik, "Nucleoside Antibiotics", Wiley-Interscience, New York, N.Y., 1970, pp 50–76.
(54) H. Fouquet, R. Wick, R. Böhme, H. W. Sauer, and K. Scheller, *Arch. Biochem. Biophys.*, **168**, 273 (1975).
(55) M. J. Robins and R. K. Robins, *J. Am. Chem. Soc.*, **86**, 3565 (1964).
(56) J. N. Brown and L. M. Trefonas, *Org. Prep. Proced.*, **2**, 317 (1970).
(57) C. D. Anderson, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **81**, 3967 (1959).

Nucleic Acid Related Compounds. 23. Transformation of Ribonucleoside 2′,3′-O-Ortho Esters into Unsaturated and Deoxy Sugar Nucleosides via Enol Ester-Substituted Iodo Intermediates[1,2]

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Abstract: Treatment of 2′,3′-*O*-methoxyethylideneadenosine (**1**) with sodium iodide and pivalic acid chloride in refluxing pyridine gave a mixture containing 6-*N*-pivalamido-9-(2-iodo-2-deoxy-3-*O*-[**4,4**-dimethyl-3-pivaloxypent-2-enoyl]-5-*O*-pivalyl-β-D-arabinofuranosyl)purine (**2a**), the corresponding 3′-iodo-2′-*O*-(**4,4**-dimethyl-3-pivaloxypent-2-enoyl) (DMPP) xylo isomer (**3a**), 6-*N*-pivalylamido-9-(2-*O*-DMPP-5-*O*-pivalyl-3-deoxy-β-D-*glycero*-pent-3-enofuranosyl)purine (**4a**), and 6-*N*-pivalamido-9-(5-pivaloxymethylfuran-2-yl)purine (**5**). These compounds were separated by column chromatography on activated carbon and fractional crystallization using solvent diffusion techniques. Deblocking of **4a** gave 9-(3-deoxy-β-D-*glycero*-pent-3-enofuranosyl)adenine (**4b**), which was hydrogenated to give 3′-deoxyadenosine (**8**) plus its 4′-epimer (**9**). Both **2a** and **3a** gave **5** on prolonged heating in pyridine. A mixture containing **4a** + **5** was observed on heating **3a** in pyridine, and **4a** was rapidly converted to **5** at 180 °C. Silver acetate converted **3a** to **4a** quantitatively. Removal of the DMPP group was effected quantitatively using potassium permanganate in cold aqueous pyridine. Such treatment of **3a** gave **3b**, which was converted to the *trans*-3′-iodo-2′-mesylate (**3c**). Elimination with concomitant deblocking occurred upon addition of **3c** to aqueous sodium iodide and sodium hydroxide to give 9-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)adenine (**7**) in 81% yield. Deblocking of **5** gave 9-(5-hydroxymethylfuran-2-yl)adenine (**10a**) which was hydrogenated to give (D,L)-2′,3′-dideoxyadenosine (**13a,14a**). Hydrogenation of **7** gave authentic **13a** for comparison. Hydrogenolysis of the pivaloxymethyl bond of **5** and deblocking gave 9-(5-methylfuran-2-yl)adenine (**10b**). Hydrogenation of **10b** gave (D,L)-2′,3′,5′-trideoxyadenosine (**13b,14b**). DMPP removal from **2a** gave **2b** which was converted to the trimethylsilyl-protected arabino iodohydrin **2c**. Elimination of hydrogen iodide was effected using 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), and the product (**6a**) was deblocked to give 9-(2-deoxy-D-*erythro*-pent-1-enofuranosyl)adenine (**6c**), the first 1′,2′-unsaturated nucleoside. Hydrogenation of **6c** gave 2′-deoxyadenosine (**11**) plus its α anomer (**12**). Spectroscopic identification of products and comparison of these procedures with other approaches in nucleoside chemistry are discussed.

Nucleoside antibiotics containing an unsaturated sugar moiety are known,[4] and unsaturated nucleoside intermediates have been postulated in biosynthetic pathways involving coenzyme B_{12} mediated reactions[5] as well as in deoxynucleoside biosynthesis.[6] Therefore, unsaturated nucleosides[7] are of interest as synthetic targets for biological investigations as well as being useful chemical intermediates for transformation into modified sugar nucleosides.

The exocyclic (4′-methylene) unsaturated products have been prepared in both the purine[8] and pyrimidine[9,10] riboside series. The antibiotic decoyinine (angustmycin A) was obtained from psicofuranine by elimination of the 6′-tosylate[8b] and a 4′,5′-unsaturated derivative of adenosine was the key intermediate in the synthesis of nucleocidin.[8c] Synthetic routes to 2′,3′-unsaturated nucleosides have generally employed pyrimidine cyclonucleoside chemistry[11] and/or naturally occurring 2′-deoxynucleosides.[12] Prior to our preliminary communication,[13] studies on 3′,4′-unsaturated nucleosides had involved C-5′ oxidized[7b,14a-c] (or electronegatively activated[14d]) derivatives. Although formation of a 1′,2′-unsaturated nucleoside by treatment of a 2′-bromo-2′-deoxyuridine derivative with reduced hydroxy cobalamine (vitamin B_{12s}) had been claimed,[15] the structure of that product was shown to be incorrect.[16]

We have been interested in developing reactions and procedures for the defined chemical transformation of naturally occurring ribonucleosides into modified sugar products. Such routes should not be dependent upon specific structural features in the base nor on the position or type of glycosyl linkage. Application of these procedures to nucleoside antibiotics could