2′,3′-*O*-Ethylideneuridine (35). (a). Perchloric acid (0.1 ml, 70%) was added to a stirred suspension of uridine (2.44 g, 10 mmol) in acetonitrile (10 ml) and acetaldehyde (5 ml) at room temperature. After 45 min a clear solution resulted and the solvents were removed *in vacuo* leaving 4 g of an oily solid. The latter was extracted several times with hot chloroform in order to remove aldehyde polymers leaving 1.9 g (70%) of crystalline **35**. Recrystallization from ethanol gave 1.50 g (56%) of **35** with mp 194–196° unchanged upon recrystallization (reported[30] mp 194–195°); λ_{max}^{MeOH} 260 nm (ε 9900).

(b). A solution of uridine (244 mg, 1 mmol) and **4** (0.49 g, 3 mmol) in DMF (1 ml) was kept at room temperature for 10 min. Solid sodium borohydride (300 mg) was added portionwise (frothing), and the semisolid mass was then diluted with chloroform, washed three times with aqueous bicarbonate and then water, dried, and evaporated leaving 370 mg of a syrup. This was treated for 1 hr with methanol–concentrated ammonium hydroxide (1:1, 4 ml) and then evaporated to dryness. The residue was separated into four bands by preparative tlc using chloroform–methanol (9:1). The slower bands corresponded to uridine and 2′-chloro-2′-deoxyuridine while elution of the next band gave 43 mg (16%) of **35** which spontaneously crystallized. Recrystallization from methylene chloride gave 30 mg of a diastereomeric mixture of **35** with mp 183–185°. The nmr spectrum of the major isomer corresponded to that above while the minor isomer was readily distinguished by the appearance of $C_{1'}H$ as a doublet ($J_{1'2'}$ = 2 Hz) at 6.32 ppm and of C_6H as a doublet ($J_{5,6}$ = 8 Hz) at 7.86 ppm.

Reactions of 2-Acyloxyisobutyryl Halides with Nucleosides. II.[1] Reactions of Adenosine[2]

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Contribution No. 99 from the Institute of Molecular Biology, Syntex Research, Palo Alto, California. Received December 11, 1972

Abstract: The reactions of adenosine with 2-acetoxyisobutyryl chloride, and the corresponding acyl bromide, give 9-(2-*O*-acetyl-3-deoxy-3-halo-β-D-xylofuranosyl)- and 9-(3-*O*-acetyl-2-deoxy-2-halo-β-D-arabinofuranosyl)-adenines (**4** and **5**) in which the 5′-hydroxy groups are present as the 2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl ethers in high yields. The dioxolanone and acetyl protecting groups can be sequentially removed by mild acidic treatment while reaction of any of these compounds with sodium methoxide gives 2′,3′-anhydroadenosine in high overall yield. Catalytic hydrogenolysis of 9-(3-bromo-3-deoxy-β-D-xylofuranosyl)adenine gives 3′-deoxyadenosine (Cordycepin), while similar treatment of the 2′-*O*-acetyl derivative (**4b**) gives equal amounts of 3′-deoxyadenosine and 2′,3′-dideoxyadenosine.

We have recently described in some detail our studies on the reactions of 2-acetoxyisobutyryl chloride (**1a**)[5] with a variety of vicinal diols including uridine.[1] In essence, our conclusions were that simple cis vicinal diols react with **1** to rapidly form trans chloroacetates *via* intermediate acetoxonium ions, while trans diols give complex mixtures of predominantly nonchlorinated products. The reaction of uridine with **1a**, however, gave principally 3′-*O*-acetyl-2′-chloro-2′-deoxyuridine derivatives, the overall cis stereochemistry being a consequence of participation of the C_2 carbonyl group of the uracil ring with the initial 2′,3′-*O*-acetoxonium ion. While intervention of N^3,3′-cyclonucleosides has been suggested several times to explain anomalous reactions of purine nucleosides,[6] it is generally thought that there is little tendency for the purine ring to participate in reactions at $C_{2'}$ or $C_{3'}$. Accordingly, it was of interest to examine the reactions of the vicinal diol function of purine nucleosides with **1**. The results of our studies with adenosine are described in this paper.

Treatment of a suspension of adenosine (**2**) and 3–4 molar equiv of **1a** in acetonitrile at 80° led to the formation of a homogeneous solution within 1 hr. Following removal of water-soluble by-products by a simple partitioning procedure, a crude reaction product that was predominantly a single uv-absorbing spot by tlc was obtained in high yield. The aqueous phase was found to contain about 20% adenine resulting from the acidic reaction conditions. Essentially identical results were obtained in reactions at 37° for 12–16 hr, but under these conditions a clear solution was not obtained since adenine (once again 20%) precipitated as the adenosine reacted. Direct crystallization of the crude product gave a homogeneous compound in 20% yield, and while the mother liquors were still predominantly material with the same tlc behavior, further crystallization could not be achieved. By analytical and spectroscopic means the crystalline product was shown to be a single diastereoisomer of 9-[2-*O*-acetyl-3-chloro-3-deoxy-5-*O*-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl)-β-D-xylofuranosyl]adenine (**4a**), the nature of the 5′ substituent being apparent from both its infrared (1810 cm^{-1}) and nmr (methyl singlets at 1.44, 1.47, and 1.72 ppm) spectra as previously discussed.[1] The mother liquors were predominantly the same material but as a diastereomeric mixture due to the chiral dioxolanone grouping. Treatment of the crude reaction product prior to crystallization of **4a** with 0.1 *N* methanolic hydrogen chloride rapidly removed the 5′ substituent and led to the isolation of crystalline 9-(2-*O*-acetyl-3-chloro-3-deoxy-β-D-xylofuranosyl)-

(1) For part I, see S. Greenberg and J. G. Moffatt, *J. Amer. Chem. Soc.*, **95**, 4016 (1973).

(2) This work has been briefly reported; see Abstracts, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, No. CARB14.

(3) Syntex Postdoctoral Fellow, 1968–1970.

(4) Syntex Postdoctoral Fellow, 1965–1967.

(5) The reactions of reagents of this type were first described by A. R. Mattocks, *J. Chem. Soc.*, 1918, 4840 (1964).

(6) (a) A. P. Martinez, W. W. Lee, and L. Goodman, *J. Org. Chem.*, **31**, 3263 (1966); (b) E. J. Reist, D. F. Calkins, and L. Goodman, *ibid.*, **31**, 2538 (1967).

Table I. Nmr Chemical Shifts at 100 MHz (DMSO-d_6)

Compd	$C_{1'}H$	$C_{2'}H$	$C_{3'}H$	$C_{4'}H$	$C_{5'a}H$	$C_{5'b}H$	C_2H and C_8H[a]	Other
4a	6.15 (d)	5.80 (dd)	4.91 (dd)	4.60 (m)	3.94 (m)		8.15, 8.23	2.08 (s, 3, OAc), 1.72 (s, 3, $MeCO_3$), 1.44, 1.47 (s, 3, CMe_2), 7.34 (s, 2, NH_2
4b	6.17 (d)	5.93 (dd)	4.91 (dd)	4.54 (m)	3.93 (m)		8.18, 8.28	2.10 (s, 3, OAc), 1.73 (s, 3, $MeCO_3$), 1.47, 1.58 (s, 3, CMe_2), 7.36 (s, 2, NH_2)
6a	6.10 (d)	5.78 (dd)	4.86 (dd)	4.92 (dt)	3.75 (dd)		8.14, 8.27	5.33 (t, 1, $C_{5'}OH$), 7.32 (s, 2, NH_2)
6b	6.10 (d)	5.90 (dd)	5.86 (dd)	4.37 (dt)	3.79 (dd)		8.16, 8.32	5.40 (t, 1, $C_{5'}OH$), 7.35 (s, 2, NH_2)
7a	5.87 (d)	4.81 (m) (dd with D_2O)	4.50 (m)	4.50 (m)	3.76 (dd)		8.17, 8.26	6.36 (d, 1, $C_{2'}OH$), 5.30 (t, 1, $C_{5'}OH$), 7.23 (br s, 2, NH_2)
7b[c]	5.90 (d)	4.95 (dd)	4.60 (dd)	4.40 (dt)	4.79 (d)		8.24, 8.36	6.42 (d, 1, $C_{2'}OH$), 5.43 (t, 1, $C_{5'}OH$), 7.39 (s, 2, NH_2)
8a	6.51 (d)	4.79 (dd)	4.59 (ddd)[b]	3.8 (m)	3.80 (m)		8.26, 8.37	5.25 (t, 1, $C_{5'}OH$), 6.10 (d, 1, $C_{3'}OH$), 7.31 (s, 2, NH_2)
8b	6.45 (d)	4.81 (dd)	4.60 (ddd)	3.78 (m)	3.78 (m)		8.17, 8.38	5.24 (t, 1, $C_{5'}OH$), 6.16 (d, 1, $C_{3'}OH$), 7.30 (s, 2, NH_2)
9	6.21 (s)	4.44 (d)	4.22 (d)	4.21 (t)	3.55 (d)		8.16, 8.33	7.26 (s, 2, NH_2), 5.05 (br s, 1, $C_{5'}OH$)
10	6.50 (d)	5.15 (dd)	5.84 (dd)	4.3 (m)	4.55 (m)		8.18, 8.29	2.04 and 2.15 (s, 3, OAc), 7.35 (s, 2, NH_2)
11	6.09 (d)	5.64 (dd)	4.63 (m)	4.27 (m)	3.8 (br m)		7.98, 8.30	1.45 (m, 18, CMe_2), 1.63, 1.67, and 1.79 (s, 3, $MeCO_3$), 7.35 (s, 2, NH_2)
13[c]	6.26 (t)	2.45 (dt)	2.08 (dt)	4.17 (m)	3.53 (dd)	3.70 (dd)	8.20, 8.41	7.30 (s, 2, NH_2)
14	5.86 (d)	4.59 (m)	1.91 (ddd) 2.28 (ddd)	4.36 (m)	3.60 (m)		8.13, 8.34	5.16 (t, 1, $C_{5'}OH$), 5.65 (d, 1, $C_{2'}OH$), 7.27 (s, 2, NH_2)

[a] Specific assignments have not been made. [b] Becoming dd, $J_{2',3'} = J_{3',4'} = 7.5$ Hz with D_2O. [c] Sugar protons reported with added D_2O.

Table II. First-Order Coupling Constants

Compd	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'a}$	$J_{4',5'b}$	$J_{5'a,5'b}$	Other
4a	3	3	4.5	*a*	*a*	*a*	
4b	3.5	3	5	*a*	*a*	*a*	
6a	3.5	3.5	5	5	5	0	$J_{5'H,OH} = 5$Hz
6b	4	4	5	5	5	0	$J_{5',OH} = 5$ Hz
7a	4	4	*a*	4	4	0	$J_{2'H,OH} = 5$ Hz, $J_{5'H,OH} = 5$ Hz
7b	4.5	4.5	4.5	4.5	4.5	0	$J_{2'H,OH} = 5$ Hz, $J_{5'H,OH} = 5.5$ Hz
8a	6.5	7.5	7.5	*a*	*a*	*a*	$J_{5'H,OH} = 5$ Hz, $J_{3'H,OH} = 5.5$ Hz
8b	6	7.5	7.5	*a*	*a*	*a*	$J_{3',OH} = 5.5$ Hz, $J_{5',OH} = 5$ Hz
9	0	2.5	0	5	5	0	
10	6	6	6	*a*	*a*	*a*	
11	6	6	*a*	*a*	*a*	*a*	
13	5	7	7	5	4	12	
14	2.5	3, 5.5	6, 8	*a*	*a*	*a*	$J_{2'H,OH} = 5$ Hz, $J_{5'H,OH} = 5$ Hz, $J_{3'a,3'b} = 13$ Hz

[a] Unresolved.

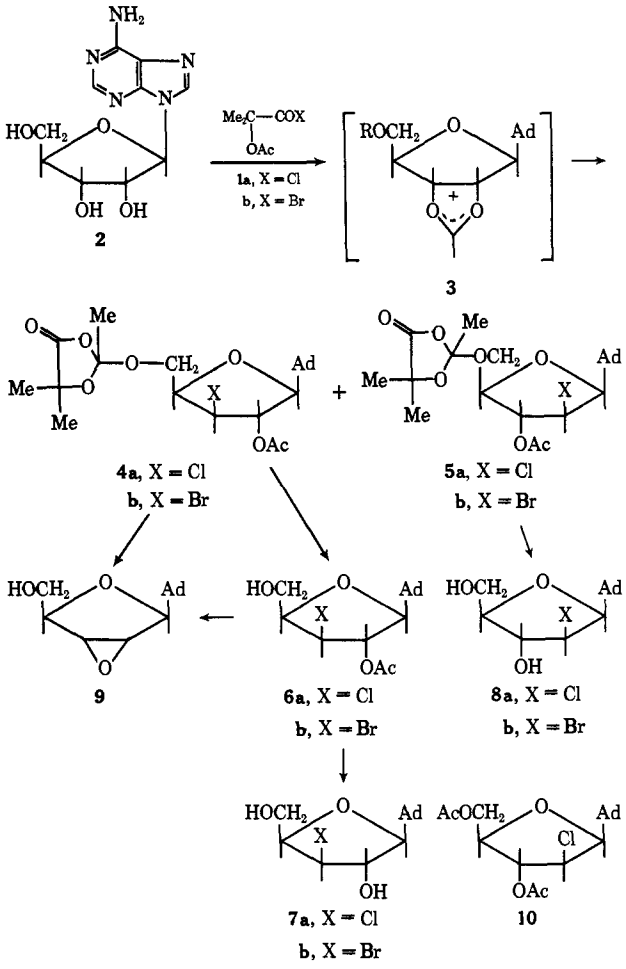
adenine (**6a**) in 60% yield. More prolonged treatment of **4a** with methanolic hydrochloric acid led to sequential removal of the dioxolanone and acetyl groups giving crystalline 9-(3-chloro-3-deoxy-β-D-xylofuranosyl)adenine (**7a**) in 84% yield. The location of the chlorine function in these molecules was clearly established by nmr spectroscopy since the signals for $C_{2'}H$ in **4a** and **6a** were located roughly 0.9 ppm downfield of those due to $C_{3'}H$. The deacetylated compound **7a**, however, showed an upfield shift of 1.0 ppm for $C_{2'}H$, this signal then being close to that of $C_{3'}H$ (Table I). The spectrum of **7a** in DMSO-d_6 clearly showed the presence of both a primary and a secondary hydroxyl group and the latter was specifically located at $C_{2'}$ since it was strongly coupled to $C_{2'}H$. All the assignments for sugar protons have been confirmed by spin-decoupling studies. The 3′-chloro function was assigned the xylo configuration because of the ease with which **4a**, **6a**, or **7a** could be converted into 9-(2,3-anhydro-β-D-ribofuranosyl)adenine (**9**) upon treatment with sodium methoxide. Thus treatment of pure **4a** with methanolic sodium methoxide gave crystalline **9** in a yield of 76%. The latter compound has been previously described *via* a seven-step synthesis from 9-(β-D-xylofuranosyl)adenine.[7] The epoxide obtained from **4a** had the same broad decomposition point described previously,[7] and its nature was clear from its elemental analysis and nmr spectrum. Typical of other 2′,3′-anhydronucleosides prepared in our work,[8] the values of $J_{1',2'}$ and of $J_{3',4'}$ equal 0 for **9** (Table II). A number of reactions of **9** will be described in a forthcoming paper.[9]

Treatment of the crude mother liquors from crystallization of **4a** with 10% methanolic ammonium hydroxide at room temperature quite rapidly removed both the acetyl and dioxolanone groups and led to extensive

(7) A. Benitez, O. P. Crews, L. Goodman, and B. R. Baker, *J. Org. Chem.*, **25**, 1946 (1960).
(8) A. F. Russell, T. C. Jain, and J. G. Moffatt, manuscript in preparation.
(9) A. F. Russell and J. G. Moffatt, manuscript in preparation.

formation of **7a** and **9** together with much smaller amounts of adenosine and a spot of intermediate mobility[10] (Scheme I). Crystallization of the crude

Scheme I



product from methanol removed almost all of the latter substance in pure form in a yield of 7%. This compound was an analytically pure chlorodeoxyadenosine to which we assign the structure 9-(2-chloro-2-deoxy-β-D-arabinofuranosyl)adenine (**8a**). The chloro function was assigned to the 2′ position since the nmr spectrum of **8a** in DMSO-d_6 shows the presence of both a primary ($C_{5'}$) and a secondary ($C_{3'}$) hydroxyl group, the latter being coupled to $C_{3'}H$. As expected, addition of D_2O to the sample caused collapse of the signal due to $C_{3'}H$ from an eight-line to a four-line pattern. In addition, acetylation of **8a** gave a crystalline diacetate (**10**) in which the signals due to $C_{3'}H$ and $C_{5'}H$ were shifted downfield by 1.32 and 0.75 ppm, respectively, while that of $C_{2'}H$ was only slightly deshielded. The D-arabino configuration is assigned on the basis of the essentially complete conversion of **8a** to **9** upon treatment with hot sodium methoxide. In addition, the relatively large value of $J_{1',2'}$ (6.5 Hz) is indicative of a cis arrangement of $C_{1'}H$ and $C_{2'}H$.[11] The large value of $J_{3',4'}$ (7.5 Hz) is also reminiscent of that shown by 2′-*C*-methyladenosine, a nucleoside forced into an unusual conformation by the presence of a fairly large substituent at $C_{2'}$ in the arabino configuration.[12]

A preparation of both the α and β anomers of **8a** has previously been reported by Vargha and Kuszmann[13] *via* condensation reactions of a suitable derivative of 2-chloro-2-deoxy-D-arabinofuranose. The reported melting point of **8a**, however, was some 20° lower than that we report and the product had a positive $[\alpha]_D$ while we have found a negative value. It seems likely that the substance isolated by the Hungarian workers was contaminated with the α anomer. A preparation of the 2′-fluoro analog of **8** has also been described starting with the fluorosugar.[14]

The formation of **4a** and **5a** from **1** and **2** as above is consistent with the proposed mechanism of the reaction of **1** with cis vicinal diols.[1] Thus, the key intermediate from **1a** and **2** will be the acetoxonium ion **3** which, in the expected absence of participation by the purine ring, will be opened by chloride ion from the β face of the sugar at either $C_{3'}$ or $C_{2'}$ giving **4a** and **5a**, respectively. From our results it is clear that attack at $C_{3'}$ is preferred, probably on steric grounds, by a factor of roughly 10.

Since, for other purposes,[9] we were interested in a facile preparation of reasonable quantities of the ribo epoxide (**9**), it was desirable to directly convert the crude reaction product from **1a** and **2** (*i.e.*, **4a** and **5a**) rather than having to isolate a single diastereoisomer of **4a** first. Treatment of the crude product with sodium methoxide at 0° for 2 days did, indeed, lead to direct crystallization of relatively pure **9**. By recrystallization and ultimate chromatography of final mother liquors pure **9** was isolated in 67% yield. It is interesting to note that while sodium methoxide at 0° efficiently converts the 3′-chloronucleoside (**7a**) to the epoxide (**9**), the 2′-chloro compound (**8a**) remains inert. Because of the low solubility of **8a** in methanol, care must be taken to avoid cocrystallization of **8a** and **9** particularly once the mixture becomes enriched in the former. Accordingly, there is a practical advantage in preparing **9** by a two-stage process in which crude **4a** and **5a** are treated first with methanolic ammonium hydroxide as above leading to almost complete removal of the 2′-chloro compound (**8a**). Subsequent treatment of the mother liquors with sodium methoxide at 0° then completes the conversion of **7a** to **9**, which can be isolated by crystallization in 53% yield. While, as mentioned above, pure **8a** could be converted into **9** in high yield with sodium methoxide in refluxing methanol, such treatment of the crude reaction product from **1** and **2** led to extensive darkening of the reaction. This is probably due to decomposition of some reducing sugar corresponding to the 20% of adenine known to be produced in the reaction.

One of our objectives in the present work was the development of facile syntheses of deoxynucleosides through hydrogenolysis of the corresponding halogenated compounds. We have, however, been generally unsuccessful in the catalytic hydrogenolysis of chloro sugar nucleosides and felt that the corre-

(10) Epoxide formation from **4a** with ammonium hydroxide or methanolic ammonia is quite slow: treatment of pure **7a** with methanol–concentrated NH_4OH (4:1) requiring roughly 4 days for 50% conversion to **9**.

(11) See, *e.g.*, T. D. Inch in *Annu. Rev. NMR (Nucl. Magn. Resonance) Spectrosc.*, **2**, 35 (1969).

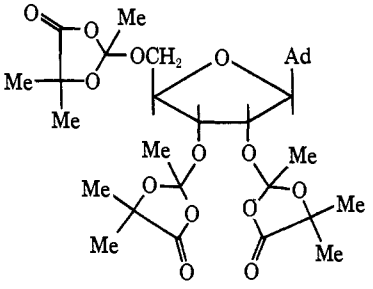
(12) S. R. Jenkins, B. Arison, and E. Walton, *J. Org. Chem.*, **33**, 2490 (1968).

(13) L. Vargha and J. Kuszmann, *Justus Liebigs Ann. Chem.*, **684**, 231 (1965).

(14) J. A. Wright, N. F. Taylor, and J. J. Fox, *J. Org. Chem.*, **34**, 2632 (1969).

sponding bromo or iodo derivatives would be more suitable. Our early attempts to react nucleosides with **1a** in the presence of a large excess of bromide ions were largely unsatisfactory. There was undoubtedly formation of the desired bromonucleosides, but always some of the chloro compounds were also present and it was usually difficult to isolate pure compounds from the mixtures in satisfactory yields. We accordingly prefer to use purified 2-acetoxyisobutyryl bromide (**1b**) as the reagent for preparing bromosugar nucleosides such as **4b**. Various attempts to convert 2-acetoxyisobutyric acid[15] to the acyl bromide (**1b**) by reaction with thionyl bromide or phosphorus tribromide proved difficult due to codistillation of reagent by-products. The preparation of pure **1b** was readily achieved by reaction of the acyl chloride (**1a**) with anhydrous lithium bromide in ethyl acetate. After removal of the precipitated sodium chloride and distillation, pure **1b** was obtained in 63% yield. It is difficult to distinguish between **1a** and **1b** by infrared spectroscopy, but a convenient confirmation of purity can be made from their nmr spectra, the *gem*-dimethyl group of **1b** resonating at 1.59 ppm while that of **1a** is at 1.61 ppm.

In general, the reactions of the acyl bromide (**1b**) with adenosine were similar to those using **1a**. The bromide was, however, much more reactive, adenosine undergoing complete reaction within 30 min at room temperature in acetonitrile, only 2–3% adenine being produced under these mild conditions. Examination of the crude product from this reaction by tlc showed two major spots in a ratio of roughly 5:1, the minor, less polar product being formed in smaller amounts in reactions conducted under more dilute conditions. The minor product was isolated in crystalline form by chromatography on silicic acid. Its nmr spectrum and elemental analysis showed this compound to be 2′,3′,5′-tris-*O*-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl)adenosine (**11**), and brief treatment

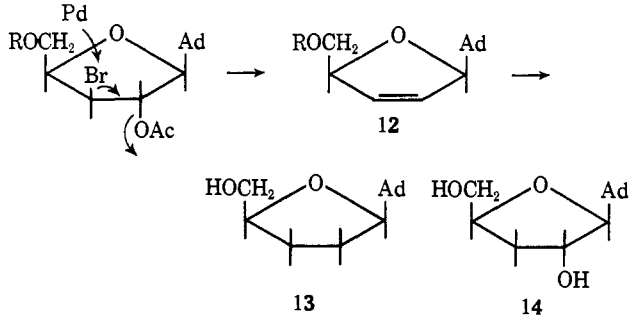


11

with sodium methoxide regenerated adenosine quantitatively. The formation of **11** seems to be less prevalent during reactions with the acyl chloride (**1a**) but becomes the exclusive reaction when adenosine is reacted with **1b** in dimethylformamide. We do not see an immediate explanation for this striking solvent effect. Direct crystallization of the crude reaction product without removal of **11** gave a single dioxolanone diastereomer of 9-[2-*O*-acetyl-3-bromo-3-deoxy-5-*O*-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl)-β-D-xylofuranosyl]adenine (**4b**) in a yield of 33%. The nmr spectrum of **4b** was very similar to that of **4a** and treatment with 0.1 *N* methanolic hydrogen chloride rapidly removed the dioxolanone group giving crystalline **6b** in 87% yield. The latter compound could also be obtained from the crude reaction product by similar treatment. The xylo configuration was confirmed by conversion of **6b** into **9** in 72% yield upon brief treatment with sodium methoxide.

Treatment of the crude product from adenosine and **1b** with methanolic ammonium hydroxide rapidly removed the acetyl and dioxolanone groups, but, unlike the chloro series, it was not possible to selectively remove the 2′-bromo isomer (**8b**) by crystallization since the epoxide (**9**) tended to cocrystallize. Pure **8b** was, however, isolated by preparative tlc and could be converted to the epoxide (**9**) by brief treatment with sodium methoxide.

Catalytic hydrogenolysis of **4b** using a palladium catalyst led to quite rapid disappearance of the starting material but unexpectedly led to the formation of two deoxynucleosides in equal amounts. These compounds were isolated in crystalline form by preparative tlc and proved to be 3′-deoxyadenosine (**14**)[16] and 2′,3′-dideoxyadenosine (**13**)[17] in yields of 46 and 40%, respectively. These compounds had physical properties identical with those described previously for samples prepared by other routes, and the structures were clearly confirmed by nmr spectroscopy. The formation of the dideoxynucleoside **13** was unexpected and is presumably a consequence of an initial, palladium catalyzed, trans elimination reaction of the bromide and acetyl groups giving an intermediate 2′,3′-olefin (**12**) which is concomitantly reduced giving **13**. A similar elimination followed by reduction has been observed during hydrogenolysis of a 2′-bromo-2′-deoxy-3′-*O*-methanesulfonyluridine derivative, but in that case the elimination is cis in nature.[18]



12 **13** **14**

In support of the above mechanism it was shown that in the absence of the 2′-*O*-acetyl function the formation of dideoxynucleosides does not occur. Thus hydrogenolysis of 9-(3-bromo-3-deoxy-β-D-xylofuranosyl)adenine (**7b**) under similar conditions to those above gives **14** as the sole product with no trace of **13**. In this way crystalline 3′-deoxyadenosine was obtained in 78% yield. In a forthcoming publication further methods for effecting elimination reactions of haloacetates such as **4** will be described.[19]

(15) R. Anschütz and O. Motschmann, *Ann.*, **392**, 100 (1912).

(16) (a) W. W. Lee, A. Benitez, C. D. Anderson, L. Goodman, and B. R. Baker, *J. Amer. Chem. Soc.*, **83**, 1906 (1961); (b) E. Walton, F. W. Holly, G. E. Boxer, R. F. Nutt, and S. R. Jenkins, *J. Med. Chem.*, **8**, 659 (1965).

(17) (a) M. J. Robins, J. R. McCarthy, and R. K. Robins, *Biochemistry*, **5**, 224 (1966); (b) G. L. Tong, W. W. Lee, and L. Goodman, *J. Org. Chem.*, **30**, 2854 (1965).

(18) Y. Furukawa, Y. Yoshioka, K. Imai, and M. Honjo, *Chem. Pharm. Bull.*, **18**, 554 (1970).

(19) I. D. Jenkins, A. F. Russell, T. C. Jain, J. P. H. Verheyden, and J. G. Moffatt, unpublished results.

From the above results it is clear that the reactions of purine nucleosides such as adenosine with 2-acetoxyisobutyryl halides provides a convenient route to 3′-bromo-3′-deoxy-β-D-xylofuranosyl analogs which can be subsequently converted into 3′-deoxy-, 2′,3′-dideoxy-, and 2′,3′-anhydronucleosides. In particular, it might be noted that sequential reaction of simple cis vicinal diols with **1a** or **1b** followed by base treatment provides a particularly facile route for the preparation of epoxides with overall retention of configuration. Such a sequence might well find considerable utility in organic synthesis.

Experimental Section

General Methods. The general methods used were similar to those described in the preceding paper.[1]

2-Acetoxyisobutyryl Bromide (1b). Lithium bromide (86.6 g, 1 mol) was dried *in vacuo* at 150° for 1 hr and then added in a drybox to anhydrous ethyl acetate (300 ml). The mixture was heated until the solid had dissolved and 2-acetoxyisobutyryl chloride (132 g, 0.80 mol) was added. The mixture was heated briefly under reflux, cooled, and filtered in the drybox. The solvent was evaporated *in vacuo* and the residue distilled giving 105.6 g (63%) of **1b** with bp 75–77° (12 mm): n^{25}D 1.4530; ν_{max} (film) 1825, 1805, 1750 cm^{-1}; nmr ($CDCl_3$) 1.59 (s, 6, CMe_2), 2.12 ppm (s, 3, OAc).

Anal. Calcd for $C_6H_9O_3Br$ (209.04): C, 34.47; H, 4.34; Br, 38.23. Found: C, 34.56; H, 4.45; Br, 38.13.

9-[2-*O*-Acetyl-3-chloro-3-deoxy-5-*O*-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl)-β-D-xylofuranosyl]adenine (4a). A suspension of adenosine (13.35 g, 50 mmol) in a solution of **1a** (33.0 g, 200 mmol) in dry acetonitrile (500 ml) was stirred and heated at 80° for 1 hr. The resulting clear solution was cooled and evaporated *in vacuo* leaving a residue that was dissolved in ethyl acetate and washed several times with 10% aqueous sodium bicarbonate and then with water. The aqueous phase was found to contain 21% of adenine. Evaporation of the dried ($MgSO_4$) organic phase left 24.1 g of crude solid product that was predominantly one spot on tlc using chloroform–methanol (9:1). Crystallization of this material from methanol gave 4.66 g (20%) of a single diastereoisomer of **4a** with mp 172–174°. Recrystallization from ethanol raised the mp to 173.5–174.5°: λ_{max} 259 nm (ε 15,000); [α]D −30.8° (*c* 0.1, dioxane); ORD negative Cotton effect $[\Phi]^{tr}_{272}$ −6300°, $[\Phi]_{258}$ 0°, $[\Phi]_{239}$ 15,600°; ν_{max} (KBr) 1810, 1760 cm^{-1}.

Anal. Calcd for $C_{18}H_{22}N_5O_7Cl$ (455.86): C, 47.42; H, 4.86; N, 15.36; Cl, 7.78. Found: C, 47.40; H, 5.11; N, 15.31; Cl, 7.73.

The mother liquors from the above crystallization were mainly a diastereomeric mixture of **4a** but no further crystals could be obtained. A comparable reaction occurred at 37° during 16 hr.

9-(2-Chloro-2-deoxy-β-D-arabinofuranosyl)adenine (8a). The mother liquors from the crystallization of **4a** were evaporated to a syrup that was dissolved in methanol (90 ml) and treated for 48 hr at room temperature with concentrated ammonium hydroxide (10 ml). The solvent was then evaporated and the residue crystallized from methanol at 0° giving 1.0 g (7%) of **8a** with mp 245–247° dec (reported[13] mp 225°): λ^{MeOH}_{max} 259 nm (ε 15,100); [α]^{23}D −10.5° (*c* 0.25, DMSO) (reported[13] [α]^{20}D 16.4° in Py–H_2O).

Anal. Calcd for $C_{10}H_{12}N_5O_3Cl$ (285.70): C, 42.04; H, 4.23; N, 24.51; Cl, 12.41. Found: C, 41.99; H, 4.16; N, 24.60; Cl, 12.68.

Acetylation of **8a** (100 mg) with acetic anhydride in pyridine followed by removal of a little 3′,5′,N^6-triacetyl derivative (λ^{MeOH}_{max} 271 nm) by preparative tlc using chloroform–methanol (9:1) gave 90 mg (70%) of **10** with mp 145–146° from ethanol: λ^{MeOH}_{max} 259 nm (ε 15,000).

Anal. Calcd for $C_{14}H_{16}N_5O_5Cl$ (369.77): C, 45.47; H, 4.36; N, 18.94. Found: C, 45.40; H, 4.46; N, 18.84.

9-(2-*O*-Acetyl-3-chloro-3-deoxy-β-D-xylofuranosyl)adenine (6a). The crude product obtained from adenosine and **1a** (1.0 g, containing 1.55 mmol of nucleoside by uv) was dissolved in 0.1 *N* methanolic hydrogen chloride and stored at room temperature for 1 hr. The solvent was then evaporated and the residue coevaporated with methanol twice. The final solid residue was washed twice with ether and purified by preparative tlc using two developments with chloroform–methanol (9:1). Elution of the major band gave 360 mg of a homogeneous foam that was crystallized from ethanol giving 305 mg (60%) of **6a** with mp 202–203°: λ^{MeOH}_{max} 258 nm (ε 15,700); [α]^{23}D −1.4° (*c* 1.0, pyridine).

Anal. Calcd for $C_{12}H_{14}N_5O_4Cl$ (327.76): C, 43.97; H, 4.31; N, 21.37. Found: C, 43.99; H, 4.47; N, 21.17.

9-(3-Chloro-3-deoxy-β-D-xylofuranosyl)adenine (7a). A solution of **4a** (2.28 g, 5 mmol) and concentrated hydrochloric acid (1 ml) in methanol (99 ml) was kept at room temperature for 8 days, at which time tlc (chloroform–methanol, 85:15) showed completion of the reaction. Silver carbonate (5 g) was added and the mixture was stirred for 3 hr and then filtered. Evaporation of the filtrates gave 1.47 g of a syrup with an R_f very similar to **9**. Crystallization from acetone–ethyl acetate gave 1.22 g (84%) of **7a** with mp 194–196°: λ^{MeOH}_{max} 259 nm (ε 15,200); [α]^{23}D −31.6° (*c* 0.14, MeOH); ORD (MeOH) negative Cotton effect $[\Phi]^{tr}_{273}$ −2700°, $[\Phi]_{247}$ 0°, $[\Phi]^{pk}_{238}$ 900°.

Anal. Calcd for $C_{10}H_{12}N_5O_3Cl$ (285.70): C, 42.04; H, 4.23; N, 24.51; Cl, 12.41. Found: C, 42.21; H, 4.35; N, 24.69; Cl, 12.26.

Treatment of **8a** (100 mg) in 0.4 *M* methanolic sodium methoxide (4 ml) under reflux for 1 hr led to direct crystallization of pure **9** (63 mg, 72%) identical with that below.

9-[2-*O*-Acetyl-3-bromo-3-deoxy-5-*O*-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl)-β-D-xylofuranosyl]adenine (4b). A mixture of adenosine (13.35 g, 50 mmol) and **1b** (31.3 g, 150 mmol) in acetonitrile (150 ml) was stirred at room temperature. A homogeneous solution was obtained after 20 min and after 45 min the solvent was largely evaporated. The residue was dissolved in ethyl acetate, washed carefully with aqueous sodium bicarbonate and water, dried, and evaporated leaving 27.5 g of a foam containing two major and several very minor products by tlc ($CHCl_3$–MeOH, 85:15). The aqueous extracts contained 2.7% of adenine. Crystallization of the product from methanol gave 8.21 g (33%) of **4b** with mp 169–172°, which was raised to 171–172° upon recrystallization from ethanol: $\lambda^{dioxane}_{max}$ 258 nm (ε 15,200); ν_{max} (KBr) 1810, 1755 cm^{-1}; [α]^{23}D −11.5° (*c* 2.5, dioxane); ORD (MeOH) negative Cotton effect $[\Phi]^{tr}_{276}$ −4000°, $[\Phi]_{258}$ 0°, $[\Phi]^{pk}_{243}$ 6900°.

Anal. Calcd for $C_{18}H_{22}N_5O_7Br$ (500.32): C, 43.21; H, 4.43; N, 14.00. Found: C, 43.24; H, 4.56; N, 14.18.

A portion of the evaporated mother liquors from crystallization of **4b** above (5 g) was chromatographed on silicic acid using chloroform–methanol (92:8) in order to separate the two principal uv-absorbing products. In this way the chromatographically homogeneous, less polar product (1.55 g, 19% from adenosine) was obtained and shown by nmr to be a mixture of diastereomeric adenosine-2′,3′,5′-trisdioxolanones (**11**). Crystallization from ether gave 0.59 g of a mixture enriched to about 70% purity with a single isomer and further crystallization from ethanol gave an essentially pure isomer with mp 145.5–146.5° (see below).

The more polar product (2.80 g, 44% from adenosine) proved to be a mixture of dioxolanone diastereomers of **4b** and **5b** in a ratio of roughly 3:2 by nmr after acidic hydrolysis of the 5′ substituent.

9-(2,3-Anhydro-β-D-ribofuranosyl)adenine (9). (a) **Via the Chloronucleosides.** The crude product from reaction of adenosine and **1a** (5.0 g, containing 7.76 mmol of nucleoside) was dissolved in 2 *M* methanolic sodium methoxide (20 ml) and kept at 0° for 48 hr. The resulting crystalline residue was collected and washed with cold methanol giving 1.3 g of cream colored solid that was chromatographically pure but contained some inorganic salts. Crystallization from water gave 0.65 g of pure **9**. The mother liquors were combined with the original filtrate, neutralized with acetic acid, and evaporated to a syrup that was dissolved in water. Repeated extraction with ethyl acetate removed most of the **9** and **8a**. By crystallization from methanol and preparative tlc of the mother liquors using three developments with chloroform–methanol (85:15), a further 0.65 g (total yield 1.30 g, 67%) of crystalline **9** was obtained in addition to 200 mg (7%) of **8a**. Pure **9** decomposed slowly above 180° without actual melting: λ^{MeOH}_{max} 258 nm (ε 14,700); [α]^{23}D −21.8° (*c* 0.2, H_2O), (reported[7] dec above 180°, [α]D −18.3°); ORD (MeOH) negative Cotton effect $[\Phi]^{tr}_{272}$ −950°, $[\Phi]_{261}$ 0°, $[\Phi]^{pk}_{241}$ 3700°.

Anal. Calcd for $C_{10}H_{11}N_5O_3$ (249.23): C, 48.19; H, 4.45; N, 28.10. Found: C, 48.04; H, 4.38; N, 28.06.

In a separate experiment the mother liquors from crystallization of **8a** were treated with methanolic sodium methoxide (60 ml of 1 *M*) at 0° for 24 hr. The crystalline residue was washed with methanol giving 5.26 g (53%) of **9** which was shown by tlc to be at least 95% pure by tlc and contaminated with a little adenosine. Recrystallization from water gave the pure epoxide identical with that above.

(b) **Via the Bromonucleosides.** The crude product from reaction of adenosine (2.76 g, 10 mmol) and **1b** as above was treated for 30 min at room temperature with methanolic sodium methoxide (20

ml of 1 *M*). The mixture was then neutralized with acetic acid and upon storage 1.98 g (80%) of essentially pure **9** was obtained.

In a separate experiment the mother liquors from crystallization of **4b** above were treated for 24 hr at 23° with methanol (90 ml) and concentrated ammonium hydroxide (10 ml). The resulting crystals (2.45 g) proved to be a mixture of **9**, **7b**, and a little adenosine. The crystals and evaporated mother liquors were accordingly treated overnight with methanolic sodium methoxide (50 ml of 1.3 *M*) giving 7.06 g (57% from adenosine and 84% after correction for the **4b** isolated) of **9** contaminated with only a trace of adenosine.

9-(2-Bromo-2-deoxy-β-D-arabinofuranosyl)adenine (8b). The crystalline product obtained from a reaction treated with methanolic ammonium hydroxide as in b above was purified by preparative tlc using chloroform–methanol (85:15) giving three bands. The fastest, major band was the epoxide **9** and the slowest band was adenosine. Elution of the middle band followed by crystallization from methanol gave homogeneous **8b** with mp 215–216°: λ_{max}^{MeOH} 259 nm (ε 14,800); $[\alpha]^{23}D$ −24.7° (*c* 0.5, DMSO).

Anal. Calcd for $C_{10}H_{12}N_5O_3Br$ (330.15): C, 36.38; H, 3.66; N, 21.21; Br, 24.21. Found: C, 36.31; H, 3.72; N, 20.92; Br, 23.98.

9-(2-*O*-Acetyl-3-bromo-3-deoxy-β-D-xylofuranosyl)adenine (6b). A solution of **4b** (200 mg, 0.4 mmol) in 0.2 *N* methanolic hydrogen chloride was kept at room temperature for 30 min. Pyridine (0.3 ml) was then added and the solution was evaporated *in vacuo* almost to dryness. The residue was dissolved in water (10 ml) containing 2 ml of saturated aqueous sodium bicarbonate and extracted three times with ethyl acetate. The extracts were dried ($MgSO_4$) and evaporated leaving 170 mg of a white froth. Crystallization from methanol gave 130 mg (87%) of **6b** contaminated with about 5% of **7b**. Complete removal of this minor impurity by crystallization was difficult but was achieved by two crystallizations from methanol giving **6b** with mp 206–207°: λ_{max}^{MeOH} 260 nm (ε 15,900); $[\alpha]^{23}D$ 10.4° (*c* 0.24, pyridine).

Anal. Calcd for $C_{12}H_{14}N_5O_4Br$ (372.19): C, 38.72; H, 3.79; N, 18.82; Br, 21.47. Found: C, 38.74; H, 4.19; N, 18.98; Br, 21.26.

Treatment of **6b** with 0.2 *N* methanolic sodium methoxide at room temperature for 30 min followed by neutralization with acetic acid, evaporation, and crystallization from ethanol gave 2′,3′-anhydroadenosine (**9**) identical with that above in 72% yield.

9-(3′-Bromo-3′-deoxy-β-D-xylofuranosyl)adenine (7b). Concentrated hydrochloric acid (1.0 ml) was added to a suspension of **4b** (2.50 g, 5 mmol) in methanol (99 ml), and the resulting solution was stored at room temperature for 8 days at which point tlc (chloroform–methanol, 85:15) showed complete reaction. Silver carbonate (5 g) was added and the mixture was stirred for 2 hr and then filtered. Evaporation of the filtrate and crystallization from methanol gave 1.20 g (73%) of **7b** with mp 131–133°: λ_{max}^{MeOH} 259 nm (ε 14,400); $[\alpha]^{28}D$ −26.4° (*c* 0.15, MeOH); ORD negative Cotton effect, $[\Phi]_{280}^{tr}$ −3800°, $[\Phi]_{252}$ 0°, $[\Phi]_{240}^{pk}$ 1800°.

Anal. Calcd for $C_{10}H_{12}N_5O_3Br$ (330.15): C, 36.38; H, 3.66; N, 21.21; Br, 24.21. Found: C, 36.12; H, 4.10; N, 21.31; Br, 23.98.

2′,3′,5′-Tris-*O*-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl)adenosine (11). Adenosine (267 mg, 1 mmol) and **1b** (836 mg, 4 mmol) were stirred in anhydrous DMF at room temperature for 1 hr and the solvent was then evaporated *in vacuo*. The residue was dissolved in ethyl acetate, washed well with aqueous sodium bicarbonate and water, dried, and evaporated leaving a foam that was predominantly one large spot. A center cut of this material was obtained by preparative tlc using chloroform–methanol (85:15) and very slowly gave a crystalline product with mp 145–147° from chloroform–hexane. This product appears to be a relatively pure diastereoisomer of **11**. Brief treatment of this substance, or its noncrystalline precursor, with methanolic sodium methoxide gave only adenosine: λ_{max}^{MeOH} 259 nm (ε 14,900); $[\alpha]^{23}D$ −22.3° (*c* 0.1, $CHCl_3$); ORD (MeOH) negative Cotton effect, $[\Phi]_{282}^{tr}$ −4500°, $[\Phi]_{258}$ 0°, $[\Phi]_{252}^{pk}$ 2900°, $[\Phi]_{240}$ 0°.

Anal. Calcd for $C_{28}H_{37}N_5O_{13}$ (651.62): C, 51.61; H, 5.72; N, 10.75. Found: C, 51.89; H, 5.62; N, 10.91.

3′-Deoxyadenosine (14). A solution of **7b** (250 mg) in methanol (50 ml) was shaken overnight in an atmosphere of hydrogen in the presence of 5% palladium on barium sulfate catalyst (100 mg)[20] and triethylamine (0.1 ml). After removal of the catalyst tlc showed the presence of a single spot identical with **14**. Evaporation of the solvent and crystallization from methanol gave 100 mg of pure **14**. Preparative tlc of the mother liquors and crystallization from methanol gave a further 53 mg (total yield 153 mg; 78%) of **14** with mp 225–226° (reported[16] mp 224–225°): $\lambda_{max}^{H^+}$ 258 nm (ε 15,100); $[\alpha]^{23}D$ −45.8° (*c* 0.6, H_2O).

Hydrogenolysis of 4b. A solution of **4b** (250 mg, 0.5 mmol) in methanol (50 ml) containing triethylamine (0.1 ml) and 10% palladium on carbon catalyst (100 mg) was vigorously stirred in an atmosphere of hydrogen for 2.5 hr. After removal of the catalyst and evaporation of the solvent the residue was treated for 1 hr with methanolic sodium methoxide and then neutralized. Preparative tlc of the residue using chloroform–methanol (85:15) gave two intense bands. Elution of the slower band followed by crystallization from 2-propanol gave 58 mg (46%) of 3′-deoxyadenosine with mp 225–226° and in all ways identical with that above. Elution of the faster band followed by crystallization from ethanol gave 47 mg (40%) of 2′,3′-dideoxyadenosine with mp 188–189° (reported[17a] mp 184–186°, 182.5–185°[17b]).

(20) Similar results were obtained using 10% palladium on charcoal catalyst.