adenosine 5′-phosphate, 61-19-8; hexabutyldistannoxane, 56-35-9; cytidine 5′-phosphate, 63-37-6; trimethyltin hydroxide, 56-24-6; 2′-deoxycytidine 5′-phosphate, 1032-65-1

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Reactions of 2-Acyloxyisobutyryl Halides with Nucleosides. IV.[1] A Facile Synthesis of 2′,3′-Unsaturated Nucleosides Using Chromous Acetate

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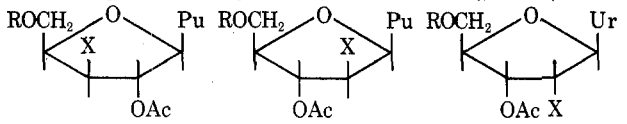
The halo acetates obtained from ribo nucleosides and 2-acetoxyisobutyryl halides have been shown to readily react with chromous acetate and ethylenediamine in ethanol at −78° to produce 2′,3′-dideoxy-β-D-*glycero*-pent-2′-enofuranosyl nucleosides. In this way 2′,3′-unsaturated analogs of adenosine, formycin, inosine, 5′,N^2-dibenzoylguanosine, and uridine have been prepared. Simple 3′-deoxy nucleosides and 3′-deoxy-β-D-*glycero*-pent-3-enofuranosyl nucleosides are sometimes obtained as by-products. An alternative synthesis of the 3′,4′-unsaturated analog of adenosine has been achieved *via* a base-catalyzed elimination reaction. Some interesting features of the nmr and ORD spectra of 2′,3′-unsaturated nucleosides are reported. An alternative synthesis of 9-(2-*O*-acetyl-3-deoxy-3-halo-β-D-xylofuranosyl)adenines has been developed *via* the reaction of 2′,3′-*O*-ethoxyethylideneadenosine with boron trifluoride etherate in the presence of anhydrous halide salts.

Nucleosides containing unsaturated sugars have been found to exist in nature in antibiotics such as Angustmycin A[3] and Blasticidin S.[4] In addition, the olefinic functionality in these molecules provides an interesting site for a variety of chemical transformations.[5,6] For these reasons considerable chemical effort has been devoted to the development of synthetic routes to 2′,3′-,[7] 3′,4′-,[8] and 4′,5′-[9] unsaturated nucleosides.[10] The available syntheses of 2′,3′-unsaturated nucleosides have generally involved base-catalyzed elimination reactions of either 3′-*O*-methanesulfonyl or O^2,3′-anhydro derivatives of 2′-deoxy nucleosides.[7] As yet, preparations starting from the more readily available ribo nucleosides have been very limited. Thus 1-(2,3-dideoxy-5-*O*-trityl-β-D-*glycero*-pent-2-enofuranosyl)uracil was obtained in the low yield *via* treatment of 5′-*O*-trityluridine 2′,3′-thionocarbonate with Raney nickel,[11a] and a blocked 2′,3′ olefin was very recently obtained from a 2′,3′-dimesyl derivative of tubercidin with zinc and sodium iodide.[11b]

Recent work from this laboratory has led to the development of efficient and novel methods for the replacement of the $C_{2'}$- or $C_{3'}$-hydroxyl groups of ribo nucleosides by chlorine or bromine atoms.[1,12] In particular, the reactions of ribo nucleosides with 2-acetoxyisobutyryl halides have led to interesting results. This reagent has been shown to react with purine nucelosides such as adenosine,[12b] tubercidin,[1] formycin,[1] and guanosine[12d] to form trans halo acetates (1 and 2) with the 2′-*O*-acetyl-3′-deoxy-3′-halo-β-D-xylofuranoside isomers (1) predominating. The formation of these trans halo acetates has been explained *via* the opening of 2′,3′-*O*-acetoxonium ion intermediates by halide ion.[12a,b] On the other hand, 2-ace-

toxyisobutyryl halides react with uridine derivatives to form 3′-*O*-acetyl-2′-deoxy-2′-halo-β-D-ribofuranosyl nucleosides (**3**), the cis halo acetate configuration being due to participation of the uracil ring with the 2′,3′-*O*-acetoxonium ion giving an O^2,2′-anhydro nucleoside which is finally opened by halide attack.[12a] In all the above compounds (**1**–**3**) the 5′-hydroxyl is substituted as either a



2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl ether or a 2-acetoxyisobutyryl ester, the choice being both solvent and substrate dependent.

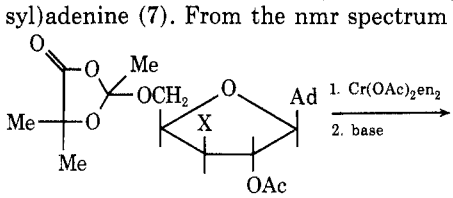
The ready availability of the above vicinal halo acetates suggested that these compounds might provide a direct route to 2′,3′-unsaturated nucleosides *via* appropriate elimination reactions.[13] A particularly attractive possibility was the use of chromous salts which, particularly when complexed with ethylenediamine, are well known to reduce simple alkyl halides[14] and to convert vicinal dihalides or halo esters to olefins.[15,16]

Most of the extensive studies by Kochi, *et al.*,[14,15] have been carried out using the ethylenediamine complex of chromous perchlorate, and our initial studies were carried out using this species as a solution in aqueous dimethylformamide.[14] In view of the extreme sensitivity of these solutions to traces of oxygen we prefer to use chromous acetate, which is a dry solid readily prepared from chromous perchlorate[17,18] and sodium acetate and readily handled in a drybox under nitrogen or argon. The acetate has previously been prepared from chromous chloride,[19] but since we have obtained consistently active preparations from the perchlorate we have continued to use this material.

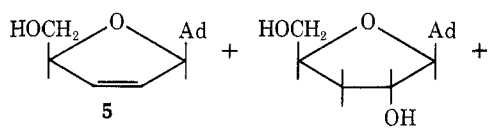
Our initial study was done using crystalline 9-[2-*O*-acetyl-3-bromo-3-deoxy-5-*O*-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl)-β-D-xylofuranosyl]adenine (**4a**), which was obtained from adenosine and 2-acetoxyisobutyryl bromide.[12b] The reaction of **4a** with 5 molar equiv of chromous acetate and 10 equiv of ethylenediamine was carried out in ethanol at −78° for 30 min. Following removal of residual protecting groups by treatment with methanolic ammonia the mixture was separated by direct crystallization and preparative tlc into two major crystalline compounds. The major product, isolated crystalline in 59% yield, proved to be the desired 9-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)adenine (**5**), a compound that has previously been prepared by both McCarthy, *et al.*,[7b] and Horwitz, *et al.*,[20] by treatment of 3′-*O*-tosyl-2′-deoxyadenosine with sodium alkoxides. The structure of **5** was unequivocal from an examination of its nmr spectrum in DMSO-d_6. The spectra of all the 2′,3′-unsaturated nucleosides prepared in this study (see Tables I and II) were all very similar and showed some interesting features. Thus the vinyl protons appear as well-defined doublets of doublets showing values of $J_{1',2'}$ = 1.5, $J_{2',3'}$ = 6, $J_{3',4'}$ = 2–2.5, and $J_{2',4'}$ = 1.5 Hz. The $C_{1'}$ proton characteristically appeared as a sharp five-line pattern with couplings to $C_{2'}$H, $C_{3'}$H, and $C_{4'}$H of 1.5, 1.5, and 3 Hz.[21] The very large 1′,4′-homoallylic coupling is noteworthy and has been previously reported in our earlier work on the thymine analog (**12c**).[23]

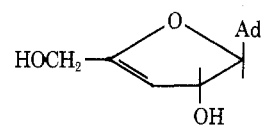
The second major product, isolated crystalline in 30% yield, proved to be 3′-deoxyadenosine (**6**), which was physically and spectrally identical with a previously prepared sample.[12b] Clearly simple chromous ion reduction of the bromo function[14] competes to some degree with the desired elimination reaction.

The presence of the chiral 5′-dioxolanone ether group allows the crystallization of a single diastereomer of **4a** in only 30–35% yield from adenosine.[12b] Accordingly, it was of practical interest to examine the chromous ion reaction with the crude mixture of 3′- and 2′-halo nucleosides (**1** and **2**, roughly 9:1) that can be obtained in greater than 90% yield from adenosine and 2-acetoxyisobutyryl halides.[12b] The reaction between the crude mixture of chloro nucleosides (**4b** and **2**, Pu = Ad, X = Cl, R = Me_3-dioxolanone) with the chromous acetate–ethylenediamine reagent was carried out exactly as with the pure 3′-bromo compound **4a**. From this reaction the crystalline 2′ olefin **5** was isolated in almost the same yield (62%) as from pure **4a**. The yield of 3′-deoxyadenosine was, however, considerably lower (10%) and a very small amount of 2′-deoxyadenosine could also be detected chromatographically. In addition to the above products a new substance was also formed in this reaction and isolated in crystalline form in 6% yield. From analytical data, a positive test for olefins upon spraying a tlc plate with aqueous potassium permanganate, and nmr spectroscopy, this compound was shown to be 9-(3-deoxy-β-D-*glycero*-pent-3-enofuranosyl)adenine (**7**). From the nmr spectrum of **7** in DMSO-d_6



4a, X = Br
b, X = Cl
c, X = I





the presence of a free 5′-hydroxyl group and a single secondary hydroxyl function were apparent. No signal for $C_{4'}$H could be detected and the $C_{2'}$ and $C_{3'}$ protons were superimposed at 5.27 ppm, suggesting the vinylic nature of $C_{3'}$.

An alternative synthesis of **7** was also achieved in 59% yield *via* treatment of **4a** with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in acetonitrile at 80°. Under these conditions a considerable amount of 2′,3′-anhydroadenosine was also produced but the two compounds could be easily separated by crystallization. Several 3′,4′-unsaturated 2′-deoxynucleosides have been prepared by Žemlička, *et al.*,[8] by base-catalyzed eliminations on 2′-deoxy nucleoside 5′-uronates followed by complex hydride reduction of the ester function.[8] The only 3′,4′-unsaturated ribo nucleosides that have been described are the result of silica gel or base-catalyzed elimination of the acetal function from 2′,3′-*O*-benzylidene nucleoside 5′-aldehydes followed by borohydride reduction of the aldehyde.[24]

In order to complete the series of 3′-halogenated adenosine derivatives it was of interest to study the iodo compound. Our previous efforts to isolate pure 2-acetoxyisobutyryl iodide were unsuccessful owing to its thermal insta-

Table I
Nmr Chemical Shifts at 100 MHz (Parts per Million)

Compd	Solvent[b]	C_1'H	C_2'H	C_3'H	C_4'H	C_5'aH	C_5'bH	C_2H, C_8H[a]	Other
4c	D	6.07 (d)	5.98 (dd)	4.75 (m)	4.14 (m)	3.77 (dd)	3.95 (dd)	8.12, 8.23	1.72 (s, 3, $MeCO_3$), 1.46 (s, 3, CMe_2), 1.50, 1.52 (s, total 3, CMe_2), 2.05 (s, 3, OAc), 7.29 (s, 2, NH_2)
5	D	6.90 (ddd)	6.42 (ddd)	6.07 (ddd)	4.84 (m)	3.55 (dd)		8.12, 8.14	4.98 (t, 1, C_5'OH), 7.21 (s, 2, NH_2)
7	D	6.31 (d)	5.27 (m)	5.27 (m)		4.07 (d)		8.20, 8.24	5.27 (t, 1, C_5'OH), 5.75 (d, 1, C_2'OH), 7.35 (s, 2, NH_2)
9	D	5.98 (ddd)	6.02 (ddd)	5.92 (ddd)	4.90 (m)	3.57 (dd)	3.74 (dd)	8.02 (s, C_5H)	
12a	D	6.86 (m)	6.58 (ddd)	6.30 (m)	5.23 (m)	4.47 (d)		With Ar	7.6–8.1 (m, 11, Ar and C_2H)
12b	D	6.78 (ddd)	6.45 (ddd)	6.09 (ddd)	4.88 (m)	3.55 (d)		8.03, 8.08	
13	D	6.21 (d)	5.12 (m)	5.22 (br d)		4.01 (s)		8.07, 8.07	
15a	D	6.80 (ddd)	6.38 (ddd)	5.90 (ddd)	4.78 (m)	3.59 (d)			5.56 (d, 1, C_5H), 7.74 (d, 1, C_6H)
15b	D	6.76 (ddd)	6.39 (ddd)	6.01 (ddd)	5.00 (m)	3.82 (d)			5.57 (d, 1, C_5H), 7.45 (d, 1, C_6H)
15c	C	7.00 (ddd)	6.28 (ddd)	5.89 (ddd)	5.07 (m)	4.22 (dd)	4.50 (dd)		1.52, 1.55 (s, 3, CMe_2), 2.01 (s, 3, OAc), 5.76 (s, 1, C_5H), 7.54 (s, 1, C_6H)
15d	C	7.09 (ddd)	6.37 (ddd)	5.99 (ddd)	5.12 (m)	4.27 (dd)	4.45 (dd)		2.08 (s, 3, OAc), 5.79 (s, 1, C_5H), 7.57 (s, 1, C_6H)
17	D	6.10 (d)	4.93 (dd)	5.20 (dd)	4.30 (m)		4.30 (br s)		5.70 (dd, 1, C_5H), 7.65 (d, 1, C_6H), 1.46 (s, 6, CMe_2), 1.96 (s, 3 *t*-OAc), 2.11 (s, 3, 3'-OAc)
18	D	6.11 (d)	4.95 (dd)	5.22 (dd)	4.25 (m)		4.25 (m)		2.04 and 2.10 (s, 3, OAc), 5.73 (dd, 1, C_5H), 7.66 (d, 1, C_6H)
21c	D	6.03 (d)	5.95 (dd)	4.75 (dd)	4.04 (m)		3.76 (m)	8.14, 8.33	2.04 (s, 3, OAc), 5.56 (t, 1, C_5'OH), 7.33 (s, 2, NH_2)

[a] Specific assignments are not implied. [b] Solvents are DMSO-d_6 (D) and $CDCl_3$ (C).

bility during distillation. We have, however, shown that the acyl iodide can be prepared *in situ* by reaction of 2-acetoxyisobutyryl chloride with carefully dried sodium iodide in acetonitrile. The direct reaction of this mixture with adenosine in the presence of an excess of sodium iodide proceeds readily to give a mixture containing only two significant ultraviolet-absorbing spots upon tlc. The faster of these (15–30% in different experiments) proved to be 2',3',5'-tris-*O*-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl) adenosine, which was isolated in crystalline form and shown to be identical with an authentic sample.[12b] The major product crystallized readily from ethyl acetate–ether and proved to be the 3'-iodoacetate **4c**. As in our earlier studies with adenosine, the 5' position was blocked as the trimethyldioxolanon-2-yl ether as shown by its infrared spectrum (ν_{max} 1810 cm^{-1}) and its nmr spectrum. While the latter clearly showed the 2'-*O*-acetyl and the CH_3CO_3 group of the dioxolanone moiety as three-proton singlets at 2.05 and 1.72 ppm, the usual pair of three-proton singlets due to the nonequivalent *gem*-dimethyl group was not present. In its place were three singlets totaling six protons and in a ratio of 2:1:1 at 1.46, 1.50, and 1.52 ppm. This suggests that the sharp-melting crystalline product is still a mixture of diastereoisomers due to the chiral dioxolanone group. Of the other protons in the molecule, only C_3'H reflected this diastereomerism and appeared as a complex multiplet while all other signals were sharp. The xylo configuration of the iodo group was apparent from the conversion of **4c** to 2',3'-anhydroadenosine[12b] upon treatment with sodium methoxide. We cannot rule out the presence of minor amounts of chloro nucleoside **4a** or of 2'-halogenated material in the crude product prior to crystallization. Nevertheless, the crude reaction product was treated with chromous acetate under the usual conditions, giving 48% of the 2' olefin **5**, 9% of 3'-deoxyadenosine (**6**), and 7% of the 3' olefin **7** in addition to adenosine coming from the trisdioxolanone.

From the above it is clear that there is relatively little difference in the distribution of products resulting from the chloro, bromo, and iodo nucleosides (**4a–c**). In view of the known relative reactivities (I > Br > Cl) of alkyl halides toward simple reduction by chromous ion,[14] it is perhaps surprising that considerably more 3'-deoxyadenosine (**6**) arose from the bromo nucleoside **4a** than from its chloro or iodo counterparts. It is established[14–16] that both chromous ion promoted reductions and eliminations involve radical and organochromium intermediates. It is assumed that the formation of the 3' olefin **7** is the consequence of an alternative pathway of decomposition of the initial C_3' radical rather than of a base-catalyzed elimination of bromide due to ethylenediamine. This conclusion is based upon the fact that the base-catalyzed conversion of **4a** to **7** using DBN requires heating in acetonitrile while the chromous reaction took place at low temperature.

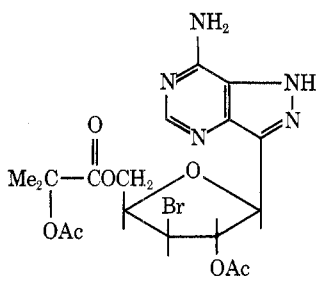
We have previously described the reaction of the biologically active adenosine analog formycin with 2-acetoxyisobutyryl bromide to give a 3:1 mixture of 7-amino-3-[5-*O*-(2-acetoxyisobutyryl)-2-*O*-acetyl-3-bromo-3-deoxy-β-D-xylofuranosyl]pyrazolo[4,3-*d*]pyrimidine (**8**) and its 3-*O*-acetyl-2-bromo-2-deoxy-β-D-arabinofuranosyl isomer in quantitative yield.[1] The reaction of this mixture with chromous acetate in the usual way followed by removal of the acetoxyisobutyryl ester with sodium methoxide gave the 2',3'-unsaturated nucleoside **9** in 43% yield. While free **9** was not obtained in crystalline form its purity was confirmed by its elemental analysis, chromatographic behavior, and characteristic nmr spectrum. In addition, a 9% yield of pure 3'-deoxyformycin (**10**) was isolated as its crystalline hydrochloride and found to be identical with a

Table II
Coupling Constants for Compounds in Table I (Hertz)

Compd	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'a}$	$J_{4',5'b}$	$J_{5'a,5'b}$	Other
4c	4	6.5	*a*	3	2.5	11.5	
5	1.5	6	2	3.5	3.5	0	$J_{1',3'} = 1.5$, $J_{1',4'} = 3$, $J_{2',4'} = 1.5$, $J_{5'H,OH} = 5$
7	2.5	*a*				0	$J_{H,OH} = 5$
9	*a*	*a*	*a*	3	3	12	
12a	1.5	5.5	*a*	4	4	0	$J_{1',3'} = 1.5$, $J_{1',4'} = 3$, $J_{2',4'} = 1.5$
12b	1.5	6	2.5	4	4	0	$J_{1',3'} = 1.5$, $J_{1',4'} = 3$, $J_{2',4'} = 1.5$
13	2.5	~2				0	$J_{3',5'} \cong 0.5$
15a	1.5	6	2	3.5	3.5	0	$J_{1',3'} = 1.5$, $J_{1',4'} = 3$, $J_{2',4'} = 1.5$, $J_{5,6} = 8$
15b	1.5	6	2.5	4.5	4.5	0	$J_{1',3'} = 1.5$, $J_{1',4'} = 3$, $J_{2',4'} = 1.5$, $J_{5,6} = 8$
15c	1.5	6	2.5	3.5	4	12.5	$J_{1',3'} = 1.5$, $J_{1',4'} = 3$, $J_{2',4'} = 1.5$, $J_{5,6} = 8$
15d	1.5	6	2.5	3.5	3.5	12	$J_{1',3'} = 1.5$, $J_{1',4'} = 3$, $J_{2',4'} = 1.5$, $J_{5,6} = 8$
17	7	6	1	~1	~1	0	$J_{5,NH} = 2$, $J_{5,6} = 8$
18	7	6	3	*a*	*a*	*a*	$J_{5,NH} = 1$
21c	4.5	4.5	5.5	*a*	*a*	*a*	$J_{5',OH} = 5$

[a] Unresolved.

sample previously obtained by catalytic hydrogenolysis of **8**.[1] While the formation of a small amount of 2′-deoxyformycin[1] in the chromous acetate reaction was indicated by tlc, this compound was not isolated.



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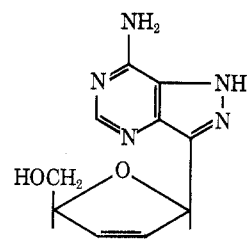

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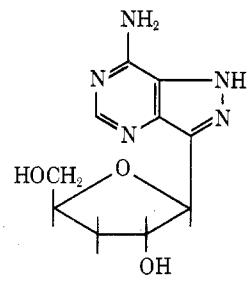
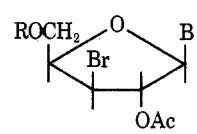
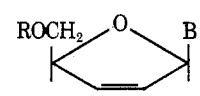


10

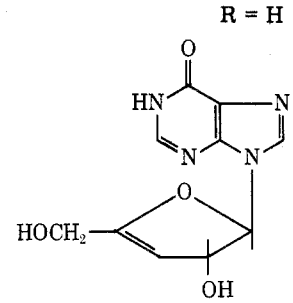
The reactions of N^6,5′-*O*-dibenzoylguanosine[25] and of inosine with α-acetoxyisobutyryl halides have also been examined and shown to lead predominantly to the 2′-*O*-acetyl-3′-bromo-3′-deoxy-β-D-xylofuranosyl nucleosides (**11a,b**).[12d] The reaction of **11a** with chromous acetate gave a mixture of products from which 9-(5-*O*-benzoyl-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-N^2-benzoylguanine (**12a**) was isolated in 24% yield by direct crystallization. Attempts to raise this yield and to isolate other products following debenzoylation of the mother liquors with methanolic dimethylamine[26] met with failure, since the mixture so obtained was not sufficiently soluble for chromatographic separation and could not be successfully crystallized. The analogous reaction with the bromo acetyl derivative **11b** in the inosine series was far more successful. Following cleavage of protecting groups with methanolic ammonia and chromatography on silicic acid, the desired 2′,3′ olefin **12b** was isolated in crystalline form in 53% yield. In addition, crystalline 9-(3-deoxy-β-D-*glycero*-pent-3-enofuranosyl)hypoxanthine (**13**) was obtained in 3% yield, and, while we have been unable to isolate it in crystalline form owing to chromatographic overlapping with residual **13**, 3′-deoxyinosine was clearly also present on the basis of tlc comparison with an authentic sample. The latter compound has previously been shown to be the biologically inactive deamination product of Cordycepin (3′-deoxyadenosine)[27] and has been obtained by synthesis.[28]



11a B = N^2-Bz-guanine; R = Bz
b, B = hypoxanthine; R = trimethyldioxolanone



12a, B = N^2-Bz-guanine; R = Bz
b, B = hypoxanthine; R = H
c, B = thymine; R = H

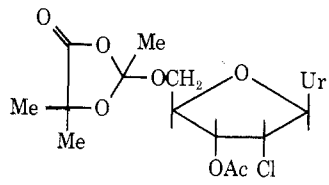


13

The above reactions using purine nucleosides have the common feature that they all are substituted with trans bromo acetate functions at $C_{2'}$ and $C_{3'}$ of the sugar moiety. Since chromous ion promoted reductive eliminations are radical in nature, Singleton and Kochi[15a] have shown that both *cis*- and *trans*-1,2-dibromocyclohexane are converted to cyclohexene, although at different rates. Accordingly, it seemed likely that the cis bromo acetates produced by reaction of uridine with 2-acetoxyisobutyryl halides[12a] should also be converted to 2′,3′ olefins. Our initial experiments were carried out on the crude product from uridine and 2-acetoxyisobutyryl chloride in acetoni-

trile which has been shown by nmr and by isolation to be predominantly (at least 80%) 3′-*O*-acetyl-2′-chloro-2′-deoxy-5′-*O*-(2,5,5,-trimethyl-1,3-dioxolan-4-on-2-yl)uridine (**14**)[12a] together with lesser amounts of the corresponding 5′-*O*-acetoxyisobutyrate. The reaction of this product with chromous acetate led, unexpectedly, to quite extensive glycosidic cleavage with release of uracil. Following removal of protecting groups with sodium methoxide and separation by preparative tlc the desired 2′,3′ olefin **15a** was isolated in crystalline form in an overall yield of 26%. This product has previously been prepared by Horwitz, *et al.*,[7a] from derivatives of 2′-deoxy-3′-*O*-methanesulfonyluridine. The only other nucleoside isolated from this reaction proved to be 2′-deoxyuridine (5%), the result of simple reduction of **14**. Another reaction was carried out using as starting material the crude product from uridine and 2-acetoxyisobutyryl chloride in dimethylformamide.[12a] This material was also shown to be predominantly the 5′-dioxolanone **14** although the proportion of by-products was somewhat higher than in the reaction in acetonitrile. In this case the distribution of products from the chromous acetate reaction was very similar to that described above, but in addition a single, less polar band was also isolated by preparative tlc. This compound, isolated crystalline in 11% yield, proved to be 1-(5-chloro-2,3,5-trideoxy-β-D-*glycero*-pent-2-enofuranosyl)uracil (**15b**), this structure being confirmed by an independent synthesis *via* chlorination of **15a** with triphenylphosphine and carbon tetrachloride.[12c] The isolation of **15b** suggests that one of the by-products accompanying reaction of uridine with 2-acetoxyisobutryl chloride in hot dimethylformamide is 3′-*O*-acetyl-2′,5′-dichloro-2′,5′-dideoxyuridine (**16**).[12c] While the chloro and acetyl functions of **16** would serve as precursors of the 2′,3′ olefin, the primary alkyl chloride would be relatively resistant to reaction with chromous ion at low temperatures.[14] In support of the above we have shown that treatment with methanolic hydrogen chloride of crude **14** from a reaction in dimethylformamide readily cleaves the dioxolanone substituent.[12a] Preparative tlc of the mother liquors from the resulting 3′-*O*-acetyl-2′-chloro-2′-deoxyuridine led to the isolation, in modest yield, of an acid-resistant fraction, the nmr spectrum of which clearly showed the major constituent to be **16**.[12c] By-products such as **16** are apparently not formed in comparable reactions between uridine and 2-acetoxyisobutyryl chloride in solvents such as acetonitrile.

In the hope that the extent of glycosidic cleavage could be reduced by using a bromo- rather than a chlorouridine, the reaction between uridine and 2-acetoxyisobutyryl bromide in acetonitrile was investigated. The crude product of this reaction, isolated in essentially quantitative yield, proved to be a roughly 9:1 mixture of two compounds. The major, less polar, product was isolated in pure form by chromatography on silicic acid and proved to be 5′-*O*-(2-acetoxyisobutyryl)-3′-*O*-acetyl-2′-bromo-2′-deoxyuridine (**17**). The unexpected formation of the acetoxyisobutyryl derivative rather than the dioxolanone found with the chloro analog **14** was confirmed by its nmr spectrum, which showed the *gem*-dimethyl group as a six-proton singlet at 1.46 ppm and the tertiary acetoxyl as a three-proton singlet at 1.96 ppm.[12a] In addition, the infrared spectrum showed only normal ester bands in the 1700–1800-cm^{-1} region and no indication of the typical dioxolanone carbonyl frequency at 1805–1810 cm^{-1}.[12a] We have previously found that during reactions of 2-acetoxyisobutyryl halides with nucleosides the choice between the dioxolanone ether and 2-acetoxyisobutyryl ester varies according to both the solvent[12a] and the nature of the heterocyclic base.[1] The present case provides yet another example of



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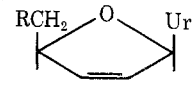
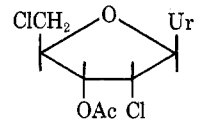


15a, R = OH
b, R = Cl
c, R = O—COCMe$_2$ (OAc)
d, R = OCOCH$_3$



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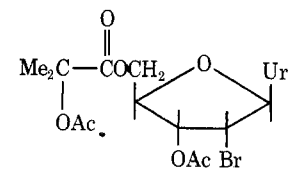

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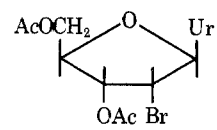


18

the delicate balance between these two alternative substituents. One possible explanation is that the 2-acyloxyisobutyryl halides are themselves in equilibrium with cyclic oxonium ion or 2-halodioxolanone tautomers, the formation of which is dependent upon both the nature of the halide and steric requirements. Examination of these compounds by infrared and nmr spectroscopy, however, reveals no indication of the presence of appreciable amounts of such species.

The minor product from the above reaction was also isolated and shown to be 3′,5′-di-*O*-acetyl-2′-bromo-2′-deoxyuridine (**18**). The chromatographic behavior and the nmr and infrared spectra of this substance were identical in every way with those of a sample of **18** prepared by acetylation of 2′-bromo-2′-deoxyuridine according to Cushley, *et al.*[29] It is interesting to note that the reaction of uridine with 2-acetoxyisobutyryl chloride and an excess of anhydrous lithium bromide rather than with pure 2-acetoxyisobutyryl bromide leads to a similar mixture of **17** and **18** in which the proportion of **18** is markedly increased. For the present purposes, of course, both **17** and **18** are equally suitable substrates for the chromous reaction. The mechanism by which the 5′-*O*-acetyl substituent arises is unclear and perhaps involves a decomposition of the reagent to acetyl bromide. The chloro analog of **18** was the sole product from uridine and 2-acetoxyisobutyryl chloride in glacial acetic acid.[12a]

The reaction of crude **17** with chromous acetate was found to give results very similar to those using the chloro nucleoside **14**. Once again, quite extensive glycosidic cleavage resulted, and following removal of the 5′ substituent and preparative tlc the 2′,3′ olefin **15a** and 2′-deoxyuridine were isolated in yields of 33 and 3%, respectively. It would appear that the extensive glycosidic cleavage leading to uracil is due to the fact that only in the uridine series the 2′ position is the principal site of halogenation. Presumably the initial chromous ion promoted 2′ radical can lead to either the desired 2′,3′ olefin or to glycosidic cleavage by alternative pathways.

In one reaction between **17** and chromous perchlorate the direct product was isolated by crystallization prior to deacylation, giving the 5′-*O*-(2-acetoxyisobutyryl) olefin

(**15c**). As part of the characterization of **15a** we have also acetylated the free 5′-hydroxyl group, giving crystalline **15d.** The nmr spectra of both **15c** and **15d** showed the expected downfield shift of the $C_{5'}$ protons relative to those of **15a.** In addition, the ester functions at $C_{5'}$ led to nonequivalence of the two $C_{5'}$ protons, presumably owing to restriction of rotation. The compound **15c** is also the first example of a 5′-*O*-(2-acetoxyisobutyryl) nucleoside that we have encountered in which the *gem*-dimethyl groups are magnetically nonequivalent and appear as a pair of three-proton singlets at 1.52 and 1.55 ppm.

It has previously been noted that the optical rotatory dispersion (ORD) spectra of the 2′,3′-unsaturated uridine and adenosine analogs **15a** and **5** are anomalous. Thus, while simple β-nucleosides in the pyrimidine and purine series normally exhibit positive and negative Cotton effects, respectively,[30] **15a** was found to be negative[11,30a] and **5** positive.[31] Our results confirm the above observations and extend them to a variety of related compounds. Thus, like **15a,** several 5′-substituted derivatives (**15b–d**) also exhibit negative Cotton effects. Similarly, the 2′,3′-unsaturated analog of formycin (**9**) showed an anomalous positive Cotton effect while that from inosine (**12b**) gave a positive plain dispersion curve. The ORD spectrum of the 5′,N^2-dibenzoylguanosine olefin (**12a**) is considerably more complex and shows a multiple Cotton effect. This is presumably related to the presence of two intense maxima in the ultraviolet spectrum of **12a.** As yet we have not debenzoylated this compound so as to obtain a more simple spectrum. It seems, nevertheless, clear that inverted Cotton effects are a general consequence of the introduction of 2′,3′ unsaturation into both purine and pyrimidine nucleosides.

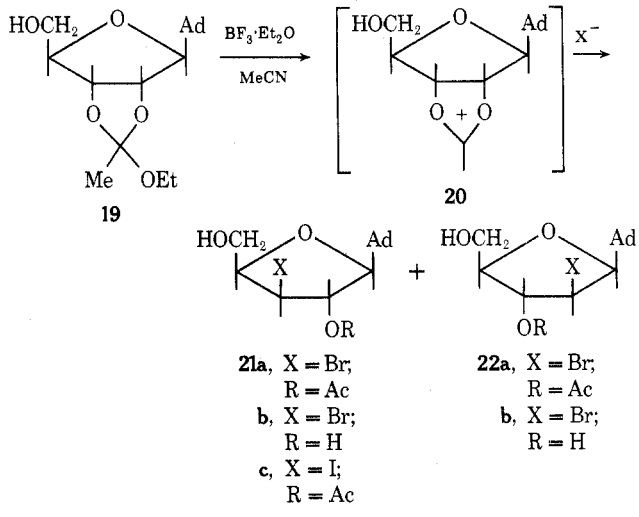
Finally, we would like to briefly describe an alternative method for the synthesis of sugar halogenated purine nucleosides of types **1** and **2** (X = Br and I) in which the 5′ hydroxyl is unsubstituted. This method is based upon the observation, made during a separate study in this laboratory,[32] that reaction of uridine 2′,3′-ortho esters with nitrosonium tetrafluoroborate in acetonitrile led readily to 3′-*O*-acyl-O^2,2′-cyclouridine derivatives, presumably *via* intermediate 2′,3′-acyloxonium ions. This is also clearly related to reports by Robins, *et al.*,[33] that treatment of 2′,3′-*O*-methoxyethylideneadenosine with pivaloyl chloride in refluxing pyridine leads, *inter alia,* to 9-(2-*O*-acetyl-3-chloro-3-deoxy-5-*O*-pivaloyl-β-D-xylofuranosyl)-N^6-pivaloyladenine, once again presumably *via* a 2′,3′-acetoxonium intermediate. In the presence of excess iodide ion a related 3′-iodo nucleoside bearing a bizarre enol ester function at $C_{2'}$ was obtained.[33b] Along similar lines, Newman and Chen[34] have recently described the conversion of simple cyclic ortho esters into chloroacetates *via* treatment with chlorotriphenylmethane.

Both the above reactions would appear to involve only the conversion of an ortho ester to an acetoxonium ion utilizing pivaloyl chloride or chlorotriphenylmethane as a source of anhydrous acid. Previous work by Meerwein[35] has shown that such a conversion can be accomplished using model cyclic ortho esters in the presence of Lewis acids such as boron trifluoride. We felt that the reaction of a nucleoside 2′,3′-ortho ester with boron trifluoride would generate the desired acyloxonium ion without the complications introduced by the presence of acylating species such as pivaloyl chloride or of nucleophilic halide ions originating from the reagent. We have accordingly treated the mixed diastereoisomers of 2′,3′-*O*-ethoxyethylideneadenosine (**19**)[36] with boron trifluoride etherate in acetonitrile at 0° in the presence of an excess of anhydrous lithium bromide. Examination of the reaction mixture by tlc showed the presence of two major spots, the more polar of which proved to be 2′(3′)-*O*-acetyladenosine arising from simple hydrolysis of the intermediate acetoxonium ion **20.** The less polar product was isolated by preparative tlc and shown by nmr to be a roughly 5:1 mixture of 9-(2′-*O*-acetyl-3-bromo-3-deoxy-β-D-xylofuranosyl)adenine (**21a**) and 9-(3-*O*-acetyl-2-bromo-2-deoxy-β-D-arabinofuranosyl)adenine (**22a**). By direct crystallization it was possible to isolate an overall 33% yield of pure **21a** which was found to be identical with a sample previously prepared by acidic hydrolysis of the corresponding 5′-*O*-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl) derivative obtained from adenosine and 2-acetoxyisobutyryl bromide.[12b]

While pure **22a** was not isolated as such, its presence was confirmed by treatment of the mother liquors from crystallization of **21a** with methanolic ammonia, which converts the 3′-bromo isomer **21a** into a mixture of the bromohydrin **21b** and 2′,3′-anhydroadenosine as previously described.[12b] At the same time **22a** is deacetylated giving, in low yield, the crystalline bromohydrin **22b** which was identical with an authentic sample.[12b]

In a very similar way, **19** was treated with boron trifluoride etherate in the presence of anhydrous sodium iodide. By a combination of chromatography on silicic acid and crystallization the pure 2′-*O*-acetyl-3′-iodo nucleoside **21c** was isolated in 35% yield. Identically the same compound was obtained by mild acidic hydrolysis of the product **4c** from adenosine and 2-acetoxyisobutyryl chloride in the presence of excess sodium iodide.

The above method constitutes a useful alternative to the use of 2-acetoxyisobutyryl halides for the preparation of compounds such as **21** and **22.** Clearly, in principle, such a reaction could also be used for the introduction of substituents other than halogen by reaction of the intermediate acetoxonium ion (**20**) with the appropriate nucleophile. Progress in this direction will be reported at a later date. Regardless of their mode of preparation, nucleoside halo acetates of types **1–3** constitute versatile intermediates for the preparation of deoxy, dideoxy, and unsaturated nucleosides.



Experimental Section

General Methods. The general methods used are similar to those described in previous papers in this series.[1] The assignments of sugar protons in the nmr spectra are generally confirmed by spin-decoupling studies and are presented in Tables I and II. We are particularly grateful to Mrs. J. Nelson and Dr. M. L. Maddox for their generous help with nmr studies.

Chromous Acetate. Electrolytically purified chromium metal chips (99.996% purity from Varlacoid Chemical Co., Elizabeth, N. J.) was rapidly, successively washed by decantation with concentrated hydrochloric acid, water, 70% perchloric acid, and water in a drybox under argon. The metal was then treated for roughly 1 min with 18% perchloric acid (40 ml) with vigorous passage of argon through the liquid. The solution was decanted, and the metal was added to 200 ml of 70% perchloric acid that had been thoroughly deoxygenated with argon. The mixture was then stored under argon for 60 hr, giving a deep blue solution which was added to a stirred, deoxygenated solution of sodium acetate (80 g) in water (160 ml). The resulting precipitate was collected under argon and successively washed with deoxygenated water, ethanol, and ether. The final material was dried and stored *in vacuo*, giving 44.3 g of chromous acetate as a brick red powder.

9-[2-*O*-Acetyl-3-deoxy-3-iodo-5-*O*-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl)-β-D-xylofuranosyl]adenine (4c). 2-Acetoxyisobutyryl chloride (6.8 ml, 48 mmol) was added to a solution of carefully dried (100° *in vacuo* for 2 days) sodium iodide (10.8 g, 72 mmol) in anhydrous acetonitrile (100 ml). After 15 min, adenosine (3.2 g, 12 mmol) was added to the resulting suspension and the mixture was stirred for 30 min. The solvent was then largely removed *in vacuo* and the residue was partitioned between ethyl acetate and aqueous sodium bicarbonate containing sodium thiosulfate. The organic phase was further washed with sodium bicarbonate, then with water, dried ($MgSO_4$), and evaporated, leaving 6.38 g of a foam which by tlc (chloroform–methanol, 9:1) contained two major spots (~3:1) with very similar mobilities and only traces of more polar products. For analytical purposes a portion of this (500 mg) was partially separated by repeated preparative tlc on two plates. The less polar, minor product was crystallized from ethyl acetate–ether, giving 40 mg of an essentially single diastereoisomer of 2′,3′,5′-tris(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl)adenosine with mp 140–141° and with an nmr spectrum identical with that of an authentic sample.[12b] Crystallization on the more polar band gave 200 mg of **4c**: mp 134.5–135.5°; λ_{max} (MeOH, H^+) 259 nm (ε 15,400); $[\alpha]^{23}D$ 16.9° (*c* 0.5, MeOH); ORD (MeOH) $[\Phi]_{242}$ (peak) 10,500°, $[\Phi]_{261}$ 0°, $[\Phi]_{278}$ (trough) −4900°.

Anal. Calcd for $C_{18}H_{22}N_5O_5I$ (547.31): C, 39.49; H, 4.05; N, 12.80; I, 23.19. Found: C, 39.66; H, 4.19; N, 12.60; I, 23.35.

Treatment of the crude product with methanolic sodium methoxide for 5 min at room temperature gave only 2′,3′-anhydroadenosine with melting point and nmr spectrum identical with those of an authentic sample[12b] and adenosine from the trisdioxolanone.

General Procedure for Chromous Acetate Reactions. The halogenated nucleoside (5 mmol) was dissolved in 100–150 ml of ethanol and deoxygenated by thorough bubbling with argon. This solution was then added, under argon, to a stirred, deoxygenated mixture of chromous acetate (4.25 g, 25 mmol) and ethylenediamine (3.4 ml, 50 mmol) in ethanol at −78° for 0.5–4 hr as specified below. Air was then bubbled through the still cooled solution for several minutes and ice (~5 g) and glacial acetic acid (4.5 ml) were added. The mixture was llowed to warm to room temperature and the purple solution was evaporated *in vacuo*. The residue was partitioned between ethyl acetate and water and the dried ($MgSO_4$) solution was treated as described below.

Reaction of Chromous Acetate with Adenosine Derivatives. A. With Crude 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 (4b). The reaction was carried out for 2.5 hr as above using 2.28 g (5 mmol) of the crude extracted product (principally **4b** and its 3′-*O*-acetyl-2′-bromo-β-D-arabino isomer in a ratio of ~9:1) from adenosine and 2-acetoxyisobutyryl chloride.[12b] The crude extract (2.0 g) was treated for 22 hr with saturated methanolic ammonia and the evaporated residue was crystallized from methanol, giving 430 mg of 9-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-adenine (**5**): mp 194–195° (reported[7b] mp 187–190°[20]); λ_{max} (MeOH) 260 nm (ε 15,200); $[\alpha]^{23}D$ 22.8° (*c* 0.25, MeOH); ORD (MeOH) $[\Phi]_{266}$ (peak) 4900°, $[\Phi]_{246}$ 0°, $[\Phi]_{234}$ (trough) −2600°.

Anal. Calcd for $C_{10}H_{11}N_5O_2$ (233.23): C, 51.49; H, 4.75; N, 30.03. Found: C, 51.21; H, 4.77; N, 30.19.

The mother liquors from **5** were separated into three major bands by preparative tlc on three plates using four developments with chloroform–methanol (9:1). Elution of the fastest band followed by crystallization from methanol gave a further 290 mg (total yield 720 mg, 62%) of **5** identical with that above. Elution of the middle band followed by crystallization from methanol gave 130 mg (10%) of pure 3′-deoxyadenosine (**6**), mp 226–228°, in every way identical with an authentic sample.[12b]

Elution of the slowest band gave 330 mg of a mixture of products containing a small amount of 2′-deoxyadenosine which was identified chromatographically. Crystallization from methanol gave 80 mg (6%) of essentially pure 9-(3-deoxy-β-D-*glycero*-pent-3-enofuranosyl)adenine (**7**) which after one further crystallization from aqueous methanol had mp 240–241°: λ_{max} (MeOH, H^+) 258 nm (ε 15,000); λ_{max} (MeOH, OH^-) 259 nm (ε 14,800); $[\alpha]D$ 307° (*c* 0.1, H_2O); ORD (MeOH) $[\Phi]_{272}$ (trough) −13,300°, $[\Phi]_{258}$ (peak) −10,300°, $[\Phi]_{226}$ (trough) −50,000°, $[\Phi]_{216}$ 0°.

Anal. Calcd for $C_{10}H_{11}N_5O_3$ (249.23): C, 48.19; H, 4.45; N, 28.10. Found: C, 48.22; H, 4.48; N, 28.13.

B. With 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 (4a). The reaction with pure crystalline **4a**[12b] was carried out for 0.5 hr, giving 1.9 g of crude ethyl acetate extract. Following treatment with methanolic ammonia, initial crystallization from methanol followed by preparative tlc as above gave 685 mg (59%) of **5**, 370 mg (30%) of **6**, and only a trace of **7**, all with physical constants similar to those above.

C. With Crude Iodo Nucleoside (4c). The crude product from adenosine, 2-acetoxyisobutyryl chloride, and sodium iodide as above (2.73 g, ~5 mmol) was treated with chromous acetate for 30 min, giving 2.1 g of crude ethyl acetate extract. This material was treated for 24 hr with saturated methanolic ammonia and evaporated to dryness. Initial crystallization from methanol followed by preparative tlc and crystallization from methanol as above gave 554 mg (48%) of **5**, 110 mg (9%) of **6**, and 90 mg (7%) of **7**, all identical with those above.

9-(3′-Deoxy-β-D-*glycero*-pent-3-enofuranosyl)adenine (7). A solution of **4a** (2.0 g, 4 mmol) and 1,5-diazabicyclo[4.3.0]non-5-ene (0.66 ml, 8 mmol) in acetonitrile (20 ml) was heated at 80° for 30 min. Methanol (20 ml) was then added to the cooled solution and the mixture was stored at room temperature for 5 hr, giving 0.83 g of crude **7** contaminated with some 2′,3′-anhydrodenosine. Crystallization from water gave 0.59 g (59%) of pure **7** which was identical with the product of the chromous acetate reaction above by tlc and by nmr and infrared spectroscopy.

7-Amino-3-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)pyrazolo[4,3-*d*]pyrimidine (9) and 3′-Deoxyformycin (10). A sample of a 3:1 mixture of **8** and its 3-*O*-acetyl-2-bromo-2-deoxy-β-D-arabinofuranosyl isomer[1] (1.0 g, 2 mmol) was treated with chromous acetate as above for 2 hr, giving 850 mg of crude ethyl acetate extract. This material was treated for 24 hr with 0.38 *N* methanolic sodium methoxide, neutralized with Dowex 50 (H^+) resin, and evaporated to dryness. The resulting syrup (500 mg) was purified by preparative tlc using three developments with chloroform–methanol (85:15) giving two major bands. Elution of the faster of these gave 200 mg (43%) of **9** as a white solid that could not be crystallized but which was pure by tlc and nmr: λ_{max} (MeOH, H^+) 237 nm (ε 5800), 296 (9000); λ_{max} (MeOH, OH^-) 236 nm (ε 14,400), 306 (5900); $[\alpha]^{23}D$ 17.6° (*c* 0.9, MeOH); ORD (MeOH) $[\Phi]_{302}$ (peak) 4700°, $[\Phi]_{280}$ (trough) 4000°, $[\Phi]_{268}$ (peak) 5100°, $[\Phi]_{246}$ 0°, $[\Phi]_{232}$ −5100°; mass spectrum (70 eV) molecular ion *m/e* 233.

Anal. Calcd for $C_{10}H_{11}N_5O_2$ (233.23): C, 51.49; H, 4.75. Found: C, 51.22; H, 5.35.

Elution of the slower band gave 120 mg of a syrup that was converted into its hydrochloride and crystallized from ethanol, giving 50 mg (9%) of 3′-deoxyformycin hydrochloride (**10**), mp 207–209°, in all ways identical with an authentic sample[1].

9-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)hypoxanthine (12b). Crude **11b** (from inosine and 2-acetoxyisobutyryl bromide)[37] was treated as usual with chromous acetate for 1 hr, giving 2.1 g of crude ethyl acetate extract. This material was chromatographed on a column of silicic acid using chloroform–methanol (19:1) to remove a lttle hypoxanthine and giving 1.4 g of a white foam. This was treated for 20 hr with methanolic ammonia at room temperature to give one major, permanganate-positive spot and several minor products. Crystallization from methanol gave a total of 606 mg (53%) of **12b**: mp above 300°; λ_{max} (MeOH, H^+) 250 nm (ε 10,300); λ_{max} (MeOH, OH^-) 255 nm (ε 12,600); $[\alpha]^{23}D$ −34.8° (*c* 0.09, H_2O); ORD (MeOH) plain positive dispersion curve with $[\Phi]_{300}$ 400°, $[\Phi]_{250}$ 3000°, $[\Phi]_{220}$ 7100°.

Anal. Calcd for $C_{10}H_{10}N_4O_3$ (234.21): C, 51.28; H, 4.30; N, 23.92. Found: C, 51.10; H, 4.28; N, 23.65.

The mother liquors from **12b** were carefully chromatographed on silicic acid using chloroform–methanol (4:1) to give 70 mg of a permanganate-positive material more polar than **12b** and with an R_f very close to that of 3′-deoxyinosine. Crystallization from methanol gave 39 mg (3%) of the pure 3′ olefin **13**: mp 206–208° dec; λ_{max} (MeOH, H^-) 251 nm (ε 10,200); λ_{max} (MeOH, OH^-)

255 nm (ε 11,600); $[\alpha]^{23}D$ −129° (c 0.1, MeOH); ORD (MeOH) $[\Phi]_{300}$ −2800°, $[\Phi]_{224}$ (trough) −22,500°, $[\Phi]_{216}$ −11,000°.

Anal. Calcd for $C_{10}H_{10}N_4O_4$ (250.21): C, 48.00; H, 4.02; N, 22.39. Found: C, 47.97; H, 4.41; N, 22.21.

The mother liquors from **13** were shown by tlc to be a mixture of **13** and 3′-deoxyinosine[37] that could not be further resolved.

9-(5-*O*-Benzoyl-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-N^2-benzoylguanine (12a). The reaction between chromous acetate and crude **11a** (3.3 g, 5 mmol, from 2-acetoxyisobutyryl bromide and N^6, 5′-dibenzoylgluanosine)[12d] was carried out for 30 min, giving 2.04 g of ethyl acetate extract. Direct crystallization of this material from methanol gave 500 mg (24%) of **12a** which softened at 280° and melted with decomposition at 289–294°: λ_{max} (MeOH, H^+) 232 nm (ε 25,100), 274 (20,000); λ_{max} (MeOH, OH^-) 231 nm (ε 27,300), 275 (14,000), 318 (17,600); $[\alpha]^{23}D$ −149° (c 0.1, pyridine); ORD (MeOH) $[\Phi]_{318}$ (trough) −4900°, $[\Phi]_{286}$ (peak) −1700°, $[\Phi]_{250}$ (trough) −8300°, $[\Phi]_{236}$ 0°, $[\Phi]_{220}$ (peak) 16,200°.

Anal. Calcd for $C_{24}H_{19}N_5O_5$ (457.43): C, 63.01; H, 4.19; N, 15.31. Found: C, 62.81; H, 4.36; N, 15.13.

5′-*O*-(2-Acetoxyisobutyryl)-3′-*O*-acetyl-2′-bromo-2′-deoxyuridine (17). 2-Acetoxyisobutyryl bromide (3.6 g, 17 mmol) was added to a suspension of uridine (1.4 g, 5.7 mmol) in acetonitrile (25 ml) and the mixture was heated at 80° for 3 hr. The resulting clear solution was largely evaporated *in vacuo* and the residue was dissolved in ethyl acetate, extracted several times with aqueous bicarbonate and then with water, dried ($MgSO_4$), and evaporated, leaving 3.0 g of a froth. This material contained one major spot and roughly 10% of a slightly more polar compound. For analytical purposes this material was chromatographed on a column of silica gel using 1% methanol in chloroform. In this way 1.57 g (58%) of pure **17** was obtained as a white froth followed by a further 1.17 g of a mixture of the two products (total yield quantitative). The major product (**17**) had λ_{max} (MeOH, H^+) 258 nm (ε 9900); $[\alpha]^{23}D$ 26.8° (c 0.22, $CHCl_3$); ν_{max} (KBr) 1755, 1700 cm^{-1}.

Anal. Calcd for $C_{17}H_{21}N_2O_9Br$ (477.27): C, 42.78; H, 4.44; N, 5.87. Found: C, 42.33; H, 4.46; N, 5.72.

A sample of the minor component was purified by preparative tlc of an enriched fraction using chloroform–methanol (19:1) giving **18** as a chromatographically homogeneous foam: λ_{max} (MeOH, H^+) 258 nm (ε 9200); $[\alpha]^{23}D$ 14.3° (c 0.6, MeOH); ORD (MeOH) $[\Phi]_{278}$ (peak) 4500°, $[\Phi]_{266}$ 0°, $[\Phi]_{250}$ (trough) −5100°. The nmr spectrum of **18** was identical with that of a sample prepared by acetylation of 2′-bromo-2′-deoxyuridine according to Cushley, *et al.*[29]

Anal. Calcd for $C_{13}H_{15}N_2O_7Br$ (391.18): N, 7.16. Found: N, 7.17.

In a separate reaction uridine (9.76 g, 40 mmol) was added to a solution of 2-acetoxyisobutyryl chloride (160 mmol) and lithium bromide (400 mmol) in acetonitrile (300 ml) and the mixture was heated at 80° for 6 hr. A work-up as above gave 20 g of a roughly 2:1 mixture of **17** and **18** as judged by tlc and nmr. This material was used directly for the preparation of **15a.**

1-(2′,3′-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)uracil (15a). A. From the Bromo Nucleoside 17. The reaction with chromous acetate was carried out in the usual way for 4 hr using crude, unchromatographed **17** (2.38 g, ~5 mmol). The ethyl acetate extract gave only 1.33 g of crude product and the aqueous phase was found to contain predominantly uracil. The organic extract was evaporated and treated for 30 min with 0.38 *M* methanolic sodium methoxide (30 ml), neutralized with Dowex 50 (H^+) resin, and evaporated. The residue was purified by preparative tlc using two developments with chloroform–methanol (85:15) giving one major and two minor bands. Elution of the fastest, major band gave 530 mg of chromatographically pure **15** which was crystallized from methanol to give 350 mg (33%): mp 154.5–155.5° (reported[7a] mp 153–154°); λ_{max} (MeOH, H^+) 260 nm (ε 9800); λ_{max} (MeOH, OH^-) 260 nm (ε 7200); $[\alpha]^{23}D$ −15.4° (c 0.2, MeOH); ORD (MeOH) $[\Phi]_{283}$ (trough) −3700°, $[\Phi]_{258}$ 0°, $[\Phi]_{220}$ 10,400°.

Anal. Calcd for $C_9H_{10}N_2O_4$ (210.19): C, 51.42; H, 4.80; N, 13.33. Found: C, 51.57; H, 4.82; N, 13.21.

Elution of the middle band and crystallization from methanol gave 30 mg (5%) of uracil with mp >300° and in all ways identical with an authentic sample. Elution of the slowest band gave 35 mg (3%) of 2′-deoxyuridine which was chromatographically identical with an authentic sample and could be distinguished from 3′-deoxyuridine by tlc using chloroform–methanol (85:15).

B. From the Chloro Nucleoside 14. The reaction with chromous acetate was carried out for 4 hr using the crude product obtained essentially quantitatively from uridine and 2-acetoxyisobutyryl chloride in acetonitrile and known to be predominantly the 5′-dioxolanone (**14**).[12a] Once again much uracil was present in the aqueous phase and the ethyl acetate extracts were treated with sodium methoxide and purified by preparative tlc as in A. In this way 270 mg (26%) of crystalline **15a,** 60 mg (11%) of uracil, and 60 mg (5%) of 2′-deoxyuridine were isolated and shown to be identical with the same compounds from A.

1-[5-*O*-(2-Acetoxyisobutyryl)-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl]uracil (15c). In one experiment on the reaction of crude **17** with chromous perchlorate and ethylenediamine in dimethylformamide, the crude ethyl acetate extract was directly crystallized from ethyl acetate without prior deacylation. In this way **15c** was obtained as white crystals, mp 159–160°, in 15% yield: λ_{max} (MeOH) 259 nm (ε 10,300); $[\alpha]^{23}D$ −25.9° (c 1, MeOH); ORD (MeOH) $[\Phi]_{270}$ (trough) −4300°, $[\Phi]_{254}$ 0°, $[\Phi]_{240}$ (sh) 5100°.

Anal. Calcd for $C_{15}H_{18}N_2O_7$ (338.31): C, 53.25; H, 5.36; N, 8.28. Found: C, 53.12; H, 5.38; N, 8.30.

1-(5-*O*-Acetyl-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)uracil (15d). Acetylation of **15a** using acetic anhydride in pyridine at room temperature for 1 hr followed by crystallization from ethyl acetate gave **15d:** mp 127–128°; λ_{max} (MeOH) 259 nm (ε 9700); ORD (MeOH) $[\Phi]_{271}$ (trough) −6600°, $[\Phi]_{255}$ 0°, $[\Phi]_{220}$ (peak) 9200°.

Anal. Calcd for $C_{11}H_{12}N_2O_5$ (252.23): C, 52.38; H, 4.80; N, 11.11. Found: C, 52.33; H, 4.83; N, 10.98.

1-(5-Chloro-2,3,5-trideoxy-β-D-*glycero*-pent-2-enofuranosyl)uracil (15b). A. A solution of **15a** (80 mg, 0.4 mmol) in dimethylformamide (1 ml) was treated overnight at room temperature with triphenylphosphine (150 mg, 0.6 mmol) and carbon tetrachloride (100 mg, 0.65 mmol). The solvent was evaporated and the residue was purified by preparative tlc using chloroform–methanol (9:1). This separated triphenylphosphine oxide from a new product which was eluted and crystallized from methanol–ethyl acetate, giving 50 mg (57%) of **15b:** mp 166.5–167.5°; λ_{max} (MeOH, H^+) 259 nm (ε 9800); λ_{max} (MeOH, OH^-) 258 nm (ε 6700); $[\alpha]^{23}D$ −67.0° (c 0.55, MeOH); ORD (MeOH) $[\Phi]_{274}$ (trough) −8700°, $[\Phi]_{257}$ 0°, $[\Phi]_{228}$ (peak) 12,800°.

Anal. Calcd for $C_9H_9N_2O_3Cl$ (228.63): C, 47.28; H, 3.97; N, 12.25; Cl, 15.51. Found: C, 47.50; H, 4.04; N, 12.07; Cl, 15.47.

Upon storage at room temperature for several weeks **15b** decomposed to a black resin.

B. A reaction between chromous acetate and the crude product from uridine and 2-acetoxyisobutyryl chloride in dimethylformamide and known to be predominantly **14**[12a] was carried out for 4 hr as above. In addition to the products isolated above as in B a new, fast-moving band was observed. Elution of this material gave 130 mg (11%) of pure **15b** which was chromatographically and spectroscopically identical with that above.

9-(2-*O*-Acetyl-3-bromo-3-deoxy-β-D-xylofuranosyl)adenine (21a). A solution of the mixed diastereoisomers of 2′,3′-*O*-ethoxyethylideneadenosine (1.68 g, 5 mmol)[35] and carefully dried (100° *in vacuo*) lithium bromide (1.74 g, 20 mmol) in acetonitrile (300 ml) was stirred at 0° while boron trifluoride etherate (5 ml) was added. After 1 hr an excess of saturated aqueous sodium bicarbonate was added and the acetonitrile was largely removed *in vacuo*. The aqueous residue was extracted several times with chloroform and some minor, fast-moving impurities were removed by chromatography on silica gel using chloroform–methanol (9:1) giving 1.40 g of a froth that showed two spots upon tlc. The slower, minor spot contained mainly 2′(3′)-*O*-acetyladenosine while the major product was a roughly 5:1 mixture of **21a** and **22a** by nmr.[12b] Preparative tlc on three plates using chloroform–methanol (9:1) gave 861 mg of the less polar band which was crystallized from methanol–chloroform, giving 646 mg (33%) of **21a,** mp 205–206°, identical with an authentic sample[12b] by nmr.

The mother liquors from **21a** were evaporated to dryness and treated for 1.5 hr with saturated methanolic ammonia. Preparative tlc using five developments with chloroform–methanol (9:1) cleanly separated a fast band containing a mixture of **21b** and 2′,3′-anhydroadenosine from a slightly more polar band which was crystallized from ethyl acetate giving 34 mg (2%) of **22b,** mp 215–216°, in every way identical with an authentic sample.[12b]

9-(2-*O*-Acetyl-3-deoxy-3-iodo-β-D-xylofuranosyl)adenine (21c). Boron trifluoride etherate (5 ml) was added to a stirred solution of **19** (1.68 g, 5 mmol) and dried sodium iodide (1.8 g, 12 mmol) in acetonitrile at 0°. After 2 hr at 0° water (3 ml) was added followed by solid sodium thiosulfate to discharge the iodine color. The solution was dried ($MgSO_4$) and evaporated, leaving

3.0 g of a yellow syrup that was directly chromatographed on a column of silicic acid using chloroform–methanol (9:1).[38] Following removal of unreacted **19** a crude product (1.35 g) was obtained which was crystallized from ethyl acetate–methanol, giving 450 mg of **21c**. Preparative tlc of the mother liquors followed by crystallization as above gave a further 300 mg (total yield 750 mg, 35%) of pure **21c**: mp 199–201°; λ_{max} (MeOH, H^+) 259 nm (ϵ 16,800); λ_{max} (MeOH, OH^-) 260 nm (ϵ 15,800); $[\alpha]^{23}D$ 30.2° (*c* 0.1, pyridine); ORD (MeOH) $[\Phi]_{280}$ (trough) −5300°, $[\Phi]_{265}$ 0°, $[\Phi]_{240}$ (peak) 11,300°; ν_{max} (KBr) 1740, 1670, 1610 cm^{-1}.

Anal. Calcd for $C_{12}H_{14}N_5O_4I$ (435.18): C, 33.12; H, 3.24; N, 16.09; I, 29.16. Found: C, 33.22; H, 3.34; N, 15.98; I, 29.10.

Registry No. **4a**, 37731-72-9; **4b**, 37731-76-3; **4c**, 42867-59-4; **5**, 7057-48-9; **6**, 73-03-0; **7**, 42867-61-8; **8**, 40627-32-5; **8** 3-*O*-acetyl-2-bromo isomer, 42867-63-0; **9**, 42867-64-1; **11a**, 42867-65-2; **11b**, 42867-66-3; **12a**, 42867-67-4; **12b**, 42867-68-5; **13**, 42867-69-6; **14**, 42867-70-9; **15a**, 5974-93-6; **15b**, 42867-72-1; **15c**, 42867-73-2; **15d**, 42867-74-3; **17**, 42867-75-4; **18**, 19325-92-9; **19**, 42867-77-6; **21a**, 42867-78-7; **21c**, 42867-79-8; chromous acetate, 628-52-4; 2-acetoxyisobutyryl chloride, 40635-66-3; adenosine, 58-61-7; 2-acetoxyisobutyryl bromide, 40635-67-4; uridine, 58-96-8.

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Synthesis and Stereochemistry of Telomers of Vinylene Carbonate as Synthetic Intermediates for Carbohydrates[1]

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Vinylene carbonate underwent smooth telomerization with various polyhalogenomethanes as telogens in the presence of the radical initiator, BPO or AIBN, to give rise to type **3** telomers which could be synthetic key intermediates for carbohydrates. Isolation and stereochemistry of the lower telomers **3** ($n \leq 3$ or 4) stereoselectively formed were described. Stereochemistry of the $n = 2$ telomers **17a** and **17b** (**18a** and **18b**) was determined as trans,syn,trans and trans,anti,trans configuration by chemical correlation with lyxose and xylose derivatives **31**, and **34**, respectively. Abnormal telomerization involving unusual hydrogen abstraction from telogens by the radicals derived from peroxide was observed in the cases of bromoform and methylene bromide employed as telogens in contrast to those of polychloromethanes.

Apart from chemical modifications of naturally occurring monosaccharides, previously reported syntheses of carbohydrates from simple nonsugar substances mostly involve nonspecific processes at the stage of extension of the carbon chain or introduction of functional groups.[2] This paper deals with the stereoselective synthesis of car-