(18) and 100 mg of anhydrous potassium carbonate in 50 ml of dry dimethylformamide was stirred and heated at reflux for 6 hr. The solvent was removed under reduced pressure, and the residue, which was washed well with water and dried, was recrystallized from acetic acid–methanol (1:1, v/v) yielding 600 mg of powder. This crude product was dissolved in a minimum amount of formic acid, and the solution was applied to a column (100 g) of silica gel packed in chloroform–acetic acid–methanol (7:2:1, v/v). Elution with the same solvent mixture yielded the desired product. A middle fraction was dissolved in hot aqueous acetic acid, treated with activated charcoal, and filtered. Cold aqueous ammonia was added to the filtrate until precipitation was complete in the slightly basic medium. The cold suspension was filtered to yield 365 mg (39%) of analytically pure material as prisms. Drying for 10 hr *in vacuo* at refluxing xylene temperature afforded an anhydrous sample: mp >320°; nmr (CF_3COOH) τ 0.83, 0.90, 1.15, and 1.30 (4 s superimposed on a br resonance, 8, $AdC_{2,8}H$ and AdC_6NH_2) 5.03 (m, 4, $AdCH_2$ and AdN_7CH_2), 7.05 (m, 2, CCH_2C); mass spectrum (70 eV) *m/e* (rel intensity) 310 (1, M^+), 176 (25), 175 (95), 174 (19), 162 (100), 149 (22), 148 (74), 136 (15), 135 (19), 108 (14).

Anal. Calcd for $C_{13}H_{14}N_{10}$: C, 50.31; H, 4.55; N, 45.14. Found: C, 50.14; H, 4.69; N, 45.20, 44.98.

8-Propyladenine was made from 4,5,6-triaminopyrimidine (**5**) and *n*-butyric acid by the general method.[37] Sublimation of the product yielded leaflets: yield 68%; mp 261–262°; nmr (CF_3COOH) τ 1.22 (s, 1, AdC_2H), 6.64 (t, 2, J = 7 Hz, AdC_8CH_2), 7.92 (m, 2, J = 7 Hz, CCH_2C), 8.81 (t, 3, J = 7 Hz, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 177 (26, M^+), 162 (19), 149 (100), 148 (26), 121 (25).

Anal. Calcd for $C_8H_{11}N_5$: C, 54.22; H, 6.26; N, 39.52. Found: C, 54.51; N, 6.15; N, 39.68.

4,6-Diamino-5-*N*-propylformylaminopyrimidine (**17**, Br = H). This intermediate was made by the general method previously described,[21] yield 77%, small prisms from 1-butanol: mp 291–292°; nmr (CF_3COOH) τ 1.53 (s, 2, PyC_2H and CHO), 3.80 (br s, 4, NH_2), 6.60 (t, J = 7 Hz, 2, NCH_2C), 7.88–8.50 (m, 2, CCH_2C), 8.97 (t, J = 7 Hz, 3, CH_3).

Anal. Calcd for $C_8H_{13}N_5O$: C, 49.23; H, 6.71; N, 35.88. Found: C, 48.96; H, 6.59; N, 36.04.

7-Propyladenine. The intermediate described above was cyclized in the usual manner[21] to give 7-propyladenine, yield 57%, prisms from 2-propanol: mp 204–205°; nmr (CF_3COOH) τ 0.83 and 1.13 (2s, 2, $AdC_{2,8}H$), 5.23 (t, 2, J = 7 Hz, AdN_7CH_2), 7.80 (m, 2, J = 7 Hz, CCH_2C), 8,86 (t, 3, J = 7 Hz, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 177 (100, M^+), 162 (17), 148 (37), 135 (76), 121 (29), 108 (24), 94 (26).

Anal. Calcd for $C_8H_{11}N_5$: C, 54.22; H, 6.26; N, 39.52. Found: C, 54.13; H, 6.28; N, 39.34.

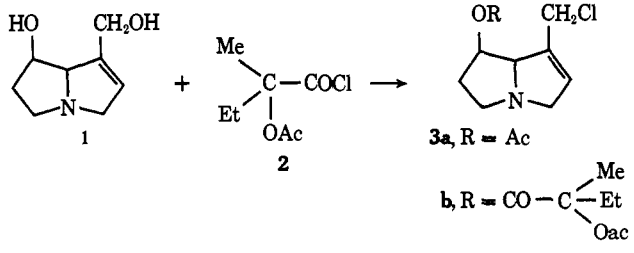
Reactions of 2-Acyloxyisobutyryl Halides with Nucleosides. I.[1] Reactions of Model Diols and of Uridine

S. Greenberg[2] and J. G. Moffatt*

Contribution No. 98 from the Institute of Molecular Biology, Syntex Research, Palo Alto, California. Received November 18, 1972

Abstract: The reaction of 2-acetoxyisobutyryl chloride with hydroxyl groups and with vicinal diols has been examined in detail. Isolated hydroxyl groups are usually converted into 2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl ethers or, under certain conditions, 2-acetoxyisobutyryl esters. *cis*-Cycloalkane-1,2-diols are converted almost quantitatively into *trans*-2-chlorocycloalkyl acetates while the corresponding *trans*-1,2-diols give many products with little incorporation of chlorine. A mechanism is proposed for these reactions. The reaction of **4** with uridine, or with 5′-protected uridine derivatives, led to the formation in high yield of 3′-*O*-acetyl-2′-chloro-2′-deoxyuridines by way of a 2′,3′-acetoxonium ion and then a 3′-*O*-acetyl-O^2,2′-cyclonucleoside. The reaction with uridine has been studied in a number of solvents, the nature of the resulting 5′ substituent being solvent dependent. Evidence in support of the proposed mechanism is provided by the isolation or trapping of the intermediates from short reactions.

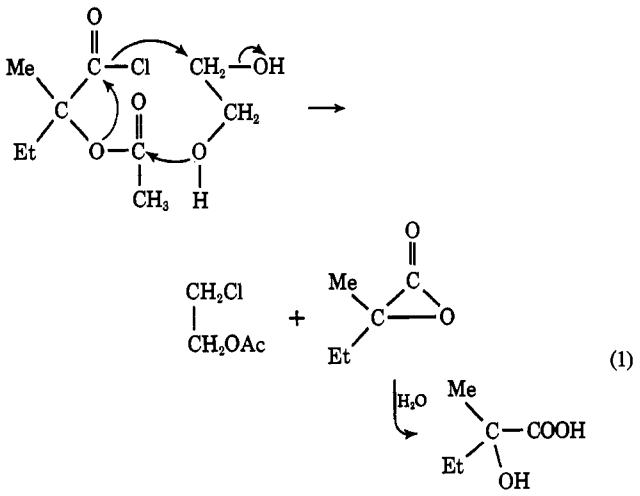
During studies by Mattocks on the chemistry of pyrrolizidine alkaloids, an abnormal reaction was observed between the 1,4-diol (**1**) and 2-acetoxy-2-methylbutyryl chloride (**2**), the unexpected products of this reaction being the chloroesters (**3a** and **3b**) in



yields of 54 and 20%.[3] Mattocks also showed that the acetoxyacyl chloride **2** reacts abnormally with 1,2- and 1,3-diols to form chloroacetates, for example, ethylene glycol reacting to form chloroethyl acetate. It was also reported that predominantly *trans*-cyclohexane-1,2-diol reacted to give four products, the major one of which was identified by vapor phase chromatography as *cis*-2-chlorocyclohexyl acetate, the reaction thus proceeding with inversion of one center.[4] On the basis of these, and other, considerations it was suggested that nucleophilic attack upon α-acyloxy acid chlorides bearing bulky substituents on the α positions occurred primarily at the acetoxy carbonyl group rather than at the acyl chloride function. A favored mechanism for these reactions is represented in eq 1.[3]

Our own interest in possible selective transformations of the vicinal diol grouping in ribonucleosides led us to reexamine this unusual reaction, and in the present paper we will discuss our interpretation of the

(1) For related work on halosugar nucleosides, see J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, 37, 2289 (1972).
(2) Syntex Postdoctoral Fellow, 1965–1967.
(3) A. R. Mattocks, *J. Chem. Soc.*, 1918, 4840 (1964).
(4) This conclusion is somewhat confused by the fact that in the Experimental Section of his paper, Mattocks identifies the major product as the *trans*-chloroacetate while in the text it is referred to as the cis isomer.



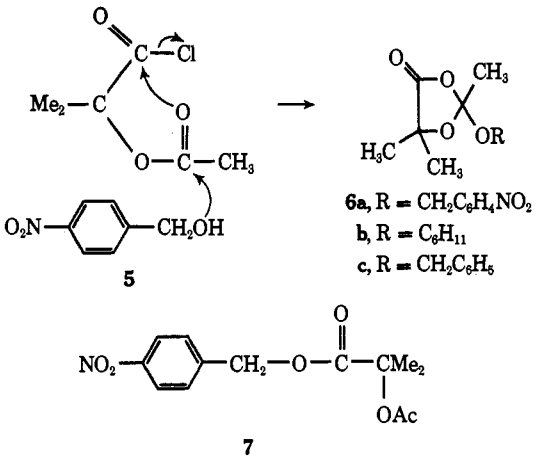
(1)

general features of the reaction and its application to uridine derivatives. The essential features of this work have been presented previously.[5] In forthcoming papers this study will be extended to reactions with other nucleosides and their analogs.[6]

Since the reagent **2** contains an asymmetric center, we have preferred to use the closely related 2-acetoxyisobutyryl chloride (**4**) in our work. The latter substance is very readily prepared by a modification of the method of Filachione, *et al.*,[7] that permits the conversion of 2-hydroxyisobutyric acid to **4** in an overall yield of 85% on a kilogram scale.

Mattocks has reported that isolated primary alcohols such as methanol and ethanol react with **2** in the presence of hindered bases such as triethylamine to form 2-alkoxy-5-ethyl-2,5-dimethyldioxolan-4-ones (*cf.* **6**), once again *via* initial nucleophilic attack upon the acetoxyl group.[3] We have confirmed and extended these observations by examining the reactions of **4** with *p*-nitrobenzyl alcohol (**5**) under different conditions. In acetonitrile a rapid reaction took place at room temperature between **5** and 2 molar equiv of **4** in the presence of 3 equiv of triethylamine. Essentially a single ultraviolet absorbing product was formed and isolated by preparative tlc in 84% yield. This substance proved to be 2,5,5-trimethyl-2-*p*-nitrobenzyloxy-1,3-dioxolan-4-one (**6a**), the formation of which clearly involves the pathway shown in eq 2.

The reaction between **4** and **5** in pure triethylamine led to a major product that was isomeric with **6a** but distinctly different chromatographically. Isolation of this substance gave the crystalline ester *p*-nitrobenzyl 2-acetoxyisobutyrate (**7**) in 47% yield. A third reaction between **4** and **5** in acetonitrile with no added base gave the dioxolanone (**6a**) as the major product isolated in 51% yield. In addition to **6a** lesser amounts of **7** and a crystalline substance, isolated in 25% yield and shown to be *p*-nitrobenzyl chloride, were formed in this reaction. Formation of the dioxolanone (**6a**) is accompanied by release of hydrogen chloride which presumably reacts directly with the rather reactive alcohol **5** to form *p*-nitrobenzyl chloride. A distinction between the isomeric dioxolanone (**6a**) and the ester (**7**) can be readily made by both infrared and nmr spectroscopy. Thus while the infrared spectrum of the ester (**7**) shows only a normal ester carbonyl band at 1735 cm^{-1}, the dioxolanone shows an intense band at 1805 cm^{-1}. This high-frequency band is very characteristic of all the alkoxydioxolanones we have examined and has been previously noted by others.[3,8] In addition, the nmr spectra of alkoxydioxolanones typically show three methyl signals at roughly 1.55, 1.58, and 1.83 ppm, the first two being the gem-dimethyl groups which are nonequivalent due to the cyclic structure and the third, the methyl group attached to carbon bearing three oxygens. The isomeric acetoxyisobutyrates, however, show a typical acetyl group at 2.05 ppm and a 6-proton singlet due to the equivalent *gem*-dimethyl functions. It might also be pointed out that the alkoxydioxolanone grouping is very sensitive to hydrolysis under both mildly alkaline and acidic conditions. We have frequently found that some decomposition of the dioxolanones accompanies their purification by preparative tlc if care is not taken to minimize their exposure to the adsorbant.



(2)

The reaction of crystalline *cis*-cyclopentane-1,2-diol (**8a**)[9] with 1.2–1.5 equiv of **4** in inert solvents such as ether, acetonitrile, or alcohol-free chloroform was rapid at room temperature, and following removal of acidic by-products [mainly 2-hydroxyisobutyric acid (**10**)] by extraction, examination of the crude reaction mixture by vpc showed at least 95% conversion to a single product. The latter was isolated in analytically pure form by distillation in 65% yield and shown to be *trans*-2-chlorocyclopentyl acetate (**9a**) which was identical with an authentic sample obtained by acetylation of *trans*-2-chlorocyclopentanol prepared by the action of hydrogen chloride on cyclopentene oxide.[10] It could be clearly differentiated by vpc from *cis*-2-chlorocyclopentyl acetate (**12a**) which was prepared by acetylation of the corresponding chloroalcohol obtained by reduction of 2-chlorocyclopentanone followed by destruction of the trans isomer by treatment with base according to Drefahl, *et al.*[11] (Scheme I).

(5) S. Greenberg and J. G. Moffatt, Abstracts, 155th National Meeting of the American Chemical Society, San Francisco, Calif., 1968, No. C-54.

(6) Papers in preparation by S. Greenberg, A. F. Russell, T. C. Jain, E. H. Hamamura, M. Prystasz, J. P. H. Verheyden, and J. G. Moffatt.

(7) E. M. Filachione, J. H. Lengel, and C. H. Fisher, *J. Amer. Chem. Soc.*, 68, 330 (1946).

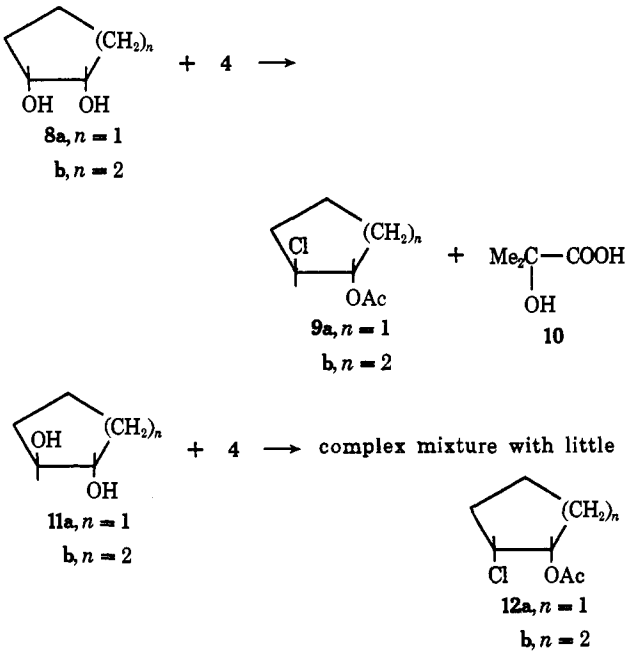
(8) M. Schulz and P. Berlin, *Angew. Chem., Int. Ed. Engl.*, 6, 950 (1967).

(9) Prepared by the wet Prevost reaction on cyclopentene according to K. B. Wiberg and K. A. Saegebarth, *J. Amer. Chem. Soc.*, 79, 6256 (1957), and shown to be free of the trans isomer by vpc on a column of 5% Chromosorb 20M at 150°.

(10) L. N. Owen and P. N. Smith, *J. Chem. Soc.*, 4026 (1952).

(11) G. Drefahl, G. Heublein, and B. Noll, *J. Prakt. Chem.*, 21, 208 (1963).

Scheme I



On the other hand, the reaction of 98.8% pure *trans*-cyclopentane-1,2-diol (**11a**)[10] with **4** was studied in several solvents and in each case gave at least ten products by vpc examination following removal of acidic by-products. Where ether was used as the solvent the formation of only 1.6% of the trans chloroacetate (**9a**) and none of its cis isomer (**12a**) was observed. In acetonitrile up to 10% of the trans chloroacetate (**9a**) was formed with less than 0.2% of the cis isomer.

In a very similar way the reaction of **4** with 99.5% pure *cis*-cyclohexane-1,2-diol (**8b**)[12] gave almost exclusively (>95%) a product that was identical with authentic *trans*-2-chlorocyclohexyl acetate (**9b**)[13] but different from the corresponding cis isomer (**12b**).[13] Once again, the corresponding reactions of **4** with 99.7% pure *trans*-cyclohexane-1,2-diol (**11b**) in different solvents gave at least 11 products. Amongst these the trans chloroacetate (**9b**) was maximally present to an extent of 15% and there was no observable cis isomer. The infrared spectrum of the mixed products arising from the trans diols (**11a,b**) was rich in ester and dioxolanone bands, and preliminary identification of some of the major products has been made through gc–mass spectrometry. These studies have shown the presence of various permutations of acetyl and 2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl derivatives of the parent diols with unknown stereochemistry. The presence of dioxolanone ethers is immediately apparent from the appearance of intense fragments at *m/e* 59, 101, and 129 in the mass spectra. In addition to **9a** and **9b** the only significant chlorine-containing products were apparently 2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl derivatives of the chlorocycloalkanols, but an understanding of the exact nature and mode of formation of these substances must await further work.

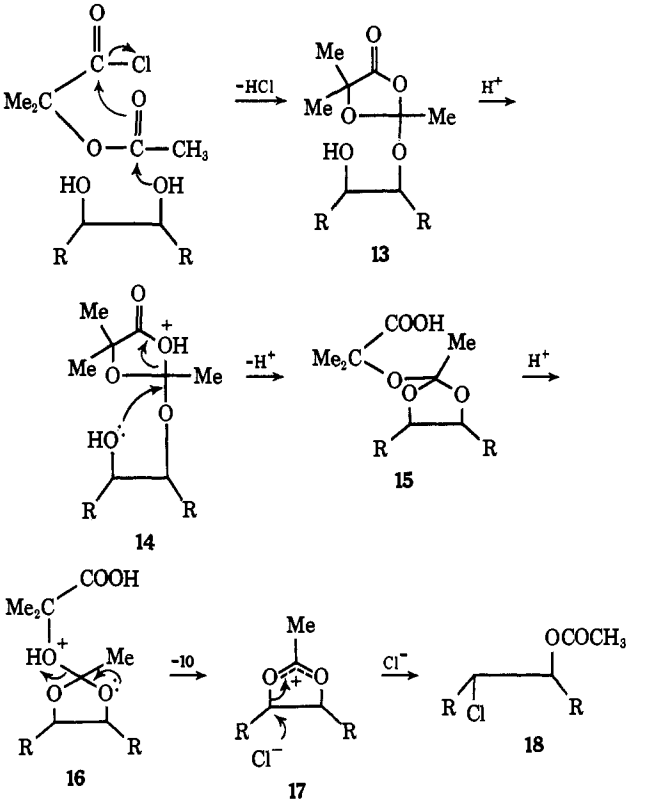
From the above results it is clear that, contrary to the conclusions of Mattocks, the formation of chloroacetates is characteristic of only cis diols and proceeds with inversion of configuration of one of the centers.

(12) Obtained from Frinton Laboratories, S. Vineland, N. J.

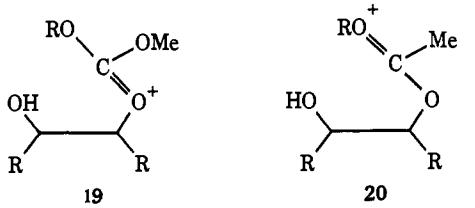
(13) S. Winstein, E. Grunwald, R. E. Buckles, and C. Hanson, *J. Amer. Chem. Soc.*, 70, 816 (1948).

The products arising from trans diols appear to be mainly simple esters and dioxolanones and contain only minor amounts of chloroacetates. On the basis of these results we propose a mechanism for the formation of chloroacetates involving the intermediate formation of acetoxonium ions as follows in Scheme II.

Scheme II



This mechanism involves initial formation of the hydroxy dioxolanone (**13**) (*cf.* isolated alcohols) followed by acid-catalyzed rearrangement involving the cis hydroxyl group to give the carboxyl substituted orthoester (**15**). In its protonated form (**16**) the latter can collapse to the acetoxonium ion (**17**) which is opened by chloride ion to the trans chloroacetate (**18**). The conversion of cyclic orthoesters to acetoxonium ions in the presence of boron trifluoride has been described by Meerwein.[14] Only protonation of the exocyclic oxygen will lead to **17**, protonation of the ring oxygens giving acyclic oxonium ions (**19,20**) that will recyclize to protonated **15**.

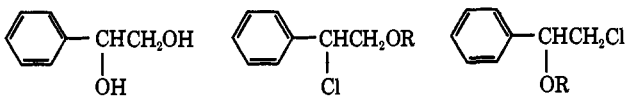


In the cyclopentane series a cyclic acetoxonium ion (**17**) can only be accommodated with cis stereochemistry. It has also been concluded that only cis-fused acyloxonium ions participate significantly in solvolysis reac-

(14) For reviews on the chemistry of orthoesters and oxonium salts, see H. Meerwein in Houben-Weyl, "Methoden der organischen Chemie," 4th ed, Vol. VI, Part 3, 1965, pp 295, 325; R. H. De Wolfe, "Carboxylic Ortho Acid Derivatives," Academic Press, New York, N. Y., 1970.

tions.[15] It is accordingly quite to be expected that, while cis diols lead cleanly to trans chloroacetates, trans diols lead to a multiplicity of products containing dioxolanyl and acetyl functions. It is significant to note that the minor amounts of chloroacetates that do arise from the trans diols (**11a,b**) retain the trans configuration. They therefore arise by a different, and as yet unexplained, mechanism. Quite compelling evidence will be provided later in this paper for the intervention of acetoxonium ions in the reactions of cis diols.

Mattocks has shown that the reaction of **2** with propane-1,2-diol gave almost exclusively 3-chloropropyl acetate with replacement of only the primary hydroxyl group by halide.[3] This, and the experiments above, show that under normal conditions the regio- and stereospecificity of the reaction is controlled mainly by steric factors. In the presence of other functionalities, however, electronic factors can assume a dominant role. Thus, the reaction of *dl*-1-phenylethane-1,2-diol (**21**) with **4** gave a single product which was isolated in 75% yield and shown by vpc and nmr to be identical with 2-chloro-2-phenylethyl acetate (**22b**) prepared by acetylation of 2-chloro-2-phenylethanol (**22a**)[16] according to Summerbell and Kland-English.[17] The product was clearly different by both vpc and nmr analysis from the isomeric 2-chloro-1-phenylethyl acetate (**23b**) prepared by acetylation of 2-chloro-1-phenylethanol (**23a**)[18] according to Sumrell, *et al.*[19]

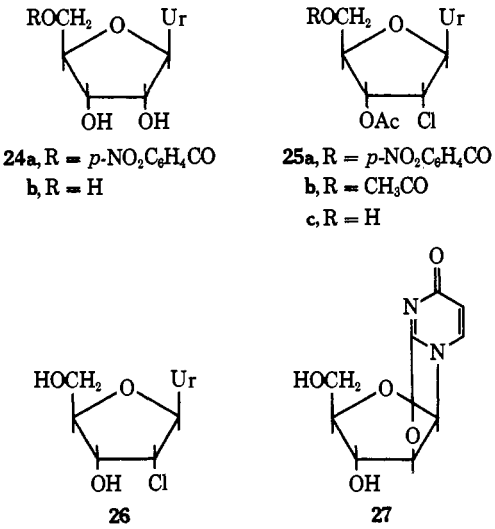


21 **22a**, R = H; **b**, R = Ac **23a**, R = H; **b**, R = Ac

Clearly, in the presence of neighboring substituents such as the phenyl ring, which can stabilize the positive charge of the acetoxonium ion in the form of an α-acetoxy carbonium ion, the normal tendency toward nucleophilic attack at the less hindered carbon can be reversed.

We then turned to the reactions of **4** with ribonucleosides, and in order to minimize potential side reactions with amino groups on the hetereocyclic rings, chose uridine as our initial target. In order to isolate the 2′,3′-diol function we first prepared 5′-*O*-nitrobenzoyluridine (**24a**) by hydrolysis of the known 2′3′-*O*-isopropylidene-5′-*O*-*p*-nitrobenzoyluridine[20] with 80% acetic acid. The resulting crystalline product (**24a**) was heated at 100° for 45 min with 4 molar equiv of **4** without added solvent. Direct crystallization of the extracted residue gave a pure halogenated nucleoside derivative in 84% yield. The nmr spectrum of this compound showed the presence of both acetyl and *p*-nitrobenzoyl groups and strongly suggested that the 3′-hydroxyl group was acylated since $C_{3'}H$ appeared at lower field (5.91 ppm) than did $C_{2'}H$ (5.55 ppm). The assignments were obvious from first-order analysis and were confirmed by spin-decoupling studies. Deacylation of the compound using methanolic sodium methoxide led to a single nucleoside that was isolated in crystalline form and shown to be identical in every way with an authentic sample of 2′-chloro-2′-deoxyuridine (**26**) prepared by an unequivocal route.[1,21] The reaction product was therefore shown to be 3′-*O*-acetyl-2′-chloro-2′-deoxy-5′-*O*-*p*-nitrobenzoyluridine (**25a**), a conclusion that was fully supported by further reactions in the uridine series.

The configuration of the chloro function was confirmed by the ready conversion in 74% yield of **26** into crystalline O^2,2′-cyclouridine (**27**) upon reaction with



24a, R = *p*-$NO_2C_6H_4CO$; **b**, R = H **25a**, R = *p*-$NO_2C_6H_4CO$; **b**, R = CH_3CO; **c**, R = H

26 **27**

potassium *tert*-butoxide in dimethylformamide according to Codington, *et al.*[22] The reaction thus proceeded with apparently exclusive introduction of the chlorine at the 2′ position and, unlike the reaction with *cis*-cyclopentane-1,2-diol, with overall retention of configuration. This can be readily explained by a rapid intramolecular participation of the C_2-carbonyl group of the uracil ring with the initial acetoxonium ion (**28**) giving the protonated 3′-*O*-acetyl-O^2,2′-cyclouridine (**29**) which is then opened once again by chloride ion giving the observed product (**25**) possessing the ribo configuration. Participation of the pyrimidine ring in other halogenation reactions involving positively charged functions at the 2′ and/or 3′ positions of the sugar has previously been noted[1,23] and the acid catalyzed opening of O^2,2′-cyclouridine (**23**) to to give **26** is a well-documented process.[21] Experiments to be reported later in this paper provide sound evidence for the participation of both **28** and **29** in this sequence (eq 3).

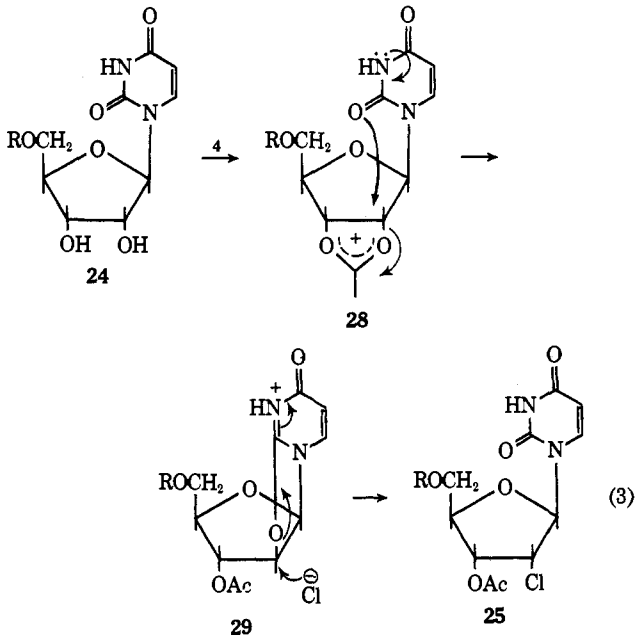
Since the reaction of primary hydroxyl groups with **4** leads only to readily removable dioxolanones (*e.g.*, **6**) or esters (*e.g.*, **7**), we next turned to the reactions of unprotected uridine. The reaction of uridine (**24**, R = H) with **4** has been examined in a variety of differ-

(15) B. Capon, *Quart. Rev., Chem. Soc.*, 18, 45 (1964).
(16) H. Bodot, E. Dieuzeide, and J. Jullien, *Bull. Soc. Chim. Fr.*, 1086 (1960).
(17) R. K. Summerbell and M. J. Kland-English, *J. Amer. Chem. Soc.*, 77, 5095 (1955).
(18) G. Sumrell, B. M. Wyman, R. G. Howell, and M. C. Harvey, *Can. J. Chem.*, **42**, 2896 (1964).
(19) G. Sumrell, R. G. Howell, B. M. Wyman, and M. C. Harvey, *J. Org. Chem.*, **30**, 84 (1965).
(20) J. P. Coat, S. David, and J. C. Fischer, *Bull. Soc. Chim. Fr.*, 2489 (1965).
(21) J. F. Codington, I. L. Doerr, and J. J. Fox, *J. Org. Chem.*, **29**, 558 (1964).
(22) J. F. Codington, I. L. Doerr, and J. J. Fox, *J. Org. Chem.*, **29**, 564 (1964).
(23) See, *e.g.*, (a) J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, **35**, 2868 (1970); (b) M. M. Ponpipom and S. Hanessian, *Can. J. Chem.*, **50**, 246, 253 (1972).

Table I. Nmr Chemical Shifts for Uridine Derivatives at 100 MHz

Compd	Solvent[a]	$C_{1'}H$	$C_{2'}H$	$C_{3'}H$	$C_{4'}H$	$C_{5'}H_a$	$C_{5'}H_b$	C_5H	C_6H	Other
24a	P	6.52 (d)	4.82 (m)	4.78 (m)	4.8 (m)	4.95 (m)		5.76 (d)	7.83 (d)	8.20 (s, 4, Ar)
25a	P	6.42 (d)	5.55 (dd)	5.91 (dd)	4.69 (dt)	4.92 (m)		5.80 (d)	7.81 (d)	2.09 (s, 3, OAc), 8.19 and 8.28 (d, 2, J_o = 8 Hz, arom.)
25b	C	6.11 (d)	4.69 (dd)	5.28 (dd)	4.42 (m)	4.42 (br s)		5.82 (d)	7.53 (d)	2.12 and 2.16 (s, 3, OAc)
25c	P	6.73 (d)	5.22 (dd)	5.80 (dd)	4.43 (m)	3.98 (dd)	4.14 (dd)	5.74 (d)	8.24 (d)	2.04 (s, 3, OAc)
26	D	5.96 (d)	4.49 (dd)	4.17 (m)	3.91 (m)	3.60 (br s)		5.61 (d)	7.86 (d)	5.16 (br s, 5'OH), 5.77 (d, $J_{H,OH}$ = 5 Hz, $C_{3'}$–OH), 11.3 (br s, 1, NH)
29 (R = H) (free base)	D[d]	6.33 (d)	5.41 (d)	5.30 (d)	4.28 (dt)	3.26 (dd)	4.44 (dd)	5.81 (d)	7.78 (d)	2.08 (s, 3, OAc), 5.06 (t, 1, $J_{H,OH}$ = 4.5 Hz, $C_{5'}$–OH)
30	C	6.12 (d)	4.52 (dd)	5.18 (dd)	4.43 (m)	4.43 (m)		5.79 (d)	7.54 (d)	1.57 (s, 6, CMe_2), 2.04 and 2.17 (s, 3, OAc)
31	C	6.16 and 6.20 (d)[e]	4.46 (dd)	5.3 (m)	4.36 (m)	3.81 (dd)	3.88 (dd)	5.74 and 5.77 (d)[e]	7.56 (d)	1.52 and 1.56 (s, 3, CMe_2), 1.78 (s, 3, $MeCO_3$), 2.18 (s, 3, OAc)
33	C	6.14 and 6.20 (d)[e]	5.3 (m)	5.3 (m)	4.31 (m)	3.79 (m)	3.92 (dd)	5.75 and 5.78[e]	7.54 and 7.56[e]	1.52 and 1.56 (s, 3, CMe_2), 1.79 (s, 3, CO_3Me), 2.08 and 2.14 (s, 3, OAc)
34	C	6.29 (d)	5.41 (d)	5.39 (s)	4.40 (m)	3.6 (m)		5.96 and 5.98[e]	7.32 and 7.34[e]	2.14 (s, 3, OAc), 1.59 (s, 3, $MeCO_3$), 1.41, 1.45 and 1.99 (s, total 6, CMe_2)[e]
35	P	6.41 (d)	5.06 (d)	5.07 (s)	4.56 (m)	3.96 (dd)	4.12 (dd)	5.72 (d)	8.02 (d)	1.45 (d, 3, J = 5 Hz, CH_3), 5.24 (q, 1, O_2CHCH_3)

[a] Solvents are designated: C ($CDCl_3$); D (DMSO-d_6); P (pyridine-d_5). [b] Virtual coupling to $C_{3'}H$. [c] Two isomers due to the chiral dioxolanone grouping. [d] The spectrum of the hydrochloride was similar except for small shifts of $C_{1'}H$, $C_{2'}H$, C_5H, and C_6H. [e] Typical of dioxolane groups in a variety of O^2,2'-cyclonucleosides we have examined,[6] the methyl signals are atypical and temperature dependent.



ent solvents and generally leads to one major and several minor products. The nature of the major product is, however, strikingly solvent dependent, the major product from the reaction in, for example, nitromethane being only a minor product in the comparable reaction using acetonitrile. The various products have, unfortunately, very similar chromatographic mobilities and clean separations on more than a small scale are difficult and wasteful. The reaction of uridine with **4** in the absence of any solvent proceeded rapidly at 100° with copious evolution of hydrogen chloride. Chromatography of the reaction product on a column of silicic acid followed by further purification of some overlapping fractions by preparative tlc permitted isolation of the major product as a syrup in 71% yield. The product had an ultraviolet spectrum typical of uridine and treatment of the crude reaction mixture with methanolic sodium methoxide gave crystalline 2'-chloro-2'-deoxyuridine (**26**) in 73% yield. By elemental analysis, nmr (see Tables I and II) and infrared spectroscopy, the major product was clearly shown to be 5'-*O*-(2-acetoxyisobutyryl)-3'-*O*-acetyl-2'-chloro-2'-deoxyuridine (**30**). The nature of the 5' substituent was apparent from the *gem*-dimethyl group as a 6-proton singlet at 1.57 ppm (*cf.* **31** below), and by the appearance of only typical ester bands (1740 cm^{-1}) in the infrared spectrum. The minor, more polar product of this reaction was still a mixture by tlc and nmr and was not examined further.

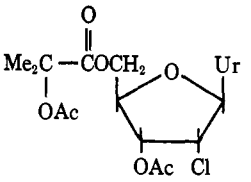
Table II. Spin–Spin Coupling Constants (Hz)

Compd	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'a}$	$J_{4',5'b}$	$J_{5'a,5'b}$	$J_{5,6}$
24a	3	*a*	*a*	*a*	*a*	*a*	8
25a	5	6	6	4	...	...	8
25b	5	5	5	0	0	0	8
25c	6.5	5	3	2	2	12	8
26	5.5	5	5	~3	~3	...	8
29 (R = H) (free base)	6	0	1	4	4	12	7.5
30	5.5	5.5	5.5	*a*	*a*	...	8
31	5.5	5.5	4	2.5	2.5	9	8
33	5	*a*	*a*	*a*	2.5	10.5	8
34	6	0	0	*a*	*a*	*a*	8
35	1.5	0	0	4	3	12	8

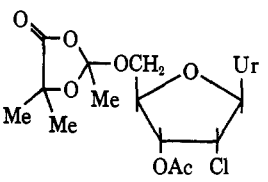
[a] Not resolved.

The reaction of uridine with **4** in acetonitrile was also rapid at 80° and led to a major product with a polarity just slightly less than that of **30**. Preparative tlc using multiple developments with chloroform–

methanol (97:3) led to the isolation of the homogeneous major product in a yield of 74%. This product proved to be isomeric with **30** and could also be converted in high yield to **26** with methanolic sodium methoxide. It was identified as 3′-*O*-acetyl-2′-chloro-2′-deoxy-5′-*O*-(2,5,5-trimethyldioxolan-4-on-2-yl)uridine (**31**) by the



30



31

presence of an intense peak at 1810 cm^{-1} in its infrared spectrum and by its nmr spectrum, which showed the typical features of a dioxolanone group (nonequivalent *gem*-dimethyl groups, and a 3-proton singlet at 1.78 ppm). In addition, the presence of a new chiral center in the dioxolanone grouping leads to double signals for both the C_5 and $C_{1'}$ protons. The minor products of this reaction were once again still mixtures and were not examined further. Brief treatment of the crude reaction product from the acetonitrile reaction with 0.1 *M* methanolic hydrogen chloride at room temperature led to cleavage of the dioxolanone group and direct crystallization of 3′-*O*-acetyl-2′-chloro-2′-deoxyuridine (**25c**) from the reaction mixture in an overall yield of 59% from uridine. No effort was made to increase this yield by chromatography of the mother liquors.

In summary, it appears that the dioxolanone **31** is the principal product from reactions of uridine with **4** in acetonitrile, dimethylformamide (DMF), ethyl acetate, dioxane, and butyrolactone. On the other hand, the corresponding reactions without solvent or in nitromethane lead to the 5′-acetoxyisobutyrate (**30**). An immediate explanation of these solvent effects is lacking.

The reaction of uridine and **4** in glacial acetic acid at 100° led to an essentially single product. This substance could be isolated in almost quantitative yield, and the crude product could be shown to be at least 95% pure by tlc and nmr analysis. Crystallization of this material proved to be very slow but the product was identical in every way with an authentic sample of 3′,5′-di-*O*-acetyl-2′-chloro-2′-deoxyuridine (**25b**) prepared by two different routes.[1,24] It is not clear whether the 5′-*O*-acetyl group arises *via* direct, acid-catalyzed acetylation[25] or by acetolysis of the intermediate dioxolanone (**31**) by several possible mechanisms. The first route seems more likely, however, since treatment at room temperature of **31** with glacial acetic acid containing 0.5 *N* hydrogen chloride led almost exclusively to the formation of **25c** and to very little **25b**.

Several types of experiments with uridine have lent considerable support to the various reaction mechanisms proposed in this paper. Thus, a suspension of uridine and **4** in nitromethane was heated under reflux for 2 min at which time a clear solution resulted. Upon cooling, the reaction mixture deposited a crystalline substance with the typical acidic ultraviolet spectrum of an O^2,2′-cyclouridine derivative. This compound was readily shown to be the hydrochloride of O^2,2′-anhydro-1-(3′-*O*-acetyl-β-D-arabinofuranosyl)-uracil (**29**, R = H) from which the free base was obtained in 73% yield upon chromatography on silicic acid. The structure of **29** (R = H) was apparent from its ultraviolet spectrum and the presence of an acetyl group in its nmr spectrum. Location of the acetyl group at $C_{3'}$ was shown by the downfield position of $C_{3'}$H and by the presence of a free 5′-hydroxyl group which appeared as a triplet at 5.06 ppm in DMSO-d_6. The isolation of this compound in quite high yield clearly confirms the intermediacy of an O^2,2′-cyclonucleoside in the formation of 2′-chloronucleosides with the ribo configuration. It is also clear that, at least in nitromethane, reaction of **4** with the cis-diol function precedes that with the 5′-hydroxyl group.

Further information was available from the results of relatively short term reaction of uridine with **4** in DMF at room temperature. The choice of DMF as the solvent for these reactions was based mainly upon the fact that uridine itself is soluble in it at room temperature. A series of reactions were set up between uridine and 3 molar equiv of **4** in DMF, and after periods of 10 min, 30 min, 1 hr, and 2 hr at room temperature the reactions were quenched by partitioning between chloroform and aqueous sodium bicarbonate. Examination of the organic phase (which contained the vast majority of the ultraviolet absorbing products) by tlc revealed that the 10-min reaction contained a major product with an R_f of roughly 0.5 in chloroform–methanol (9:1) together with a more polar substance and lesser amount of two nonpolar spots. As the reaction proceeded this major spot diminished in intensity, being replaced by the more polar substance and, to a minor degree, by the fast moving substances. By use of less polar solvent systems it could be shown that the principal nonpolar substance was **31** identical with the product obtained in hot DMF. Preparative tlc of the ethyl acetate soluble portion of the 10-min reaction mixture[26] gave a chromatographically homogeneous substance, the nmr spectrum of which showed the presence of a dioxolanone grouping. In addition, there were three acetyl singlets totaling 3 protons and multiple signals for C_6H, C_5H, and $C_{1'}$H. In spite of this, the compound gave a satisfactory elemental analysis consistent with its being a mixture of 2′- and 3′-*O*-acetyl-5′-*O*-(2,5,5-trimethyldioxolan-4-on-2-yl)uridine (**32**). In support of this assignment it was shown that brief treatment with methanolic hydrogen chloride converted **32** into a material that was chromatographically identical with 2′(3′)-*O*-acetyluridine[27] together with a little uridine, whereas hydrolysis with ammonia gave only uridine, the ribo configuration being confirmed by borate electrophoresis.[28] Acetylation of **32** gave the analytically pure 2′,3′-di-*O*-acetate (**33**) in 90% yield. As expected, the nmr spectrum of **33** now showed only two sharp 3-proton acetyl singlets and the signals for

(24) I. L. Doerr and J. J. Fox, *J. Org. Chem.*, 32, 1462 (1967).

(25) Acetylation of uridine through heating with glacial acetic acid has been described by Codington, *et al.*,[21] and has been confirmed by us in the presence of hydrogen chloride.

(26) The use of ethyl acetate almost completely eliminates the polar product which is found in the aqueous phase but can be extracted into chloroform.

(27) H. P. M. Fromageot, B. E. Griffin, C. B. Reese, and J. E. Sulston, *Tetrahedron*, 23, 2315 (1967).

(28) J. F. Codington, R. Fecher, and J. J. Fox, *J. Amer. Chem. Soc.*, 82, 2794 (1960).

$C_{1'}H$, C_5H, and C_6H all became sharp although each still occurred as pairs of signals due to the chirality of the dioxolanone group.

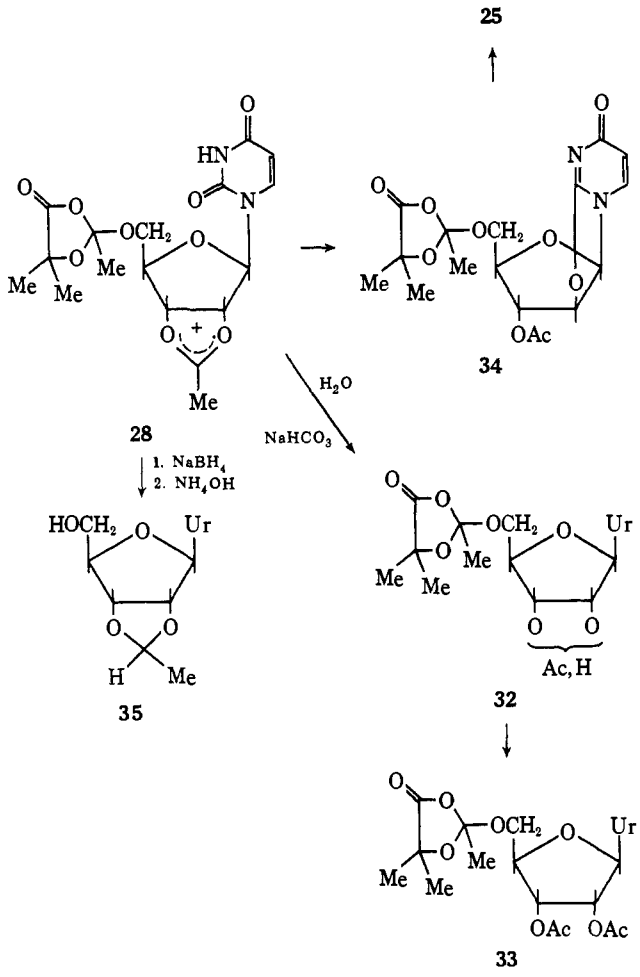
We interpret the formation of the two isomeric monoacetates (**32**) as being due to the accumulation of the acetoxonium ion (**28**) which is quenched by sodium bicarbonate before it can undergo attack by the C_2-carbonyl group to give the 3′-*O*-acetyl-O^2,2′-cyclonucleoside (**29**). It is well known that the quenching of acyloxonium ions with water leads to mixtures of cis hydroxy acetates.[29]

A similar work-up of the reaction mixture after 2 hr in DMF at room temperature still gave some **32** and increased amounts of fast moving chlorinated products (**31**) soluble in ethyl acetate. Extraction of the aqueous phases with chloroform, however, recovered a 43% yield of crystalline O^2,2′-anhydro-1-[3′-*O*-acetyl-5′-*O*-(2,5,5-trimethyldioxolan-4-on-2-yl)-β-D-arabinofuranosyl]uracil (**34**). The structure of **34** was apparent from its ultraviolet and nmr spectra and, as expected, selective removal of the dioxolanone group by brief treatment with 0.1 *M* methanolic hydrogen chloride gave in 84% yield the crystalline hydrochloride of O^2,2′-anhydro-1-(3′-*O*-acetyl-β-D-arabinofuranosyl)uracil (**29**, R = H) identical with a sample prepared as above.

Final confirmation of the intermediacy of a 2′,3′-acetoxonium ion came from a direct trapping of this species. Thus a reaction of uridine with **4** in DMF at room temperature for 10 min as above was directly treated with an excess of sodium borohydride. Acetyl and dioxolanone groups were then removed with methanolic ammonium hydroxide giving a mixture of four substances, three of which (uridine, 2′-chloro-2′-deoxyuridine, and an unidentified compound) were also present in an identical reaction omitting the borohydride step. Isolation of the unique product by preparative tlc gave crystalline 2′,3′-*O*-ethylideneuridine (**35**) in an overall yield of 16%. The nmr spectrum of **35** showed it to be a roughly 2:1 mixture of two diastereoisomers due to the chiral nature of the acetal function. A preparation of **35** has recently been described by Zemlicka[30] *via* reaction of uridine with dioxane and acetonitrile containing hydrogen chloride. This compound can also be conveniently prepared by direct condensation of uridine with acetaldehyde in the presence of a trace of perchloric acid at room temperature for 45 min. As obtained in this fashion **35** was a single diastereoisomer with properties similar to those described by Zemlicka and showing nmr signals identical with those of the major isomer obtained by borohydride reduction. Clearly, in the presence of excess acetaldehyde **35** can undergo acid-catalyzed equilibration leading to the most stable diastereoisomer while borohydride reduction of the acetoxonium ion is irreversible and leads to a mixture of isomers. While the yield of crystalline **35** was not high due, at least in part, to the complexity of the mixture undergoing borohydride reduction, the isolation of this substance must be considered as compelling evidence for the intermediacy of an acetoxonium ion. The overall scheme for the above reactions follows (Scheme III).

(29) L. Goodman, *Advan. Carbohyd. Chem.*, 22, 109 (1967).
(30) J. Zemlicka, *J. Org. Chem.*, 36, 2383 (1971).

Scheme III



The work described in this paper demonstrates the utility of 2-acetoxyisobutyryl chloride as a reagent for the selective 2′-chlorination of uridine derivatives. Subsequent publications will describe the reactions of this reagent with many other ribonucleosides as well as the use of the corresponding acyl bromide for the facile conversion of ribonucleosides into various deoxynucleosides *via* hydrogenation of the intermediate bromo compounds.

Experimental Section

General Methods. Thin layer chromatography was done on 0.25-mm layers of Merck silica gel GF and preparative tlc on 20 × 100 cm glass plates coated with a 1.3-mm layer of Merck silica gel HF. Spots were detected by ultraviolet examination or by spraying with a 5% solution of ammonium molybdate followed by brief heating at 150°. Nmr spectra were obtained using Varian A-60 and HA-100 spectrometers and are reported in ppm downfield of an internal standard of tetramethylsilane. Vapor phase chromatography (vpc) was done on a Hewlett-Packard Model 402 instrument and vpc coupled mass spectrometry using a Varian MAT CH-7 G-C mass spectrometer. We are grateful to Dr. M. L. Maddox, Dr. J. Murphy, and Mrs. J. Nelson for their help with nmr determinations, and to Dr. L. Tökés, and Mr. B. Amos for mass spectrometry.

Elemental analyses were obtained by Dr. A. Bernhardt, Mulheim, Germany, and other instrumental analyses are by the staff of the Analytical Laboratories of Syntex Research.

2-Acetoxyisobutyryl Chloride (4). Acetyl chloride (2.0 kg, 25.5 mol) was added slowly with stirring and ice cooling to 2-hydroxyisobutyric acid (1.0 kg, 9.6 mol). After gas evolution had ceased, the mixture was heated under reflux for 2 hr and then excess acetyl chloride was removed by distillation at 25-mm pressure. Thionyl chloride (1 kg, 8.40 mol) was then added to the residue and the resulting solution was heated at a bath temperature of 100° for 2

hr. The product was then distilled *in vacuo* giving 1169 g (84.6%) of 2-acetoxyisobutyryl chloride: bp 55–56° (6 mm); $n^{25}D$ 1.4278; ν_{max} (film) 1810, 1750 cm^{-1}; nmr ($CDCl_3$) 1.61 ppm (s, 6, CMe_2), 2.11 (s, 3, OAc).[31]

Anal. Calcd for $C_6H_9O_3Cl$ (164.58): C, 43.78; H, 5.51; Cl, 21.54. Found: C, 43.88; H, 5.57; Cl, 21.34.

Reactions of 2-Acetoxyisobutyryl Chloride with *p*-Nitrobenzyl Alcohol. (a) With Limited Base. 2-Acetoxyisobutyryl chloride (3.29 g, 20 mmol) was added to a solution of *p*-nitrobenzyl alcohol (1.53 g, 10 mmol) and triethylamine (0.45 ml, 30 mmol) in anhydrous acetonitrile (5 ml). After 1.5 hr at room temperature the solvent was evaporated *in vacuo* and the residue was dissolved in ether, washed thoroughly with aqueous sodium bicarbonate, dried, and evaporated. The resulting yellow oil (2.70 g) was purified on four preparative tlc plates using chloroform giving 2.35 g (84%) of **6a** as a pale yellow syrup: λ_{max}^{MeOH} 247 nm (ϵ 11,300); ν_{max} (film) 1805, 1740, 1615, 1525, 1370 cm^{-1}; nmr ($CDCl_3$) 1.55 and 1.58 (s, 3, CMe_2), 1.83 (s, 3, $MeCO_3$), 4.73 (s, 2, $ArCH_2O$), 7.50 and 8.22 (d, 2, J_o = 8 Hz, Ar).

Anal. Calcd for $C_{13}H_{15}NO_6$ (281.26): C, 55.51; H, 5.38; N, 4.98. Found: C, 55.14; H, 5.44; N, 5.25.

(b) Without Base. A reaction as above except that the triethylamine was omitted was worked up after 30 min. Preparative tlc using chloroform–hexane (7:3) gave a major product (1.43 g, 51%) identical with **6a** above. In addition, there were smaller amounts of a more polar product (**7**, see below) and a fast band. Elution of the latter gave 0.43 g (25%) of crystalline *p*-nitrobenzyl chloride with mp 72.5–73° after recrystallization from hexane. This material was identical with an authentic sample by melting point and infrared and nmr spectroscopy.

(c) In Triethylamine. A solution of *p*-nitrobenzyl alcohol (0.77 g, 5 mmol) and **4** (0.90 g, 5.5 mmol) in triethylamine (5 ml) was kept for 1 hr at 23° and then evaporated *in vacuo*. A solution of the residue in ether was carefully extracted with aqueous bicarbonate, dried, and purified by preparative tlc using two developments with chloroform. Elution of the major band and crystallization from hexane gave 0.66 g (47%) of *p*-nitrobenzyl 2-acetoxyisobutyrate (**7**) with mp 54.5–55.5°; λ_{max}^{MeOH} 265 nm (ϵ 10,700); ν_{max} (KBr) 1735, 1610, 1525, 1345 cm^{-1}; nmr ($CDCl_3$) 1.59 (s, 6, CMe_2), 2.05 (s, 3, OAc), 5.28 (s, 2, $ArCH_2O$), 7.53 and 8.25 (d, 2, J_o = 8 Hz, Ar).

Anal. Calcd for $C_{13}H_{15}NO_6$ (281.26): C, 55.51; H, 5.38; N, 4.98. Found: C, 55.63; H, 5.46; N, 5.10.

2-Cyclohexyloxy-2,5,5-trimethyl-1,3-dioxolan-4-one (6b). A solution of cyclohexanol (1.0 g, 10 mmol) and **4** (3.28 g, 20 mmol) in ether (10 ml) was kept overnight at room temperature. It was diluted with ethyl acetate and carefully extracted twice with saturated aqueous sodium bicarbonate and then water, dried, and evaporated. The residue was distilled giving 1.25 g (55%) of **6b**: bp 87–89° (1 mm); ν_{max} (film) 1800 cm^{-1}; nmr ($CDCl_3$) 1.47 and 1.53 ppm (s, 3, CMe_2), 1.69 (s, 3, $MeCO_3$), 1.0–2.0 (m, 10, cyclohexyl), 3.65 (m, 1, CHO).

Anal. Calcd for $C_{12}H_{20}O_4$ (228.28): C, 63.14; H, 8.83. Found: C, 63.70; H, 9.20.

2-Benzyloxy-2,5,5-trimethyl-1,3-dioxolan-4-one (6c). A reaction between benzyl alcohol (1.08 g, 10 mmol) and **4** (1.80 g, 11 mmol) in ether (5 ml) at room temperature for 1 hr was worked up as above giving 1.0 g (42%) of **6c**: bp 100° (1 mm); ν_{max} (film) 1800 cm^{-1}; nmr ($CDCl_3$) 1.52 and 1.58 ppm (s, 3, CMe_2), 1.77 (s, 3, $MeCO_3$), 4.48 and 4.70 (d, 1, J_{gem} = 11 Hz, $ArCH_2O$), 7.32 (s, 5, Ar).

Anal. Calcd for $C_{13}H_{16}O_4$ (236.26): C, 66.08; H, 6.83. Found: C, 65.63; H, 6.62.

Reaction of 4 with 1-Phenylethane-1,2-diol (21). A solution of **21** (1.38 g, 10 mmol) and **4** (1.81 g, 11 mmol) in ether (10 ml) was kept at room temperature for 16 hr and then washed carefully with aqueous sodium bicarbonate. Distillation of the ether soluble material gave 1.48 g (75%) of 2-chloro-2-phenylethyl acetate (**22b**) with bp 105–108° (2 mm) (reported[17] bp 105–110° (3 mm): $n^{26}D$ 1.5156; ν_{max} (film) 1740, 1240 cm^{-1}; nmr ($CDCl_3$) 2.02 ppm (s, 3, OAc), 4.42 (d, 2, J = 7 Hz, CH_2OAc), 5.07 (t, 1, J = 7 Hz, Ar-CHCl), 7.33 (s, 5, Ar).

Anal. Calcd for $C_{10}H_{11}ClO_2$ (198.65): C, 60.46; H, 5.58; Cl, 17.85. Found: C, 60.32; H, 5.70; Cl, 17.73.

The nmr spectrum above is identical with that of **22b** prepared by a different route[17] and clearly different from that of 2-chloro-1-phenylethyl acetate (**23b**).[19] The latter compound showed nmr ($CDCl_3$) 2.12 (s, 3, OAc), 3.77 (d, 2, J = 7 Hz, CH_2Cl), 6.00 (t, 1, J = 7 Hz, ArCHOAc), 7.37 (s, 5, Ar). The two compounds were also clearly separated by vpc on a column of 10% NPGS on Gas-Chrom Q[32] at 103°.

Reaction of *cis*-Cyclopentane-1,2-diol (8a) with 4. A solution of crystalline *cis*-cyclopentane-1,2-diol[9] (1.17 g, 11.5 mmol) in 5 ml of alcohol-free chloroform (5 ml) was added dropwise with cooling to a solution of **4** (2.27 g, 13.8 mmol) in chloroform. After 15 min at room temperature the solution was thoroughly extracted with aqueous sodium bicarbonate and then with water, dried ($MgSO_4$), and evaporated. The residue was distilled giving 1.22 g (65%) of *trans*-2-chlorocyclopentyl acetate (**9a**): bp 70–73° (9 mm) (reported[10] bp 83° (15 mm)); $n^{27}D$ 1.4510; ν_{max} (film) 1750, 1235 cm^{-1}; nmr ($CDCl_3$) 1.5–2.3 ppm (m, 6, CH_2's), 2.00 (s, 3, OAc), 4.15 (m, 1, CHCl), 5.12 (m, 1, CHOAc).

Anal. Calcd for $C_7H_{11}ClO_2$ (162.62): C, 51.70; H, 6.82; Cl, 21.80. Found: C, 51.60; H, 6.98; Cl, 21.74.

The above compound could be clearly separated from its cis isomer (**12a**)[11] by vpc on a 10% Carbowax 20M on Gas-Chrom WAW column at 120°, the trans isomer having a shorter retention time. The nmr spectrum of **12a** showed 1.5–2.2 ppm (m, 6, CH_2's), 2.06 (s, 3, OAc), 4.35 (m, 1, CHCl), 5.05 (m, 1, CHOAc).

Reaction of *trans*-Cyclopentane-1,2-diol (11a) with 4. A solution of **11a** (0.51 g, 5 mmol, 99.7% trans by glc)[10] and **4** (2.46 g, 15 mmol) in ether (5 ml) was kept at room temperature for 16 hr and then diluted with ether. This solution was carefully extracted with 10% aqueous sodium bicarbonate and then with water, dried ($MgSO_4$), and evaporated leaving 1.4 g of a colorless syrup. Examination of this material by glc using either a Carbowax 20M column programmed from 120 to 220° or a silicone SE-30 on Chromosorb W column programmed from 90 to 220° showed the presence of at least nine products. Of these only a trace component (1.6%) had the retention time of the trans chloroacetate (**9a**) and there was no indication of the cis isomer (**12a**). The nature of the major products is discussed in the text.

A reaction between **4** and **11a** exactly as above except that acetonitrile was used as the solvent gave 1.15 g of a light colored oil that was examined by glc as above. In this case the trans chloroacetate (**9a**) was present to the extent of 10%, the cis isomer (**12a**) being absent. The major products were similar to those in ether but the relative amounts were considerably different.

Reaction of *cis*-Cyclohexane-1,2-diol (8b) with 4. A solution of crystalline **8b** (0.46 g, 4 mmol, 99.5% trans by glc) and **4** (0.82 g, 5 mmol) in ether (10 ml) was stirred at room temperature for 1 hr. The solution was then diluted with ether, extracted several times with aqueous sodium bicarbonate, dried, and evaporated. Examination by vpc using the columns described above showed the presence of a single peak with a retention time identical with that of the trans chloroacetate (**9b**) and only a trace (~5%) of a by-product with a long retention time. Distillation of the residue gave 0.48 g (68%) of *trans*-2-chlorocyclohexyl acetate (**9b**) with bp 103° (15 mm) (reported[13] bp 98° (12 mm)) that was homogeneous and identical with an authentic sample by vpc, nmr, and ir: ν_{max} (film) 1750 cm^{-1}; nmr ($CDCl_3$) 1.0–2.0 ppm (m, 8, CH_2's), 2.05 (s, 3, OAc), 3.85 (m, 1, CHCl), 4.80 (m, 1, CHOAc).

Anal. Calcd for $C_8H_{13}O_2Cl$ (176.64): C, 54.39; H, 7.42; Cl, 20.07. Found: C, 54.50; H, 7.51; Cl, 19.92.

Reaction of *trans*-Cyclohexane-1,2-diol (11b) with 4. A solution of **11b** (1.16 g, 10 mmol, 99.7% trans by glc) and **4** (2.82 ml, 20 mmol) in acetonitrile was kept at room temperature for 16 hr and then worked up exactly as above giving 2.38 g of a clear syrup. Examination of this material by glc using the columns described above showed the presence of at least ten products, the major of which were tentatively identified by gc–mass spectrometry as described in the text. One peak (2–10% in different experiments) had a retention time identical with that of the trans chloroacetate (**9b**). A comparable reaction in ether gave very little **9b**.

5′-*O*-*p*-Nitrobenzoyluridine (24a). 5′-*O*-*p*-Nitrobenzoyl-2′,3′-*O*-isopropylideneuridine was prepared in 97% yield from 2′,3′-*O*-isopropylideneuridine and *p*-nitrobenzoyl chloride in pyridine. The product had mp 208–208.5° from chloroform (reported[20] mp 212°). A solution of this product (4.2 g) in 80% acetic acid (35 ml) was heated at 100° for 4 hr and then evaporated to dryness. The residue was crystallized from ethyl acetate giving 2.18 g (68%) of **24a** with mp 184–185°.

(31) *Cf.* 2-hydroxyisobutyric acid, 1.50 (s, 6, CMe_2), 7.30 (s, 2, COOH and OH) and 2-acetoxyisobutyric acid, 1.58 (s, 6, CMe_2), 2.06 (s, 3, OAc), 11.65 (s, 1, COOH).

(32) Applied Science Laboratories, State College, Pa.

Anal. Calcd for $C_{18}H_{15}N_3O_9$ (393.30): C, 48.86; H, 3.84; N, 10.68. Found: C, 49.15; H, 3.91; N, 10.51.

Reaction of 5′-*O*-*p*-Nitrobenzoyluridine (24a) with 4. A mixture of **24a** (800 mg, 2.04 mmol) and **4** (1.34 g, 8.17 mol) was heated at 100° for 45 min. The cooled mixture was then dissolved in methylene chloride, washed carefully with aqueous sodium bicarbonate, dried, and evaporated. Crystallization of the residue from chloroform gave 780 mg (84%) of 3′-*O*-acetyl-2′-chloro-2′-deoxy-5′-*O*-*p*-nitrobenzoyluridine (**25a**) with mp 197–198°. An analytical sample from ethanol had mp 197–197.5°; λ_{max}^{MeOH} 257 nm (ε 22,600).

Anal. Calcd for $C_{18}H_{16}N_3O_9Cl$ (453.79): C, 47.64; H, 3.55; N, 9.26; Cl, 7.81. Found: C, 47.20; H, 3.34; N, 9.07; Cl, 7.67.

In some experiments a hemihydrochloride of **25a** was obtained if the product was directly crystallized from chloroform. This material also has mp 197–198°.

Anal. Calcd for $C_{18}H_{16}N_3O_9Cl \cdot {}^1/_2HCl$: C, 45.79; H, 3.52; N, 8.90; Cl, 11.27. Found: C, 46.08; H, 3.34; N, 9.01; Cl, 11.18

5′-*O*-(2-Acetoxyisobutyryl)-3′-*O*-acetyl-2′-chloro-2′-deoxyuridine (30). A mixture of uridine (2.44 g, 10 mmol) and **4** (4.92 g, 30 mmol) was heated at 100° for 30 min during which time there was gas evolution (HCl) and the mixture became homogeneous. The product was dissolved in ethyl acetate, washed twice with 10% aqueous sodium bicarbonate and then water, dried ($MgSO_4$), and evaporated leaving 4.40 g of a clear syrup. This material was chromatographed on a column of silicic acid (400 g) using a gradient (2 l.) of 0 to 50% ethyl acetate in chloroform giving two main products. Further purification of some overlapping fractions was achieved by preparative tlc using benzene–ethyl acetate (1:1) and giving a total of 3.06 g (71%) of **30** as a homogeneous white froth that could not be crystallized: λ_{max}^{MeOH} 258 nm (ε 9900); ν_{max} (KBr) 1690, 1740 cm^{-1}.

Anal. Calcd for $C_{17}H_{21}N_2O_9Cl$ (432.82): C, 47.17; H, 4.89; N, 6.47; Cl, 8.19. Found: C, 47.25; H, 5.24; N, 6.45; Cl, 8.01.

The more polar product (20%) was still a mixture and was not examined further.

3′-*O*-Acetyl-2′-chloro-2′-deoxy-5′-*O*-(2,5,5-trimethyldioxolan-4-on-2-yl)uridine (31). Uridine (2.44 g, 10 mmol) and **4** (4.92 g, 30 mmol) were heated under reflux in acetonitrile (10 ml) for 30 min. The resulting clear solution was evaporated and the residue was dissolved in ethyl acetate, washed with aqueous bicarbonate and water, dried, and evaporated leaving 4.48 g of a white froth. A 0.50-g sample of this was purified by preparative tlc using multiple developments with chloroform–methanol (97:3). Elution of the faster, major band gave 0.36 g (74%) of **31** as a noncrystalline froth: λ_{max}^{MeOH} 259 nm (ε 9800); ν_{max} (KBr) 1690, 1740, 1810 cm^{-1}.

Anal. Calcd for $C_{17}H_{21}N_2O_9Cl$ (432.82): C, 47.17; H, 4.89; N, 6.47. Found: C, 46.82; H, 4.96; N, 6.25.

3′-*O*-Acetyl-2′-chloro-2′-deoxyuridine (25c). A sample of the crude extracted product during preparation of **31** above (1.0 g) was dissolved in 0.1 *M* methanolic hydrogen chloride (5 ml) and kept at room temperature for 2 hr. The mixture was cooled to complete crystallization and filtered giving 0.40 g (59% from uridine) of **25c** with mp 181–183°. An analytical sample from methanol had mp 183–184°: λ_{max}^{MeOH} 258 nm (ε 9900); $[\alpha]^{23}D$ +13.7° (*c* 0.76, MeOH).

Anal. Calcd for $C_{11}H_{13}N_2O_6Cl$ (304.69): C, 43.35; H, 4.29; N, 9.19; Cl, 11.63. Found: C, 43.39; H, 4.31; N, 9.06; Cl, 11.75.

2′-Chloro-2′-deoxyuridine (26). The crude extracted product from reaction of uridine (2.44 g) and **4** (4.92 g) without solvent as above was dissolved in 0.5 *M* methanolic sodium methoxide (50 ml) and stored at room temperature for 30 min. The solution was neutralized by rapid addition of 50 ml of Dowex 50 (H^+) resin and filtered, and the filtrate was evaporated to dryness. Crystallization of the residue from methanol gave 1.90 g (73%) of **26** with mp 206–207° (reported[21] mp 207–212°). This product was identical in all ways with a sample prepared by an alternative route.[1,21]

Similar methanolysis of **25a** and **31** gave **26** identical with that above in high yield.

O^2,2′-Anhydro-1-(β-D-arabinofuranosyl)uracil (27). A solution of **26** (750 mg) and potassium *tert*-butoxide (1.0 g) in a mixture of *tert*-butyl alcohol (20 ml) and DMF (40 ml) was heated at 100° for 2 hr. After filtration and evaporation of the solvents the residue was triturated with ether and then crystallized from methanol giving 475 mg of **27** with mp 244–245°. The material was identical in every way with an authentic sample of **27** prepared by a different route.[33]

(33) A. Hampton and A. W. Nichol, *Biochemistry*, **5**, 2076 (1966).

3′,5′-Di-*O*-acetyl-2′-chloro-2′-deoxyuridine (25b). A solution o uridine (2.44 g, 10 mmol) and **4** (4.92 g, 30 mmol) in glacial acetic acid (10 ml) was heated at 100° for 2 hr. The solvent was removed *in vacuo* and a solution of the residue was washed three times with aqueous bicarbonate, dried, and evaporated leaving 3.38 g (98%) of chromatographically and spectroscopically homogeneous **25b**. This material could be crystallized only very slowly from chloroform–hexane or 2-propanol giving **25b** with mp 128–130° (reported[24] mp 127–130°); λ_{max}^{MeOH} 257 nm (ε 9900).

Anal. Calcd $C_{13}H_{15}N_2O_7Cl$ (346.73): C, 45.03; H, 4.36; N, 8.08; Cl, 10.23. Found: C, 45.24; H, 4.54; N, 7.93; Cl, 10.07.

Treatment of **25b** with methanolic sodium methoxide gave crystalline **26** identical with that above in 83% yield. Reactylation of **26** regenerated **25b** quantitatively.

O^2,2′-Anhydro-1-(3′-*O*-acetyl-β-D-arabinofuranosyl)uracil Hydrochloride (29, R = H). A mixture of uridine (2.44 g, 10 mmol) and **4** (3.29 g, 20 mmol) in nitromethane (25 ml) was heated under reflux for 2 min, and the resulting clear solution was immediately cooled. The resulting crystals were collected and washed with ether giving 1.84 g (61%) of **29** (R = H) with a broad mp of 140–145°, unimproved by recrystallization from ethanol: λ_{max}^{MeOH} 223 nm (ε 8800), 251 mμ (ε 7800).

Anal. Calcd for $C_{11}H_{12}N_2O_6 \cdot HCl$ (304.69): C, 43.36; H, 4.30; N, 9.20; Cl, 11.64. Found: C, 43.05; H, 4.33; N, 9.04; Cl, 11.58.

O^2,2′-Anhydro-1-(3′-*O*-acetyl-β-D-arabinofuranosyl)uracil. A methanolic solution of **29** (R = H) (500 mg) was applied to a preparative tlc plate and developed with chloroform–methanol (4:1) giving a single band. Elution of this band followed by crystallization from methanol–ether gave 320 mg (73%) of the free base of **29** (R = H) with mp 202–204°: λ_{max}^{MeOH} 224 nm (ε 9400), 250 (8100).

Anal. Calcd for $C_{11}H_{12}N_2O_6$ (268.22): C, 49.25; H, 4.51; N, 10.45. Found: C, 49.09; H, 4.84; N, 10.57.

Reactions of Uridine with 4 in DMF at Room Temperature. A solution of uridine (2.44 g, 10 mmol) in anhydrous DMF (5 ml) was cooled, mixed with **4** (4.26 g, 30 mmol), and stored at room temperature. After the designated times the solutions were diluted with ethyl acetate and extracted three times with 10% aqueous sodium bicarbonate and then with water, dried ($MgSO_4$), and evaporated.

(a) Ten-Minute Reaction. The ethyl acetate phase contained 3.0 g of a foam which contained two major products. A portion of this (900 mg) was purified by preparative tlc on two plates using chloroform–methanol (9:1). Elution of the major band gave 350 mg (28%) of chromatographically homogeneous 2′(3′)-*O*-acetyl-5′-*O*-(2,5,5-trimethyldioxolan-4-on-2-yl)uridine (**32**): λ_{max}^{MeOH} 261 nm (ε 8000); ν_{max} (KBr) 1810, 1740, 1690 cm^{-1}; nmr ($CDCl_3$) multiple signals for C_5, C_6, and $C_{1'}$ protons, 1.51, 1.56 (s, 3, CMe_2), 1.77 (s, 3, CO_3Me), 2.12, 2.13, and 2.17 (s, total 3, OAc).

Anal. Calcd for $C_{17}H_{22}N_2O_{10}$ (414.36): C, 49.27; H, 5.36; N, 6.76. Found: C, 49.00; H, 5.43; N, 6.45.

Hydrolysis of this material with methanolic ammonium hydroxide gave only uridine while treatment with 0.1 *M* methanolic hydrogen chloride at 20° for 30 min gave mainly a spot with the same R_f as 2′(3′)-*O*-acetyluridine.[27] Treatment of **32** (50 mg) with acetic anhydride (0.2 ml) in pyridine (0.25ml) for 1 hr followed by preparative tlc using chloroform–methanol (9:1) gave 49 mg (90%) of the diacetate **33**: λ_{max}^{MeOH} 259 nm (ε 11.700); ν_{max} (KBr) 1810, 1750, 1690 cm^{-1}.

Anal. Calcd for $C_{19}H_{24}N_2O_{11}$ (456.40): C, 50.00; H, 5.30; N, 6.14. Found: C, 50.10; H, 5.56; N, 5.71.

From the aqueous phase of reaction a, 900 mg (23%) of **34** was isolated as in b.

(b) Two-Hour Reaction. A reaction exactly as in a was kept for 2 hr at room temperature and worked up using ethyl acetate. The combined aqueous phases were extracted three times with chloroform and the extracts were dried and evaporated. The crystalline residue was washed with ether and dried giving 1.68 g (43%) of pure **34** with mp 156–158°. Recrystallization from chloroform–ether gave mp 158–159°: λ_{max}^{MeOH} 225 nm (ε 9400), 249 (7900); ν_{max} (KBr) 1805, 1750, 1655 cm^{-1}; $[\alpha]^{23}D$ −42.9° (*c* 0.39, $CHCl_3$).

Anal. Calcd for $C_{17}H_{20}N_2O_9$ (396.35): C, 51.51; H, 5.09; N, 7.07. Found: C, 51.52, H, 4.97; N, 7.20.

Treatment of **34** (100 mg) with 0.25 ml of 0.1 *M* methanolic hydrogen chloride at room temperature for 45 min followed by gradual addition of ether gave 65 mg (84%) of **29** (R = H) which was identical with a sample prepared as above.

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_8H 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]

A. F. Russell,[3] S. Greenberg,[4] and J. G. Moffatt*

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).