Preparation and Synthetic Utility of Some Organotin Derivatives of Nucleosides

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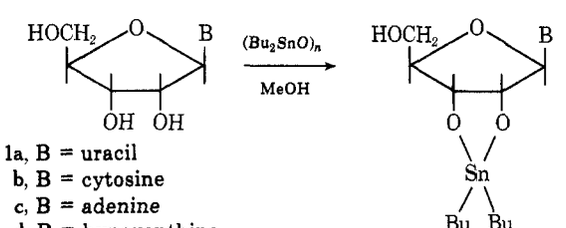
The reaction of ribo nucleosides with dibutyltin oxide in hot methanol gives rise to 2′,3′-*O*-(dibutylstannylene)nucleosides (**2**) that can be isolated in high yield and crystalline form. The dibutylstannylene function serves, not as a protecting group, but rather as an activating group for the 2′- and 3′-oxygen functions. Thus, the reactions of **2** prepared *in situ* in methanol with acyl chlorides or anhydrides leads to the selective formation of 2′(3′)-*O*-acyl nucleosides from which the pure 3′-*O*-acyl derivatives can be isolated in good yield by crystallization. In a similar way the reaction of methanolic solutions of **2** with *p*-toluenesulfonyl chloride leads quite selectively to the formation and isolation of 2′-*O*-*p*-toluenesulfonyl nucleosides. The related reaction with phosphorus oxychloride leads, after hydrolysis, to the selective formation of mixed nucleoside 2′(3′)-phosphates. Alkylation reactions are more restricted but reaction of 2′,3′-*O*-(dibutylstannylene)uridine with benzyl bromide and methyl iodide in dimethylformamide leads selectively to the monobenzylation and monomethylation of the 2′ and 3′ oxygens. The reaction of nucleoside 5′-phosphates with hexabutyldistannoxane leads to the formation, in high yield, of crystalline bis(tributyltin) esters with significant antifungal and antibacterial properties.

The ever-increasing interest in the chemistry of nucleosides and nucleotides has led to a continuing search for new and selective reactions that can be applied to predetermined sugar hydroxyl groups. Recent years have also witnessed an expanding interest in the chemistry of organotin compounds,[2] including the development of effective means for the synthesis of cyclic dialkoxytin derivatives.[3] It was therefore of interest to investigate the synthesis of some 2′,3′-*O*-stannylene derivatives of nucleosides (**2**), these compounds being tin analogs of the frequently used 2′,3′-*O*-alkylidene (*e.g.*, isopropylidene) nucleosides. Since tin–oxygen bonds have rather varied stabilities, the stannylene function could either serve as a protecting group for the 2′,3′-diol or as an activating group for further reactions.

The preparation of 2′,3′-*O*-(dibutylstannylene) nucleosides (**2**) proved to be very simple and was achieved by heating a methanolic suspension of the nucleoside (**1**) and an equimolar amount of dibutyltin oxide. A homogeneous solution resulted, usually within 30 min, and the solvent was then evaporated, leaving a solid residue that can be readily crystallized. In this way the 2′,3′-*O*-dibutylstannylene derivatives of uridine (**2a**), cytidine (**2b**), and adenosine (**2c**) were obtained in crystalline form in yields of 96, 91, and 70%, respectively. The reduced yield (70%) of **2c** was due to the necessity of two recrystallizations in order

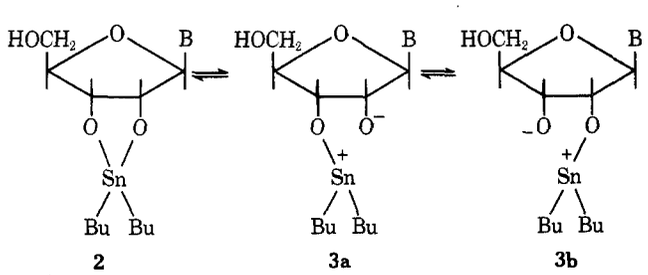


1a, B = uracil
b, B = cytosine
c, B = adenine
d, B = hypoxanthine

2a, B = uracil
b, B = cytosine
c, B = adenine
d, B = hypoxanthine

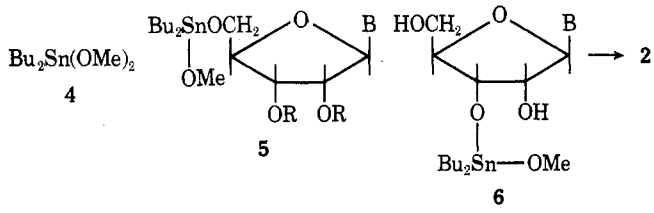
to remove a trace impurity. In all cases the reactions appear to be essentially quantitative and for practical purposes we usually generate the derivatives *in situ* as above and use them directly without crystallization.

The stannylene derivatives (**2**) have reasonable solubilities in polar solvents such as methanol, ethanol, and dimethylformamide but are poorly soluble in chloroform, acetone, and ether. On attempted thin layer chromatography on silica gel, and to a lesser degree on cellulose plates, the stannylene derivatives reverted to the parent nucleosides. The primary covalent nature of the compounds was, however, assured by mass spectrometry, which showed small but significant multiple peaks (tin isotopes) corresponding to the expected molecular ions. Other significant fragments in the higher molecular weight region corresponded to loss of butyl groups and of the heterocyclic bases. Unfortunately, we have been consistently unable to obtain well-resolved nmr spectra for these compounds, most signals being broad and lacking in fine structure. The nmr spectra of alkoxytin compounds have been a source of some confusion, since in some cases tin–hydrogen coupling is observed[4] while in others it is not.[5] Factors such as partial ionic character,[5] facile intermolecular alkoxy exchange,[4a] and self-association[4b] have been suggested to explain these effects. In the present case a general broadening of all signals can probably be attributed to intermolecular exchange. In support of this it was observed that the signals generally sharpened as the temperature was lowered until viscosity became a problem. Also, the spectrum of a mixture of **2a** and uridine showed broadened signals for, *e.g.*, the C_1·H of both compounds and these signals gradually coalesced as the temperature was raised. Upon recooling the original broad signals returned. Because of the problems described above in examining compounds of type **2** by either thin layer chromatography or nmr, it is difficult to determine with any precision the chemical stabilities of these substances.



2 **3a** **3b**

The selective formation of the 2′,3′-*O*-stannylene derivatives (**2**) is clearly a consequence of the greater thermodynamic stability of the cyclic 2-stanna-1,3-dioxolane structure relative to acyclic alkoxytin derivatives.[3b] It is well known that dibutyltin oxide and methanol rapidly form dibutyldimethoxytin (**4**),[2] which is presumably the reactive intermediate in subsequent condensations.

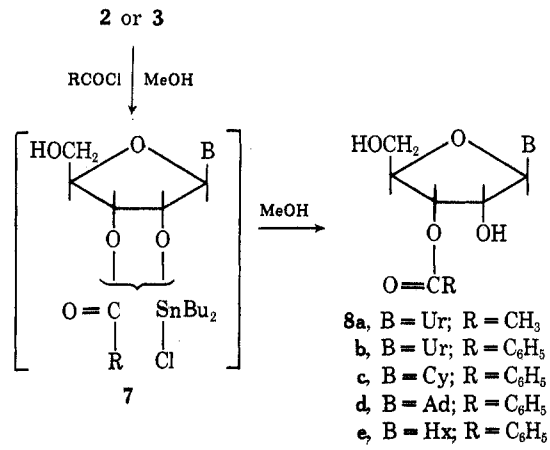


Whenever 4 undergoes alkoxy exchange with the 5′-hydroxyl group of the nucleoside the resulting derivative (5) can exchange once again with the solvent, regenerating 4. On the other hand, a single exchange reaction involving either the 2′ or 3′ hydroxyl group gives an intermediate (*e.g.*, 6) which undergoes an extremely rapid, second exchange to form the cyclic derivative (2) before methanolysis can occur. Since 2 is far more stable than 5 to methanol, or to traces of water formed during preparation of 4, the above process leads essentially quantitatively to this substance.

In an initial effort to determine the role of the stannylene derivative in other reactions of the nucleoside sugar moiety, pure **2a** was treated in dimethylformamide with a slight excess of acetic anhydride at 0°. Examination by thin layer chromatography (tlc) showed one major product which gave a negative test for vicinal diols using a periodate–benzidine spray.[6] Following extraction of tin compounds with chloroform the residue was shown by nmr spectroscopy to be a roughly equal mixture of 2′-*O*-acetyl- and 3′-*O*-acetyluridine similar to that prepared by mild hydrolysis of 2′,3′-*O*-(ethoxyethylidene)uridine.[7] As was shown by Fromageot, *et al.*,[7] crystallization of such a mixture from a polar solvent led to equilibration of the acyl functions and isolation of pure 3′-*O*-acetyluridine (**8a**) in 54% yield. From this experiment it was clear that the stannylidene group functions not as a protecting group, but rather as an activating group for the 2′- and 3′-hydroxyl functions of a nucleoside. It has previously been shown that various monoalkoxytin derivatives react with acid anhydrides or acid chlorides to form esters and the appropriate tin acetate or tin chloride.[8] Such a reaction has proved to be valuable in effecting a mild sulfamoylation in previous work from this laboratory,[9] but comparable acylations or alkylations do not appear to have been reported using cyclic stannylene derivatives. It is not clear whether such acylations are a direct consequence of equilibrium concentrations of ionic species (**3a,b**) or simply involve the well-known addition of tin alkoxides to reactive bonds, perhaps *via* a four-center transition state.[2,10]

In order to avoid multiple acylation in the above reaction only a slight excess of acetic anhydride was used. The apparent reactivity of the tin–oxygen bond, however, suggested that it might be possible to directly acylate the stannylene derivatives prepared *in situ* in methanol. In fact, the addition of 5–10 equiv each of acetyl chloride and triethylamine to a solution of **2a** prepared in methanol led to a very rapid and selective monoacetylation reaction. By crystallization of the mixed 2′(3′)-acetates, pure 3′-*O*-acetyluridine (**8a**) was obtained in 69% yield. Similar results were obtained using acetic anhydride rather than acetyl chloride but the yield of pure **8a** was lower.

From a preparative point of view the direct benzoylation of the stannylene derivatives was of greater interest. Treatment of a methanolic solution of **2a** with benzoyl chloride and triethylamine gave pure 3′-*O*-benzoyluridine (**8b**) in 78% yield following crystallization from aqueous ethanol. Very similar results were obtained from reactions of the other 2′,3′-*O*-stannylene nucleosides (**2b–d**) with acylating agents. Thus the reaction of methanolic **2b** with acetic anhydride and triethylamine gave a roughly 3:1 mixture of 3′-*O*-acetyl- and 2′-*O*-acetylcytidines in essentially quantitative yield. In this case, however, no selective crystallization of one isomer could be achieved. A similar reaction using benzoyl chloride gave pure crystalline 3′-*O*-benzoylcytidine (**8c**) in 87% yield. The method was also suitable in the purine series, since reactions of 2′,3′-*O*-(dibutylstannylene)adenosine (**2c**) and its inosine counterpart **2d** gave the crystalline 3′-*O*-benzoyl nucleosides (**8d, 8e**) in yields of 70 and 50%, respectively. In all cases the homogeneity of the final products and the location of the acyl group were readily apparent by nmr spectroscopy. The spectra of the crude products prior to crystallization always showed signals characteristic of both the 2′- and 3′-acyl derivatives, the relative assignments being possible through application of the rules developed by Fromageot, *et al.*[11] Following crystallization, the pure 3′-*O*-acyl derivatives (**8a–e**) were identified by use of the

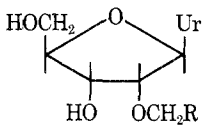


above rules,[11] by the characteristic downfield shift of the C_3′H signals, and by the presence of signals due to the C_2′OH and C_5′OH groups. The absolute location of those groups was confirmed by spin-decoupling studies in DMSO-d_6. The ribo configuration was in each case confirmed by deacylation and examination of the parent nucleosides by borate electrophoresis.[12]

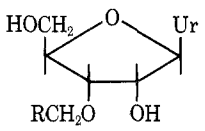
The useful feature of all the above reactions is the complete selectivity for acylation at C_2′ or C_3′ with no observable reaction at C_5′ or on heterocyclic amino groups. This is doubtless a consequence of the initial high reactivity of the Sn–O bonds, perhaps *via* intervention of equilibrium concentrations of ionic species such as **3a,b.** This reactivity leads to almost immediate reaction with the acyl halide, giving a mixture of monoacyl–monotin ethers (*e.g.*, 7). The lability of acyclic tin ethers such as 7 in methanol or in the presence of the mole of water released during formation of **2** then leads to rapid methanolysis or hydrolysis of the remaining Sn–O bond, giving, after crystallization, the monoester **8** before a second acylation can occur. In the absence of tin activation at C_5′OH and at amino functions, these groups cannot compete effectively with methanol and remain unreacted. In contrast, it is known that selective N-acylation of cytidine can be accomplished using acid anhydrides in methanol[13] but these reactions occur in the absence of any base and require many hours under reflux. It should also be recalled that some selectivity for 2′(3′)-*O*-mono- and diacylation results from reaction of nucleosides with benzoic anhydride and tributylamine in aqueous ethanol.[14]

In the uridine series, the 2′,3′-*O*-stannylene function also provides an opportunity for selective monoalkylation of the 2′- and 3′-oxygen functions. Thus the reaction of **2a** with a slight excess of benzyl bromide in dimethylformamide led to the formation of a roughly equal (nmr) mix-

ture of 2′-*O*-benzyluridine (**9a**) and 3′-*O*-benzyluridine (**10a**) in a combined yield of 65% and with no indication of other benzylation products. The mixture could not be preparatively separated by chromatography under a variety of conditions, but it was possible to almost completely resolve the mixture by fractional crystallization, giving pure **9a** (31%) and **10a** (26%). Unequivocal syntheses of **9a** and **10a** have been described by Reese, *et al.*,[15] and by Blank and Pfleiderer[16] *via* benzylation of the appropriate di-*O*-trityluridines. Also, recent work by Christensen and Broom[17] has demonstrated the direct 2′(3′)-*O*-benzylation of unprotected uridine through reaction with phenyldiazomethane in the presence of stannous chloride. A similar reaction between **2a** and a large excess of methyl iodide in dimethylformamide at 37° led to a mixture of 2′-*O*-methyluridine (**9b**)[18] and 3′-*O*-methyluridine (**10b**)[18] in a ratio



9a, R = C_6H_5
b, R = H

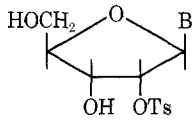


10a, R = C_6H_5
b, R = H

of 45:55 (by nmr) in 70% yield. There was once again no indication of methylation of C_5′OH or of the uracil ring. A preparative separation of these two compounds could not be achieved.

Unfortunately, extension of the selective alkylation reaction to the adenosine and cytidine series was not successful. Thus reaction of **2c** with a large excess of methyl iodide led to the predominant formation of N^1-methyladenosine, which was isolated in crystalline form and directly compared with an authentic sample.[19] In a similar way, reaction of the cytidine derivative (**2b**) led predominantly to a positively charged, periodate-positive material with an ultraviolet spectrum similar to that of N^3-methylcytidine.[20] An attempt to avoid base alkylation *via* preparation of the stannylene derivative of N^4-benzoylcytidine also failed, since the reaction was accompanied by debenzoylation. It is interesting that we observed no sign of *O*-alkylation during the above reactions.

The reactions of the stannylene derivatives of uridine and adenosine (**2a**, **2c**) with *p*-toluenesulfonyl chloride in methanol were extremely rapid and led to the isolation of the pure, crystalline 2′-*O*-*p*-toluenesulfonyl derivatives (**11a,b**) in yields of 62 and 70%, respectively. Since it is generally accepted that sulfonyl esters, unlike their carboxylate counterparts, do not undergo "acyl" migration,[21] this suggests a distinct preference for reaction at C_2′OH rather than at C_3′OH. Similar preference has previously been noted during sulfonylation of 5′-substituted nucleosides[22] and 5′-nucleotides[23] as well as during alkylation of unprotected nucleosides.[24] The present method provides a uniquely facile route to 2′-*O*-*p*-toluenesulfonyladenosine (**11b**), a versatile type of precursor to 8,2′-anhydro nucleosides,[25] which has previously been difficult to prepare in pure form and high yield.[22c] It is interesting to note that **11b** proves, rather unexpectedly, to be labile in base, brief



11a, B = Ur
b, B = Ad
c, B = Cy

treatment with ethanolic sodium hydroxide leading to complete glycosidic cleavage and release of adenine. Similar cleavage was not observed upon treatment with aqueous pyridine or triethylamine at 100°, but attempted displacement of the sulfonyl group with sodium benzoate or lithium azide in dimethylformamide at 150° once again gave only adenine. The mechanism of this glycosidic cleavage is not at all certain at this time. One possibility involves the intermediacy of a 1′,2′-unsaturated nucleoside arising *via* an elimination reaction, and studies with such nucleosides[26] are currently underway.

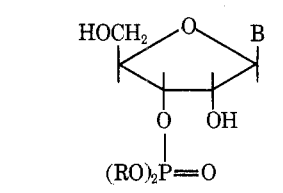
The reaction of 2′,3′-*O*-(dibutylstannylene)cytidine (**2b**) with *p*-toluenesulfonyl chloride in methanol under conditions similar to those above led to a more complex mixture. At least in part this can be explained by the expected tendency of 2′-*O*-*p*-toluenesulfonylcytidine (**11c**) to undergo internal displacement with formation of *O*2,2′-cyclocytidine. Indeed, an examination of the crude reaction product by paper chromatography and electrophoresis demonstrated the presence of *O*2,2′-cyclocytidine. It has recently been demonstrated by Ikehara and Uesugi[27] that attempted tosylation of cytidine 5′-phosphate in aqueous base leads to a complex mixture of products mostly derived from initial reaction at C_2′ followed by cyclonucleoside formation. A clarification of the nature of the other products must await further work.

Finally, we have examined the reaction of the 2′,3′-*O*-stannylene nucleosides with phosphorochloridates. Our original studies made use of substituted phosphorylating agents such as diphenyl phosphorochloridate and it was shown that such compounds react with, *e.g.*, **2c** in methanol in the presence of triethylamine to form an unstable, neutral species which is presumably either a 2′(3′)-phospho triester (*e.g.*, **12a**) or a 2′,3′-cyclic triester. As expected,[28] this material was very sensitive to water and was very unstable in both acid and base, being rapidly converted to a monoanion as judged by paper electrophoresis at pH 7.5. Accordingly, it could not be freed from salts or obtained in a pure form.

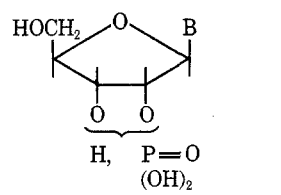
A similar product could be obtained by reaction of a methanolic solution of **2c** with an excess of phosphorus oxychloride. In order to avoid the presence of water-soluble salts, hexabutyldistannoxane was used as a base, since both the compound itself and the resulting acid addition products (*e.g.*, Bu_3SnCl) are soluble in ether. Following the very rapid reaction of **2c** with phosphorus oxychloride as above, the adenosine derivatives were precipitated with ether. The nmr spectrum of the resulting product showed it to be a roughly 9:1 mixture of two compounds, the major one being dimethyladenosine 3′-phosphate (**12b**). There is no doubt that the compound is a dimethyl ester, the methyl groups appearing as a pair of three-proton doublets ($J_{P,H}$ = 11 Hz) at 3.84 and 3.91 ppm in DMSO-d_6 due to the diastereotopic nature of phospho triesters containing asymmetric functions.[29] The minor constituent, presumably the 2′-dimethylphosphoryl isomer, showed methyl ester protons, once again as a pair of doublets, at 3.60 and 3.65 ppm. The location of the phosphate ester grouping at C_3′ in the major isomer was apparent both from the fact that signal for C_3′H was shifted downfield and was superimposed upon that of C_2′H, and from the relative chemical shifts of the C_1′ protons in the two isomers,[11] the major signal being a doublet ($J_{1',2'}$ = 7 Hz) at 6.60, and the minor one a doublet at 6.66 ppm ($J_{1',2'}$ = 5 Hz). For the moment we have no evidence as to whether the formation of **12b** involves predominant opening of the stannylene derivative at C_3′ or an equilibration of the 2′- and 3′-phosphoryl derivatives with **12b** being the thermodynamically more stable product.

Storage of the above crude product in the presence of moisture led to the appearance of ionic materials and

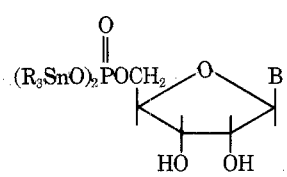
completion of this hydrolysis with aqueous sodium hydroxide at room temperature led to the isolation of the pure mixed barium salts of adenosine 2′(3′)-phosphates (**13a**, 60% 3′-phosphate by paper chromatography) in an overall yield of 78% from adenosine. The alkaline hydrolysis of compounds such as **12b** is well known and involves a series of events involving participation of the adjacent hydroxyl function.[28] In essentially the same way, the reactions of **2a** and **2b** with phosphorus oxychloride and hexabutyldistannoxane led to the isolation of the mixed uridine 2′(3′)-phosphates (**13b**) and cytidine 2′(3′)-phosphates (**13c**) in yields of 87 and 73%, respectively. The absence of any 5′-phosphate esters was confirmed by borate electrophoresis at pH 8 and by the complete resistance of the products toward dephosphorylation by the 5′-nucleotidase activity of crude *Crotalus adamanteus* venom.[30] The above method thus provides a novel and highly selective method for the direct 2′(3′)-phosphorylation of unprotected ribo nucleosides. Complementary methods involving reaction of nucleosides with aqueous trimetaphosphate[31] or with phosphite esters[32] have also been described.



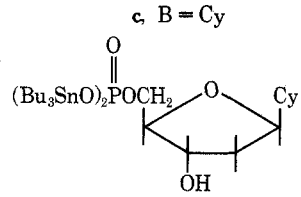
12a, B = Ad; R = C_6H_5
b, B = Ad; R = CH_3



13a, B = Ad
b, B = Ur
c, B = Cy



14a, B = Ad; R = C_4H_9
b, B = Cy; R = C_4H_9
c, B = Cy; R = CH_3



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In the past many organotin esters of phosphoric acid and related derivatives have been prepared and examined for antifungal and insecticidal activities.[2,33] It seemed of interest to prepare some trialkyltin esters of nucleotides both for the above reasons and in the hope that such esters might serve as phosphate protected, organic solvent soluble derivatives suitable for chemical manipulations. Such esters have, in general, been prepared *via* reaction of the sodium salt of the phosphate with a tin halide. We have preferred, however, to briefly heat the free acid nucleoside 5′-phosphate with an equivalent amount of hexabutyldistannoxane or trimethyltin hydroxide in methanol or ethanol until a clear solution results. Evaporation of the solvent followed by crystallization then gives the pure bis(trialkyltin) nucleoside 5′-phosphates (**14**, **15**) in good yields.

The esters were indeed very stable in the crystalline form and freely soluble in solvents such as pyridine. By analogy with extensive studies on trialkyltin esters of a variety of acids, these compounds are considered to be covalent.[2] Their reactions are, however, polar in nature and strongly dependent upon the solvent. The ready polarization of the ester bond is apparent from the fact that they behave similarly to the parent nucleotide during chromatography and electrophoresis. The ester groups also do not appear to prevent participation of the phosphate group during attempted carbodiimide promoted phosphorylations of the sugar hydroxyl functions. The utility of compounds such as **14** or **15** as phosphate protected nucleotides thus appears to be severely limited.

Some biological properties of **14** and **15** have also been examined.[34] They were thus quite cytotoxic to mammalian cells in tissue culture (ED_{50} ~0.1–1 μg/ml) and showed a broad activity against a variety of gram-positive bacteria and fungi (minimum inhibitory concentrations of 0.3–5.0 μg/ml). Both the spectra of activities and the absolute activities are very similar to those shown by a variety of trialkyltin esters[2,33,35] and the present compounds do not appear to show any unique properties.

Thus, while the tin esters of nucleotides do not appear to be particularly useful compounds, the 2′,3′-*O*-dialkylstannylene nucleosides (**2**) have proved to be readily available and interesting intermediates permitting highly selective reactions at the $C_{2'}$- and $C_{3'}$-hydroxyl functions. Examples of the use of these compounds for specific purposes will be found in future publications.

Experimental Section

Thin layer chromatography (tlc) was conducted on commercial 250-μ thick layers of silica gel GF obtained from Analtech, Inc., Newark, Del., and preparative tlc on 20 × 100 cm glass plates coated with a 1.3-mm layer of silica gel HF. Nuclear magnetic resonance spectroscopy was performed using a Varian HA-100 spectrometer and is reported in parts per million downfield from an internal standard of tetramethylsilane. Elemental analyses were by Dr. A. Bernhardt, Mulheim, Germany, and other instrumental analyses were obtained by the staff of the Analytical Laboratory of Syntex Research. We are particularly grateful to Dr. M. L. Maddox and Mrs. J. Nelson for their cooperation with nmr spectroscopy.

2′,3′-*O*-(Dibutylstannylene)uridine (2a). A suspension of uridine (488 mg, 2 mmol) and dibutyltin oxide (500 mg, 2 mmol) in methanol (100 ml) was heated under reflux for 30 min and the resulting clear solution was then evaporated to dryness and dried *in vacuo*. The resulting crystalline residue (915 mg, 96%) was analytically pure and showed mp 232–234°. Recrystallization from ethanol did not change this melting point: λ_{max} (MeOH) 261 nm (ε 9400); mass spectrum (70 eV) *m/e* 473–481 (M^+), 415–423 (M − C_4H_9), 361–369 (M − uracil), 301–309 (M − uracil − C_4H_9).

Anal. Calcd for $C_{17}H_{28}N_2O_6Sn$ (475.10): C, 42.97; H, 5.94; N, 5.90. Found: C, 42.91; H, 5.91; N, 5.86.

2′,3′-*O*-(Dibutylstannylene)cytidine (2b). A suspension of cytidine (243 mg, 1 mmol) in methanol (25 ml) was heated under reflux in methanol (25 ml) in the presence of dibutyltin oxide (250 mg, 1 mmol). After 2 hr the resulting clear solution was evaporated to dryness and the residue was crystallized from ethanol–ether, giving 430 mg (91%) of **2b**: mp 217–218°; λ_{max} (H^+, MeOH) 282 nm (ε 13,300); λ_{max} (OH^-, MeOH) 275 nm (ε 8200); nmr (MeOh-d_4) 0.90 (t. 6, CH_3's), 1.2–1.8 (m, 12, CH_2's), 3.88 (m, 2, $C_5{\cdot}H_2$), 4.3 (m, 2, $C_2{\cdot}H$ and $C_3{\cdot}H$), 5.88 (s, 1, $C_1{\cdot}H$), 5.92 (d, 1, $J_{5,6}$ = 7.5 Hz, C_5H), 7.97 ppm (d, 1, C_6H).

Anal. Calcd for $C_{17}H_{29}N_3O_5Sn$ (474.11): C, 43.06; H, 6.17; N, 8.86; Sn, 25.03. Found: C, 42.66; H, 6.23; N, 8.78; Sn, 24.69.

2′,3′-*O*-(Dibutylstannylene)adenosine (2c). A mixture of adenosine (267 mg, 1 mmol), dibutyltin oxide (250 mg, 1 mmol), and methanol (25 ml) was heated under reflux for 30 min and then evaporated to dryness. Two crystallizations from ethanol–acetone gave 350 mg (70%) of **2c**: mp 154–156°; λ_{max} (MeOH) 259 nm (ε 14,700); mass spectrum (70 eV) *m/e* 496–504 (M^+), 438–446 (M − C_4H_9), 361–369 (M − adenine).

Anal. Calcd for $C_{18}H_{29}N_5O_4Sn$ (498.14): C, 43.39; H, 5.86; N, 14.05; Sn, 23.82. Found: C, 43.23; H, 6.05; N, 14.11; Sn, 23.56.

3′-*O*-Acetyluridine (8a). A. A mixture of uridine (1.22 g, 5 mmol) and dibutyltin oxide (1.25 g, 5 mmol) was heated under reflux in methanol (150 ml) for 30 min. The resulting clear solution was cooled and to it was added triethylamine (7.0 ml, 50 mmol) and then acetyl chloride (3.56 ml, 50 mmol). After 10 min at room temperature the solution was evaporated to dryness and a solution of the residue in chloroform was applied to a 2 × 30 cm column of silicic acid. Elution with ethyl acetate–acetone (1:1) gave a mixture of 2′(3′)-*O*-acetyluridines (roughly 70% 3′ by nmr)[11] which was crystallized twice from ethanol, giving 992 mg (69%) of pure **8a**: mp 171–172° (reported[7] mp 172–174°); λ_{max} (MeOH) 260 nm (ε 10,200); nmr (DMSO-d_6) 2.08 (s, 3, OAc), 3.63 (br s, 2, $C_5{\cdot}H_2$), 4.05 (br d, 1, $J_{3',4'}$ = 2.5 Hz, $C_4{\cdot}H$), 4.31 (m, 1,

becoming dd, $J_{1',2'}$ = 6.5, $J_{2',3'}$ = 5.5 Hz, C_2·H), 5.15 (dd, 1, C_3·H), 5.28 (t, 1, C_5·OH), 5.72 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 5.72 (d, 1, $J_{H,OH}$ = 6 Hz, C_2·OH), 5.86 (d, 1, C_1·H), 7.91 ppm (d, 1, C_6H).

B. A solution of **2a** (475 mg, 1 mmol) and acetic anhydride (0.1 ml, 1.05 mmol) in dimethylformamide (10 ml) was kept at 0° for 4 hr, the reaction being followed by tlc using chloroform–methanol (85:15). The mixture was then evaporated to dryness *in vacuo* and the residue was partitioned between water and chloroform. The aqueous phase was evaporated to dryness and the residue was crystallized from ethanol (1 ml) giving 154 mg (54%) of pure **8a** identical with that above.

C. A solution of **2a** in methanol (30 ml) was prepared *in situ* from uridine (488 mg, 2 mmol) and dibutyltin oxide (500 mg) as in A. Triethylamine (2.8 ml, 20 mmol) and acetic anhydride (2.0 ml, 20 mmol) were added and after 3 min at room temperature the mixture was evaporated to dryness. The residue was coevaporated several times with ethanol and then partitioned between methylene chloride and water. The aqueous phase was evaporated to dryness and the residue was crystallized from ethanol, giving 230 mg (34%) of pure **8a**, the purity being confirmed by tlc and nmr as above.

3′-*O*-Benzoyluridine (8b). A solution of **2a** (2 mmol) in methanol (100 ml) was prepared *in situ* as above. Triethylamine (1.4 ml, 10 mmol) and benzoyl chloride (1.2 ml, 10 mmol) were added and the mixture was stirred at room temperature for 10 min, at which point tlc using ethyl acetate–acetone (1:1) showed no remaining uridine. The solvent was evaporated *in vacuo* and the residue was partitioned between ether (100 ml) and water and filtered. The aqueous phase was concentrated to about 30 ml and allowed to crystallize. Recrystallization from aqueous ethanol gave 570 mg (78%) of pure (nmr and tlc) **8b** as the dihydrate: mp 213–214° (reported[7] mp 212–214° for the anhydrous compound); λ_{max} (MeOH) 230 nm (ε 16,000), 260 (11,800); ORD (MeOH) $[\Phi]_{284}$ 0°, $[\Phi]_{282}$ (peak) 400°, $[\Phi]_{280}$ 0°, $[\Phi]_{253}$ (trough) −1300°, $[\Phi]_{226}$ 0°; nmr (DMSO-d_6) 3.70 (dd, 2, $J_{4',5'}$ = 3, $J_{H,OH}$ = 5 Hz, C_5·H_2, becoming d with D_2O), 4.23 (dt, 1, $J_{3',4'}$ = 3 Hz, C_4·H), 4.42 (ddd, 1, $J_{1',2'}$ = 7, $J_{2',3'}$ = 6, $J_{H,OH}$ = 6 Hz, C_2·H), 5.41 (dd, 1, C_3·H), 5.33 (t, 1, C_5·OH), 5.74 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 5.84 (d, 1, C_2·OH), 5.97 (d, 1, C_1·H), 7.6 and 8.05 (m, total 5, Ar), 7.93 (d, 1, C_6H), 11.38 ppm (br s, 1, NH).

Anal. Calcd for $C_{16}H_{16}N_2O_7 \cdot 2H_2O$ (366.33): C, 52.46; H, 4.95; N, 7.64. Found: C, 52.40; H, 5.04; N, 7.59.

After drying *in vacuo* at 100° the anhydrous compound (mp 212–213°) was obtained.

Anal. Calcd for $C_{16}H_{16}N_2O_7$ (348.31): C, 55.17; H, 4.63; N, 8.04. Found: C, 55.07; H, 4.76; N, 8.03.

2′-*O*-Benzyluridine (9a) and 3′-*O*-Benzyluridine (10a). A solution of **2a** (2.375 g, 5 mmol) and benzyl bromide (1.7 g, 10 mmol) in dimethylformamide (30 ml) was heated at 100° for 1 hr, at which point tlc using ethyl acetate–acetone (1:1) showed no uridine remaining. Following evaporation of the solvent the residue was chromatographed on a column of silicic acid using chloroform and chloroform–methanol (19:1) giving 1.2 g (65%) of a roughly equal mixture (nmr) of **9a** and **10a**. Crystallization of the mixture from ethanol removed almost all of the 3′-*O*-benzyl isomer (**10a**), giving 440 mg (26%) of the pure compound: mp 206–208°, raised to 208.5–209° upon recrystallization of an analytical sample (reported[15a] mp 204–206°, 205–207°[17]); λ_{max} (MeOH) 262 nm (ε 10,200); nmr (DMSO-d_6) 3.58 (br s, 2, C_5·H_2), 3.95 (m, 2, C_3·H and C_4·H), 4.22 (ddd, 1, $J_{1',2'}$ = 5.5, $J_{2',3'}$ = 5.5, $J_{H,OH}$ = 5 Hz, C_2·H), 4.53 and 4.70 (d, 1, J_{gem} = 12.5 Hz, ArCH_2), 5.10 (t, 1, C_5·OH), 5.46 (d, 1, C_2·OH), 5.61 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 5.80 (d, 1, C_1·H), 7.33 (s, 5, Ar), 7.86 ppm (d, 1, C_6H).

Anal. Calcd for $C_{16}H_{18}N_2O_6$ (334.33): C, 57.48; H, 5.42; N, 8.37. Found: C, 57.31; H, 5.48; N, 8.58.

Continued crystallization from ethanol gave 510 mg (31%) of pure **9a** in three crops: mp 178.5–180° (reported[15b] mp 181–182°, 177–179°[17]); λ_{max} (MeOH) 262 nm (ε 9800); nmr (DMSO-d_6) 3.63 (br s, 2, C_5·H_2), 3.97 (dd, 1, $J_{1',2'}$ = 5, $J_{2',3'}$ = 5 Hz, C_2·H), 3.95 (m, 1, C_4·H), 4.18 (ddd, 1, $J_{3',4'}$ = 5, $J_{H,OH}$ = 5 Hz, becoming dd with D_2O, C_3·H), 4.55 and 4.74 (d, 1, J_{gem} = 12 Hz, ArCH_2), 5.10 (t, 1, C_5·OH), 5.19 (d, 1, C_3·OH), 5.56 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 5.96 (d, 1, C_1·H), 7.32 (s 5, Ar), 7.90 ppm (d, 1, C_6H).

Anal. Calcd for $C_{16}H_{18}N_2O_6$ (334.33): C, 57.48; H, 5.42; N, 8.37. Found: C, 57.15; H, 5.36; N, 8.07.

2′(3′)-*O*-Methyluridine (9b, 10b). A solution of **2a** (475 mg, 1 mmol) and methyl iodide (2.0 ml) in dimethylformamide (15 ml) was kept at 37° for 18 hr, at which point tlc using ethyl acetate–acetone (1:1) showed a major spot giving a negative test with the periodate–benzidine spray.[6] After evaporating the solvent and washing the residue with hexane, the mixture was purified by preparative tlc using ethyl acetate–acetone (45:55) giving 180 mg (70%) of a clean mixture of **9b** and **10b** in a ratio of 55:45 by nmr. No resolution of this mixture was achieved.

2′-*O*-*p*-Toluenesulfonyluridine (11a). A solution of **2a** in methanol (250 ml) was prepared *in situ* as above from 1.22 g (5 mmol) of uridine. Triethylamine (8.5 ml, 60 mmol) was added followed by a solution of *p*-toluenesulfonyl chloride (11.5 g, 60 mmol) in acetone (20 ml). After 10 min at room temperature the solution was evaporated to dryness and the residue was dissolved in acetone and filtered to remove 4.8 g of triethylamine hydrochloride. The filtrate was evaporated and partitioned between water and ether, and the aqueous phase was concentrated to a small volume, giving 1.75 g (88%) of **11a** that was at least 90% pure by nmr. Recrystallization from water gave 1.23 g (62%) of pure **11a**: mp 172–174° (reported[36] mp 175–177°); λ_{max} (MeOH) 225 nm (ε 14,500), 261 (ε 9600); nmr (DMSO-d_6) 2.37 (s, 3, ArCH_3), 3.57 (m, 2, C_5·H_2), 3.95 (m, 1, C_4·H), 4.17 (ddd, 1, $J_{2',3'}$ = 5, $J_{3',4'}$ = 2, $J_{H,OH}$ = 5 Hz, becoming dd with D_2O, C_3·H), 4.88 (dd, 1, $J_{1',2'}$ = 7 Hz, C_2·H), 5.28 (t, 1, C_5·OH), 5.47 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 5.91 (d, 1, C_3·OH), 6.03 (d, 1, C_1·H), 7.40 and 7.73 (d, 2, J = 8.5 Hz, Ar), 7.60 ppm (d, 1, C_6H).

Anal. Calcd for $C_{16}H_{18}N_2O_8S$ (398.39): C, 48.23; H, 4.56; N, 7.03. Found: C, 48.26; H, 4.57; N, 6.73.

Treatment of 10 mg of **11a** with 0.1 *N* sodium hydroxide (0.3 ml) at room temperature for 2 hr led to almost complete conversion to 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil which was identified by tlc (EtOAc–MeOH, 3:2) and uv (λ_{max} 223, 250 nm).

Uridine 2′(3′)-Phosphate (13b). A solution of **2a** (2 mmol) was prepared *in situ* in methanol (100 ml) and cooled to room temperature. After addition of hexamethyldistannoxane (6 ml, 12 mmol), phosphorus oxychloride (0.70 ml, 7.6 mmol) was added and the solution was kept at room temperature for 20 min before evaporation to dryness. The residue was shaken several times with 100-ml portions of ether to remove tin compounds and finally dissolved in water. After extraction with ether, the aqueous phase contained a predominant spot with the electrophoretic mobility of a monoanion. This material was treated overnight with 0.5 *N* sodium hydroxide and the solution was then adjusted to pH 8 with Dowex 50 (H^+) resin. The solvent was evaporated and the residue was crystallized from aqueous ethanol, giving 644 mg (87%) of the disodium salts of **13b** (3′:2′ = 3:2 by nmr). The product contained no uridine 5′-phosphate as judged by borate electrophoresis at pH 8[37] and by its complete resistance to incubation with crude *Crotalus adamanteus* venom,[30] λ_{max} (pH 2) 260 nm (ε 9200).

Anal. Calcd for $C_9H_{11}N_2O_9PNa_2$ (368.13): C, 29.36; H, 3.00; N, 7.60; P, 8.41. Found: C, 29.17; H, 3.34; N, 7.60; P, 8.27.

2′(3′)-*O*-Acetylcytidine. Triethylamine (2.8 ml, 20 mmol) and acetic anhydride (2.0 ml, 20 mmol) were added to a solution of **2b** in methanol (50 ml) prepared *in situ* from cytidine (973 mg, 4 mmol) as above. After 5 min at room temperature the mixture was evaporated to dryness and the residue was extracted several times with boiling ether. The final residue was dissolved in isopropyl alcohol (10 ml) and upon addition of ether gave 1.10 g (96%) of a mixture of 3′-*O*-acetylcytidine and its 2′ isomer in a ratio of 3:1 by nmr. The mixture had mp 120–130° and no selective crystallization could be achieved: λ_{max} (pH 2) 278 nm (ε 12,300), 211 (9600); λ_{max} (pH 12) 229 nm (ε 8000), 270 (8600).

Anal. Calcd for $C_{11}H_{15}N_3O_6$ (285.26): C, 46.31; H, 5.30; N, 14.73. Found: C, 45.83; H, 5.04; N, 14.84.

3′-*O*-Benzoylcytidine (8c). Triethylamine (1.4 ml, 10 mmol) and benzoyl chloride (1.20 ml, 10 mmol) were added to a solution of **2b** prepared *in situ* in methanol (25 ml) from cytidine (486 mg, 2 mmol) and dibutyltin oxide (500 mg, 2 mmol) as above. After 5 min at room temperature the solvent was evaporated and the residue was partitioned between water (100 ml) and ether. The aqueous phase was concentrated to about 15 ml and upon storage gave 670 mg (87%) of pure 3′-*O*-benzoylcytidine (**8c**) as the dihydrate: mp 136–137°; λ_{max} (pH 1) 230 nm (ε 16,300), 278 (14,600); λ_{max} (pH 12) 221 nm (ε 16,200), 271 (9200); ORD (pH 2) $[\Phi]_{298}$ (peak) 3000°, $[\Phi]_{284}$ 0°, $[\Phi]_{235}$ (trough) −5900°, $[\Phi]_{226}$ 0°; nmr (DMSO-d_6) 3.68 (m, 2, C_5·H_2), 4.21 (dt, 1, $J_{4',5'}$ = 3.5, $J_{3',4'}$ = 3.5 Hz, C_4·H), 4.41 (ddd, 1, $J_{1',2'}$ = 6, $J_{2',3'}$ = 5.5, $J_{H,OH}$ = 6 Hz, becoming dd with D_2O, C2·H), 5.34 (dd, 1, C_3·H), 5.25 (t, 1, C_5·OH), 5.73 (d, 1, C_2·OH), 5.79 (d, 1, $J_{5,6}$ = 6.5 Hz, C_5H), 5.96 (d, 1, C_1·H), 7.22 (br s, 2, NH_2), 7.6 and 8.07 (m, total 5, Ar), 7.88 ppm (d, 1, C_6H).

Anal. Calcd for $C_{16}H_{17}N_3O_6 \cdot 2H_2O$ (383.36): C, 50.15; H, 5.51; N, 10.96. Found: C, 50.33; H, 5.34; N, 10.89.

Upon drying *in vacuo* at 100° the compound lost its crystalline form and gave anhydrous **8c** which sintered at 136° but did not fully melt until 144.5°.

Anal. Calcd for $C_{16}H_{17}N_3O_6$ (347.33): C, 55.33; H, 4.93; N, 12.10. Found: C, 54.99; H, 5.47; N, 12.19.

Cytidine 2′(3′)-Phosphate (13c). Hexabutyldistannoxane (6 ml, 12 mmol) and then phosphorus oxychloride (0.7 ml, 7.5 mmol) were added at room temperature to a solution of **2b** (2 mmol) prepared *in situ* in methanol (60 ml) as above. After 20 min the mixture was evaporated to dryness and the residue was extracted several times with boiling ether. The final residue was dissolved in 1 *N* sodium hydroxide and stored overnight. The solution was then adjusted to pH 8 by addition of Dowex 50 (H^+) resin, and then passed through a column of Dowex 50 (Et_3N) resin. The eluates were evaporated to dryness, dissolved in water (1 ml) and ethanol (6 ml), and adjusted to pH 2 with concentrated hydrochloric acid, giving 460 mg (73%) of a crystalline mixture of cytidine 2′(3′)-phosphates with chromatographic and electrophoretic mobilities identical with those of the authentic compounds: λ_{max} (pH 2) 278 nm (ϵ 12,700); λ_{max} (pH 12) 230 nm (sh, ϵ 8300), 270 (9100).

Anal. Calcd for $C_9H_{14}N_3O_8P$ (323.21): C, 33.44; H, 4.36; N, 13.00; P, 9.58. Found: C, 33.48; H, 4.48; N, 12.89; P, 9.66.

3′-*O*-Benzoyladenosine (8d). Triethylamine (14.0 ml, 100 mmol) and benzoyl chloride (12 ml, 100 mmol) were added to a solution of **2c** (20 mmol) prepared *in situ* in methanol (250 ml). After 15 min at room temperature the solvent was evaporated and the residue was thoroughly triturated with ether (250 ml) several times. The residue was then triturated twice with 50-ml portions of water and then dried *in vacuo*. Two crystallizations from aqueous ethanol gave 5.14 g (70%) of pure **8d:** mp 205–206°; λ_{max} (pH 2) 237 nm (ϵ 17,100), 256 (15,800); λ_{max} (ph 11) 231 nm (ϵ 13,100), 259 (14,900); nmr (DMSO-d_6) 3.76 (br s, 2, $C_5{}'H_2$), 4.36 (br d, 1, $J_{3',4'}$ = 2 Hz, $C_4{}'H$), 5.05 (ddd, 1, $J_{1',2'}$ = 7.5, $J_{2',3'}$ = 5.5, $J_{H,OH}$ = 5.5 Hz, becoming dd with D_2O, $C_2{}'H$), 5.58 (dd, 1, $C_3{}'H$), 5.91 (d, 1, $C_2{}'OH$), 6.06 (d, 1, $C_1{}'H$), 7.39 (s, 2, NH_2), 7.1 and 8.13 (m, total 5, Ar), 8.20 and 8.44 ppm (s, 1, C_2H and C_8H).

Anal. Calcd for $C_{17}H_{17}N_5O_5$ (371.36): C, 54.98; H, 4.61; N, 18.86. Found: C, 54.75; H, 5.02; N, 18.73.

2′-*O*-*p*-Toluenesulfonyladenosine (11b). Triethylamine (10.5 ml, 75 mmol) and *p*-toluenesulfonyl chloride (14.25 g, 75 mmol) were added to a solution of **2c** (5 mmol) prepared *in situ* in methanol (100 ml). After 5 min at room temperature the solvent was evaporated and the residue was partitioned between water and ether. The aqueous phase was concentrated and stored at 4°, giving 1.47 g (70%) of **11b:** mp 229–230° (reported[22c] mp 224°); λ_{max} (pH 2) 229 nm (ϵ 12,900), 257 (12,400); λ_{max} (pH 11) 228 nm (ϵ 12,300), 261 (12,700); nmr (DMSO-d_6) 2.25 (s, 3, $ArCH_3$), 3.62 (m, 2, $C_5{}'H_2$), 4.07 (br d, 1, $J_{3',4'}$ = 2 Hz, $C_4{}'H$), 4.39 (ddd, 1, $J_{2',3'}$ = 5, $J_{H,OH}$ = 5 Hz, becoming dd with D_2O, $C_3{}'H$), 5.49 (dd, 1, $J_{1',2'}$ = 7.5 Hz, $C_2{}'H$), 5.75 (t, 1, $C_5{}'OH$), 6.03 (d, 1, $C_3{}'OH$), 6.11 (d, 1, $C_1{}'H$), 7.03 and 7.42 (d, 2, Ar), 7.37 (s, 2, NH_2), 8.02 and 8.19 ppm (s, 1, C_2H and C_8H).

Anal. Calcd for $C_{17}H_{19}N_5O_6S$ (421.44): C, 48.45; H, 4.54; N, 16.61; S, 7.60. Found: C, 48.29; H, 5.18; N, 16.52; S, 7.71.

Reaction of 11b with Alkali. Sodium hydroxide (4 ml of 1 *N*) was added to a solution of **11b** (421 mg, 1 mmol) in ethanol (20 ml) and the mixture was heated under reflux for 10 min. Tlc using ethyl acetate–methanol (4:1) showed complete conversion to adenine. The mixture was evaporated and purified by preparative tlc using the above solvent, and crystallization from water gave 110 mg (81%) of adenine, mp >300°, having a uv spectrum identical with that of an authentic sample. Treatment of **11b** with 90% pyridine at 100° for 24 hr or with aqueous triethylamine did not lead to any change, but treatment with sodium benzoate or lithium azide in dimethylformamide at 150° for 10 min gave only adenine.

Adenosine 2′(3′)-Phosphate (13a). Hexabutyldistannoxane (6.0 ml, 11.8 mmol) and phosphorus oxychloride (0.70 ml, 7.5 mmol) were added to a solution of **2c** (2 mmol) prepared *in situ* in methanol (30 ml). After 20 min the solvent was evaporated and the residue was washed carefully with ether, leaving 525 mg of a dry, white precipitate, the nmr spectrum of which suggested it to be dimethyl adenosine 3′-phosphate and its 2′ isomer in a ratio of 9:1 (see text). Upon storage of the mother liquors in an open flask a further 280 mg of precipitate separated and was shown by paper electrophoresis to be a monoanion. The combined precipitates were dissolved in 1 *N* sodium hydroxide and kept overnight before being adjusted to pH 8 with Dowex 50 (H^+) resin. Addition of barium acetate (2 ml of 2 *M*) followed by two volumes of ethanol gave a white precipitate that was collected by centrifugation and reprecipitated twice with aqueous ethanol. The final precipitate was washed with ethanol and ether and dried *in vacuo* at 100°, giving 750 mg (78%) of the barium salt of adenosine 2′- and 3′-phosphates [roughly 2:3 by paper chromatography using saturated ammonium sulfate–2-propanol–1 *M* sodium acetate (80:2:18)]: λ_{max} (pH 2) 256 nm (ϵ 14,200); λ_{max} (pH 12) 259 nm (ϵ 15,000).

Anal. Calcd for $C_{10}H_{12}N_5O_7PBa$ (482.54): C, 24.89; H, 2.51; N, 14.51; P, 6.42. Found: C, 24.81; H, 3.12; N, 14.41; P, 6.24.

3′-*O*-Benzoylinosine (8e). A suspension of inosine (536 mg, 2 mmol) in methanol (100 ml) containing dibutyltin oxide (500 mg, 2 mmol) and triethylamine (2.8 ml, 20 mmol) was heated under reflux for 30 min.[38] After cooling, benzoyl chloride (2.4 ml, 20 mmol) was added and after 10 min the solvent was evaporated. The residue was washed thoroughly with ether and then partitioned between water and ether. The aqueous phase was evaporated to dryness and the residue was extracted with acetone, leaving much of the triethylamine hydrochloride as white crystals. Evaporation of the acetone solution and crystallization from water gave 465 mg (63%) of a 2:1 mixture of 3′-*O*-benzoyl- and 2′-*O*-benzoylinosine ($C_1{}'H$ 6.04 ppm in 3′-OBz and 6.35 ppm in 2′-OBz). Recrystallization from aqueous ethanol gave 372 mg (50%) of the pure 3′-*O*-benzoate (**8e**): mp 155–159°, unchanged upon recrystallization; λ_{max} (pH 2) 234 nm (ϵ 20,400), 248 (sh, 16,300); λ_{max} (pH 11) 230 nm (ϵ 13,700), 254 (11,900); nmr (DMSO-d_6) 3.75 (m, 2, $C_5{}'H_2$), 4.35 (br d, 1, $J_{3',4'}$ = 2 Hz, $C_4{}'H$), 4.95 (ddd, 1, $J_{1',2'}$ = 7, $J_{2',3'}$ = 5.5, $J_{H,OH}$ = 5.5 Hz, becoming dd with D_2O, $C_2{}'H$), 5.33 (t, 1, $C_5{}'OH$), 5.56 (dd, 1, $C_3{}'H$), 5.97 (d, 1, $C_2{}'OH$), 6.04 (d, 1, $C_1{}'H$), 7.65 and 8.12 (m, total 5, Ar), 8.44 ppm (s, 1, C_8H).

Anal. Calcd for $C_{17}H_{16}N_4O_6$ (372.34): C, 54.83; H, 4.33; N, 15.05. Found: C, 54.80; H, 4.43; N, 14.96.

Bis(tributyltin) Adenosine 5′-Phosphate (14a). A suspension of adenosine 5′-phosphate (346 mg, 1 mmol) and hexabutyldistannoxane (606 mg, 1.02 mmol) in ethanol (60 ml) was heated under reflux for 10 min, giving a clear solution. The solvent was then concentrated to 10 ml, and water (50 ml) was gradually added, giving 740 mg (80%) of **14a:** mp 197–198°; λ_{max} (MeOH) 259 nm (ϵ 14,500); nmr (DMSO-d_6) 0.7–1.8 (m, 54, Bu), 4.66 (dd, 1, $J_{1',2'}$ = 5, $J_{2',3'}$ = 5 Hz, $C_2{}'H$), 5.90 (d, 1, $C_1{}'H$), 8.17 and 8.21 ppm (s, 1, C_2H and C_8H).

Anal. Calcd for $C_{34}H_{66}N_5O_7PSn_2$ (925.24): C, 44.13; H, 7.19; N, 7.57; P, 3.35. Found: C, 43.75; H, 6.99; N, 7.74; P, 3.37.

Bis(tributyltin) Cytidine 5′-Phosphate (14b). A suspension of cytidine 5′-phosphate (646 mg, 2 mmol) and hexabutyldistannoxane (1.19 g, 2 mmol) in methanol (30 ml) was heated under reflux for 2 hr and the resulting clear solution was then evaporated to dryness. The resulting residue was crystallized twice from ethanol–ether, giving 1.25 g (69%) of **14b:** mp 163–166°; λ_{max} (MeOH, H^+) 283 nm (ϵ 13,700); λ_{max} (MeOH, OH^-) 273 nm (ϵ 8300).

Anal. Calcd for $C_{33}H_{66}N_3O_8PSn_2$ (901.27): C, 43.98; H, 7.38; N, 4.66. Found: C, 43.95; H, 7.30; N, 4.98.

Bis(trimethyltin) Cytidine 5′-Phosphate (14c). A suspension of cytidine 5′-phosphate (323 mg, 1 mmol) and trimethyltin hydroxide (360 mg, 2 mmol) in ethanol (30 ml) was heated under reflux for 1 hr and the resulting clear solution was evaporated to dryness. Crystallization from ethanol–chloroform gave 584 mg (90%) of **14c:** mp >300°; λ_{max} (MeOH, H^+) 279 nm (ϵ 12,200); λ_{max} (MeOH, OH^-) 227 nm (sh, ϵ 8200), 271 (8600).

Anal. Calcd for $C_{15}H_{30}N_3O_8PSn_2$ (648.80): C, 27.77; H, 4.66; N, 6.47; P, 4.77. Found: C, 27.76; H, 4.87; N, 6.29; P, 4.70.

Bis(tributyltin) 2′-Deoxycytidine 5′-Phosphate (15). An ethanolic suspension (35 ml) of 2′-deoxycytidine 5′-phosphate (1 mmol) and hexabutyldistannoxane (1 mmol) was heated under reflux for 10 min and then evaporated to dryness. Crystallization of the residue from ethanol–acetone and then from ethanol–ether gave 725 mg (82%) of **15:** mp 190–191°, λ_{max} (MeOH) 273 mm (ϵ 10,000).

Anal. Calcd for $C_{33}H_{66}N_3O_7PSn_2$ (885.27): C, 44.77; H, 7.51; N, 4.74; P, 3.49. Found: C, 44.44; H, 7.83; N, 5.22; P, 3.29.

Registry No. 2a, 42822-78-6; **2b,** 42822-79-7; **2c,** 42822-80-0; **8a,** 4873-68-1; **8b,** 16667-60-0; **8c,** 42822-83-3; **8d,** 42822-84-4; **8e,** 42822-85-5; **9a,** 6554-02-5; **9b,** 2140-76-3; **10a,** 4710-74-1; **10b,** 6038-59-1; **11a,** 6206-10-6; **11b,** 42776-78-3; **13a** 2′ isomer barium salt, 42829-41-4; **13a** 3′ isomer barium salt, 42829-42-5; **13b** 2′ isomer disodium salt, 42829-43-6; **13b** 3′ isomer disodium salt, 35170-03-7; **13c** 2′ isomer, 85-94-9; **13c** 3′ isomer, 84-52-6; **14a,** 42829-47-0; **14b,** 42829-48-1; **14c,** 42829-49-2; **15,** 42829-50-5; uridine, 58-96-8; dibutyltin oxide, 818-08-6; cytidine, 65-46-3; adenosine, 58-61-7; 2′-*O*-acetylcytidine, 36963-55-0; 3′-*O*-acetylcytidine, 42829-52-7;

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-