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Studies on Nucleosides and Nucleotides. VIII.[1] Preparation and Reactions of Triphenylphosphoranediylnucleosides

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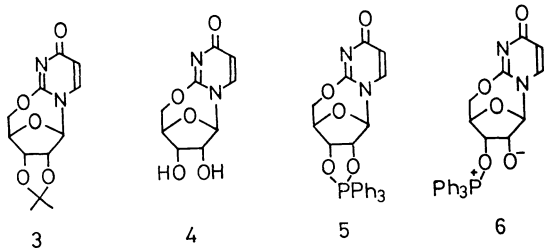
The reaction of uridine, N^4-benzoylcytidine, guanosine, and N^6-*p*-toluoyladenosine with diethyl azodicarboxylate and triphenylphosphine resulted in the formation of the corresponding 2′,3′-*O*-(triphenylphosphoranediyl)-cyclonucleosides. On the other hand, adenosine afforded, under similar conditions, 3′,5′-*O*-(triphenylphosphoranediyl)adenosine (**19**). The difference can be explained in terms of the acidity of base moieties of the nucleosides. The reaction of 2′,3′-*O*-(triphenylphosphoranediyl)-O^2,5′-cyclouridine, N^4-benzoyl-2′,3′-*O*-(triphenylphosphoranediyl)-O^2,5′-cyclocytidine, 2′,3′-*O*-(triphenylphosphoranediyl)-N^3,5′-cycloguanosine, or N^6-*p*-toluoyl-2′,3′-*O*-(triphenylphosphoranediyl)-N^3,5′-cycloadenosine with nucleophiles and with electrophiles addorded the corresponding nucleoside derivatives with free 2′- and 3′-hydroxyl groups. Thus the 2′,3′-*O*-triphenylphosphoranediyl group serves as a protecting group which is readily removed during work-up of the reaction products. **19** reacted with phenyl isocyanate to give 5′-*O*-phenylcarbamoyladenosine and N^6,5′-*O*-bis(phenylcarbamoyl)adenosine. The reaction of **19** with diphenylketene also afforded acyladenosines with free 2′- and 3′-hydroxyl groups. These results suggested that 3′,5′-*O*-triphenylphosphoranediyl group activates the 5′-carbon atom of adenosine.

Since the discovery of 2′,3′-*O*-isopropylidene-N^3,5′-cycloadenosine by Todd and his coworkers, many cyclonucleosides have been synthesized and utilized in synthetic organic chemistry and pharmaceutical as well as in genetic studies.[2] Cyclonucleosides are generally prepared by two stage reactions which involve transformation of a hydroxyl group of the sugar moiety into a leaving group and subsequent intramolecular displacement. Recent study in this laboratory has shown that 2′,3′-*O*-isopropylideneuridine reacts with diethyl azodicarboxylate (**1**) and triphenylphosphine (**2**) giving 2′,3′-*O*-isopropylidene-O^2,5′-cyclouridine (**3**).[3]

In the present paper, we describe the synthesis of triphenylphosphoranediylnucleosides and the use of these compounds in the preparation of nucleoside derivatives.[4]

2′,3′-O-(Triphenylphosphoranediyl)-O²,5′-cyclouridine. In order to obtain unprotected O^2,5′-cyclouridine (**4**), the reaction of uridine with 3 molar equivalents each of **1** and **2** was carried out at room temperature, 2′,3′-*O*-(triphenylphosphoranediyl)-O^2,5′-cyclouridine (**5**) and not the expected **4** being isolated in 65% yield. An alternative structure, **6**, or its position isomer was ruled out by NMR study. A signal is observed in the ^{31}P-NMR spectrum at $\delta = +27.60$, lying in the region characteristic for a phosphorane and not for a phosphonium salt (Table 1).[5] Further support for the structure **5** was provided by the following reactions.

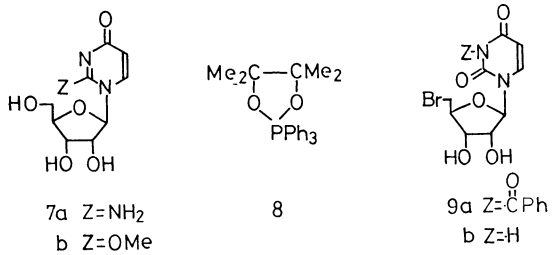


3 4 5 6

Acid or alkaline hydrolysis of **5** afforded uridine and triphenylphosphine oxide in a *ca.* 1 : 1 ratio, **4** being obtained in 70% yield[6] on treatment with H_2O–tetrahydrofuran (THF) at room temperature for 3 d. **4** reacted with **1** and **2** to regenerate **5** in 73% yield. When **5** was treated with ammonia in methanol, isocytidine (**7a**) was isolated which was subsequently converted into 2′,3′-*O*-isopropylideneisocytidine. The results indicate that the removal of triphenylphosphine oxide proceeds smoothly with retention of the configuration of 2′- and 3′-hydroxyl groups.

Bartlett *et al.* reported that 2,2,2-triphenyl-4,4,5,5-tetramethyl-1,3,2-dioxaphospholane (**8**) decomposes into tetramethyloxirane even at room temperature.[7] Unlike **8**, **5** is thermally stable and can be recrystallized from *N*,*N*-dimethylformamide (DMF) at 80 °C. As compared with the isopropylidene group, the –O–P–O– bond of the phosphoranediyl group is somewhat more labile but still stable enough to be treated without difficulty under ordinary atmosphere. **5** could therefore be utilized as a protected O^2,5′-cyclouridine.

The reaction of **5** with methanol under reflux for 10 h afforded O^2-methyluridine (**7b**) in 80% yield. As in the case of **3**,[8] **5** reacted smoothly with benzoyl bromide and with acetyl bromide to give 5′-bromo-5′-deoxy-N^3-benzoyluridine (**9a**; 72%) and 5′-bromo-5′-deoxyuridine (**9b**; 60%), respectively. The fact that no 2′- and/or 3′-acylated products could be detected in these reactions indicates that the phosphoranediyl group is stable under the reaction conditions used.



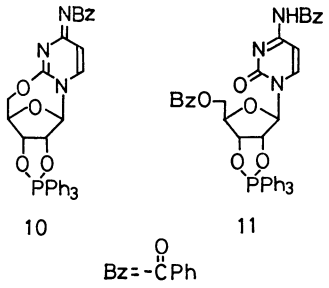
7a Z=NH₂ b Z=OMe 8 9a Z=C(=O)Ph b Z=H

In the reactions of triphenylphosphoranediyl nucleosides with nucleophiles and electrophiles, the isolated

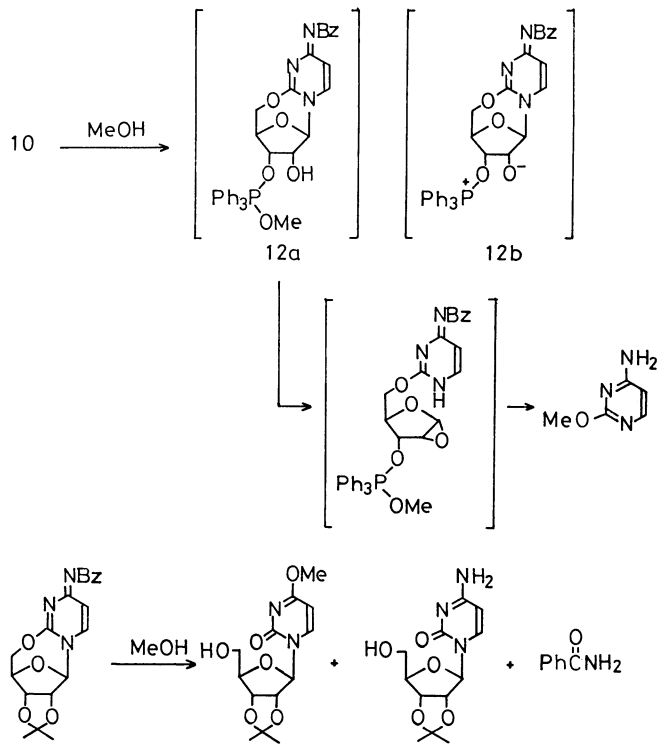
products has no phosphorane ring, presumably because triphenylphosphine oxide was eliminated during the work-up.

N⁴-Benzoyl-2′,3′-O-(triphenylphosphoranediyl)-O′,5′-cyclocytidine. When cytidine was allowed to react with **1** and **2** in a similar manner to that described above, unidentified products were formed. The reaction of N^4-benzoylcytidine with **1** and **2**, however, gave N^4-benzoyl-2′,3′-*O*-(triphenylphosphoranediyl)-O^2,5′-cyclocytidine (**10**) in 71% yield.

The O^2,5′-anhydro bond of 2′,3′-*O*-isopropylidene-O^2,5′-cyclocytidine methanesulfonate is known to be more reactive than that of **3**.[9] This is also the case with phosphoranediylcyclonucleosides **5** and **10**. Thus when **10** was treated with acetonitrile–H_2O at room temperature for 2 d, N^4-benzoylcytidine and triphenylphosphine oxide were formed in a *ca.* 1 : 1 ratio. **10** reacted smoothly at room temperature with benzoic acid giving N^4,5′-*O*-dibenzoylcytidine quantitatively.[10] By the reaction with **1** and **2**, N^4,5′-*O*-dibenzoylcytidine afforded N^4,5′-*O*-dibenzoyl-2′,3′-*O*-(triphenylphosphoranediyl)cytidine (**11**) in 49% yield. The configuration of 2′- and 3′-hydroxyl group was thus retained during the migration of the phosphoranediyl group.



Both the anhydro and glycosidic bonds were cleaved by treatment of **10** in methanol at room temperature overnight, O^2-methylcytosine being obtained in 65% yield. Attempts to isolate and identify the products from the sugar moiety were unsuccessful. On the other hand, no glycosidic bond cleavage took place when N^4-benzoyl-2′,3′-*O*-isopropylidene-O^2,5′-cyclocytidine was treated in methanol under the same conditions.

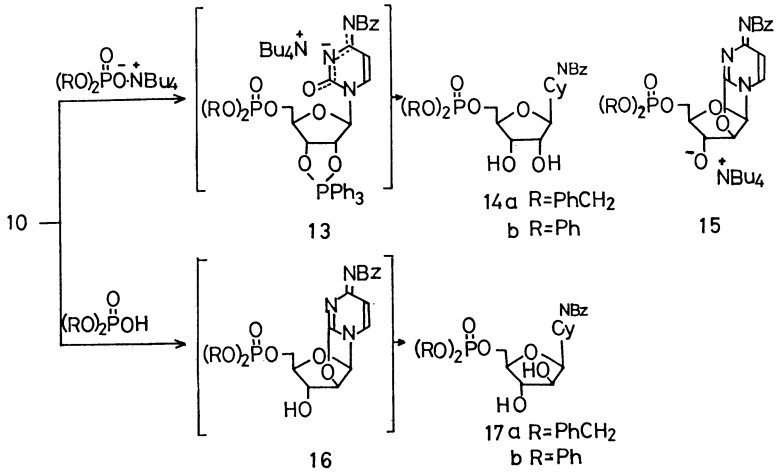


Scheme 1.

In this case O^4-methyl-2′,3′-*O*-isopropylideneuridine, 2′,3′-*O*-isopropylidenecytidine, and benzamide were isolated in 33, 23, and 36% yields, respectively (Scheme 1).

The formation of O^2-methylcytosine might be explained by the initial formation of phosphorane (**12a**) or betaine (**12b**). The glycosidic and O^2,5′-anhydro bonds were successively cleaved by intramolecular nucleophilic displacement and methanolysis as shown in Scheme 1.

The reaction of **10** with phosphoric diesters was studied. As expected, **10** reacted with tetrabutylammonium dibenzyl phosphate at room temperature to afford N^4-benzoylcytidin-5′-yl dibenzyl phosphate (**14a**; 35% isolated yield) which was converted into the corresponding isopropylidene derivatives. Similarly the reaction



Scheme 2.

of **10** with tetrabutylammonium diphenyl phosphate gave **14b** in 15% isolated yield (Scheme 2). On the other hand, when **10** was allowed to react with dibenzyl hydrogenphosphate or diphenyl hydrogenphosphate under the same conditions, neither **14a** nor **14b** could be isolated, but 1-(β-D-arabinofuranosyl)-N^4-benzoylcytosin-5'-yl dibenzyl phosphate (**17a**) and 1-(β-D-arabinofuranosyl)-N^4-benzoylcytosin-5'-yl diphenyl phosphate (**17b**) were isolated in 38 and 52% yields, respectively (Scheme 2).[11] The structure of **17b** was determined by comparison of physical properties with those of an authentic sample prepared by the reaction of 1-(β-D-arabinofuranosyl)-N^4-benzoylcytidine with diphenyl phosphorochloridate.

The difference between the reaction of **10** with a phosphoric diester and with its tetrabutylammonium salt might be explained by the mechanism illustrated in Scheme 2. When a phosphoric diester attacks the 5'-carbon atom of **10**, rearrangement of O^2,5'-anhydro bond takes place with liberation of triphenylphosphine oxide, forming O^2,2'-cyclocytidine 5'-phosphate (**16**) which is hydrolyzed to **17** during the course of manipulation.[12] Since no evidence of the formation of O^2,2'-anhydro bond was obtained in the reaction of **10** with benzoic acid, the anhydro bond rearrangement would be an acid catalyzed process. Since no proton source exists in the reaction of **10** with a tetrabutylammonium salt of phosphoric diester, the anhydro bond rearrangement is unfavorable because of instability of the resulting alkoxide (**15**). The reaction stops at the stage of the formation of **13**.

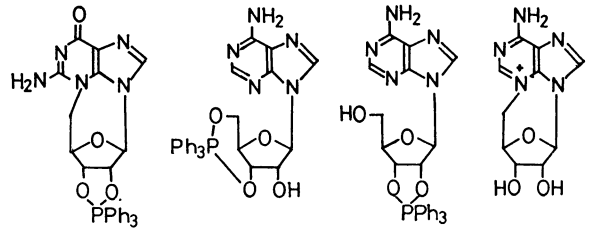
2',3'-O-(Triphenylphosphoranediyl)-N^3,5'*-cycloguanosine.* Guanosine also reacted with **1** and **2** at 70 °C to give 2',3'-*O*-(triphenylphosphoranediyl)-N^3,5'-cycloguanosine (**18**) which was readily hydrolyzed to N^3,5'-cycloguanosine and triphenylphosphine oxide in a 1 : 1 ratio. ^{31}P-NMR spectrum also supports the phosphorane structure (Table 1).

TABLE 1. YIELD AND PHYSICAL CONSTANTS OF TRIPHENYLPHOSPHRANEDIYLNUCLEOSIDES

Compound	**5**	**10**	**18**	**19**	**29**
Yield/%	62	71	67	75	24
Mp/°C	>250	200—201	>250	171—172	200—204
UV_{max} (MeCN)/nm	232	235^{sh}, 318	259	260	
$\varepsilon \times 10^{-4}$	2.65	1.46	1.25	0.74	
^{31}P-NMR(δ)[a]	+27.60	+27.54	+26.58	+29.33	

a) Recorded on a Hitachi R-22 spectrometer at 36.414 MHz±1 Hz (^{1}H decoupled; solvent, DMF). Triphenylphosphine sulfide (δ −42.07; Ref. 85% H_3PO_4) was used as an internal standard, the reported chemical shift being relative to 85% H_3PO_4.

3',5'-O-(Triphenylphosphoranediyl)adenosine. When adenosine was allowed to react with **1** and **2** in dioxane at 70 °C, a phosphorus-containing compound was obtained, showing UV_{max} 260 nm, and a ^{31}P-NMR singlet at +29.33 ppm (Table 1). This compound was hydrolyzed to adenosine and triphenylphosphine oxide in a 1 : 1 ratio. As the structure of the product, both 3',5'-*O*-(triphenylphosphoranediyl)- and 2',3'-*O*-(triphenylphosphoranediyl)adenosine (**19** and **20**) are conceivable.



18 19 20 21

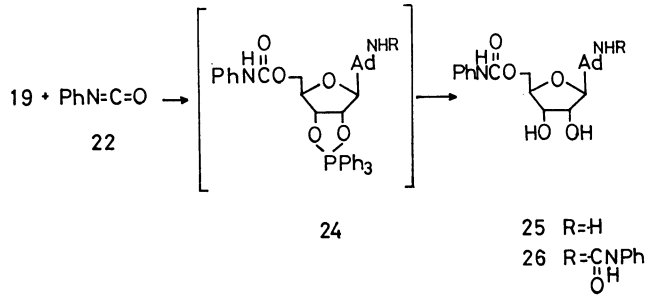
In order to confirm the structure, the product was allowed to react with benzoic acid to form 5'-*O*-benzoyladenosine and N^3,5'-cycloadenosine (**21**) in 59 and 16% yields, respectively. A similar treatment with thiobenzoic acid gave 5'-benzoylthio-5'-deoxyadenosine in 63% yield. It can be concluded that the product obtained by the reaction of adenosine with **1** and **2** is **19** rather than **20**.

The fact that **19** is readily hydrolyzed to adenosine under mild conditions suggests that the compound can be utilized as a starting material for the protection of 2'-hydroxyl group of adenosine. Contrary to expectation, reactions of **19** with acyl halide, acid anhydride or dihydropyran were complicated, giving rise to significant side reactions and affording unidentified products.

The reaction of **19** with phenyl isocyanate (**22**) and diphenylketene (**23**), however, led to definite products. **19** reacted with **22** in pyridine to give 5'-*O*-phenylcarbamoyladenosine (**25**) and N^6,5'-*O*-bis(phenylcarbamoyl)adenosine (**26**) in 34 and 45% yields, respectively. The products were identified by comparison with samples prepared by the reaction of **22** with 2',3'-*O*-isopropylideneadenosine, followed by removal of the protecting group.

Similarly, **19** reacted with **23** to give 5'-*O*-(diphenylacetyl)adenosine and N^6,5'-*O*-bis(diphenylacetyl)-adenosine in 21 and 41% yields, respectively.

In the reaction of **19** with **22** and with **23**, no 2'- and/or 3'-*O*-carbamoyl- or acyladenosine could be obtained. The results lead to the hypothesis that the 3',5'-*O*-triphenylphosphoranediyl group "activates" the 5'-carbon atom of **19**. The electrophilic attack at the 5'-carbon atom accompanies 5'-O–P bond rearrangement giving 2',3'-*O*-(triphenylphosphoranediyl)-



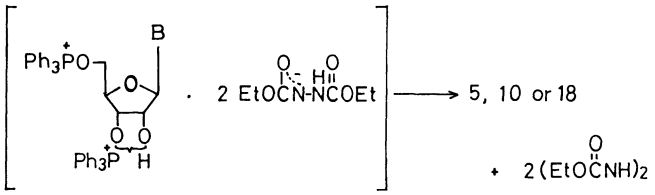
22 24 25 R=H 26 R=CNPh

Scheme 3.

adenosine derivative (**24**) in which the phosphoranediyl group protects 2'- and 3'-hydroxyl groups from further attack of the electrophiles (Scheme 3).[13]

On the basis of NMR studies, Mengel and Bartke have demonstrated that the product obtained by the reaction of adenosine with **1** and **2** is not **19** but **20**.[14] However, it is difficult to explain the formation of 5'-*O*-benzoyladenosine and N^3,5'-cycloadenosine by the structure **20**. A plausible interpretation might be given if we assume equilibrium between **19** and **20** in which the former is reactive species.

Reaction Mechanism. 2'(or 3'),5'-*O*-Bis(triphenylphosphonio)nucleoside (**27**) can be assumed to be a key intermediate for the formation of 2',3'-*O*-(triphenylphosphoranediyl)cyclonucleoside.[1,4] *N,N'*-Bis(ethoxycarbonyl)hydrazinide anion subsequently abstracts hydrogen atoms from the base and the hydroxyl group to form **5**, **10**, and **18** (Scheme 4).



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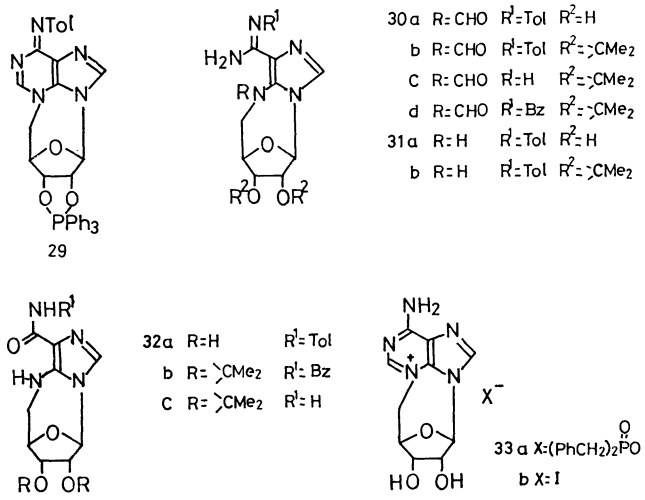
Scheme 4.

5 was obtained as the sole product derived from the nucleoside when the reaction of uridine with equimolar amounts of **1** and **2** was carried out with the intention of preparing **4**. This suggests that phosphorane ring formation is essential for the formation of the anhydro bond.[15]

The reaction of adenosine with **1** and **2** would also proceed through the initial formation of 5'-*O*-(triphenylphosphinio)adenosine (**28**). Since the hydrogen atom of the adenine ring is not so acidic as to be abstracted by hydrazinide anion, the 3'-hydroxyl group of **28** attacks the phosphorus atom giving **19**. Whether anhydro bond is formed or not would depend on the relative acidity of the base moiety of nucleoside and *N,N'*-bis(ethoxycarbonyl)hydrazine. In order to confirm the assumption, we carried out the reaction of N^6-*p*-toluoyladenosine in which N^6-hydrogen atom was expected to become more acidic than *N,N'*-bis(ethoxycarbonyl)hydrazine by the electron withdrawing effect of the *p*-toluoyl group.

The reaction of N^6-*p*-toluoyladenosine with **1** and **2** resulted in the formation of N^6-*p*-toluoyl-2',3'-*O*-(triphenylphosphoranediyl)-N^3,5'-cycloadenosine(**29**) in 24% isolated yield. Since purification of the product was difficult, the crude products obtained under separate experiment were treated with water under reflux to afford N^5,5'-anhydro-5-formamido-4-(*N*-*p*-toluoylamidino)-1-(β-D-ribofuranosyl)imidazole (**30a**) in 74% yield. By treatment with ammonia in methanol, **30a** was converted into **31a** which was hydrolyzed to **32a** under mild acidic conditions.

N^3,5'-Anhydro bond formation also took place when N^6-*p*-toluoyl-2',3'-*O*-isopropylideneadenosine was used. Thus the reaction of the fully protected nucleoside with **1** and **2** afforded imidazole nucleoside (**30b**) in a nearly quantitative yield rather than N^6-*p*-toluoyl-2',3'-*O*-isopropylidene-N^3,5'-cycloadenosine. Thus the precursor of **30b** should be N^6-*p*-toluoyl-2',3'-*O*-isopropylidene-N^3,5'-cycloadenosine which was hydrolyzed to **30b** during the work-up involving preparative layer chromatography. By subsequent treatment with ammonia in methanol, **30b** was converted into deformylated imidazole nucleoside (**31b**).



Reports have been given on the cleavage of N(1)–C(2) bond of N^3,5'-cycloadenosine derivatives. Anzai and Matsui[16] reported that treatment of 2',3'-*O*-isopropylidene-N^3,5'-cycloadenosine methanesulfonate and 5'-*O*-methylsulfonyl-N^6,N^6-dibenzoyl-2',3'-*O*-isopropylideneadenosine with alkali leads to imidazole cyclonucleoside **30c** and **30d**, respectively; they also reported the transformation of **30d** into **32b** and **32c**.

When the reaction of adenosine with **1** and **2** is carried out in the presence of dibenzyl hydrogenphosphate, N^3,5'-cycloadenosine dibenzyl phosphate (**33a**) is formed in good yield.[1] The reaction of adenosine with methyltriphenylphosphonium iodide gave N^3,5'-cycloadenosine iodide (**33b**).[17] It can thus be concluded that the N^3,5'-anhydro bond of adenosine is formed only when the reaction system involves a conjugate base of strong acid which stabilizes the N^3,5'-cycloadenosine cation.

The methods described make phosphoranediylnucleosides readily available. That the phosphoranediyl function serves as a protecting group as well as an activating group suggests a number of possibilities for the transformation of nucleosides.

Experimental

Methods. Preparative layer chromatography (TLC) was carried out on 20 cm×20 cm or 20 cm×30 cm glass plates coated with Merck silica gel PF_{254}. ^{1}H-Nuclear magnetic resonance (NMR) spectra were measured on a Hitachi R-20 spectrometer (60 MHz) using tetramethylsilane as an internal standard. We are grateful to Dr. G. Miyajima of Hitachi Co. Ltd. for the measurement of ^{31}P-NMR spectra. Ultraviolet absorption spectra were obtained with a Hitachi EPS-3T

recording spectrometer. Elemental analyses were carried out at the Institute of Physical and Chemical Research, Wako-shi, Saitama.

2′,3′-O-(Triphenylphosphoranediyl)-O²,5′-cyclouridine (5). A solution of **1** (2.61 g, 15 mmol) in THF (2 ml) was added to a mixture of uridine (1.22 g, 5 mmol) and **2** (3.93 g, 15 mmol) in THF (10 ml) at room temperature. The nucleoside dissolved on addition of **1**, precipitation taking place shortly afterwards. After the mixture had been kept stirred at room temperature overnight, the precipitate was collected by centrifugation, washed successively with THF and ether. Recrystallization from DMF (80 °C) gave **5** not melting below 250 °C; UV_{max} (MeCN) 232 nm; NMR (DMSO-d_6) δ=4.32, 4.50, 4.70 (m, 5, $C_2'H$, $C_3'H$, $C_4'H$, $C_5'H$), 5.86 (br. s, 1, $C_1'H$), 7.28 (15, aromatic H). Found: C, 66.65; H, 4.82; N, 5.81%. Calcd for $C_{27}H_{23}N_2O_5P$: C, 66.67; H, 4.76; N, 5.76%.

When **5** was treated with AcOH–H_2O or dil aqueous ammonia, uridine and triphenylphosphine oxide were formed in a 1 : 1 ratio.

O²,5′-Cyclouridine (4). A solution of **5** (486 mg, 1 mmol) in THF–H_2O (1 : 1 v/v, 10 ml) was stirred over a period of 3 d at room temperature and then evaporated. The residue was washed with acetone in order to remove triphenylphosphine oxide giving **4** (70%), which melted with decomposition at *ca.* 265 °C (lit,[6] dec 212—214 °C). UV_{max} (MeOH) 238 nm. Found: C, 47.75; H, 4.54; N, 12.34%. Calcd for $C_9H_{10}N_2O_5$: C, 47.79; H, 4.46; N, 12.39%.

When **4** was allowed to react with 1.5 molar equivalent each of **1** and **2** in THF at room temperature overnight, **5** was obtained in 73% yield.

O²-Methyl- and O²-Ethyluridine. **5** (1.458 g, 3 mmol) was treated with methanol (100 ml) under reflux for 10 h and then evaporated. The residue was washed with acetone, recrystallization from methanol giving *O²*-methyluridine with mp 171—172 °C (lit,[18] mp 173 °C). UV_{max} (H_2O) 229, 253 nm, UV_{min} 213, 238 nm.

Similarly, *O²*-ethyluridine was isolated in 41% yield, mp 176—177 °C. UV_{max}(H_2O) 228, 253 nm; UV_{min} 213, 237 nm.

Isocytidine. A solution of **5** (120 mg, 0.125 mmol) in saturated methanolic ammonia (10 ml) was left to stand at room temperature for 5 d and then separated by TLC using $CHCl_3$–MeOH (10 : 1) to give isocytidine as a glass almost quantitatively. UV_{max}(MeOH) 230^{sh}, 255 nm, UV_{min} 250 nm. Found: C, 44.23; H, 5.39; N, 17.28%. Calcd for $C_9H_{13}N_3O_5$: C, 44.44; H, 5.72; N, 17.10%.

Isocytidine (100 mg, 0.41 mmol) dissolved in 2,2-dimethoxypropane (2 ml) in the presence of a catalytic amount of *p*-toluenesulfonic acid was stirred for 2 h at room temperature and then neutralized with sodium methoxide. The resulting mixture was separated by TLC using $CHCl_3$–MeOH (10 : 1), giving 50% of 2′,3′-*O*-isopropylideneisocytidine which was purified by re-precipitation from ethanol–ether, mp 191—192 °C (lit,[18] mp 206—207 °C).

Reaction of 5 with Acyl Bromide. A mixture of **5** (484 mg, 1 mmol) and acetyl bromide (492 mg, 4 mmol) in THF (5 ml) was kept stirred at room temperature for 3 h and then evaporated. The residue was separated by TLC using $CHCl_3$–MeOH (95 : 5) giving 173 mg (73%) of **9b** with mp 183—185 °C (lit,[19] mp 180—183 °C).

In a similar way, **5** was treated with benzoyl bromide to give **9a** (300 mg, 73%). The substance softens at 78 °C, showing no definite mp. UV_{max}(MeOH) 255 nm, UV_{min} 226 nm. Found: C, 46.62; H, 3.53; N, 6.60%. Calcd for $C_{15}H_{15}N_2O_5Br$: C, 46.73; H, 3.77; N, 6.81%.

N⁴-Benzoyl-2′,3′-O-(triphenylphosphoranediyl)-O²,5′-cyclocytidine (10). A solution of **1** (4 mmol) in THF (2 ml) was added to a mixture of *N⁴*-benzoylcytidine (694 mg, 2 mmol) and **2** (4 mmol) in THF (4 ml) at room temperature. The nucleoside dissolved as **1** was added and shortly afterwards pale yellow solid began to precipitate. After the mixture had been stored at room temperature for 2 d, the precipitate was collect and recrystallized from dry acetonitrile, giving 830 mg (71%) of **10** which decomposed at 200—201 °C. UV_{max} (MeCN) 235^{sh}, 318 nm (ε 14600), UV_{min} 290 nm; NMR ($CDCl_3$) δ=4.16—4.66 (m, 5, $C_2'H$, $C_3'H$, $C_4'H$, $C_5'H$), 5.17 (d, 1, $C_1'H$), 6.60 (d, 1, C_5H), 8.20—8.30 (m, 21, aromatic-H, C_6H). Found: C, 69.27; H, 4.79; N, 6.93%. Calcd for $C_{34}H_{28}N_3O_5P$: C, 69.26; H, 4.79; N, 7.13%.

A solution of **10** in MeCN–H_2O (1 : 1) was kept stirred at room temperature for 2 d and then evaporated. The residue was washed with acetone to remove triphenylphosphine oxide, giving *N⁴*-benzoylcytidine in nearly quantitative yield with mp 222—225 °C (lit,[20] mp 219—220 °C). The substance was identical with an authentic sample as confirmed by IR analysis.

N⁴-Benzoyl-2′,3′-O-isopropylidene-O²,5′-cyclocytidine. A solution of **1** (4.5 mmol) in THF (2 ml) was added dropwise at room temperature to a solution of *N⁴*-benzoyl-2′,3′-*O*-isopropylidenecytidine (1.161 g, 3 mmol) and **2** (4.5 mmol) in THF (5 ml). After the mixture had been kept stirred overnight, the precipitate was filtered and recrystallized from $CHCl_3$ giving 484 mg (44%) of the compound with mp 290 °C. UV_{max} (MeCN) 252, 316 nm, UV_{min} 220, 290 nm; NMR (DMF-d_7 and acetone-d_6) δ=1.32 and 1.55 (two s, 6, isopropylidene methyl), 4.02—4.70 (m, 3, $C_4'H$, $C_5'H$), 5.06 (m, 2, $C_2'H$, $C_3'H$), 5.55 (d, 1, $C_1'H$), 6.51 (d, 1, C_5H), 7.36—8.11 ppm (m, 6, aromatic-H, C_6H).

N⁴,5′-O-Dibenzoylcytidine. *a) With Use of Benzoic Acid*: **10** (589 mg, 1 mmol) was allowed to react with benzoic acid (366 mg, 3 mmol) in THF (8 ml) at room temperature overnight or under reflux for 2.5 h. The TLC of the crude reaction mixture showed that **10** was completely converted into *N⁴*,5′-*O*-dibenzoylcytidine. The solvent was evaporated and the residue was purified by TLC ($CHCl_3$–MeOH= 10 : 1) giving the compound (70%) with mp 187—189 °C (lit,[21] mp 186—190 °C). UV_{max}(EtOH) 229, 261, 305 nm, UV_{min} 245, 289 nm.

b) With Use of Tetrabutylammonium Benzoate: Benzoic acid (1.5 mmol) was added to a 10% solution of tetrabutylammonium hydroxide in methanol (3 ml) and evaporated to dryness. The salt was rendered anhydrous by repeated evaporation of added portion of dry benzene. To the salt was added **10** (1 mmol) and THF (5 ml), and the mixture was kept stirred overnight. The mixture was then worked up as above giving the compound in nearly quantitative yield.

N⁴,5′-O-Dibenzoyl-2′,3′-O-(triphenylphosphoranediyl)cytidine (11). A solution of **1** (3 mmol) in THF (2 ml) was added dropwise at room temperature to a mixture of *N⁴*,5′-*O*-dibenzoylcytidine (910 mg, 2 mmol) prepared as described above and **2** (3 mmol) in THF (8 ml). The nucleoside dissolved as **1** was added, precipitation taking place shortly afterwards. The mixture was kept stirred overnight and filtered to give crude product (1.12 g, 80%) which was dissolved in acetone–$CHCl_3$ and concentrated to small volume *in vacuo*. The concentrated solution was kept standing to precipitate 700 mg (49%) of pure phosphorane which was collected by filtration, mp 183—184 °C (dec). UV_{max}(MeCN) 231, 259, 311 nm, UV_{min} 222, 246, 288 nm. NMR (DMSO-d_6) δ=4.1—4.8 (m, 5, $C_2'H$, $C_3'H$, $C_4'H$, $C_5'H$), 5.85 (d, 1, $C_1'H$), 7.1—8.2 (m, 27, aromatic-H, C_5H, C_6H), 11.25 ppm (br. s, 1, NH). Found: C, 68.74; H, 4.85; N, 5.44%. Calcd for $C_{40}H_{34}N_3O_7P$: C, 69.19; H, 4.87; N, 5.90%.

The phosphorane was hydrolyzed by treatment with THF–H_2O for 24 h to give N^4,5′-*O*-dibenzoylcytidine and triphenylphosphine oxide in a *ca.* 1 : 1 ratio.

Methanolysis of N^4-*Benzoyl-2′,3′-O-(triphenylphosphoranediyl)-*O^2,*5′-cyclocytidine (10).* One mmol of **10** was treated with methanol (50 ml) under reflux for 5 h or kept stirred at room temperature overnight and then evaporated. O^2-Methylcytosine was isolated in 65% yield (81 mg) by TLC using ethyl acetate. UV_{max} (H_2O) 228, 264 nm, UV_{min} 243 nm. NMR (DMSO-d_6) δ=3.82 (s, 3, CH_3O), 6.16 (d, 1, C_5H), 7.00 (br. s, 2, NH_2), 7.96 ppm (d, 1, C_6H).

Methanolysis of N^4-*Benzoyl-2′,3′-O-isopropylidene-*O^2,*5′-cyclocytidine.* When the title compound was treated with methanol as in the methanolysis of **10**, O^4-methyl-2′,3′-*O*-isopropylideneuridine with mp 235—236 °C was isolated in 33% yield (80 mg) by TLC using $CHCl_3$–MeOH (10 : 1). UV_{max} (MeOH) 276 nm, UV_{min} 240 nm. Found: C, 51.80; H, 6.05; N, 9.37%. Calcd for $C_{13}H_{18}N_2O_6$: C, 52.34; H, 6.08; N, 9.37%. Benzamide (53 mg, 36%, mp 125—128 °C) and 2′,3′-*O*-isopropylidenecytidine (36 mg, 23%, glass) were also obtained.

N^4-*Benzoylcytidin-5′-yl Dibenzyl Phosphate (14a) and Diphenyl-Phosphate (14b).* Tetrabutylammonium dibenzyl phosphate was prepared from dibenzyl hydrogenphosphate (417 mg, 1.5 mmol) and tetrabutylammonium hydroxide (3 ml of 10% solution in methanol) by a procedure similar to that for N^4,5′-*O*-dibenzoylcytidine. The salt was allowed to react with **10** (489 mg, 1 mmol) at room temperature overnight, and then evaporated. The residue was purified by TLC using $CHCl_3$–MeOH (10 : 1) giving 210 mg (35%) of **14a** which was recrystallized from MeCN, melting at 136—137 °C. UV_{max} (MeOH) 262 (ε 24100), 306 nm, UV_{min} 235.5, 288 nm. NMR ($CDCl_3$+D_2O) δ=4.0—4.5 (m, 5, $C_2'H$, $C_3'H$, $C_4'H$, $C_5'H$), 5.07 (d, 4, $PhC\underline{H}_2$), 5.92 (d, 1, $C_1'H$), 7.3—8.3 ppm (m, 17, aromatic-H, C_5H, C_6H). Found: C, 59.31; H, 4.98; N, 6.92%. Calcd for $C_{30}H_{30}N_3O_9P$: C, 59.22; H, 5.03; N, 7.06%.

14a (58 mg) was converted into 2′,3′-*O*-isopropylidene derivative by treatment with acetone (1 ml) and 2,2-dimethoxypropane (2 ml) in the presence of *p*-toluenesulfonic acid (20 mg). The NMR spectrum of the product was identical with that of N^4-benzoyl-2′,3′-*O*-isopropylidenecytidin-5′-yl dibenzyl phosphate prepared by the procedure described below.

A similar treatment of **10** with tetrabutylammonium diphenyl phosphate afforded **14b** (15%) with mp 191—192 °C (from MeCN). NMR (DMSO-d_6) δ=5.35, 5.60 (2, 2′-OH, 3′-OH), 5.81 (d, 1, $C_1'H$), 11.10 ppm (br. s, 1, NH).

N^4-*Benzoyl-2′,3′-O-isopropylidenecytidin-5′-yl Dibenzyl Phosphate.* Dibenzyl hydrogenphosphate (417 mg, 1.5 mmol) was converted into tetrabutylammonium salt and allowed to react with N^4-benzoyl-2′,3′-*O*-isopropylidene-O^2,5′-cyclocytidine (484 mg, 1 mmol) in THF (5 ml) at room temperature overnight. After being evaporated, the products were separated by TLC ($CHCl_3$–MeOH=19 : 1), giving 422 mg (65%) of the compound which was recrystallized from petroleum ether, melting at 123—124 °C. Found: C, 61.20; H, 5.29; N, 6.49%. Calcd for $C_{33}H_{34}N_3O_9P$: C, 61.14; H, 5.32; N, 6.51%.

*1-(β-*D*-Arabinofuranosyl)-*N^4*-benzoylcytosin-5′-yl Dibenzyl Phosphate (17a).* Dibenzyl hydrogenphosphate (1.5 mmol) was allowed to react with **10** (1 mmol) in THF (5 ml) at room temperature overnight and then evaporated. **17a** (233 mg, 38%) was isolated by TLC using $CHCl_3$–MeOH (10 : 1). After recrystallization from MeCN, mp 166—169 °C. UV_{max} (EtOH) 261 (ε 24500), 308 nm, UV_{min} 235, 288 nm. NMR (DMSO-d_6) δ=3.86—4.38 (m, 5, $C_2'H$, $C_3'H$, $C_4'H$, $C_5'H$), 5.03 (d, 4, $PhC\underline{H}_2$), 5.70 (2, 2′-OH, 3′-OH), 6.20 (d, 1, $C_1'H$), 7.0—8.2 ppm (m, 17, aromatic-H, C_5H, C_6H).

*1-(β-*D*-Arabinofuranosyl)-*N^4*-benzoylcytosin-5′-yl Diphenyl Phosphate (17b).* *a) Reaction of* ***10*** *with Diphenyl Hydrogenphosphate*: The compound was prepared in 52% yield by a procedure similar to that for **17a**. This compound was recrystallized from MeCN, melting at 196—197 °C. NMR (DMSO-d_6) δ=5.78 (2, 2′-OH, 3′-OH), 6.25 (d, 1, $C_1'H$), 11.15 ppm (br. s, 1, NH). Found: C, 58.08; H, 4.61; N, 7.39%. Calcd for $C_{28}H_{26}N_3O_9P$: C, 58.03; H, 4.52; N, 7.25%.

*b) Reaction of 1-(β-*D*-Arabinofuranosyl)-*N^4*-benzoylcytosine with Diphenyl Phosphorochloridate*: 1-(β-D-Arabinofuranosyl)-N^4-benzoylcytosine[22] (80 mg, 0.23 mmol) was treated with diphenyl phosphorochloridate (100 mg, 0.37 mmol) in pyridine (1 ml) at room temperature overnight. After the work-up as described in a), **17b** was obtained in 51% yield. The products prepared by procedures a) and b) were identical.

2′,3′-O-(Triphenylphosphoranediyl)-N^3*,5′-cycloguanosine (18).* A solution of **1** (6 mmol) in dioxane (2 ml) was added dropwise to a suspension of guanosine (566 mg, 2 mmol) and **2** (6 mmol) in dioxane (5 ml) at 70 °C. Guanosine dissolved as **1** was added. The homogeneous solution was kept stirred at 70 °C for 3 h and then allowed to cool to room temperature. The resulting precipitate was filtered. The solid was dissolved in DMF (15 ml) and reprecipitated by the addition of THF (60 ml) giving 700 mg (67%) of **18**, not melting below 250 °C. UV_{max} (MeCN) 235 (ε 26500), 258 (ε 13300) nm, UV_{min} 223, 253 nm. NMR (DMSO-d_6) δ=3.95 (m, 2, $C_5'H$), 4.58—5.00 (m, 3, $C_2'H$, $C_3'H$, $C_4'H$), 6.37 (s, 1, $C_1'H$), 7.00—7.95 ppm (m, 18, aromatic-H, NH_2, C_6H). Found: C, 63.41; H, 4.68; N, 12.80%. Calcd for $C_{28}H_{24}N_5O_4P$: C, 64.00; H, 4.60; N, 13.33%.

18 (400 mg, 0.76 mmol) was treated with 0.1 mol dm^{-3} HCl for 1 h at room temperature, triphenylphosphine oxide (187 mg, 94%) precipitated being filtered off. The filtrate was neutralized with aqueous ammonia and then evaporated. The residue was washed with acetone and recrystallized from H_2O giving N^3,5′-cycloguanosine (177 mg, 88%); mp 265 °C. UV_{max} (H_2O, pH 1) 249 nm, UV_{min} 222 nm. UV_{max} (H_2O, pH 11) 268 nm, UV_{min} 250 nm.

3′,5′-O-(Triphenylphosphoranediyl)adenosine (19). A solution of **1** (15 mmol) in dioxane (10 ml) was added to a mixture of adenosine (2.67 g, 10 mmol) and **2** (15 mmol) suspended in dioxane (20 ml) at 70 °C. Adenosine dissolved as **1** was added. The solution was stirred at 70 °C for 3 h, and then allowed to cool to room temperature. The precipitate thus formed was filtered and recrystallized from dioxane giving 3.95 g (75%) of **19** with mp 171—172 °C. UV_{max} (MeCN) 260 (ε 7400) nm, UV_{min} 245 nm. NMR (DMSO-d_6) δ=4.10—4.84 (m, 5, $C_2'H$, $C_3'H$, $C_4'H$, $C_5'H$), 6.01 (d, 1, $C_1'H$), 7.59 ppm (m, 15, aromatic-H). Found: C, 63.66; H, 5.08; N, 13.20%. Calcd for $C_{28}H_{26}N_5O_4P$: C, 63.75; H, 4.98; N, 13.28%.

On treatment with AcOH–H_2O or dil aqueous ammonia, **19** was hydrolized to adenosine and triphenylphosphine oxide in a 1 : 1 ratio.

Reaction of 19 with Benzoic Acid. A mixture of **19** (1 mmol) and benzoic acid (3 mmol) in dioxane (5 ml) was heated at 70 °C for 5 h. The solution was made up to 50 ml. A certain volume of the resulting solution was chromatographed on Toyo Roshi 51A paper using solvent system of 1-BuOH–AcOH–H_2O=5 : 2 : 3 (v/v), the spots and blank areas of the paper being eluted by soaking in water of standard volume and their concentrations determined spectrophotometrically. The yields of 5′-*O*-benzoyladenosine (UV_{max} (H_2O) 238, 260 nm, UV_{min} 224, 252 nm) and N^3,5′-cycloadenosine (**21**; UV_{max} (H_2O) 273 nm, UV_{min} 229 nm) were

determined to be 59 and 16%, respectively. The following molar extinction values of the compounds were used: 5′-*O*-benzoyladenosine, 11000 (260 nm) and N^3,5′-cycloadenosine, 13500 (273 nm).

5′-Thiobenzoyl-5′-deoxyadenosine. Thiobenzoic acid (414 mg, 3 mmol) and **19** (529 mg, 1 mmol) in pyridine (5 ml) was kept stirred under N_2 at room temperature overnight, and then evaporated. The compound was obtained by TLC using $CHCl_3$–MeOH (10 : 1), followed by recrystallization from MeCN–MeOH; 244 mg (63%), mp 159—160 °C. UV_{max} (H_2O) 248, 262 (ε 13800) nm, UV_{min} 225 nm. Found: C, 52.33; H, 4.54; N, 18.10%. Calcd for $C_{10}H_{13}N_5O_3S$: C, 52.71; H, 4.42; N, 18.08%.

*Reaction of **19** with Phenyl Isocyanate.* A mixture of **19** (1 mmol) and phenyl isocyanate (357 mg, 3 mmol) in pyridine (5 ml) was kept stirred at room temperature overnight and then evaporated. 5′-*O*-Phenylcarbamoyladenosine (**25**; 134 mg, 34%) and N^6,5′-*O*-bis(phenylcarbamoyl)adenosine (**26**; 225 mg, 45%), isolated by TLC using ethyl acetate, had the following physical properties.

25 was recrystallized from MeOH, mp 181—183 °C. UV_{max} (H_2O) 237, 259 (ε 12100) nm, UV_{min} 223, 252 nm. Found: C, 50.49; H, 4.99; N, 20.78%. Calcd for $C_{17}H_{18}N_6O_5 \cdot H_2O$: C, 50.75; H 4.86; N, 20.79%.

26 was recrystallized from MeOH, softing at 145 °C, but showing no definite melting point. UV_{max} (MeOH) 235, 280 (ε 29900)[23] nm, UV_{min} 225, 253 nm.

Reaction of 2′,3′-O-Isopropylideneadenosine with Phenyl Isocyanate. A mixture of 2′,3′-*O*-isopropylideneadenosine (307 mg, 1 mmol) and phenyl isocyanate (3 mmol) in pyridine (5 ml) was kept stirred for 1 d and then evaporated. Ethanol was added to the residue which was evaporated. The residue was treated with 10% aqueous AcOH (40 ml) under reflux for 1.5 h in order to remove isopropylidene group. The products were separated by TLC using MeOH–$CHCl_3$ (10 : 1) giving N^6,5′-*O*-bis(phenylcarbamoyl)adenosine (374 mg, 69%) which was identical with **26** obtained by the procedure described above.

*Reaction of **19** with Diphenylketene.* A mixture of **19** (1 mmol) and diphenylketene (582 mg, 3 mmol) in pyridine (5 ml) was kept stirred at room temperature overnight and then evaporated. The following products were isolated by TLC using $CHCl_3$–MeOH (10 : 1).

5′-*O*-(Diphenylacetyl)adenosine was obtained in 20% (94 mg) yield and recrystallized from MeCN. It began to soften at 180 °C but showed no definite melting point. UV_{max} (MeOH) 260 (ε 12600) nm, UV_{min} 235 nm. Found: C, 62.46; H, 4.69; N, 14.94%. Calcd for $C_{24}H_{23}N_2O_5$: C, 62.46; H, 5.02; N, 15.18%.

N^6,5′-*O*-Bis(diphenylacetyl)adenosine was obtained in 46% (298 mg) yield and recrystallized from benzene–ether. It began to soften at 95 °C. UV_{min} (MeOH) 278 (ε 17500) nm, UV_{min} 240 nm. Found: C, 68.55; H, 5.09; N, 10.32%. Calcd for $C_{38}H_{33}N_5O_6$: C, 69.60; H, 5.07; N, 10.68%.

Reaction of N^6-p-*Toluoyladenosine with **1** and **2**. a)* N^6-p-*Toluoyl-2′,3′-O-(triphenylphosphoranediyl)-*N^3,*5′-cycloadenosine (**29**).* A solution of **1** (4.1 mmol) in dioxane (1.5 ml) was added dropwise over a period of 1 h to a mixture of N^6-*p*-toluoyladenosine (577 mg, 1.5 mmol) and **2** (4 mmol) in dioxane (1.5 ml) at 70 °C. After the nucleoside had dissolved, the mixture was allowed to cool to room temperature and then kept stirred overnight. The precipitate formed was filtered and washed with ether and dioxane to give **29** (201 mg, 24%). An analytical sample was prepared by recrystallization twice from dioxane–ether. It turned brown above 190 °C, melting at 200—204 °C. UV_{max} (dioxane) 243^{sh}, 307 nm, UV_{min} 289 nm. NMR ($CDCl_3$) δ=2.2 (s, 3, CH_3), 3.7—5.0 (m, 5, C_2′H, C_3′H, C_4′H, C_5′H), 5.92 (s, 1, C_1′H), 6.6—8.0 ppm (m, 21, aromatic-H, C_2H, C_8H). Found: C, 67.55; H, 4.82; N, 11.57%. Calcd for $C_{36}H_{30}N_5O_4P \cdot 1/2H_2O$: C, 67.91; H, 4.91; N, 11.00%.

b) N^5,*5′-Anhydro-5-formamido-4-(*N-p-*toluoylamidino)-1-(β-*D-*ribofuranosyl)imidazole (**30a**):* N^6-*p*-Toluoyladenosine (770 mg, 2 mmol) was allowed to react with 6 mmol each of **1** and **2** in dioxane (15 ml) in a similar manner to that described in a). The resulting mixture was treated with H_2O (2 ml) under reflux for 1 h, and then evaporated. The residue was separated by TLC ($CHCl_3$–MeOH=10 : 1) giving **30a** in 74% (532 mg) yield. This was recrystallized from acetone, mp 181—183 °C (dec). UV_{max} (MeOH) 270, 309 nm, UV_{min} 245, 290 nm.

N^5,*5′-Anhydro-5-amino-4-(*N-p-*toluoylamidino)-1-(β-*D-*ribofuranosyl)imidazole (**31a**).* **30a** (162 mg, 0.42 mmol) was treated with saturated methanolic ammonia (15 ml) at room temperature for 1 d and evaporated. **31a** was isolated in 64% yield and recrystallized from acetone–ethanol; dec at 214—216 °C. UV_{max} (MeOH) 255^{sh}, 273, 337 nm, UV_{min} 234, 296 nm.

N^5,*5′-Anhydro-5-amino-4-(*N-p-*toluoylcarbamoyl)-1-(β-*D-*ribofuranosyl)imidazole (**32a**).* **31a** (90 mg, 0.27 mmol) was treated with *p*-toluenesulfonic acid hydrate (190 mg, 1 mmol) in THF (3 ml) at room temperature for 8 h. The solution was neutralized with triethylamine. The precipitate wa· collected by filtration and washed with water and methanol giving **32a** in 64% yield. The product was recrystallized from acetone, mp 215—217 °C (dec). UV_{max} (MeOH) 252, 314 nm, UV_{min} 237, 275 nm. Found: C, 56.21; H, 5.13; N, 15.37%. Calcd for $C_{17}H_{18}N_4O_5$: C, 56.98; H, 5.06; N, 15.64%.

N^5,*5′-Anhydro-5-formamido-4-(*N-p-*toluoylamidino)-1-(2,3-*O-*isopropylidene-β-*D-*ribofuranosyl)imidazole (**30b**).* A solution of **1** (1.5 mmol) in THF (1 ml) was added dropwise at room temperature over a period of 1 h to a mixture of N^6-*p*-toluoyl-2′,3′-*O*-isopropylideneadenosine (425 mg, 1 mmol) and **2** (1.5 mmol) in THF (2 ml). The homogeneous solution was kept standing overnight and then evaporated. **30b** was obtained nearly quantitatively by TLC using ethyl acetate–benzene (1 : 1). It was recrystallized from MeOH, mp 240—242 °C. UV_{max} (MeOH) 270, 310 nm, UV_{min} 253, 290 nm. Found: C, 59.11; H, 5.41; N, 16.71%. Calcd for $C_{21}H_{23}N_5O_5$: C, 59.28; H, 5.45; N, 16.46%.

N^5,*5′-Anhydro-5-amino-4-(*N-p-*toluoylamidino)-1-(2,3-*O-*isopropylidene-β-*D-*ribofuranosyl)imidazole (**31b**).* **30b** (558 mg, 1.31 mmol) was treated with saturated methanolic ammonia (120 ml) at room temperature for 8 h and then evaporated. The residue was separated by TLC ($CHCl_3$–MeOH=10 : 1) giving **31b** (52%) with mp 250—251 °C (lit,[16a] mp 245—247 °C). UV_{max} (MeOH) 250^{sh}, 272 (ε 18500), 336 (ε 16800) nm, UV_{min} 244, 296 nm (lit,[16a] UV_{max} (MeOH) 270 (ε 18500), 333 (ε 16800) nm. NMR ($CDCl_3$) δ=1.32, 1.43 (two s, 6, isopropylidene-CH_3), 2.37 (s, 3, CH_3), 3.38 (m, 2, C_5′H), 4.53, 4.94 (a pair of d, 2, C_2′H, C_3′H), 4.6 (m, 1, C_4′H), 5.71 (s, 1, C_1′H), 7.11, 7.85 ($A'_2B'_2$, 4, aromatic-H), 7.07 ppm (s, 1, C_2H). Found: C, 60.34; H, 5.86; N, 17.74%. Calcd for $C_{20}H_{23}N_5O_4$: C, 60.44; H, 5.83; N, 17.62%.

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11) The thin layer chromatography of the crude reaction mixture resulting from the reaction of **10** with the tetrabutylammonium salt of phosphate diester indicates the presence of a trace of **17a** and of **17b**. Similarly, a small amount of **14a** or **14b** was also formed in the reaction of **10** with free phosphate diesters.

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22) This compound was prepared by the reaction of 1-(β-D-arabinofuranosyl)cytosine (243 mg, 1 mmol) with benzoic anhydride (399 mg, 1.5 mmol) in DMF (2 ml) at room temperature and recrystallized from H_2O–ethanol, mp 180—182 °C.

23) N^6,3′,5′-*O*-Tris(phenylcarbamoyl)deoxyadenosine is reported to have UV_{max} (EtOH) 278 nm. K. L. Agarwal and H. G. Khorana, *J. Am. Chem. Soc.*, **94**, 3578 (1972).