s ($PhCHO_2$), 4.92 d (C-1-H, $J_{1,2}$ = 4 cps), 6.53 s (OCH_3), 7.83 s (CH_3 of tosyl).

Anal. Calcd for $C_{28}H_{28}O_8S_2$: C, 60.4; H, 5.07. Found: C, 60.2; H, 4.80.

Registry No.—**2**, 16136-65-5; **3**, 16136-66-6; **5**, 16136-67-7; **7**, 16136-68-8; **8**, 16136-69-9; **11**, 16136-70-2; **12**, 73-03-0; **15**, 16136-72-4; **17**, 16136-73-5; **18**, 16136-77-9; **19**, 16136-78-0; **20**, 16136-74-6; **21**, 16136-75-7; **22**, 16136-76-8; **23**, 16170-23-3.

Acknowledgment.—The authors are indebted to Dr. Peter Lim and staff for infrared and ultraviolet spectra and for optical rotation data. The authors are indebted to Mr. O. P. Crews and staff for large-scale preparation of intermediates.

Branched-Chain Sugar Nucleosides. III. 3′-*C*-Methyladenosine

RUTH F. NUTT, MARY J. DICKINSON, FREDERICK W. HOLLY, AND EDWARD WALTON

Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., Rahway, New Jersey

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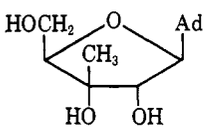
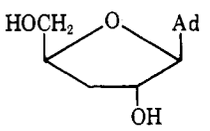
The synthesis of 3′-*C*-methyladenosine (**1**), the first example of a branched-chain sugar nucleoside, is described. The required derivative of the previously unknown 3-*C*-methyl-D-ribofuranose was prepared starting with 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-xylofuranose (**3**). Oxidation of **3** with RuO_4 produced 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranos-3-ulose (**4**) which when treated with methyl Grignard led to 5-*O*-benzoyl-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-ribofuranose (**9**). Removal of the 1,2-*O*-isopropylidene moiety of **9** in acidic methanol gave methyl 5-*O*-benzoyl-3-*C*-methyl-D-ribofuranoside (**11**). Benzoylation of **11** produced methyl 2,3,5-tri-*O*-benzoyl-3-*C*-methyl-D-ribofuranoside (**13**). Conversion of **13** into 2,3,5-tri-*O*-benzoyl-3-*C*-methyl-D-ribofuranosyl bromide (**19**) followed by reaction with chloromercuri-6-benzamidopurine gave the acylated nucleoside (**22**) which was deacylated to yield 3′-*C*-methyladenosine (**1**). The β anomeric configuration of **1**, assigned on the basis of the *trans* rule and rotational properties, was proved through oxidation studies as well as by conversion of **1** into a 3,5′ cyclo nucleoside. Some reactions and properties of several 3-*C*-methyl-D-ribofuranose derivatives are described. As part of a short discussion of some conformational aspects of the 3-*C*-methyl-D-ribofuranosyl moiety based on nmr spectral measurements and construction of molecular models, it is suggested that the carbohydrate part of **1** exists in a T_3^2 conformation.

We became interested in the synthesis of nucleosides of branched-chain sugars[1] through earlier work on 3′-deoxyadenosine (**2**),[2] a potent inhibitor of RNA synthesis in Ehrlich ascites cells.[3] Available biological evidence[4] indicates that it is incorporated into the RNA chain where, having no 3′-hydroxyl group, it acts as a chain terminator. The biological properties of 3′-deoxyadenosine led us to undertake the synthesis of an adenosine analog having a 3′-hydroxyl group, but one of altered chemical reactivity. This was accomplished by the substitution of a methyl group for the proton at C-3′ of the ribose moiety thereby converting the normal secondary 3′-hydroxyl into a tertiary alcohol. The resultant nucleoside, 3′-*C*-methyladenosine (**1**), is the first[5] synthetic nucleoside containing a branched-chain sugar. This is not surprising in view of the rather limited availability of branched-chain sugars.[6]



1



2

It was felt that the change of the normal secondary 3′-hydroxyl of adenosine into the tertiary 3′-hydroxyl group in 3′-*C*-methyladenosine represented a more subtle alteration at the 3′-carbon than that in 3′-deoxyadenosine (**2**) where the 3′-hydroxyl is absent. The presence of the 3′-hydroxyl in **1** may permit certain enzymic reactions for which it is required; on the other hand, its reduced chemical reactivity might be expected to interfere with other biological processes. It is apparent that, in addition to changing the chemical reactivity of the 3′-hydroxyl group, the branching at C-3′ will have other consequences. The methyl group occupies more space above the furanose ring as depicted in **1** than does the C-3′ proton of adenosine. It also introduces an additional bulky-group eclipsing interaction with its predictable effect on the conformation of the furanose ring. Both of these factors would be expected to play a role in the biochemistry of 3′-*C*-methyladenosine.

For the synthesis of 3′-*C*-methyladenosine (**1**), a suitable derivative of the unknown 3-*C*-methyl-D-ribose was required. The key intermediate for its synthesis was 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-*erythro*-pentos-3-ulose (**4**), the synthesis of which was described recently[7] by us and earlier by Oka and Wada.[8] In both cases, the osulose **4** was obtained by the oxidation of the unblocked 3-hydroxyl group in

(1) (a) E. Walton, F. W. Holly, and R. F. Nutt, Winter Meeting of the American Chemical Society, Phoenix, Ariz., Jan 1966, Abstract 37C; (b) E. Walton, S. R. Jenkins, R. F. Nutt, M. Zimmerman, and F. W. Holly, *J. Amer. Chem. Soc.*, **88**, 4524 (1966); (c) R. F. Nutt and E. Walton, *J. Med. Chem.*, **10**, 151 (1967).

(2) E. Walton, F. W. Holly, G. E. Boxer, R. F. Nutt, and S. R. Jenkins, *ibid.*, **8**, 659 (1965).

(3) (a) H. Klenow and S. Frederickson, Abstracts, the VIth International Congress of Biochemistry, New York, N. Y., July 1964, p 66; (b) H. T. Shigeura and C. N. Gordon, *J. Biol. Chem.*, **240**, 806 (1965).

(4) H. T. Shigeura and G. E. Boxer, *Biochem. Biophys. Res. Commun.*, **17**, 758 (1964).

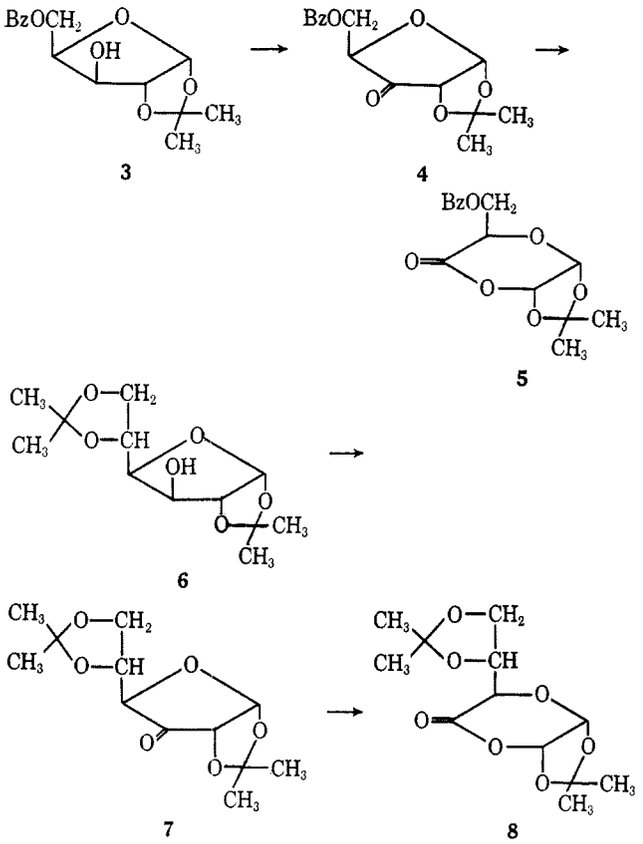
(5) After our preliminary report (ref 1b and 1c) on the synthesis of **1**, F. W. Lichtenthaler and H. Zinke [*Angew. Chem.*, **78**, 774 (1966)] described the synthesis of 1-(3-deoxy-3-*C*-methyl-3-nitro-β-D-glucopyranosyl)uracil from "uridine dialdehyde" and nitroethane.

(6) The chemistry of naturally occurring branched-chain sugars was reviewed by R. Shaeffer, *Advan. Carbohyd. Chem.*, **11**, 263 (1956). Since that time notable progress has been made in the synthesis of branched-chain sugars; for example, the synthesis of the streptoses by J. R. Dyer, W. E. McGonigal, and K. C. Rice [*J. Amer. Chem. Soc.*, **87**, 654 (1965)], the synthesis of hamamelose by W. G. Overend and N. R. Williams [*J. Chem. Soc.*, 3446 (1965)] and also by J. J. K. Novak and F. Šorm [*Collect. Czech. Chem. Commun.*, **30**, 3303 (1965)], and the synthesis of noviose by B. P. Vaterlaus, J. Kiss, and H. Spiegelburg [*Helv. Chim. Acta*, **47**, 381 (1964)], among others.

(7) R. F. Nutt, B. Arison, F. W. Holly, and E. Walton, *J. Amer. Chem. Soc.*, **87**, 3273 (1965).

(8) K. Oka and H. Wada, *Yakugaku Zasshi*, **83**, 890 (1963); *Chem. Abstr.*, **60**, 1825 (1964).

SCHEME I

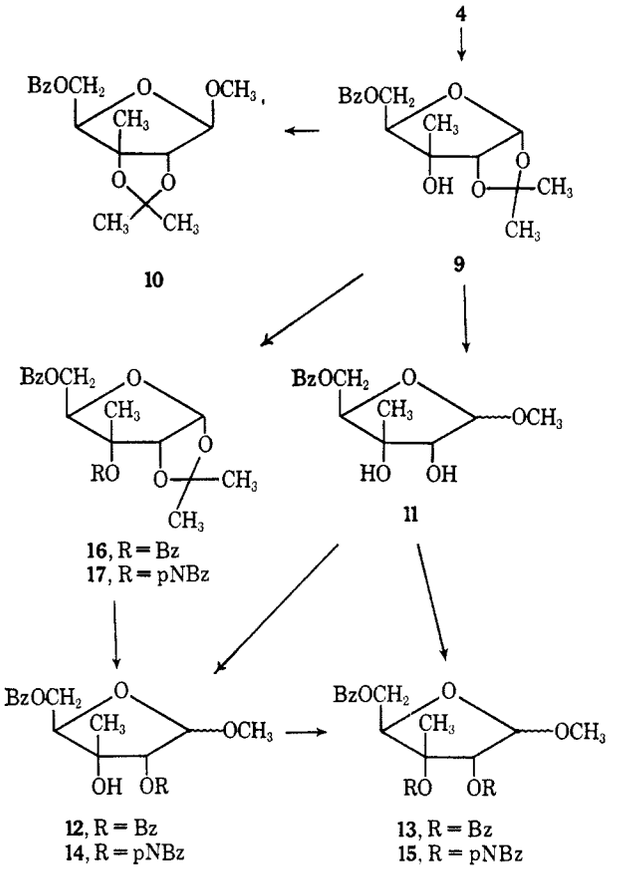


5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-xylofuranose[9] (**3**) (Scheme I).

Considerable difficulty was experienced in carrying out this oxidation, probably because of unfavorable steric factors.[10] Oxidizing agents such as chromium trioxide in pyridine, acetone and/or acetic acid, aluminum isopropoxide in acetone, potassium permanganate in acetone as well as lead tetraacetate in benzene gave either complex mixtures or unchanged starting material. The method of Oka and Wada[8] using chromium trioxide in *t*-butyl alcohol was tried, but, in our hands, the yields were too low to be useful. During the course of this work a new method for oxidizing sterically hindered hydroxyl groups in carbohydrate derivatives with ruthenium tetroxide was reported,[11] whereby 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**6**) was converted into 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**7**) in 80% yield. When we applied this reagent to the oxidation of **3**, 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-*erythro*-pentos-3-ulose (**4**) was isolated in 50% yield in spite of the concomitant formation of the product of oxygen insertion, 6-*O*-benzoyl-3-deoxy-1,2-*O*-isopropylidene-3-oxa-α-D-*erythro*-hexos-4-ulose (**5**). When the time of reaction was extended, the by-product of **5** became the major product. The oxidation of **6** with ruthenium tetroxide was repeated and, as reported,[11] after a few hours the product **7** was produced, while after 48 hr the product of oxygen insertion 1,2:6,7-di-*O*-isopropylidene-3-deoxy-3-oxa-α-D-*ribo*-heptos-4-ulose (**8**) was obtained.[12]

Reaction of **4** with methylmagnesium iodide was essentially stereospecific and afforded 5-*O*-benzoyl-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-ribofuranose (**9**) (Scheme II). The bulky isopropylidene group blocking the C-1 and C-2 hydroxyls in **4** interferes with the addition of the Grignard reagent from the underside of the ring as depicted and none of the corresponding 3-*C*-methylxylose derivative was detected among the reaction products. Conversion of **9** into methyl 5-*O*-benzoyl-2,3-*O*-isopropylidene-3-*C*-methyl-β-D-ribofuranoside (**10**) in a mixture of anhydrous methanol, acetone, and hydrogen chloride indicated the *cis* nature of the C-2 and C-3 hydroxyls and confirmed the ribose configuration of the Grignard addition product. The β-glycoside (**10**) was the only detectable product of this reaction. The assignment of the β configuration to **10** was made on the basis of the low value of the coupling constant for the C-1 and C-2 protons ($J_{1,2} \sim 0$ cps) observed in its nmr spectrum.

SCHEME II



The next step in the synthesis required the conversion of the 3-*C*-methylribose derivative (**9**) into a form suitable for reaction with an appropriate derivative of adenine. Acidic methanolysis of **9** under essentially anhydrous conditions produced methyl 5-*O*-benzoyl-3-*C*-methyl-D-ribofuranoside (**11**) as a mixture of α and β anomers, but in only 50% yield. The remainder appeared in the form of the 2,3-*O*-isopropylidene derivative (**10**). However, when some water was added

(9) P. A. Levene and A. L. Raymond, *J. Biol. Chem.*, **102**, 317 (1933).

(10) (a) B. R. Baker and D. H. Buss [*J. Org. Chem.*, **30**, 2304, 2308 (1965)] have commented on the difficulty of oxidizing sterically hindered hydroxyls in carbohydrate derivatives. (b) The oxidation of **3** with DMSO to give **4** has recently been reported by G. L. Tong, W. W. Lee, and L. Goodman, *ibid.*, **32**, 1984 (1967).

(11) P. J. Beynon, P. M. Collins, and W. G. Overend, *Proc. Chem. Soc.*, 342 (1964).

(12) V. M. Parikh and J. K. N. Jones [*Can. J. Chem.*, **43**, 3452 (1965)] have described a buffered, catalytic ruthenium tetroxide oxidation of carbohydrate derivatives which does not give oxygen inserted products.

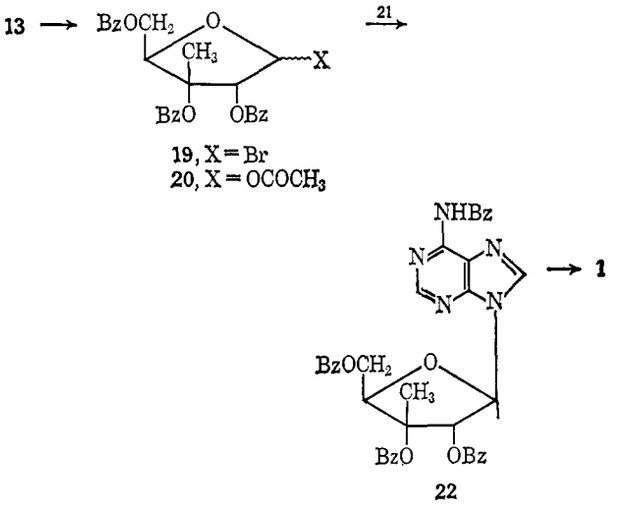
to the methanolysis solution, the formation of **10** was avoided and the anomeric mixture (**11**) was produced in good yield. Benzoylation of **11** in pyridine at room temperature rapidly produced methyl 2,5-di-*O*-benzoyl-3-*C*-methyl-α- (and β-) ribofuranoside (**12**); practically no benzoylation of the tertiary C-3 hydroxyl was noted under these conditions even though an excess of benzoyl chloride was used. After chromatography of the anomeric mixture of products on silica gel, it was possible to obtain the major component (β-**12**) as a crystalline solid. Again, the *trans* nature of the protons at C-1 and C-2 was indicated by the low coupling constant ($J_{1,2}$ = 0.5 cps) shown in its nmr spectrum. When **12** was heated with benzoyl chloride in pyridine at 100° for several hours, the tertiary C-3 hydroxyl was acylated, and methyl 2,3,5-tri-*O*-benzoyl-3-*C*-methyl-β-D-ribofuranoside (**13**) was obtained as an oil. An interesting characteristic of 3-*C*-methyl-D-ribofuranose is that each of the hydroxyl groups has a different functionality—primary at C-5, secondary at C-2, and tertiary at C-3. This feature makes the selective acylation of the different hydroxyl groups feasible.

Similarly, treatment of **11** with *p*-nitrobenzoyl chloride at 65° for 4.5 hr produced methyl 5-*O*-benzoyl-2,3-di-*O*-*p*-nitrobenzoyl-α- (and β-) D-ribofuranoside from which the β anomer (**15**) ($J_{1,2}$ < 0.5 cps) was isolated as a crystalline product. In this case, no attempt was made to isolate the intermediate 2,5-di-*O*-acylated derivative (**14**) which was noted on tlc very early during the course of the reaction. As expected, *p*-nitrobenzoylation occurred under milder conditions than those required for benzoylation.

Some acylations of 5-*O*-benzoyl-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-ribofuranose (**9**) were also investigated. Treatment of **9** with benzoyl chloride in pyridine at room temperature for 20 hr produced the crystalline 3,5-di-*O*-benzoyl derivative (**16**). The conditions for benzoylation of the tertiary C-3 hydroxy group were much milder than those (100° for 16 hr) required for the benzoylation of **12** wherein the tertiary hydroxyl is flanked by a 2-*O*-benzoyl group. Likewise *p*-nitrobenzoylation of **9** occurred readily at room temperature in a few hours, whereas the corresponding reaction with **14** required heating at 65° for 4.5 hr.

It was expected that acidic methanolysis of **16** would give methyl 3,5-di-*O*-benzoyl-3-*C*-methyl-β-D-ribofuranoside. However, examination of the products of such a reaction revealed that a rearranged product had been produced. Migration of the benzoyl group from the C-3 tertiary hydroxyl to the secondary hydroxyl at C-2 had occurred—undoubtedly *via* an intermediate cyclic form. A crystalline anomer was isolated and found to be identical with methyl 2,5-di-*O*-benzoyl-3-*C*-methyl-β-D-ribofuranoside (**12**), prepared earlier by direct benzoylation of methyl 5-*O*-benzoyl-3-*C*-methyl-D-ribofuranoside (**11**).

For the synthesis of 3′-*C*-methyladenosine, methyl 2,3,5-tri-*O*-benzoyl-3-*C*-methyl-α- (and β-) D-ribofuranoside (**13**) obtained by a one-step benzoylation of **11** was used. Treatment of the anomeric mixture with hydrogen bromide in acetic acid gave the desired bromo sugar (**19**) but as part of a mixture of products as indicated by tlc and nmr. Examination of the nmr spectrum of the crude reaction product showed that, in addition to the α and β anomers of 2,3,5-tri-*O*-benzoyl-3-*C*-methyl-D-ribofuranosyl bromide (**19**), a considerable amount of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-3-*C*-methyl-α- (and β-) D-ribofuranose (**20**) had been produced. A typical band for acetyl methyl protons was noted at τ 7.92, and resonances for the α and β anomeric protons were observed at τ 4.28 and 4.12. The nmr spectrum also indicated the presence of one other minor but unidentified impurity. When the crude bromo sugar was retreated with hydrogen bromide, but this time in ether solution, the 1-*O*-acetyl derivatives (**20**) were converted into the desired product (**19**).[13] In an attempt to eliminate the two-step process for the preparation of the bromo sugar (**19**), reaction of **13** with hydrogen bromide at 25° in both ether and methylene chloride was tried. However, in neither case was the C-1 methoxyl group cleaved and none of the bromo sugar (**19**) was obtained.



Reaction of the bromo sugar (**19**) with chloromercuri-6-benzamidopurine (**21**)[14] produced the acylated nucleoside, 6-benzamido-9-(2,3,5-tri-*O*-benzoyl-3-*C*-methyl-β-D-ribofuranosyl)purine (**22**), isolated as a glass. Analytically pure product was obtained by column chromatography. Catalytic removal of the benzoyl groups from (**22**) in methanolic sodium methoxide gave crystalline 3′-*C*-methyladenosine (**1**).

Assignment of the β configuration to the product was based on the following: (1) as applied by Baker[15] to reactions of 2-*O*-acylhalogenoses with heavy metal derivatives of purines, the "*trans*" rule[16a] requires that the product in this case be β (*trans*); (2) both the negative optical rotation at the sodium D line as well as the negative Cotton effect shown by ORD measurements[16b] are consistent with a β configuration.

From the evidence at hand, there was little doubt that the product was of the β configuration. However, because there was no prior experience with nucleosides containing branched-chain sugars, a more direct proof of the configuration seemed desirable. Following the

(13) G. L. Tong, K. J. Ryan, W. W. Lee, E. M. Acton, and L. Goodman [*J. Org. Chem.*, **32**, 859 (1967)] have reported similar observations in their synthesis of 2,5-di-*O*-benzoyl-3-deoxy-D-*erythro*-pentofuranosyl chloride.

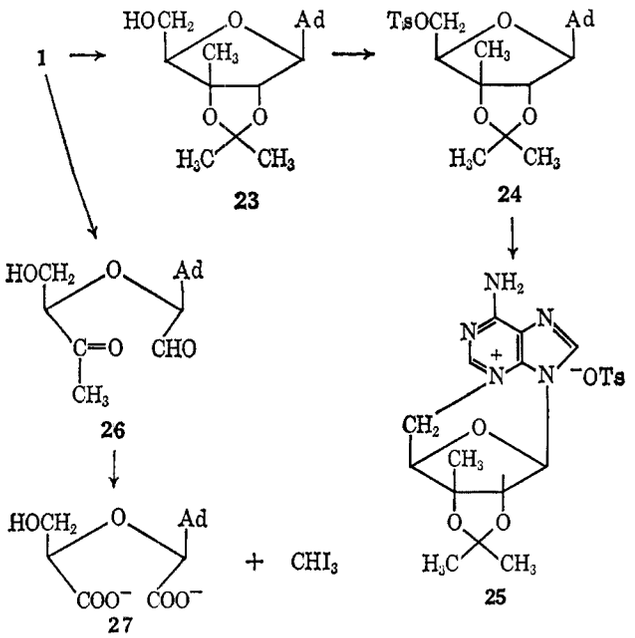
(14) J. Davoll and B. A. Lowy, *J. Amer. Chem. Soc.*, **73**, 1650 (1951).

(15) B. R. Baker, Ciba Foundation Symposium, Chemistry and Biology of Purines, Little, Brown, and Co., Boston, Mass., 1957, p 120.

(16) (a) R. S. Tipson, *J. Biol. Chem.*, **130**, 55 (1939); (b) See, for example, T. L. V. Ulbricht, J. P. Jennings, P. M. Scopes, and W. Klyne, *Tetrahedron Lett.*, No. 13, 695 (1964).

approach used by Clark, Todd, and Zussman[17a] for demonstrating the β configuration of adenosine, 3′-*C*-methyladenosine (**1**) was converted, by the method of Hampton,[17b] into its 2′,3′-*O*-isopropylidene derivative (**23**) (Scheme III). The synthesis of **23** was unexpectedly difficult; after stirring a mixture of **1** in acetone, 2,2-dimethoxypropane and 3.4 equiv of di-*p*-nitrophenyl hydrogen phosphate for 5 days, a small amount of starting material still remained and evidence for cleavage of the base from the sugar was noted by tlc. Under similar conditions (1.2 equiv of di-*p*-nitrophenyl hydrogen phosphate), adenosine was cleanly converted into its 2′,3′-*O*-isopropylidene derivative in good yield in 5 hr. Tosylation of **23** gave the corresponding 5′-*O*-tosyl derivative (**24**) which on heating in dioxane gave the 3,5′ cyclo nucleoside (**25**) proving the proposed β configuration as the α form could not be expected to undergo cyclization. The time (6.5 hr) required for the cyclization of **24** was considerably more than that (1 hr) required[17a] for the cyclization of the corresponding adenosine derivative. The compounds **24** and **25** were not isolated but were characterized by nmr and ultraviolet absorption spectra as well as their behavior on tlc.

SCHEME III



3′-*C*-Methyladenosine reacts rapidly with sodium metaperiodate. The keto aldehyde (**26**), presumably the product of this reaction, yields iodoform on further treatment with alkaline iodine. The formation of iodoform confirms the presence of the branched methyl group in the nucleoside (**1**). After removal of the iodoform, the filtrate, containing the dianion **27**, showed a molecular rotation of +14,800°. When adenosine was subjected to the same series of oxidations, which should also produce **27**, the final solution showed a molecular rotation of +13,200°. The reasonably good agreement of these rotational values is a further proof that **1** is of the β configuration.

The nmr spectrum of **1** was of no value for determining the configuration at C-1′. The resonance for the anomeric proton at τ 4.08 appears as a doublet with the rather large $H_{1',2'}$ coupling constant of 8.2 cps, far above the value of ≤ 2 cps[18] which would permit a comfortable assignment of a β (*trans*) anomeric configuration through application of the Karplus relationship.

The magnitude of $J_{1',2'}$ of **1** does, however, have implications concerning its conformation in solution. Table I lists the $J_{1',2'}$ values for 3′-deoxyadenosine, adenosine, and 3′-*C*-methyladenosine as well as the dihedral angles (ϕ) calculated[19] from these values. The values for ϕ ($H_{1'}$–$H_{2'}$) indicate that there is a greater amount of twist about the C-1′ to C-2′ bond in 3′-*C*-methyladenosine than in adenosine which is in turn greater than that in 3′-deoxyadenosine. This increasing amount of deformation of the furanose ring away from five-atom planarity parallels the increase in the number of bulky-group eclipsing interactions. Examination of space-filling (Courtauld) molecular models of the three purine nucleosides listed above clearly shows the requirement for a greater deformation of the furanose ring of 3′-*C*-methyladenosine than that required by the other two compounds. In fact, the models indicate that only one conformation of 3′-*C*-methyladenosine would be likely. Using the notational system of Jardetsky,[20a] this would be the twist conformation wherein C-3′ is *exo* and C-2′ is *endo*;[20b] in Hall's[20c] notation the conformation would be designated T_3^2. Inspection of the model of 3′-*C*-methyladenosine in the suggested T_3^2 conformation shows that the dihedral angle formed by $H_{1'}$ and $H_{2'}$ is very close to that (151°) calculated[19] from the spin–spin coupling constant. Of course, the methyl group at C-3′ eliminates vicinal proton couplings between C-2′ and C-3′ and C-3′ and C-4′; hence dihedral angles for these bonds are not obtainable by nmr spectral measurements. Examination of the $J_{1,2}$ values for the various derivatives of methyl 3-*C*-methyl-β-D-ribofuranoside show that they are all less than 1 cps which indicates an H_1–H_2 dihedral angle in the vicinity of 90°. From this it is clear that the methyl glycosides exist in a conformation that is quite different from that of the corresponding adenine nucleoside. A similar observation was made earlier[21] with 5′,5′-di-*C*-methyladenosine and the derivatives of methyl 5′,5′-di-*C*-methyl-β-D-ribofuranoside. It is suggested that the nucleoside (**1**) exists in

TABLE I

	$J_{1,'2'}$, cps	ϕ ($H_{1'}$–$H_{2'}$), deg	Nonproton eclipsing interactions
3′-Deoxydenosine	2.3	116	0
Adenosine	6.0	138	1
3′-*C*-Methyladenosine	8.2	151	2

(17) (a) V. M. Clark, A. R. Todd, and J. Zussman, *J. Chem. Soc.*, 2952 (1951); (b) A. Hampton, *J. Amer. Chem. Soc.*, **83**, 3640 (1961).

(18) R. U. Lemieux and D. R. Lineback, *Ann. Rev. Biochem.*, **32**, 155 (1963).

(19) Calculated using the equation given by R. J. Abraham, L. D. Hall, L. Hough, and K. A. McLauchlan, *J. Chem. Soc.*, 3699 (1962). Although the actual dihedral angles for these compounds in solution may differ somewhat from those obtained by nmr measurements, the relative variation of ϕ indicated in Table I can hardly be doubted.

(20) (a) C. D. Jardetsky, *J. Amer. Chem. Soc.*, **84**, 62 (1962). (b) From the values of $J_{1',2'}$ calculated for maximally puckered five-membered ring conformations, the C-2′ *endo* envelope (V^2) conformation is also possible; however, this must be considered unlikely because the eclipsing interaction between the C-3′ methyl and C-5′ is minimized if C-3′ is *exo*, as are contacts between the C-3′ methyl and the purine. (c) L. D. Hall, *Chem. Ind.* (London), 950 (1963).

(21) R. F. Nutt and E. Walton, *J. Med. Chem.*, **11**, 151 (1967).

the T_3^2 conformation, whereas the methyl glycosides favor the T_2^3 conformation. The apparent change in conformation in going from the methyl glycoside to the nucleoside may be due to interactions of N-3 or the C-8 proton[22] with the bulky substituents at C-3′ and C-4′ in the T_2^3 conformation which is relieved in the T_3^2 form as indicated by the molecular models.

The difficult conversion of 3′-*C*-methyladenosine (**1**) into its 2′,3′-*O*-isopropylidene derivative (**23**) can be explained by the resistance of **1** to assume the conformation required for isopropylidene formation. It is likely that the dihedral angle O–C_2′–C_3′–O in **1** is too large[23] to accommodate the facile formation of a dioxolane ring. The nmr spectra show that $J_{1',2'}$ of 8.2 cps in 3′-*C*-methyladenosine (**1**) has been reduced to 2.2 cps in its isopropylidene derivative (**23**) with a corresponding reduction in the calculated[19] dihedral angle from 151 to 116°. This reduction of twist about $C_{1'}$–$C_{2'}$ would be accompanied by corresponding reduction of the dihedral angle O–C_2′–C_3′–O to one small enough to accommodate the formation of a dioxolane ring.[24] The resultant flattening of the furanose ring would increase steric contacts between the purine moiety with the C-3′ methyl and the C-2′ proton.[22] The resistance to this conformational change would account for the slow formation of 2′,3′-*O*-isopropylidene-3′-*C*-methyladenosine (**23**).

Experimental Section[25]

5-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-*erythro*-pentos-3-ulose (4).—A solution of 125 g of $NaIO_4$ in 1.5 l. of water was cooled in an ice bath and added portionwise to a vigorously stirred suspension of 15 g of RuO_2 (Engelhard Industries)[26] in 1.5 l. of CCl_4 cooled in an ice bath. About 30 min after the addition was complete, most of the black, insoluble RuO_2 had been converted into soluble, yellow RuO_4. The CCl_4 solution of RuO_4 was separated from the water layer and added over 15 min to a stirred solution of 18 g (0.06 mol) of **3**[9] in 1.5 l. of CCl_4 covered by 100 ml of water. After 1 hr, the reaction mixture, which now contained RuO_2, was warmed to room temperature and stirred for an additional 2 hr. Tlc in chloroform–ethyl acetate (4:1) showed zones at R_f 0.35 (blue, starting material **3**), R_f 0.40 (brown, product **4**),[27] and R_f 0.80 (purple, by-product **5**). The reaction mixture was treated with 10 ml of isopropyl alcohol in 50 ml of CCl_4 to decompose unchanged RuO_4. The RuO_2 was filtered off and washed with 50 ml of water and 100 ml of CCl_4, and the CCl_4 in the combined filtrates was washed with 100 ml of saturated $NaHCO_3$ solution. The CCl_4 layer was concentrated, and the residue was crystallized from ether. A total of 9.9 g (55%) of **4** was obtained: mp 98–99°; $[\alpha]_D$ +136°, $[\alpha]_{578}$ +144° (*c* 1, $CHCl_3$) (lit.[8] mp 93–94.5°; $[\alpha]_D$ 135°); λ_{max}^{Nujol} 5.62 μ (cyclic ketone), 5.77 (ester); τ^{CDCl_3} 3.87 (d, C-1 H, $J_{1,2}$ = 4.5 cps), 8.50 and 8.58 [s, s, >$C(CH_3)_2$].

6-*O*-Benzoyl-3-deoxy-1,2-*O*-isopropylidene-3-oxa-α-D-*erythro*-hexos-4-ulose (5).—A CCl_4 solution (300 ml) of RuO_4, prepared from 3.18 g (23.8 mmol) of RuO_2, was added to a solution of 3.0 g (10.2 mmol) of **3** in 300 ml of CCl_4 and the mixture was stirred at 25° for 24 hr. The remaining intermediate **4** was removed by hydrolysis by the addition of 17.5 ml of 0.1 *N* LiOH. The reaction mixture was filtered and the CCl_4 layer was separated and concentrated leaving a residue of 1.82 g of solid, R_f 0.79, tlc in chloroform–ethyl acetate (9:1). The crude product when recrystallized from ether gave a total of 1.1 g (35%) of **5**: mp 111–112°; $[\alpha]_D$ +81°, $[\alpha]_{578}$ +86° (*c* 1.03, $CHCl_3$); λ_{max}^{Nujol} 5.71 and 5.80 μ (ester); τ^{CDCl_3} 4.08 (d, C-2 H), 4.32 (d, C-1 H, $J_{1,2}$ = 3.6 cps), 8.43 and 8.58 [s, s, >$C(CH_3)_2$].

Anal. Calcd for $C_{15}H_{16}O_7$: C, 58.44; H, 5.23. Found: C, 58.61; H, 5.41.

When 10 mg (0.034 mmol) of **4** was treated with a large excess (0.475 mmol) of RuO_4 in 10 ml of CCl_4 at 25° for 48 hr, the conversion into **5** was essentially complete as indicated by a single zone (R_f 0.79, purple) on tlc.

3-Deoxy-1,2:6,7-di-*O*-isopropylidene-3-oxa-α-D-*ribo*-heptos-4-ulose (8).—A solution of 3 g (11.4 mmol) of **6** in 200 ml of CCl_4 was stirred with a solution of RuO_4 (from 2.5 g of RuO_2) in 170 ml of CCl_4. After 25 hr, additional RuO_4 (from 1.5 g of RuO_2) in 150 ml of CCl_4 was added and stirring was continued for an additional 25 hr at 25°. About 2 ml of isopropyl alcohol in 3 ml of CCl_4 was added. The mixture was filtered and the filtrate was concentrated to a residual oil (2.09 g). Chromatography on 40 g of silica gel in chloroform–ethyl acetate (19:1) gave fractions containing a total of 870 mg of crude **8**, R_f 0.70 (purple), tlc in chloroform–ethyl acetate (4:1). Crystallization of a 320-mg portion of the crude product from 0.5 ml of ether plus 1 ml of petroleum ether (bp 30–60°) gave a total of 137 mg of **8**: mp 62–64°; $[\alpha]_D$ +86°, $[\alpha]_{578}$ +90 (*c* 0.5, $CHCl_3$); λ_{max}^{Nujol} 5.68 μ (ester); τ^{CDCl_3} 4.12 (d, C-2 H), 4.29 (d, C-1 H, $J_{1,2}$ = 3.9 cps).

Anal. Calcd for $C_{12}H_{18}O_7$: C, 52.55; H, 6.62. Found: C, 52.81; H, 6.68.

Later fractions from the chromatography contained mostly **7**, part of which was isolated as an oil (300 mg) after concentration of the solvents: λ_{max}^{neat} 5.63 μ (ketone); $[\alpha]_D$ +98°, $[\alpha]_{578}$ +103° (*c* 0.86, $CHCl_3$) (lit.[11] $[\alpha]_D$ +107°). On standing in the open for 72 hr, the oil crystallized. The crystals were triturated with ether and 110 mg of the hydrate of **7** was obtained: mp 105–110° (lit.[11] mp 109–112°); λ_{max}^{Nujol} 2.9 μ (OH) (no band at 5.63 μ for ketone); $[\alpha]_D$ +33°, $[\alpha]_{578}$ +35° (*c* 1.06, $CHCl_3$) (lit.[11] $[\alpha]_D$ +45°).

5-*O*-Benzoyl-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-ribofuranose (9).—A solution of methylmagnesium iodide was prepared by adding 29.6 g (0.208 mol) of methyl iodide in 100 ml of dry ether to a stirred mixture of 6.4 g (0.264 g-atom) of Mg shavings in 80 ml ofdry ether; it was added to a stirred solution of 7.7 g (0.026 mol) of **4** in 600 ml of dry ether at 5°. A heavy, white precipitate formed immediately. The reaction mixture was poured into

(22) R. A. Long, R. K. Robins, and L. B. Townsend [*J. Org. Chem.*, **32**, 2751 (1967)] have made note of an increased value of $J_{1',2'}$ (*trans*) in several 8-amino-2′-deoxyadenosines and suggest that the increase may be due to a steric interaction of the bulky group at C-8 (presumably with C-5′ or C-3′ H). Here, of course, the bulky group is on C-8, whereas in **1** it is on C-3′ and in 5′,5′-dimethyladenosine it is on C-5′. From calculations based on crystallographic measurements, A. E. V. Haschemeyer and A. Rich [*J. Mol. Biol.*, **27**, 369 (1967)] have noted the important steric interactions of N-3 and C-8 H with parts of the sugar moiety in purine nucleosides in the solid state. From their data, steric contacts in **1** would appear to be minimized in the T_3^2 conformation. See also M. Sundaralingam, *J. Amer. Chem. Soc.*, **87**, 599 (1965).

(23) It is known [E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis." Interscience Publishers, Inc., New York, N. Y., 1965, p 360] that a dihedral angle of 60° is too large to be incorporated into a dioxolane ring. Furthermore, R. U. Lemieux, J. D. Stevens, and R. R. Fraser [*Can. J. Chem.*, **40**, 1955 (1962)] have determined the dihedral angle between the vicinal carbons in 2,2-dimethyldioxolane to be 41°. Examination of the nmr spectra of adenosine (i) and 2′,3′-*O*-isopropylideneadenosine (ii) yielded the following *J* values from which the dihedral angles (ϕ) were calculated.[19] Here $\phi_{2',3'}$ in adenosine has been reduced by 6°

	i		ii	
Protons	*J*, cps	ϕ, deg	*J*, cps	ϕ, deg
1′,2′	6.0	138	3.0	121
2′,3′	5.0	44	6.0	38
3′,4′	3.2	122	2.3	116

to a value of 38° in the isopropylidene derivative and is accompanied by a general flattening of the furanose ring.

(24) From the observation that $\phi_{1',2'}$ in **1** (151°) is larger than that in adenosine (138°), it is proposed that $\phi_{2',3'}$ in **1** is also larger than $\phi_{1',2'}$ (44°) in adenosine. If this is so then formation of the dioxolane ring in **1** would be expected to require a greater reduction in $\phi_{1',2'}$ than that (17°) observed in the case of adenosine. The calculated reduction of 35° in $\phi_{1',2'}$ in going from **1** to **23** is in keeping with this proposal.

(25) Microanalyses were performed by Mr. R. N. Boos and his associates, and the ultraviolet spectral measurements were done by Mr. E. A. MacMullin and his associates. The ORD curve was determined by Dr. J. J. Wittick. All melting points were determined on a micro hot stage and are corrected. Except where noted, R_f data were obtained by tlc on silica gel and the zones were made visible by spraying the plates with a solution of 100 mg of 1,3-dihydroxynaphthalene in 50 ml of ethanol containing 2.5 ml of H_3PO_4 and warming them on the steam cone until the colors developed. Fritted-glass Büchner funnels of medium porosity were used for column chromatographic separations. The silica gel (J. T. Baker, 100–200 mesh) packing had a height to diameter ratio of about 1:1. Unless noted otherwise, all concentrations were carried out in a rotary evaporator at reduced pressure. The nmr spectra were determined with a Varian Associates Model A-60 spectrometer.

(26) RuO_2 from other commercial sources was not oxidized by sodium metaperiodate under these conditions.

(27) The zones for **3** and **4** were resolved only if the silica gel plates were dried at 100° for 30 min prior to use.

a cold, stirred mixture of 800 ml of ether and 250 g of NH_4Cl dissolved in 1200 ml of water. The water layer was separated and extracted with three 400-ml portions of ether. The ether layers were combined, washed with 200 ml of saturated sodium chloride solution, and dried over anhydrous $MgSO_4$. Concentration of the ether solution gave a residue which, when crystallized from ether–petroleum ether, gave a total of 5.4 g (67%) of **9**: mp 109–111°; $[\alpha]_D$ +12.6°, $[\alpha]_{578}$ +12.6° (*c* 2.4, $CHCl_3$).

Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.32; H, 6.54. Found: C, 62.35; H, 6.45.

Methyl 5-*O*-Benzoyl-2,3-*O*-isopropylidene-3-*C*-methyl-β-D-ribofuranoside (10) from 9.—A solution of 1.0 g (3.24 mmol) of **9** in 10 ml of acetone was treated with 15 ml of 3% (w/w) HCl in methanol. The solution was kept at 25° for 16 hr and 1.5 g of $NaHCO_3$ was added. The mixture was filtered and concentrated and the residue was leached with three 50-ml portions of methylene chloride. Concentration of the methylene chloride solution gave 1.16 g of an oil which showed a single zone (R_f 0.59) on tlc in chloroform–ethyl acetate (19:1). Glpc on 4% EGSS-Y on gas Chromosorb P showed a single peak at 15 min. The oil was evaporatively distilled at 120–130° (<1 mm), and 800 mg (77%) of **10** was obtained: $n^{22}D$ 1.5006; $[\alpha]_D$ −17.5°, $[\alpha]_{578}$ −18.2° (*c* 2.41, $CHCl_3$); λ_{max}^{neat} 3.30, 3.36 μ (CH), 5.77 μ (COOR), 11.54 μ [$C(CH_3)_2$]; τ^{CDCl_3} 5.05 (s, C-1 H), 5.73 (s, C-2 H), 6.66 (s, OCH_3), 8.45 (s, C-3 CH_3), 8.52 and 8.59 [s, s, $>C(CH_3)_2$].

Anal. Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.47; H, 6.79.

When the above reaction was carried out in 25 ml of methanolic hydrogen chloride, an oil (940 mg) was obtained which consisted of a mixture of **11** and **10** in a ratio of 1:1. The oil was chromatographed on 20 g of silica gel in chloroform–ethyl acetate (9:1). Initial fractions gave 500 mg of **10** followed by fractions yielding 420 mg of **11**.

Methyl 5-*O*-Benzoyl-3-*C*-methyl-α- (and β-) D-ribofuranoside (11).—A solution of 7.8 g (0.025 mol) of **9** in 320 ml of 20% (w/w) hydrogen chloride in methanol and 80 ml of water was stirred at 25° for 80 min. After the addition of 120 g of $NaHCO_3$, the mixture was concentrated to dryness and the residue was leached with two 100-ml portions of warm methylene chloride. The methylene chloride solution was concentrated and the residual oil (6.6 g) was chromatographed on a column of 170 g of silica gel in chloroform–ethyl acetate (4:1). Elution of the column was followed by tlc in chloroform–ethyl acetate (4:1): R_f 0.7, **9**; R_f 0.2, **11**. After the elution of a small amount of impurities, fractions containing **11** were obtained. The solvents were removed and the yield of liquid **11** was 5.75 g (80%): τ^{CDCl_3} (α-**11**) 5.02 (d, C-1 H, $J_{1,2}$ = 4.5 cps), 6.48 (s, OCH_3), 8.65 (s, C-3 CH_3); (β-**11**) 5.12 (d, C-1 H, $J_{1,2}$ = 2.5 cps), 6.60 (s, OCH_3), 8.59 (s, C-3 CH_3); α/β ratio 1:3.

Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.56; H, 6.43. Found: C, 59.49; H, 6.32.

Methyl 2,5-Di-*O*-benzoyl-3-*C*-methyl-β-D-ribofuranoside (β-12).—A solution of 420 mg (1.49 mmol) of α- and β-**11** in 7.5 ml of pyridine was cooled to 5° and treated with 463 mg (3.3 mmol) of benzoyl chloride. After a few minutes, at 25°, the reaction was complete as indicated by tlc in chloroform–ethyl acetate (4:1): R_f 0.2 (**11**), 0.6 (**12**). No further change was observed after 16 hr and the reaction mixture was treated for 15 min with 0.5 ml of water, added to 30 ml of cold water, and extracted with three 30-ml portions of chloroform. The chloroform extracts were washed with 5% HCl, 10% NaHCO, and saturated NaCl and concentrated. The residue was crystallized from ether–petroleum ether and gave 300 mg (52%) of β-**12**: mp 106.5–108°; $[\alpha]_D$ +2.3°, $[\alpha]_{578}$ +2.5° (*c* 1.58, $CHCl_3$); τ^{CDCl_3} 4.91 (d, C-1 H), 4.84 (d, C-2 H, $J_{1,2}$ = 0.5 cps), 6.57 (s, OCH_3), 8.45 (s, C-3 CH_3).

Anal. Calcd for $C_{21}H_{22}O_7$: C, 65.27; H, 5.74. Found: C, 65.08; H, 6.02.

Methyl 2,3,5-Tri-*O*-benzoyl-3-*C*-methyl-β-D-ribofuranoside (β-13).—A solution of 230 mg (0.595 mmol) of β-**12** in 3 ml of pyridine was treated with 270 mg (1.89 mmol) of benzoyl chloride and heated at 100° for 8 hr. The mixture was cooled, added to water and ice, and extracted with chloroform. The chloroform extracts were washed with dilute HCl and 10% $NaHCO_3$ and concentrated. The residual oil was chromatographed on 8 g of silica gel in chloroform–ethyl acetate (49:1). Fractions containing only material having R_f 0.7, tlc in chloroform–ethyl acetate (19:1), were combined and concentrated and gave 280 mg (95%) of β-**13**: $[\alpha]_D$ +13°, $[\alpha]_{578}$ +14° (*c* 0.5, $CHCl_3$); λ_{max}^{neat} 5.77 μ (ester); τ^{CDCl_3} 4.27 (s, C-2 H), 4.88 (s, C-1 H), 6.48 (s, OCH_3), 8.07 (s, C-3 CH_3).

Anal. Calcd for $C_{28}H_{26}O_8$: C, 68.56; H, 5.34. Found: C, 68.47; H, 5.52.

Methyl 5-*O*-Benzoyl-2,3-di-*O*-*p*-nitrobenzoyl-3-*C*-methyl-β-D-ribofuranoside (β-15).—A solution of 510 mg (1.81 mmol) of **11** in 10 ml of pyridine was cooled to 5° and treated with 1.0 g (5.43 mmol) of *p*-nitrobenzoyl chloride. After 5 min, tlc indicated that the 2-hydroxyl was completely acylated (R_f 0.1, **11**; 0.5, **14**; 0.71, **15**) in chloroform–ethyl acetate (4:1). The mixture was heated at 65° for 4.5 hr, cooled, and worked up as in the preparation of β-**13**. The crude product (1.23 g) was chromatographed on 30 g of silica gel in chloroform–ethyl acetate (19:1) and fractions containing only β-**15** by tlc were combined and concentrated. The residue was crystallized from benzene–petroleum ether and gave a total of 700 mg (66%) of β-**15**: mp 125–126.5°; $[\alpha]_D$ +18°, $[\alpha]_{578}$ +19° (*c* 0.79, $CHCl_3$); λ_{max}^{Nujol} 5.72 and 5.79 μ (ester), 6.55 and 6.59 μ (NO_2), τ^{CDCl_3} 4.27 (d, C-2 H), 4.88 (d, C-1 H), $J_{1,2}$ = 0.5 cps), 6.47 (s, OCH_3), 8.03 (s, C-3 CH_3).

Anal. Calcd for $C_{20}H_{24}N_2O_{12}$: C, 57.93; H, 4.17; N, 4.83. Found: C, 57.91; H, 3.90; N, 5.00.

3,5-Di-*O*-benzoyl-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-ribofuranose (16).—A solution of 1.0 g (3.54 mmol) of **9** in 12 ml of pyridine was cooled and treated with 750 mg (5.3 mmol) of benzoyl chloride. The mixture was kept at 25° for 72 hr and worked up as in preparation of β-**13**. The crude product (1.5 g) was crystallized from 1 ml benzene and 25 ml of petroleum ether and gave 700 mg of **16**: mp 82–84°; $[\alpha]_D$ +63°, $[\alpha]_{578}$ +66° (*c* 2.39, $CHCl_3$); λ_{max}^{Nujol} 5.77 μ (ester); R_f 0.64, tlc in chloroform–ethyl acetate (9:1).

Anal. Calcd for $C_{23}H_{24}O_7$: C, 66.96; H, 5.87. Found: C, 66.75; H, 5.63.

The residue from the filtrates, following chromatography on silica gel in chloroform–ethyl acetate (19:1) and crystallization from benzene–petroleum ether, yielded an additional 380 mg (total, 74%) of **16**.

Acidic Methanolysis of 3,5-Di-*O*-benzoyl-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-ribofuranose.—A mixture of 920 mg (2.23 mmol) of **16** in 23 ml of 20% hydrogen chloride in methanol was stirred at 25° for 15 hr. Complete solution was obtained in 15 min. The solution was concentrated and the residue in 80 ml of chloroform was washed with 30 ml of saturated $NaHCO_3$ solution. The chloroform layer was concentrated and the residue (950 mg) was chromatographed on 20 g of silica gel. Elution with chloroform–ethyl acetate (19:1) gave a total of 780 mg of a mixture of the α and β forms of **12**. Crystallization gave 420 mg (50%) of β-**12**, mp 107–108°, identical in all other respects with β-**12** prepared previously from **11**.

5-*O*-Benzoyl-1,2-*O*-isopropylidene-3-*O*-*p*-nitrobenzoyl-3-*C*-methyl-α-D-ribofuranose (17).—A solution of 1.0 g (3.54 mmol) of **9** in 12 ml of pyridine was treated with 980 mg (5.3 mmol) of *p*-nitrobenzoyl chloride. The mixture was kept at 25° for 5.5 hr and worked up as in the preparation of β-**13**. The crude product (1.67 g) was crystallized from benzene–petroleum ether and gave a total of 1.32 g (82%) of **17**: mp 109–110.5°; $[\alpha]_D$ +63°, $[\alpha]_{578}$ +66° (*c* 1.18, $CHCl_3$); λ_{max}^{Nujol} 5.76 and 5.81 shoulder (ester); R_f 0.69, tlc in chloroform–ethyl acetate (9:1).

Anal. Calcd for $C_{23}H_{23}NO_9$: C, 60.39; H, 5.07; N, 3.06. Found: C, 60.11; H, 4.91; N, 3.39.

Methyl 2,3,5-Tri-*O*-benzoyl-3-*C*-methyl-α- (and β-) D-ribofuranoside (13).—An 8.65-g (0.0307 mol) portion of **11** in 91 ml of dry (BaO) pyridine was acylated with 15.4 g (0.106 mol) of benzoyl chloride in the manner described for the preparation of β-**13** and the crude product (14.9 g) obtained was chromatographed on 375 g of silica gel in chloroform. Elution of the column was followed by tlc in chloroform–ethyl acetate (19:1): R_f 0.7, **13**; R_f 0.1, **11**. The product (**13**) was eluted in the first several fractions and, after removal of the solvent, amounted to 14.4 g (97%): τ^{CDCl_3} (α-**13**) 4.55 (d, C-2 H), 4.67 (d, C-1 H, $J_{1,2}$ = 4.5 cps), 6.60 (s, OCH_3), 8.17 (s, C-3 CH_3); (β-**13**) 4.32 (d, C-2 H), 4.93 (d, C-1 H, $J_{1,2}$ = 1.0 cps), 6.53 (s, OCH_3), 8.11 (s, C-3 CH_3).

Anal. Calcd for $C_{28}H_{26}O_8$: C, 68.56; H, 5.34. Found: C, 68.47; H, 5.52.

2,3,5-Tri-*O*-benzoyl-3-methyl-α- (and β-) D-ribofuranosyl Bromide (19).—A solution of 2.0 g (4.08 mmol) of **13** in 10 ml of acetic acid was treated with 0.5 ml of acetyl bromide, cooled to 10°, and treated with 10 ml of 30% (w/w) HBr in acetic acid. The reaction solution was warmed to 25° and after 40 min was

concentrated at a bath temperature of <40°. The residue was a mixture of **19** and **20**.[28] For the conversion of **20** into **19**, the mixture was dissolved in 100 ml of ether saturated with HBr at 0°. After being kept at 25° for 80 min, the solution was concentrated to a residual oil at a bath temperature of <40°. Four 30-ml portions of dry toluene were concentrated successively from the residue and a residue of **19** was obtained: τ^{CDCl_3} (α-**19**) 3.07 (d, C-2 H), 4.63 (d, C-1 H, $J_{1,2}$ 4.5 cps), 8.08 (s, C-3 CH_3); (β-**19**) 3.55 (d, C-2 H), 3.78 (d, C-1 H, $J_{1,2}$ = 1.0 cps), 8.05 (s, C-3 CH_3); the ratio of α-**19** to β-**19** was about 2:1.

6-Benzamido-(2,3,5-tri-*O*-benzoyl-3-*C*-methyl-β-D-ribofuranosyl)purine (22).—A suspension of 1.92 g (4.04 mmol) of finely ground **21**[14] in 170 ml of xylene was dried by distilling 90 ml of the xylene. The stirred mixture was cooled to about 60° and **19**, prepared from 2.0 g (4.04 mmol) of **13**, in 20 ml of dry xylene was added. The mixture was stirred and refluxed for 40 min and most of the suspended solid dissolved. The hot mixture was filtered and the filtrate was diluted with 400 ml of petroleum ether and cooled to 5° for several hours and the precipitated solid was removed. The solid was dissolved in 150 ml of chloroform and the solution was washed with two 30-ml portions of 30% KI solution and two 30-ml portions of water. After removal of the chloroform, the residue (1.93 g) was chromatographed on a short column of 40 g of alumina (Merck, acid washed) in benzene–chloroform (9:1). Fractions containing the product **22** R_f 0.28, tlc on alumina in benzene–chloroform (9:1) (zones visualized with iodine vapor) were combined and concentrated. A total of 1.36 g (48%) of **22** was obtained as a glass: $[\alpha]_D$ −146°, $[\alpha]_{578}$ −155° (*c* 1.5, $CHCl_3$); λ_{max}^{EtOH} [mμ ($\epsilon \times 10^{-3}$)] 232 (51), 279 (23.4); τ^{CDCl_3} 3.44 (s, unresolved C-1′ and C-2′ H's), 7.92 (s, C-3′ CH_3).

Anal. Calcd for $C_{39}H_{31}N_5O_5$: C, 67.14; H, 4.48; N, 10.04. Found: C, 66.94; H, 4.43; N, 9.91.

9-(3-*C*-Methyl-β-D-ribofuranosyl)adenine (1).—A mixture of 8.14 g (11.6 mmol) of **22** and 200 ml of dry (molecular sieves) methanol and a sodium methoxide solution, prepared from 400 mg (17 mg-atoms) of Na and 10 ml of dry methanol, was refluxed for 45 min. The solution was concentrated and the residue was dissolved in 200 ml of water. The water solution was neutralized (pH 7–8) with acetic acid, extracted with three 100-ml portions of chloroform, and filtered. The filtrate was concentrated to about 30 ml, seeded, and kept at 25° for 45 hr. Crystalline **1** (2.0 g) was removed by filtration and washed with two 3-ml portions of cold water. The filtrate and washings were concentrated to dryness and the residue was leached with a total of 100 ml of hot ethanol in several portions. The ethanol extracts were concentrated to dryness and the residue was crystallized from a minimum volume of hot water. A total of 2.7 g (83%) of 9-(3-*C*-methyl-β-D-ribofuranosyl)adenine (**1**) was obtained: mp 213–215° (transition at 165°); $\lambda_{max}^{H_2O}$ [mμ ($\epsilon \times 10^{-3}$)] (pH 1) 257.5 (14.8), (pH 7) 260 (14.9), (pH 13) 260 (14.3); $[\alpha]_D$ −58°, $[\alpha]_{578}$ −61° (*c* 1, H_2O); $[\phi]_{400}$ −518°, $[\phi]_{281}$ −3730° (tr), $[\phi]_{264}$ 0°, $[\phi]_{255}$ +700° (pk) (*c* 0.05, MeOH); τ^{D_2O} 4.08 (d, C-1′ H), 5.43 (d, C-2′ H, $J_{1',2'}$ 8.2 cps), 5.83 (m, C-4′ H), 6.18 (m, C-5′ H_2), 8.57 (C-3′ CH_3), 1.82 and 2.03 (2s, C-8 and C-2 H).

Anal. Calcd for $C_{17}H_{18}N_8O_{11}$: C, 46.97; H, 5.38; N, 24.90. Found: C, 46.90; H, 5.24; N, 25.13.

(28) Tlc on alumina in benzene–chloroform (1:1) showed zones (visualized with iodine vapor) at R_f 0.1, **19**; R_f 0.6, α-**20**; R_f 0.85, β-**20**. In this system **13** shows zones at R_f 0.8, α, and R_f 0.9, β. Nmr spectroscopy indicates the ratio of **19** to **20** is about 1:1: τ^{CDCl_3} (α-**20**) 3.31 (d, C-2 H), 4.28 (d, C-1 H, $J_{1,2}$ = 5.0 cps); (β-**20**) 3.62 (d, C-2 H), 4.14 (d, C-1 H, $J_{1,2}$ = 1.5 cps).

2′,3′-*O*-Isopropylidene-3′-*C*-methyladenosine (23).—A solution of 150 mg (0.53 mmol) of **1** in 12 ml of acetone and 2 ml of 2,2-dimethoxypropane was treated with 654 mg (1.82 mmol) of di-*p*-nitrophenyl hydrogen phosphate and the mixture was stirred at 25° for 5 days. The course of the reaction was followed by tlc in ethyl acetate–ethanol (4:1). Samples of the reaction mixture were spotted on plates previously spotted with saturated $NaHCO_3$ solution. Zones were noted at R_f 0.33 (**1**), 0.50 (**23**), 0.68 (sugar cleavage product). The reaction solution was added to 18 ml of 0.1 *N* $NaHCO_3$ and the mixture was concentrated to about 15 ml. The residual solution was extracted with four 20-ml portions of chloroform and the chloroform extracts were concentrated to dryness. The residue was chromatographed on 20 g of silica gel in ethyl acetate. Fractions containing the product were pooled and concentrated and the residue was crystallized from methanol–petroleum ether affording 80 mg (50%) of **23**: mp 205–207°; $[\alpha]_D$ −39°, $[\alpha]_{578}$ −42° (*c* 5.0, pyridine); λ_{max}^{MeOH} [mμ ($\epsilon \times 10^{-3}$)] (0.1 *N* HCl) 209 (21.8), 259 (14.7); (neutral) 209 (20.0), 259 (14.8); (0.1 *N* NaOH) 259 (14.6); τ^{CDCl_3} 3.43 (d, C-1′ H), 4.27 (d, C-2′ H, $J_{1',2'}$ = 2.2 cps), 5.38 (m, C-4′ H), 5.82 (m, C-5′ H_2), 8.16, 8.36 and 8.52 (3s, three CH_3 protons).

Anal. Calcd for $C_{14}H_{19}N_5O_4$: C, 52.33; H, 5.96; N, 21.80. Found: C, 52.60; H, 6.16; N, 22.01.

2′,3′-*O*-Isopropylidene-5′-*O*-tosyl-3′-*C*-methyladenosine (24).—A solution of 47 mg (0.07 mmol) of **23** in 1 ml of cold pyridine was treated with 40 mg (0.185 mmol) of tosyl chloride. The mixture was kept at 25° for 20 hr and decomposed (cold) with 2 drops of water and 2 ml of saturated $NaHCO_3$. The mixture was extracted with four 3-ml portions of chloroform. The chloroform extracts were washed with four 2-ml portions of water and concentrated. The residue was chromatographed on 10 g of silica gel in ethyl acetate. Fractions containing the desired product were pooled and concentrated giving 40 mg of **24**: R_f 0.81, tlc in ethyl acetate–ethanol (4:1); τ^{CDCl_3} 3.60 (d, C-1′ H), 4.72 (d, C-2′ H, $J_{1',2'}$ = 2.0 cps), 5.37 (broad s, C-4′ and C-5′ H); λ_{max}^{MeOH} [mμ ($\epsilon \times 10^{-3}$)] 215 (*ca.* 22), 225 shoulder (*ca.* 14), 259 (*ca.* 11).

3,5′-Cyclo-2′,3′-*O*-isopropyledene-3′-*C*-methyladenosine Tosylate (25).—A solution of 25 mg of **24** in 2 ml of dioxane was heated at 100°. The course of the reaction was followed by tlc in ethyl acetate–ethanol (4:1). Cyclization was complete in 6.5 hr. Concentration of the reaction solution gave 25 mg of **25**: R_f 0.06, tlc in ethyl acetate–ethanol (4:1); τ^{CDCl_3} 3.45 (s, C-1′ H), 5.48 (s, C-2′ H); λ_{max}^{MeOH} [mμ ($\epsilon \times 10^{-3}$)] 214 (*ca.* 20), 268 (*ca.* 12); λ_{min}^{MeOH} 239 (*ca.* 6).

Periodate Oxidation.—A solution of 36 mg (0.128 mmol) of 3′-*C*-methyladenosine in 4 ml of water was treated with 3 ml of 0.197 *N* $NaIO_4$. The optical rotation of the solution was constant after 2 hr, $[\alpha]_{578}$ −27.2° (*c* 0.514). A 1-ml aliquot of the oxidation solution was titrated by the Fleury–Lange method[29] and its was determined that 1.19 mmol of $NaIO_4$ was consumed by 1 mmol of **1**. A 2.0-ml aliquot of the oxidation solution (containing the ketoaldehyde **26**) was treated with 50 mg of Na_2CO_3, 70 mg of iodine, and 3 drops of 20% KI solution. Very rapidly the brown iodine color disappeared and a yellow solid precipitated. The mixture was shaken periodically and after 4 hr the yellow iodoform (mp 125°) was removed. The filtrate was decolorized with 30 mg of $NaAsO_2$ and the optical rotation was determined: $[\alpha]_{578}$ +53°, $[M]_{578}$ +14,700° (*c* 0.514). In an identical experiment, starting with adenosine, the solution obtained after oxidation with $NaIO_4$ followed by iodine and Na_2CO_3 showed $[\alpha]_{578}$ +49°, [M] +13,200° (*c* 0.8).

(29) R. D. Guthrie, *Methods Carbohyd. Chem.*, **1**, 437 (1962).