ca. 290; nmr ($CDCl_3$) δ 1.16 [9H, s, $(CH_3)_3CCOO$], 2.1–3.4 (2H, vbm, 3′-CH_2), 4.80 [3H, e, 5′-CH_2 and 4′-CH(?)], 6.04 [1H, e, 2′-CH(?)], 6.57 (1H, bs, 1′-CH), 6.88 (2H, bs, $COOCH_2$-N), 7.23–7.67 (6H, m, *m*- and *p*-C_6H_5COO), 7.88–8.20 (4H, m, *o*-C_6H_5COO), 8.48 and 9.20 (1H each, s,s, purine H's), 9.05 (2H, be, NH_2). The resolution of the nmr spectrum was low owing to slow decomposition and precipitation of solid from the solution. Compound **3** was essentially pure as judged by tlc and was used directly in the next reaction.

3-β-(2′,5′-Di-*O*-benzoyl-3′-deoxy-D-ribofuranosyl)adenine (4).—Compound **3** (4.26 g, 6.51 mmol) was dissolved in 12 ml of methanol saturated with ammonia. After 40 min at room temperature, the reaction mixture was filtered, giving 2.31 g of almost colorless microcrystals. Nmr spectroscopy (trifluoroacetic acid solution) established this material to be a mixture of 3-β-(2′,5′-di-*O*-benzoyl-3′-deoxy-D-ribofuranosyl)adenine (**4**) and its N^6-pivaloyl derivative in a ratio of about 4:1. The crude product was triturated with 30 ml of boiling chloroform, and this mixture was evaporated on a water bath with periodic addition of methanol until most of the chloroform had been replaced by methanol. Filtration of the cooled mixture then gave 1.775 g (59%) of 3-β-(2′,5′-di-*O*-benzoyl-3′-deoxy-D-ribofuranosyl)adenine (**4**) as colorless microcrystals: mp 244–246° dec; ν_{max} 3220 cm^{-1} (b, NH_2), 1724 (sh), 1716, 1272, and 1261 (st, ester) 1686 and 1621 (med, purine); λ_{max} 230 mμ (ε × 10^{-3} 33.8), 274–282 (13.5), *ca.* 293 (sh, 10.7), λ_{min} 251 (5.6), λ_{max} (pH 1) 229 (33.8) and 277 (20.2), λ_{min} 250 (8.7); nmr (CF_3COOH) δ 2.70 (2H, m, 3′-CH_2), 4.78 (2H, m, 5′-CH_2), 5.13 (1H, e, 4′-CH), 5.86 [1H, bps, 2′-CH(?)], 6.75 (0.8H, s, 1′-CH), 7.35–7.80 (6H, m, *m*- and *p*-C_6H_5COO), 8.00–8.28 (4H, m, *o*-C_6H_5-COO), 8.87 and 9.24 (1H each, s,s, purine H's).

Anal. Calcd for $C_{24}H_{21}N_5O_5$: C, 62.74; H, 4.61; N, 15.24. Found: C, 62.53; H, 4.64; N, 15.34.

From the original chloroform–methanol mother liquors long needles (0.166 g) deposited on standing. Recrystallization from acetonitrile gave glistening colorless needles of nearly pure **3-β-(2′,5′-di-*O*-benzoyl-3′-deoxy-D-ribofuranosyl)-N^6-pivaloyladenine**: softens and melts indistinctly at 113°; λ_{max} 229, 283 (sh), and 295 mμ, λ_{min} 255, λ_{max} (pH 1) 228, 283 (sh), 293, and 302 (sh), λ_{min} 251, λ_{max} (pH 13) 228, 273 (sh), 282 and 329, λ_{min} 263 and 288; nmr ($CDCl_3$) δ 1.46 (9H, s, $(CH_3)_3CCON$), 2.22–3.22 (2H, m, 3′-CH_2), 4.72 (2H, ps and d, J = ~4.2 cps av, 5′-CH_2), 4.68–5.22 (1H, m, 4′-CH), 6.02 and 6.11 (1H, d of bpt, J = 5.2, 1.5 cps, 2′-CH), 6.48 (1H, bs half-height width 2.5 cps, 1′-CH), 6.87–7.22 (1H, e, NH), 7.22–7.63 (6H, m, *m*- and *p*-C_6H_5COO), 7.92–8.13 (4H, m, *o*-C_6H_5COO), 8.14 and 8.81 (1H each, s,s, purine H's).

3-β-(3′-Deoxy-D-ribofuranosyl)adenine (5).—Sodium methoxide (0.206 g, 3.81 mmol) in 15 ml of methanol was added to a stirred suspension of 0.372 g (0.81 mmol) of 3-β-(2′,5′-di-*O*-benzoyl-3′-deoxy-D-ribofuranosyl)adenine (**4**) in 5 ml of dimethyl sulfoxide. The reaction mixture became homogeneous after being stirred for 40 min at room temperature and was treated with 7 drops of glacial acetic acid. The resulting solution was concentrated *in vacuo* (30°) to a translucent gel. This crude product was suspended in 50 ml of 19:1 chloroform–methanol, and the suspension was applied to a column of silica gel (70 g). Elution with 1:4–3:7 methanol–chloroform gave 0.185 g (91%) of pale cream crystals. Recrystallization from absolute ethanol gave 0.132 g of **3-β-(3′-deoxy-D-ribofuranosyl)adenine (5)** as analytically pure, glistening, colorless plates: mp 222–223° dec (further recrystallization raised the melting point to 224.5–225°); ν_{max} 2300–3500 cm^{-1} (b, st, NH_2 and OH); λ_{max} 214 mμ (ε × 10^{-3} 16.1) and 277 (12.9), λ_{min} 244 (2.9), λ_{max} (pH 1) 219 (sh, 11.4) and 276 (17.6), λ_{min} 237 (3.2); nmr (DMSO-d_6) δ 1.67–2.50 (2H, m, 3′-CH_2), 3.27–4.07 (2H, m, 5′-CH_2), 4.32–5.00 (2H, m, 2′-CH and 4′-CH), 5.84 and 6.12 [*ca.* 0.8H each, e (D), e (D), 2′-COH and 5′-COH], 5.96 (1H, d, J = 3.2 cps, 1′-CH), 8.21 [1.4H, e (D), NH_2], 7.85 and 9.05 (1H each, s,s, purine H's).

Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.80; H, 5.22; N, 27.88. Found: C, 47.98; H, 5.25; N, 27.98.

Increased yields of the nucleoside **5** could be obtained by using small solvent/solute ratios. Under these more concentrated conditions the reaction mixture would not become homogeneous but, after 2 hr or less, substantially pure nucleoside **5** could be obtained directly by filtration. Work-up of the filtrate would then give additional amounts of **5**.

Registry No.—**3**, 16136-37-1; **4**, 16136-34-8; **5**, 16136-35-9; 3-β-(2′,5′-di-*O*-benzoyl-3′-deoxy-D-ribofuranosyl-N^6-pivaloyladenine, 16136-36-0.

Branched-Chain Sugar Nucleosides. IV. 2′-*C*-Methyladenosine

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The synthesis of 2′-*C*-methyladenosine is described. The required derivative of the previously unknown 2-*C*-methyl-D-ribofuranose was prepared starting with 2-*C*-methyl-D-ribono-γ-lactone. The lactone was completely benzoylated and the benzoyl derivative was reduced with bis(3-methyl-2-butylborane) which produced a mixture of 2,3,5-tri-*O*-benzoyl-2-*C*-methyl-α- (and -β-) D-ribofuranose and 3,5-di-*O*-benzoyl-2-*C*-methyl-α- (and -β-) D-ribofuranose. This mixture was benzoylated to give a mixture of α and β tetrabenzoates which was converted into 2,3,5-tri-*O*-benzoyl-2-*C*-methyl-β-D-ribofuranosyl chloride. The chloro sugar reacted with chloromercuri-6-benzamidopurine to give the completely acylated nucleoside. Catalytic removal of the benzoyl blocking groups with sodium methoxide in methanol led to the isolation of crystalline 2′-*C*-methyladenosine. From nmr spectral measurements and consideration of steric interactions, it is suggested that 2′-*C*-methyladenosine exists in a 2′-*exo*,3′-*endo* (T_2^3) conformation and is, therefore, conformationally unrelated to adenosine.

In a preliminary communication,[1] we reported the synthesis of 2′-*C*-methyladenosine (**13**), the second of a series of branched-chain sugar nucleosides. We now wish to describe the synthesis of **13** in detail.

Our interest in 2′-*C*-methyladenosine stemmed from the biological activity evinced by 3′-*C*-methyladenosine,[1] the first compound of this series. Our objective in the synthesis of a 2′-*C*-methyl nucleoside was to produce a compound which might mimic a 2′-deoxy nucleoside, either through the lowered chemical activity of the tertiary 2′-hydroxyl or because conformational changes produced by the steric interaction of the 2′-*C*-methyl group with the purine moiety might move the 2′-hydroxyl group to a location where it would no longer be recognized enzymically as the 2′-hydroxyl group of a normal nucleoside. There is evidence that a tertiary alcohol in a nucleoside is not a satisfactory substrate for enzymic reactions in the finding that 5′,5′-di-*C*-methyladenosine,[2] a branched-chain sugar nucleoside having a tertiary C-5′ hydroxyl, is not phosphorylated by Ehrlich ascites cells.[3] It seemed possible that a nucleoside possessing a non-

(1) (a) E. Walton, S. R. Jenkins, R. F. Nutt, M. Zimmerman, and F. W. Holly, *J. Amer. Chem. Soc.*, **88**, 4524 (1966).

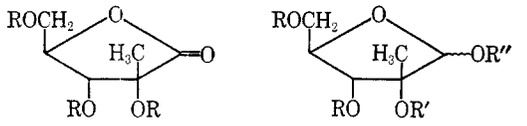
(2) R. F. Nutt and E. Walton, *J. Med. Chem.*, **11**, 151 (1958).

(3) H. T. Shigeura and S. D. Sampson, *Nature*, **215**, 419 (1967).

functioning 2′-hydroxyl group might indeed resemble a 2′-deoxy nucleoside in biological systems.

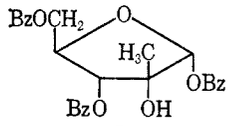
For the synthesis of 2′-*C*-methyladenosine, a source of the previously undescribed 2-*C*-methyl-D-ribofuranose was required. Aldoses branched at C-2 are not completely unknown. The naturally-occurring sugar hamamelose, 2-*C*-hydroxymethyl-D-ribose, has been available for some time and its synthesis in the pyranoid form was described by two groups[4a,b] of workers.

More recently the synthesis of methyl 3,4-*O*-isopropylidene-2-*C*-methyl-β-L-ribopyranoside was reported.[4c] The method of introducing branching at C-2 used by these workers involved addition of suitable reagents to a 2-keto aldopyranose. This approach might have been useful in the synthesis of 2′-*C*-methyl-D-ribofuranose, but what appeared to be a more attractive starting point was found in 2-*C*-methyl-D-ribono-γ-lactone (**1**) (α-glucosaccharinic acid lactone). This lactone, easily prepared[5a] in low yield by an alkaline rearrangement of invert sugar, has been known for about 90 years[5b] although its exact structure was finally proven only recently.[5c] Reaction of **1** in pyridine with benzoyl chloride gave the 2,3,5-tri-*O*-benzoyl-2-*C*-methyl-D-ribono-γ-lactone (**2**). Although benzoylation of the primary C-5 hydroxyl and the secondary C-3 hydroxyl proceeded at 25°, acylation of the tertiary C-2 hydroxyl required heating at 70° for several hours. The tri-*O*-benzoyllactone (**2**) was then reduced to the corresponding aldose using disiamylborane (bis-3-methyl-2-butylborane). This reagent had been used previously[6] in the reduction of several straight-chain poly-*O*-acyl-hexono-γ-lactones. The reduction of **2** yielded, along with the expected 2,3,5-tri-*O*-benzoyl-2-*C*-methyl-α- (and -β-) D-ribofuranose (**3**), a considerable amount of 3,5-di-*O*-benzoyl-2-*C*-methyl-α- (and -β-) D-ribofuranose (**4**). Not all of the di-*O*-benzoyl derivative (**4**) resulted from hydrolysis of the 2-*O*-benzoyl group but was produced in great measure by reductive cleavage as demonstrated by the isolation of benzyl benzoate following rebenzoylation of the crude reduction mixture. The 2,3,5-tri-*O*-benzoyl and 3,5-di-*O*-benzoyl derivatives (**3** and **4**) could be separated by chromatography on silica gel from which the α and β anomeric mixtures **3** and **4** were isolated as oils. For further characterization, both **3** and **4** were completely acylated with *p*-nitrobenzoyl chloride and crystalline 2,3,5-tri-*O*-benzoyl-1-*O*-*p*-nitrobenzoyl-2-*C*-methyl-β-D-ribofuranose (**5**) and 3,5-di-*O*-benzoyl-1,2-di-*O*-*p*-nitrobenzoyl-2-*C*-methyl-β-D-ribofuranose (**6**) were obtained, respectively. For preparative purposes, the mixture of **3** and **4** was benzoylated in pyridine at 70° to produce a mixture of α- and β-1,2,3,5-tetra-*O*-benzoyl-2-*C*-methyl-D-ribofuranose (**8**) from which most of the β anomer (β **8**) was separated by crystallization from ether. The pure α anomer (α **8**) was obtained by chromatography of the residue obtained from the filtrate from the crystallization. In an attempt to separate the α and β anomers of 2,3,5-tri-*O*-benzoyl-2-*C*-methyl-D-ribofuranose (**3**) by chromatography on acid-washed alumina, a rearrangement occurred and practically all of the product was converted into 1,3,5-tri-*O*-benzoyl-2-*C*-methyl-α-D-ribofuranose (**7**) by a migration of the 2-*O*-benzoyl group to the anomeric position. Only one anomer was obtained and, as the migration undoubtedly occurred through a cyclic intermediate, it must be the α anomer.



1, R = H
2, R = Bz

3, R = R′ = Bz; R″ = H
4, R = Bz; R′ = R″ = H
5, R = R′ = Bz; R″ = pNBz
6, R = Bz; R′ = R″ = pNBz
8, R = R′ = R″ = Bz



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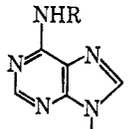
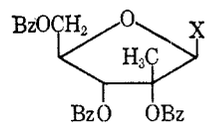
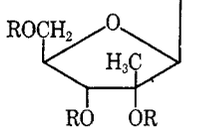
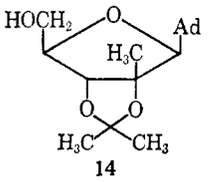




9, X = OCOCH3
10, X = Cl



12, R = Bz
13, R = H



14

Both anomers of **8** were convertable into 2,3,5-tri-*O*-benzoyl-2-*C*-methyl-β-D-ribofuranosyl chloride (**10**); however, the reaction conditions required for the conversion of α **8** were quite different from those used for β **8**. In the case of β **8**, **10** was obtained in good yield by treatment with ethereal hydrogen chloride at 25° for about 2 hr. Under the same conditions, α **8** remained virtually unchanged after 5 days. Even when hydrogen chloride in acetic acid was used, 24 hr at 25° was required for complete conversion of α **8** into a mixture of **10** and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-2-*C*-methyl-β-D-ribofuranose (**9**). Retreatment of this mixture with ethereal hydrogen chloride at 25° for 2 hr resulted in complete conversion into **10**.[7]

From both α **8** and β **8** only one anomer, 2,3,5-tri-*O*-benzoyl-2-*C*-methyl-β-D-ribofuranosyl chloride, is obtained. This is also true of the 1-*O*-acetyl intermediate (**9**) formed during the first stage of conversion of α **8** into **10**. Ness and Fletcher[8] have reported that the reaction of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide with water in acetone leads to the formation of approxi-

(4) (a) W. G. Overend and N. R. Williams, *J. Chem. Soc.*, 3446 (1965); (b) J. J. K. Novak and F. Sörm, *Collect. Czech. Chem. Commun.*, **30**, 3303 (1965); (c) A. A. J. Feast, W. G. Overend, and N. R. Williams, *J. Chem. Soc.*, 303 (1966).

(5) (a) R. L. Whistler and J. N. BeMiller, *Methods Carbohyd. Chem.*, **2**, 484 (1963); (b) E. Peligot, *Compt. Rend.*, **89**, 918 (1879); (c) J. C. Sowden and D. R. Strobach, *J. Amer. Chem. Soc.*, **82**, 3707 (1960).

(6) P. Kohn, R. H. Samaritano, and L. M. Lerner, *ibid.*, **86**, 1457 (1964); P. Kohn and L. M. Lerner, *J. Org. Chem.*, **31**, 1503 (1966).

(7) Tlc of the acetic acid, hydrogen chloride reaction solution in the conversion of α **8** into **10** showed a sizable zone for **10** at R_f 0.3 and a moderate zone for **9** at R_f 0.5. However, tlc of the product obtained after concentration of the reaction solution indicated that almost all of the isolated product was **9** and very little was **10**. This was confirmed by the nmr spectra, which indicated a ratio of **9** to **10** of about 9:1. This reversion of **10** to **9** during work-up is reasonable if one assumes that the reaction mixture is a mobile equilibrium. During concentration Cl^-, as volatile hydrogen chloride, is removed faster than AcO^- thereby driving the reaction in the direction of **9**. In the reaction carried out in ether solution, there is no competing anion, and **10** is the sole product isolated after concentration of the reaction solution.

(8) R. K. Ness and H. G. Fletcher, Jr., *J. Amer. Chem. Soc.*, **78**, 4710 (1956).

mately equal amounts of 2,3,5-tri-*O*-benzoyl-D-ribofuranose and 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose. We have repeated this reaction using the chloro sugar in place of the bromo sugar and have obtained a similar result. However, when **10** was subjected to the same conditions, 1,3,5-tri-*O*-benzoyl-2-*C*-methyl-α-D-ribofuranose was the only product. In the case of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride and bromide, the rearranged product 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose arises from the β-glycosyl halide *via* a cyclic carbonium ion whereas the 2,3,5-tri-*O*-benzoyl-D-ribofuranose comes from unassisted hydrolysis of the α anomer of the chloro sugar. The quantitative recovery of rearranged product **7** from **10** indicates that **10** is entirely in the β form.

The assignment of anomeric configurations to β **5**, β **6**, α **8**, β **8**, and **10** is based in part on the obvious α configuration of the rearrangement product **7**. The nmr spectrum of **7** shows the C-3 proton resonance as a broad singlet; the C-3 proton resonance of α **8** is also a broad singlet. On the other hand, all of the β anomers show the C-3 proton resonance as a doublet ($J_{3,4}$ = 7.3–7.5 cps). The resonance for the C-1 proton of both α and β anomers appears as a singlet because of the absence of vicinal protons at C-2. It was noted that the resonances for H-1 of the β anomers were about 0.2 ppm downfield relative to the resonances for H-1 of the related α anomers.

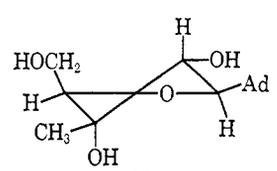
Benzoylation of **7** in pyridine with benzoyl chloride produced mainly α **8**; however, this does not constitute an unambiguous proof of the configuration of α **8** because a sizable amount of β **8** was also recovered from the reaction products. It is assumed that β **8** was obtained from 2,3,5-tri-*O*-benzoyl-2-*C*-methyl-D-ribofuranose (**3**) produced by reconversion of **7** into **3** during the essentially basic (pyridine) conditions of the benzoylation reaction. It has been reported[8] that 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose is rearranged to 2,3,5-tri-*O*-benzoyl-D-ribofuranose under basic conditions.

Additional confirmation of the anomeric configurational assignments of α and β **8** is obtained from the difference in the ease of conversion of these two compounds into the halo sugar **10**. Neighboring-group assistance in the β *trans* anomer of **8** would be expected to result in easy conversion into **10**, whereas the unassisted reaction in the case of the α anomer would be expected to require more strenuous conditions. The quite different experimental conditions required for the preparation of **10** from α and β **8** are in keeping with the configurational assignments.

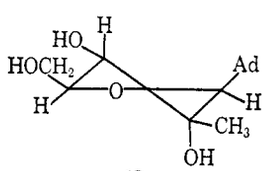
Reaction of **10** in boiling xylene with chloromercuri-6-benzamidopurine (**11**)[9] gave 6-benzamido-9-(2,3,5-tri-*O*-benzoyl-2-*C*-methyl-β-D-ribofuranosyl)purine (**12**) which was purified by chromatography on silica gel. Attempts to purify **12** on acid-washed alumina led to extensive decomposition into 6-benzamidopurine and a carbohydrate fragment whose physical properties indicated that it was 1,3,5-tri-*O*-benzoyl-2-*C*-methyl-α-D-ribofuranose (**7**).

Following purification, **12** was deblocked in methanol with a catalytic amount of sodium methoxide and 2′-*C*-methyladenosine (**13**) was isolated and crystallized from water.

Configurational Assignment.—The assignment of the β configuration to 2′-*C*-methyladenosine (**13**) was based on the following: (1) the *trans* rule;[10] (2) the negative Cotton effect shown by ORD measurements is consistent with the proposals advanced[11] for purine β-D-nucleosides; (3) the facile decomposition of the polyacylated nucleoside (**12**) on acid-washed alumina giving **11** and **7**, which undoubtedly requires the anchimeric assistance of the neighboring 2′-acyloxy moiety, is in keeping with a *trans* configuration of the functional groups at C-1′ and C-2′. Although nmr measurements were of little direct value toward establishing the anomeric configuration of **13**, the magnitude of $J_{3',4'}$ (8.8 cps) is of interest. In the case of 5′,5′-di-*C*-methyladenosine (**15**)[2] $J_{1',2'}$ was found to be about 7.0 cps whereas $J_{3',4'}$ was about 1.5 cps. On the other hand, 3′-*C*-methyladenosine (**16**)[12] showed $J_{1',2'} \simeq$ 8.2 cps. The rather large value for $J_{1',2'}$ in both **15** and **16** indicated a rather large dihedral angle for the *trans* protons on C-1′ and C-2′, and led to the proposal that C-2′ in these compounds, is in an *endo*[13] conformation. In 2′-*C*-methyladenosine (**13**), however, the dihedral angle H-3′–H-4′, is large, ∽155°,[14] and is in keeping with a C-3′ *endo*[13] conformation. The potential steric interaction of the C-2′ methyl group with the purine moiety at C-1′ would be maximumly relieved if C-2′ were *exo*.[15] For these reasons, and examination of molecular models, it is proposed that **13** exists in a twist conformation wherein C-2′ is *exo* and C-3′ is *endo* (T_2^3),[16] which would make 2′-*C*-methyladenosine the "conformational mirror image" of 3′-*C*-methyladenosine, and is, therefore, not related to adenosine conformationally.



16



13

2′-*C*-Methyladenosine (**13**) was converted, by a modification of the method of Hampton,[17] into its 2′,3′-*O*-isopropylidene derivative (**14**). As in the synthesis of 2′,3′-*O*-isopropylidene-3′-*C*-methyladenosine,[12] the conversion was very slow and gave a low yield of product. The nmr spectrum of **14** showed that $J_{3'4'}$ was 2.1 cps, a considerable reduction from the value of 8.8 cps shown by **13**, and indicates a reduction in the dihedral angle H-3′–H-4′ from 155° in **13** to ∽115° in **14**. As was proposed in the case of 3′-*C*-methyladenosine,[12] this would be accompanied by a reduction in the dihedral angle O–C-2′–C-3′–O to a size which would accommodate a dioxolane ring. The resultant flattening of the furanose ring would increase steric contacts between the

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

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

(11) T. R. Emerson, R. J. Swan, and T. L. V. Ulbricht, *Biochem. Biophys. Res. Commun.*, **22**, 505 (1966).

(12) R. F. Nutt, M. J. Dickinson, F. W. Holly, and E. Walton, *J. Org. Chem.*, **33**, 1789 (1968).

(13) C. D. Jardetsky, *J. Amer. Chem. Soc.*, **84**, 62 (1960).

(14) Calculated using $J_{3',4'}$ in the equation given by R. J. Abraham, L. D. Hall, L. Hough, and K. A. McLauchlan, *J. Chem. Soc.*, 3699 (1962).

(15) See A. E. V. Haschemeyer and A. Rich, *J. Mol. Biol.*, **27**, (1967), for data concerning steric interactions of the purine with parts of the carbohydrate moiety in nucleosides.

(16) Notation of L. D. Hall, *Chem. Ind.* (London), 950 (1963).

(17) A. Hampton, *J. Amer. Chem. Soc.*, **83**, 3640 (1961).

purine and sugar moieties[15] which impedes the conversion of **13** into **14**.

Experimental Section[18]

2,3,5-Tri-*O*-benzoyl-2-*C*-methyl-D-ribono-γ-lactone (2).—A solution of 5 g (30.8 mmol) of **1**[5] in 100 ml of dry pyridine was cooled, stirred, and treated with 17 ml of benzoyl chloride. The mixture was heated at 65–70° for 4 hr, then cooled, and stirred while 20 ml of water was added. After 25 min, the mixture was concentrated to a thick semisolid which was dissolved in 100 ml of chloroform and washed with three 50-ml portions of 10% hydrochloric acid, two 50-ml portions of 1 *N* sodium hydrogen carbonate, and two 50-ml portions of water. The dried chloroform layer was concentrated and the residue was crystallized from ether. The yield of **2** was 10.8 g (74%): mp 141–142°; $[\alpha]_D$ −79° (*c* 1, chloroform); λ_{max}^{Nujol} 5.57 (lactone) and 5.70 and 5.78 μ (ester); τ^{CDCl_3} 4.48 (d, C-3 H, $J_{3,4}$ = 6.0 cps), 4.82 (m, C-4 H), 5.25 (m, C-5 H_2), 8.06 ppm (s, C-2 CH_3).

Anal. Calcd for $C_{27}H_{22}O_8$: C, 68.35; H, 4.67. Found: C, 68.26; H, 4.76.

2,3,5-Tri-*O*-benzoyl-2-*C*-methyl-α- (and -β-) D-ribofuranose (3) and 3,5-Di-*O*-benzoyl-2-*C*-methyl-α- (and -β-) D-ribofuranose (4).—To a stirred solution of 30 g (63 mmol) of **2** in 125 ml of dry tetrahydrofuran at 0° under a nitrogen atmosphere was added dropwise 175 ml of 1 *M* bis(3-methyl-2-butyl)borane. After 16 hr at 25°, the reaction solution was cooled to 0° and 26 ml of water was carefully added. After the evolution of gas had subsided, the mixture was refluxed for 30 min and concentrated and the residual oil was dissolved in 250 ml of acetone and 75 ml of water. The solution was cooled (0–5°) and stirred during the dropwise addition of 33 ml of 30% H_2O_2 while the pH was maintained between 7 and 8 by the addition of 3 *N* NaOH. The excess H_2O_2 was decomposed at 25° by the cautious addition of 500 mg of 5% platinum on carbon. Stirring was continued until the evolution of gas was complete. The catalyst was removed and the filtrate was extracted with four 200-ml portions of chloroform. The chloroform solution was concentrated to a residual oil (42 g). Tlc in chloroform–ethyl acetate (19:1) showed zones at R_f 0.7 (by-product), 0.5 (**3**), 0.4 (**4**), 0.2, and 0.1 (by-products).

The residue was chromatographed on 650 g of silica gel in chloroform–ethyl acetate (99:1). Fractions containing materials of R_f (tlc) 0.7, 0.5, and 0.4 were combined and concentrated to an oil (32 g). Rechromatography of the oil on 650 g of silica gel in benzene–ethyl acetate (19:1) gave 15 g of a mixture of **3** and **4** which was satisfactory for use in the preparation of **8**.

A similar reduction of 5.5 g (11 mmol) of **2** gave 6 g of crude product which showed tlc zones at R_f 0.0, 0.18, 0.33, 0.45, and 0.65, on silica plates in benzene–ethyl acetate (4:1). It was chromatographed on 300 g of silica gel in the same solvent system which yielded 1.9 g of **3** (R_f 0.65) and 0.5 g of **4** (R_f 0.33) as oils which were further characterized by the synthesis of crystalline *p*-nitrobenzoyl derivatives **5** and **6** described below.

2,3,5-Tri-*O*-benzoyl-1-*O*-*p*-nitrobenzoyl-2-*C*-methyl-β-D-ribofuranose (5).—A solution of 0.5 g (1 mmol) of **3** in 8 ml of pyridine was treated with 370 mg (2 mmol) of *p*-nitrobenzoyl chloride. After being kept at 25° for 16 hr, the reaction was worked up in the usual manner. Crystallization of the crude product from ether gave 200 mg of β **5**: mp 211–212°; $[\alpha]_D$ +70°; $[\alpha]_{578}$ + 74° (*c* 1, $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 5.77 μ (C=O); R_f 0.55, tlc in benzene–ethyl acetate (19:1); τ^{CDCl_3} 2.90 (s, C-1 H), 4.00 (d, C-3 H, $J_{3,4}$ = 7.5 cps), 5.20 (m, C-4 H and C-5 H_2), 8.04 ppm (s, C-2 CH_3).

Anal. Calcd for $C_{34}H_{27}NO_{11}$: C, 65.28; H, 4.35; N, 2.24. Found: C, 65.30; H, 4.38; N, 2.37.

The filtrates from the crystallization of β **5** were concentrated and the residue (400 mg) was chromatographed on 20 g of silica gel in benzene–ethyl acetate (9:1). Fractions were obtained from which 100 mg of α **5** was obtained as an oil: R_f 0.6, tlc in benzene–ethyl acetate (19:1); λ^{CDCl_3} 3.08 (s, C-1 H), 4.30 (broad s, C-3 H, w_h = 4.5 cps), 5.16 (s, C-4 H and C-5 H_2), 8.01 ppm (s, C-2 CH_3).

3,5-Di-*O*-benzoyl-1,2-di-*O*-*p*-nitrobenzoyl-2-*C*-methyl-β-D-ribofuranose (β 6).—A solution of 290 mg (0.78 mmol) of **4** in 10 ml of dry pyridine was treated with 445 mg (2.4 mmol) of *p*-nitrobenzoyl chloride. After being heated at 45° for 3 hr the mixture was worked up in the usual manner. The crude product, as a residual oil, crystallized on the addition of ether. The solid was recrystallized from benzene–petroleum ether (30–60°) which gave 102 mg (20%) of β **6**: mp 207–208°; $[\alpha]_D$ +80°, $[\alpha]_{578}$ +85° (*c* 1, $CHCl_3$); τ^{CDCl_3} 2.97 (s, C-1 H), 4.02 ppm (d, C-3 H, $J_{3',4'}$ = 7.5 cps).

Anal. Calcd for $C_{34}H_{26}N_2O_{13}$: C, 60.89; H, 3.91; N, 4.18. Found: C, 61.09; H, 3.69; N, 4.12.

1,2,3,5-Tetra-*O*-benzoyl-2-*C*-methyl-α- (and -β-) D-ribofuranose (8).—A mixture of 15 g (~32 mmol) of **3** and **4** in 250 ml of dry pyridine was treated with 15.2 ml of benzoyl chloride. The mixture was heated for 5 hr at 80°, and the product was worked up as in the preparation of **2**. The chloroform solution of the product was concentrated and the residue (18 g) was dissolved in 55 ml of ether and kept at 5° for several hours. The precipitated β **8** (8.25 g, 23%) was removed by filtration: mp 156.5–157.5°; $[\alpha]_D$ +68°, $[\alpha]_{578}$ +72° (*c* 1, $CHCl_3$); R_f 0.8, tlc in chloroform–ethyl acetate (19:1); τ^{CDCl_3} 2.90 (s, C-1 H), 4.02 (d, C-3 H; $J_{3,4}$ = 7.3 cps), 5.14 (m, C-4 H), 5.33 (m, C-5 H_2), 8.04 ppm (s, C-2 CH_3); λ_{max}^{Nujol} 5.72 and 5.80 μ (C=O).

Anal. Calcd for $C_{34}H_{28}O_9$: C, 70.34; H, 4.86. Found: C, 70.22; H, 4.84.

The combined filtrates were concentrated to a residual oil (10 g) containing mostly α **8** and a small amount of the β **8**. Chromatography of the oil on 650 g of silica gel in chloroform–ethyl acetate (19:1) gave 9 g (25%) of pure α **8**: $[\alpha]_D$ +68°, $[\alpha]_{578}$ +71° (*c* 1, $CHCl_3$); R_f 0.65, tlc in chloroform–ethyl acetate (19:1); τ^{CDCl_3} 3.12 (s, C-1 H), 4.30 (broad s, w_h = 4.5 cps), 5.17 (s, C-4 H and C-5 H_2), 8.02 ppm (s, C-2 CH_3); $\lambda_{max}^{CHCl_3}$ 5.78 μ (C=O).

Anal. Found: C, 69.90; H, 4.98.

Rearrangement of 2,3,5-Tri-*O*-benzoyl-2-*C*-methyl-α- (and -β-) D-ribofuranose (3) to 1,3,5-Tri-*O*-benzoyl-2-*C*-methyl-α-D-ribofuranose (7).—A 3.1-g sample of **3** (R_f 0.5, tlc on alumina in chloroform) was chromatographed on 120 g of acid-washed alumina (Merck) in chloroform. All of the material obtained from the column had R_f 0.7. The column fractions were combined and concentrated and gave 2.9 g (95%) of **7** as an oil: $[\alpha]_D$ +92°, $[\alpha]_{578}$ +96° (*c* 1, $CHCl_3$); τ^{CDCl_3} 3.68 (s, C-1 H), 4.78 (broad s, C-3 H, w_h = 4.5 cps), 5.28 (s, C-4 H and C-5 H_2), 8.34 ppm (s, C-2 CH_3).

Anal. Calcd for $C_{27}H_{24}O_8$: C, 68.06; H, 5.08. Found: C, 68.00; H, 5.16.

1,2,3,5-Tetra-*O*-benzoyl-2-*C*-methyl-α- (and -β-) D-ribofuranose (8) from 1,2,5-Tri-*O*-benzoyl-2-*C*-methyl-α-D-ribofuranose (7).—A solution of 1.9 g (4.0 mmol) of **7** in 32 ml of pyridine was treated with 1.5 ml of benzoyl chloride and heated at 80° for 5 hr. The reaction mixture was worked up in the usual manner and the crude product (2.2 g) was dissolved in a small amount of ether and cooled. Crystalline β **8** {$[\alpha]_D$ +66°, $[\alpha]_{578}$ +70° (*c* 0.65, $CHCl_3$), R_f 0.8, tlc on silica in chloroform–ethyl acetate (19:1) (400 mg, mp 155–156°)} was obtained. The filtrate was concentrated and the residue was chromatographed on 100 g of silica gel in chloroform–ethyl acetate (19:1) and fractions were obtained which on concentration yielded 800 mg of α **8**: $[\alpha]_D$ +67°, $[\alpha]_{578}$ +71° (*c* 1, $CHCl_3$); R_f 0.65, tlc on silica gel in chloroform–ethyl acetate (19:1).

2,3,5-Tri-*O*-benzoyl-2-*C*-methyl-β-D-ribofuranosyl Chloride (10). From 1,2,3,5-Tetra-*O*-benzoyl-2-*C*-methyl-β-D-ribofuranose (β 8).—To 300 ml of dry ether saturated at 0° with hydrogen chloride in a round-bottomed flask was added 12 ml of acetyl chloride and 6 g (10 mmol) of β **8**. The flask was tightly stoppered and kept at 25° for 2.5 hr. The tetra benzoate dissolved during the first hour. The solvent was removed and 75 ml of dry toluene distilled from the residue. The residue was dissolved in 300 ml of dry ether and rapidly extracted with three 120-ml portions of cold, saturated $NaHCO_3$ and two 120-ml portions of cold water. The ether layer was dried ($MgSO_4$) and concentrated and the product (**10**, 5.0 g) was obtained as an oil: tlc on alumina in benzene–chloroform (1:1), R_f 0.3; τ^{CDCl_3} 3.13 (s, C-1

(18) 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, silica gel was used for tlc and the zones were made visible with I_2 vapor. The naphthalene-1,2-diol spray used previously[2] was not useful with the 2-*C*-methyl sugars in that the colors were slow to develop and very weak. 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 values were determined with a Varian Associates Model A-60 spectrometer.

H), 3.92 (d, C-3 H, $J_{3,4}$ = 7.5 cps), 5.27 (m, C-4 H and C-5 H_2), 8.02 ppm (s, C-2 CH_3).

2,3,5-Tri-*O*-benzoyl-2-*C*-methyl-β-D-ribofuranosyl Chloride (10). From 1,2,3,5-Tetra-*O*-benzoyl-2-*C*-methyl-α-D-ribofuranose (α 8).—A solution of 5.9 g (10 mmol) of α **8** in 105 ml of acetic acid containing 5 ml of acetyl chloride was added to 260 ml of ether containing 4 ml of acetyl chloride saturated with hydrogen chloride at 0° in a round-bottomed flask. The flask was tightly stoppered and kept at 25° for 48 hr. The solvents were removed and the residue was dissolved in 150 ml of ether and was extracted with three 75-ml portions of cold, saturated $NaHCO_3$ and three 75-ml portions of cold water. The ether layer was dried ($MgSO_4$) and concentrated. The residue (5.8 g) which consisted of a mixture of **10** and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-2-*C*-methyl-β-D-ribofuranose (**9**) [τ^{CDCl_3} 3.14 (s, C-1 H), 4.15 (d, C-3 H, $J_{3,4}$ = 7.0 cps), 5.30 (m, C-4 H and C-5 H_2), 7.98 (s, C-1 CH_3COO), 8.16 ppm (s, C-2 CH_3)] was dissolved in 250 ml of ether containing 0.5 ml of acetyl chloride and saturated with hydrogen chloride. After being kept at 25° for 2.5 hr, the solution was concentrated. Three 50-ml portions of dry toluene were distilled from the residue at reduced pressure. The residual **10** (5.5 g) had the same physical properties as the product obtained from β **8**.

1,3,5-Tri-*O*-benzoyl-2-*C*-methyl-α-D-ribofuranose (7) from 2,3,5-Tri-*O*-benzoyl-2-*C*-methyl-β-D-ribofuranosyl Chloride (10).—A solution of 200 mg of **10** in 0.5 ml of acetone was treated with 0.03 ml of water. Tlc on alumina in benzene–chloroform (1:1) indicated that the reaction was essentially complete in 10 min. The reaction solution was diluted with 25 ml of chloroform and washed with cold dilute HCl, $NaHCO_3$, and water. Concentration of the chloroform solution gave 175 mg of essentially pure **7** with physical properties identical with those of an authentic sample of **7**.

6-Benzamido-9-(2,3,5-tri-*O*-benzoyl-2-*C*-methyl-β-D-ribofuranosyl)purine (12).—About 400 ml of xylene was distilled, at atmospheric pressure, from a suspension of 4.86 g (10.3 mmol) of finely powdered chloromercuri-6-benzamidopurine (**11**). The last 90 ml of xylene distilled was used to dissolve 5.5 g of chloro sugar **10**, and the solution of **10** was added to the stirred xylene suspension of **11** at 60–80°. The mixture was heated to the reflux temperature and refluxing was continued for 1.25 hr. The mixture was concentrated to 150 ml and partially cooled, and 500 ml of petroleum ether was added. After being kept at 5° several hours, the precipitate was removed and added to 200 ml of chloroform. A small amount of chloroform-insoluble material was removed and the filtrate was washed with three 150-ml portions of 30% KI and two 150-ml portions of water. Concentration of the dried ($MgSO_4$) chloroform layer gave a residual glass (5.7 g). Tlc in chloroform–ethyl acetate (9:1) showed a large zone for **12** at R_f 0.3 and faint zones due to impurities at R_f 0.0, 0.1, 0.5, and 0.9. The crude product was chromatographed on 200 g of silica gel in chloroform–ethyl acetate (4:1) and 4.4 g (61%) of purified **12** was obtained: $[\alpha]_D$ −66°, $[\alpha]_{578}$ −66° (*c* 1, $CHCl_3$); λ_{max}^{MeOH} mμ (ε × 10^{-3}), 278 (12.5), 262 (8.0), 231 (27); τ^{CDCl_3} 3.13 (s, C-1 H), 3.22 ppm (d, C-3 H, $J_{3',4'}$ = 6.0 cps).

Anal. Calcd for $C_{39}H_{31}N_5O_8$: C, 67.14; H, 4.48; N, 10.04. Found: C, 67.42; H, 4.71; N, 9.74.

Decomposition of 12 on Acid-Washed Alumina.—A 1.37-g sample of **12** was chromatographed on 50 g of acid-washed alumina (Merck) in chloroform–ethyl acetate (9:1). Several fractions were obtained which contained only the desired product (**12**), R_f 0.6 – tlc on alumina. These fractions were concentrated and gave a total of 580 mg (24%) of **12**. All of the remaining fractions from the column showed three distinct tlc zones when the plates were viewed in ultraviolet light. These zones were scraped from the tlc plates and eluted with methanol. The ultraviolet and infrared spectra as well as R_f values indicated that the zone at R_f 0.1 was 6-benzamidopurine, that at R_f 0.6 was **25**, and that at R_f 0.8 was **7**.

2′-*C*-Methyladenosine (13).—To a suspension of 4.4 g (6.3 mmol) of **11** in dry methanol was added a solution prepared from 240 mg (10.5 mg-atom) of sodium and 50 ml of dry methanol. The solution was refluxed for 30 min and concentrated, and the residue was dissolved in 66 ml of water. The pH was adjusted to 7 with acetic acid and the water solution was extracted with four 100-ml portions of ether. The water layer was concentrated to ~20 ml during which process the product precipitated. After the mixture was kept at 5° for several hours, the product (1.35 g) was removed and recrystallized from 30 ml of hot water. The cooled mixture was filtered and 1.3 g (74%) of **13** was obtained: mp 256–258°; $[\alpha]_D$ −21°, $[\alpha]_{578}$ −22° (*c* 0.5, water); $[\phi]$ (λ, mμ), −1000° (292), −2250° tr (278), 0° (267), +8900° pk (248), 6950° tr (235) (*c* 0.0516, H_2O); $\lambda_{max}^{H_2O}$ mμ (ε × 10^{-3}), pH 1 258 (15.1), pH 7 260 (15.1), pH 13 260 (14.9); $\tau^{deuteriopyridine}$ 3.10 (s, C-1′ H), 4.93 (d, C-3′ H, $J_{3',4'}$ = 8.8 cps), 5.22 (d, C-4 H), 5.52 (s, C-5 H_2), 8.65 ppm (s, C-2 CH_3).

Anal. Calcd for $C_{11}H_{15}N_5O_4$: C, 46.97; H, 5.38; N, 24.90. Found: C, 46.77; H, 5.26; N, 25.20.

2′,3′-*O*-Isopropylidene-2′-*C*-methyladenosine (14).—A suspension of 150 mg (0.52 mmol) of **13** in 12 ml of dry acetone, 0.7 ml of 2,2-dimethoxypropane and 436 mg (1.28 mmol) of di-*p*-nitrophenylphosphoric acid was stirred at 25° for 3.5 days at which time a small amount of **13** [R_f 0.33, tlc on silica gel in ethyl acetate–ethanol (4:1)] remained unreacted. Complete solution was obtained in 1 hr. The reaction mixture was neutralized with 20 ml of 0.1 *N* $NaHCO_3$, and the acetone was removed at reduced pressure. The aqueous solution was extracted with three 40-ml portions of chloroform which were combined and washed with 40 ml of water. The chloroform was removed and the residue was dissolved in 8 ml of methanol, concentrated to 3 ml and kept at 5° for 20 hr. The crystalline product (88 mg) was removed and recrystallized from 1.5 ml of methanol, which yielded 77 mg (45%) of **14**: mp 291–292°; $[\alpha]_D$ −89° $[\alpha]_{578}$ −94° (*c* 0.5, CH_3OH); λ_{max}^{MeOH} mμ (ε × 10^{-3}), 0.1 *N* HCl 211 (20.0), 257.5 (14.8), neutral 260 (15.1), 0.1 *N* NaOH 259 (14.9); $\tau^{deuteriopyridine}$ 3.20 (s, C-1′ H), 5.02 (d), C-3′ H, $J_{3',4'}$ = 2.1 cps), 5.33 (m, C-4′ H), 5.84 (m, C-5′ H_2), 8.31 (s, C-2′ CH_3), 8.55 ppm [s, >C $(CH_3)_2$].

Anal. Calcd for $C_{14}H_{19}N_5O_4$: C, 52.33; H, 5.96; N, 21.80. Found: C, 52.77; H, 5.87; N, 22.14.

Registry No.—**2**, 7392-74-7; α **5**, 16434-45-0; β **5**, 16434-46-1; β **6**, 16434-47-2; **7**, 16434-48-3; α **8**, 15397-16-7; β **8**, 15397-15-6; **10**, 16434-51-8; **12**, 16434-52-9; **13**, 15397-12-3; **14**, 16434-54-1.