The Synthesis of 3-β-(3′-Deoxy-D-ribofuranosyl)adenine, an Isomer of Cordycepin[1]

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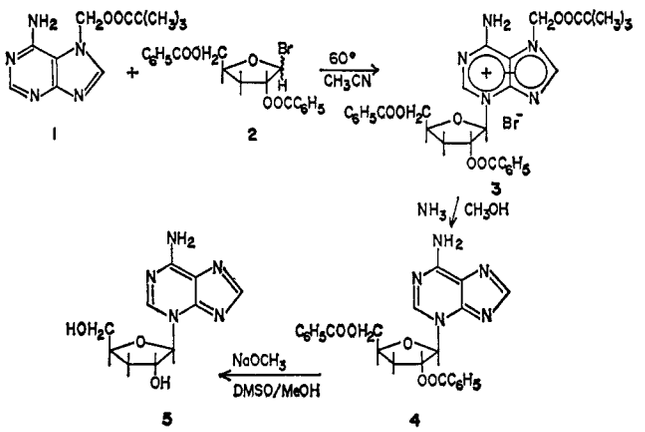
In an application of the use of the pivaloyloxymethyl protecting group, 3-β-(3′-deoxy-D-ribofuranosyl)adenine (**5**), an isomer of cordycepin, has been synthesized in good yield. The route involves the alkylation of 7-pivaloyloxymethyladenine (**1**) with 2,5-di-*O*-benzoyl-3-deoxy-D-ribofuranosyl bromide (**2**) to give 3-β-(2′,5′-di-*O*-benzoyl-3′-deoxy-D-ribofuranosyl)-7-pivaloyloxymethyladenine (hydrobromide **3**) and successive removal of the pivaloyloxymethyl and benzoyl groups.

Interest in 3′-deoxyribofuranosyl nucleosides stems from the identification[2,3] of the metabolite cordycepin from *Cordyceps militaris* (Linn.) Link[4-6] and from the fermentation broth of *Aspergillus nidulans* (Eidam) Wint. as 9-β-(3′-deoxy-D-ribofuranosyl)adenine[7-12] (3′-deoxyadenosine). This 3′-deoxyribofuranosyl nucleoside inhibits nucleic acid synthesis in Ehrlich ascites cells[13-18] and in *Bacillus subtilis*.[19] Parallel interest has developed in the isonucleosides of adenine in which the sugar moiety is attached to N-3 instead of N-9, such as 3-β-D-ribofuranosyladenine (3-isoadenosine)[20] and 3-β-(2′-deoxy-D-ribofuranosyl)adenine[21] especially because of the unusual biological activity exhibited by the former.[20c,22-24] Accordingly, we were encouraged to prepare 3-β-(3′-deoxy-D-ribofuranosyl)-adenine (**5**) (3′-deoxy-3-isoadenosine or 3-isocordycepin), which contains the characteristic structural features of both cordycepin and 3-isoadenosine.

The mild synthetic route to 3-substituted adenine derivatives employing the pivaloyloxymethyl (Pom) protecting group[21] seemed eminently suited for the preparation of **5**. Of the several synthetic procedures developed for providing a 3-deoxypentose moiety on purine or pyrimidine bases,[7-12,25-31] that involving alkylation by a preformed 3-deoxyribofuranosyl halide[10,26] appeared simplest. 7-Pivaloyloxymethyladenine (**1**), obtained from sodium adenide and chloromethyl pivalate,[21] was treated with 2,5-di-*O*-benzoyl-3-deoxy-D-ribofuranosyl bromide (**2**)[10] in acetonitrile at about 60°. The reaction was essentially complete within 5 min, and crude product (**3**) was obtained in



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yields up to 95%. Characterization of the product as 3-β-(2′,5′-di-*O*-benzoyl-3′-deoxy-D-ribofuranosyl)-7-pivaloyloxymethyladenine hydrobromide (**3**) followed from the ultraviolet[32] and nmr spectra. Since the compound showed instability in solution, it was not purified further but was subjected directly to reaction with methanolic ammonia at room temperature. This treatment led to rapid removal of the 7-pivaloyloxymethyl group but gave, in place of the expected nucleo-

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(2) E. A. Kaczka, E. L. Dulaney, C. O. Gitterman, H. B. Woodruff, and K. Folkers, *Biochem. Biophys. Res. Commun.*, **14**, 452 (1964).

(3) E. A. Kaczka, N. R. Trenner, B. Arison, R. W. Walker, and K. Folkers, *ibid.*, **14**, 456 (1964).

(4) (a) K. G. Cunningham, S. A. Hutchinson, W. Manson, and F. S. Spring, *J. Chem. Soc.*, 2299 (1951); (b) H. R. Bentley, K. G. Cunningham, and F. S. Spring, *ibid.*, 2301 (1951).

(5) N. M. Kredich and A. J. Guarino, *Biochim. Biophys. Acta*, **41**, 363 (1960); **47**, 529 (1961).

(6) S. Frederiksen, H. Malling, and H. Klenow, *ibid.*, **95**, 189 (1965).

(7) A. Todd and T. L. V. Ulbright, *J. Chem. Soc.*, 3275 (1960).

(8) W. W. Lee, A. Benitez, C. D. Anderson, L. Goodman, and B. R. Baker, *J. Amer. Chem. Soc.*, **83**, 1906 (1961).

(9) E. Walton, R. F. Nutt, S. R. Jenkins, and F. W. Holly, *ibid.*, **86**, 2952 (1964).

(10) E. Walton, F. W. Holly, G. E. Boxer, R. F. Nutt, and S. R. Jenkins, *J. Med. Chem.*, **8**, 659 (1965).

(11) D. H. Murray and J. Prokop, *J. Pharm. Sci.*, **54**, 1468 (1965).

(12) M. Ikehara and H. Tada, *Chem. Pharm. Bull.* (Tokyo), **15**, 94 (1967).

(13) (a) H. Klenow, *Biochim. Biophys. Acta*, **76**, 347 (1953); (b) H. Klenow, *ibid.*, **76**, 354 (1953); (c) H. Klenow, *Biochem. Biophys. Res. Commun.*, **5**, 156 (1961); (d) H. Klenow and K. Overgaard-Hansen, *Biochim. Biophys. Acta*, **80**, 500 (1964).

(14) (a) S. Frederiksen and H. Klenow, *Biochem. Biophys. Res. Commun.*, **17**, 165 (1964); (b) H. Klenow and S. Frederiksen, *Biochim. Biophys. Acta*, **87**, 495 (1964).

(15) H. T. Shigeura and C. N. Gordon, *J. Biol. Chem.*, **240**, 806 (1965).

(16) H. T. Shigeura, G. E. Boxer, M. L. Meloni, and S. D. Sampson, *Biochemistry*, **5**, 994 (1966).

(17) C. O. Gitterman, R. W. Burg, G. E. Boxer, D. Meltz, and J. Hitt, *J. Med. Chem.*, **8**, 664 (1965).

(18) D. V. Jagger, N. M. Kredich, and A. J. Guarino, *Cancer Res.*, **21**, 216 (1961).

(19) F. Rottman and A. J. Guarino, *Biochim. Biophys. Acta*, **80**, 632 (1964).

(20) (a) N. J. Leonard and R. A. Laursen, *J. Amer. Chem. Soc.*, **85**, 2026 (1963); (b) N. J. Leonard and R. A. Laursen, *Biochemistry*, **4**, 354 (1965); (c) N. J. Leonard and R. A. Laursen, *ibid.*, **4**, 365 (1965).

(21) M. Rasmussen and N. J. Leonard, *J. Amer. Chem. Soc.*, **89**, 5439 (1967).

(22) A. M. Michelson, C. Monny, R. A. Laursen, and N. J. Leonard, *Biochim. Biophys. Acta*, **119**, 258 (1966).

(23) K. Gerzon, I. S. Johnson, G. B. Boder, J. C. Cline, P. J. Simpson, and C. Speth, *ibid.*, **119**, 445 (1966).

(24) K. Gerzon, Annual Meeting, American Association for Cancer Research, Denver, Colo., May 28, 1966; see K. Gerzon, G. B. Boder, C. R. Speth, P. J. Simpson, and I. S. Johnson, *Proc. Amer. Assoc. Cancer Res.* **7**, 23 (1966).

(25) D. M. Brown, D. B. Parihar, A. Todd, and S. Varadarajan, *J. Chem. Soc.*, 3028 (1958).

(26) E. Walton, F. Holly, G. E. Boxer, and R. F. Nutt, *J. Org. Chem.*, **31** 1163 (1966).

(27) D. M. Brown and G. H. Jones, *J. Chem. Soc.*, 249, 252 (1967).

(28) P. Szabò and L. Szabò, *ibid.*, 2944 (1965).

(29) S. R. Jenkins, F. W. Holly, and E. Walton, *J. Org. Chem.*, **30**, 2851 (1965).

(30) J. Prokop and D. H. Murray, *J. Pharm. Sci.*, **54**, 359 (1965).

(31) A. P. Martinez, W. W. Lee, and L. Goodman, *J. Org. Chem.*, **31**, 3263 (1963).

(32) N. J. Leonard, K. L. Carraway, and J. P. Helgeson, *J. Heterocycl. Chem.*, **2**, 291 (1965).

side **5**, a mixture of 3-β-(2′,5′-di-*O*-benzoyl-3′-deoxy-D-ribofuranosyl)adenine (**4**) and 3-β-(2′,5′-di-*O*-benzoyl-3′-deoxy-D-ribofuranosyl)-N_6-pivaloyladenine (N^6-pivaloyl derivative of **4**) in a ratio of about 4:1. The latter, minor component, formed by intermolecular rearrangement of the pivaloyl group,[21] was readily separated from the sparingly soluble **4** and was identified by its spectroscopic characteristics. The debenzoylation of **4**, isolated in 59% yield from the ammonia–methanol treatment, was accomplished with sodium methoxide in dimethyl sulfoxide–methanol at room temperature in 79% yield.

The structure of the debenzoylated product, mp 224.5–225°, homogeneous by tlc, was indicated as 3-β-(3′-deoxy-D-ribofuranosyl)adenine (**5**) by microanalysis and the route of synthesis. The position of attachment of the sugar to adenine was confirmed as **3** by the nmr and uv spectral data.[33,34] The assignment of the β configuration required further inspection. Participation of the 2′-*O*-benzoyl group during the alkylation reaction (**1** + **2**) should have given preponderantly the β anomer, following the *trans* rule.[35,36] Similar use of 2,5-di-*O*-benzoyl-3-deoxy-D-ribofuranosyl bromide (**2**) had produced the β-ribofuranoside cordycepin,[10] and direct alkylation of adenine with 2,3,5-tri-O-benzoylribofuranosyl bromide had given two β-ribofuranosides, precursors of adenosine and 3-isoadenosine.[20b] In the light of the synthetic precedents, the fairly high over-all yield from 7-pivaloyloxymethyladenine of pure **5** (43%), with its sharp melting point and homogeneity indicated by tlc, was suggestive of the β configuration. The ORD curve for **5** was difficult to measure owing to the high $\epsilon/[M]$ ratios in the region of the absorption maximum but indicated a negative Cotton effect. Application of Hudson's rules of isorotation[38] is not secure for a new, single example as represented by **5**, and anomeric assignments by ORD have been limited mainly to cyclo nucleosides, pyrimidine nucleosides, purine N-9 nucleosides,[39,40] and series of nucleosides containing unnatural sugar moieties.[41] From our experience with 3-substituted adenines.[20b,21] we consider the optical rotation data to be further suggestive of the β configuration in **5**.

Further support for the assignments of anomeric configuration emerges from the nmr spectrum through judicious application of the Karplus equations[42,43] to the relation between the coupling constant $J_{1',2'}$ and the dihedral angle between the intersecting planes defined by H-1′–C–C and H-2′–C–C and empirically by analogy. In the nmr spectra of several anomeric pairs of 3′-deoxyribofuranosylpyrimidine nucleosides[26] there appears to be a small but distinct difference between the *trans* $J_{1',2'}$ coupling, 1.3–1.8 cps, of the β anomers and the *cis* $J_{1',2'}$ coupling, 3.5–3.9 cps, of the α anomers. The related 9-β-(3′-deoxy-D-ribofuranosyl)adenine (cordycepin) in D_2O has been noted[44] to have a low $J_{1',2'}$ coupling, 2.2 cps, relative to that of adenosine, 6.1 cps. The value of $J_{1',2'}$ which we observed for 3′-deoxy-3-isoadenosine (**5**) in hexadeuteriodimethyl sulfoxide was 3.2 ± 0.5 cps, which did not permit a firm conclusion concerning the anomeric configuration. However, the observed $J_{1',2'}$ coupling was solvent dependent, and the addition of a few drops of deuterium oxide to the DMSO-d_6 solution of **5** caused $J_{1',2'}$ to decrease to 2.7 cps. Moreover, the signal for the anomeric C-1′ proton of **5** in D_2O acidified with deuteriosulfuric acid occurred as a broadened *singlet* with half-height width of 2.2 cps.[45] Supportive nmr evidence was also available from the signal for the C-1′ proton in the precursors **4** (singlet) and **3** (broad singlet). Further, the chemical shift of H-1′ appears in the region to be expected for a proton *cis* to the C-2′ hydroxyl group.[21,44,46] The chemical shift and coupling constant are consistent with a β configuration for **5**, but no final correlation between nmr spectra and configuration can be made in the absence of the α anomer. In conclusion, the structural formulas **3**, **4**, and **5** indicate the most probable stereochemistry of the products synthesized in this sequence, which, by the use of the Pom protecting group, provides a good yield of 3-β-(3′-deoxy-D-ribofuranosyl)adenine.[47]

Experimental Section[48]

2,5-Di-*O*-benzoyl-3-deoxy-D-ribofuranosyl bromide (**2**) was obtained as a pale brown oil by following the ten-step procedure of Walton, Holly, Boxer, Nutt, and Jenkins[10] (4.6% over-all yield from D-xylose).

3-β-(2′,5′-Di-*O*-benzoyl-3′-deoxy-D-ribofuranosyl)-7-pivaloyloxymethyladenine Hydrobromide (**3**).—To a solution of 0.611 g (2.46 mmol) of 7-pivaloyloxymethyladenine (**1**)[21] in 100 ml of anhydrous acetonitrile at 57° was added 1.8 g (4.4 mmol) of 2,5-di-*O*-benzoyl-3-deoxy-D-ribofuranosyl bromide[10] in 10 ml of acetonitrile. After 10 min at 57–60°, the solution was cooled and then evaporated *in vacuo* (below 30°). The residual foam was dissolved in 10 ml of acetonitrile, and the solution was diluted with *ca.* 100 ml of ether. After trituration, the crude product was collected by filtration as fawn-colored microcrystals, yield 1.488 g (94%), which softened at 115°, gradually decomposed above *ca.* 150°, and melted with evolution of a gas and extensive decomposition at *ca.* 206° (rapid heating): λ_{max} 228, 279, and 288 (sh) mμ, λ_{min} 250, λ_{max} (pH 1) 229, 277, and 288 (sh), λ_{min} 250, λ_{max} (pH 13) (unstable) *ca.* 275 (sh), 281, and 326, λ_{min} 258 and

(33) N. J. Leonard and J. A. Deyrup, *J. Amer. Chem. Soc.*, **84**, 2148 (1962).

(34) L. B. Townsend, R. K. Robins, R. N. Loeppky, and N. J. Leonard, *ibid.*, **86**, 5320 (1964), and references therein.

(35) B. R. Baker, in "Ciba Foundation Symposium, Chemistry and Biology of Purines," G. E. W. Wolstenholme and C. M. O'Connor, Ed., J. and A. Churchill Ltd., London, 1957, p 120.

(36) The *trans/cis* (β/α for ribosides) ratio may be lower when the 2-*O*-acyl group is acetyl or when it is benzoyl substituted with electron-withdrawing groups.[26,37]

(37) M. Prystaš and F. Šorm, *Collect. Czech. Chem. Commun.*, **29**, 2956 (1964).

(38) C. S. Hudson, *J. Amer. Chem. Soc.*, **31**, 66 (1909).

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

(40) P. Crabbé and W. Klyne, *Tetrahedron*, **23**, 3449 (1967).

(41) Dr. I. Iwai, Sankyo Co., Ltd., Tokyo, private communication.

(42) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(43) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

(44) A. D. Broom, M. P. Schweizer, and P. O. P. Ts'o, *ibid.*, **89**, 3612 (1967).

(45) (a) R. U. Lemieux and J. W. Lown, *Can. J. Chem.*, **41**, 889 (1963); (b) L. Goldman and J. W. Marsico, *J. Med. Chem.*, **6**, 413 (1963).

(46) L. Gatlin and J. C. Davis, *J. Amer. Chem. Soc.*, **84**, 4464 (1962).

(47) This compound has been mentioned by H. T. Shigeura and S. D. Sampson, *Nature*, **215**, 419 (1967), in the summary of their study on the structural basis for phosphorylation of adenosine congeners.

(48) All melting points are corrected. The ir spectra were recorded as Nujol mulls on a Perkin-Elmer 337 grating infrared spectrophotometer at slow scan. The uv spectra were recorded on a Cary Model 15 spectrophotometer on samples dissolved in 95% aqueous ethanol and 0.1 *M* hydrochloric acid in 95% aqueous ethanol (pH 1).[32] The pmr spectra were determined with a Varian A-60A spectrometer. Chemical shifts are reported in δ units (ppm downfield from internal tetramethylsilane) and coupling constants in cps with estimated error ±0.5 cps. The following conventions for abbreviations are used: m = multiplet, e = envelope, t = triplet, d = doublet, s = singlet, b = broad, p = pseudo, D = signal disappears on exchange with D_2O, sh = shoulder, st = strong, med = medium, v = very. Thin layer chromatography (tlc) was performed on Eastman silica gel strips (with fluorescent indicator) routinely using 1:19 to 1:4 methanol–chloroform solvent systems.

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).