Branched-Chain N-Sugar Nucleosides. 1. Nucleosides of Branched-Chain Cyanomethyl, Aminoethyl, and *N,N*-Dimethylcarbamoylmethyl Allo Sugars. 6-*N,N*-Dimethylamino-9-[3′-*C*-(*N,N*-dimethylcarbamoylmethyl)-3′-deoxy-β-D-allofuranosyl]purine[1]

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The synthesis of two novel branched-chain N-sugar nucleosides is described. Condensation of diethyl cyanomethylphosphonate with 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**1**) by a Wittig reaction afforded, after stereoselective reduction of the unsaturated sugars over palladium on charcoal, 3-*C*-cyanomethyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**2**) in 78% yield. Compound **2** was reduced over rhodium on Al_2O_3 to yield an amino sugar **3** (isolated as its acetamido derivative **4**). Compound **2** was also converted by alkaline hydrogen peroxide hydrolysis into the branched-chain 3-*C*-carbamoylmethyl-3-deoxy sugar **5** in 70% yield. Compound **2** was hydrolyzed selectively to the 1,2-monoisopropylidene derivative **6**, which was converted *via* benzoylation, hydrolysis with trifluoroacetic acid, and then acetylation into the 1,2-diacetate **7**. Fusion of **7** with 6-chloropurine afforded the blocked allo nucleoside **8** in 69% yield. Treatment of the latter with methanolic aqueous dimethylamine gave the novel branched-chain allo sugar nucleoside **9** containing a 3′-*C*-(*N,N*-dimethylcarbamoylmethyl) branched chain in 45% yield. Sodium metaperiodate oxidation of **9** followed by sodium borohydride reduction of the aldehydo nucleoside gave the branched-chain ribo nucleoside **10**. Compound **7** was also converted into the benzamido nucleoside **11**. Treatment of **11** with lithium aluminum hydride afforded 9-[3′-*C*-(2′-aminoethyl)-3′-deoxy-β-D-allofuranosyl]adenine (**12**).

The occurrence of unique and unusual amino, deoxy, and branched-chain sugars in some of the antibiotics has stimulated increased interest in the distribution of unusual carbohydrates in nature, and an extensive list of unusual sugars has resulted from chemical investigations on bacterial cell walls, capsular materials, and other naturally occurring macromolecules.[2a] A classification of the sugar-containing antibiotics in addition to a discussion of the chemistry of those members whose complete structures were known to 1969 has been made.[2b] The chemistry and biochemistry of branched-chain sugars from 1969 to the present have just been reviewed.[3]

The discovery that nucleosides with branched-chain sugars can exhibit cytostatic and virostatic activity has heightened the interest in the development of general methods for the synthesis of branched-chain sugars.[3] The isolation of nucleoside antibiotics containing carbamoyl and peptide groups (gougerotin and puromycin[4]) has probably helped to stimulate a continued interest in the synthesis of analogs of these substances. With the recent report of the synthesis of 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (virazole) by Witkowski of I. C. N. and the finding that it has significant and reproducible activity against a broad spectrum of DNA and RNA viruses,[5] there might be expected to be a further continued interest in nucleosides containing the carbamoyl group. In this connection, it is interesting to note that adenosine 5′-carboxamides are reported to affect blood circulation when administered orally or parenterally.[6] Recently, appropriately blocked amino acids and peptides have been coupled to a purine 5′-amino-5′-deoxy nucleoside derivative[7] and to a nucleoside containing a free carboxylic acid moiety to afford novel nucleoside peptides.[8] Reasons for the preparation of this class of compounds have been outlined.[7]

The objective of the research outlined in this and in the following paper was to develop a general synthetic procedure for the substitution of the 3′-hydroxyl on adenosine and related nucleosides by cyanomethyl, carbamoylmethyl, *N,N*-dimethylcarbamoylmethyl, aminoethyl, and a peptide branched chain.

In the preliminary communication,[9] we have reported the synthesis of 3-*C*-cyanomethyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**2**) and its subsequent utilization in the synthesis of a nucleoside containing a branched-chain cyano sugar **8**. We now wish to describe in detail this synthesis and, in addition, to outline the utilization of **8** in the synthesis of other novel branched-chain N-sugar nucleosides.

Condensation of 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose[10] (**1**) with diethyl cyanomethylphosphonate in the presence of sodium hydride followed by hydrogenation over 10% palladium on charcoal according to a procedure already published[11] afforded the key intermediate in our synthesis, namely, 3-*C*-cyanomethyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**2**), in over 80% yield. The assignment of configuration of **2** was deduced from its nuclear magnetic resonance spectrum. Based on the fact that trans H_2–H_3 of the furanose sugars have small cou-

(1) Preliminary communication: Abstracts, Third International Congress of Heterocyclic Chemistry, Sendai, Japan, Aug 1971, p 106.

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(3) H. Grisebach and R. Schmid, *Angew. Chem., Int. Ed. Engl.*, **11**, 159 (1972).

(4) J. J. Fox, K. A. Watanabe, and A. Block, *Progr. Nucl. Acid Res. Mol. Biol.*, **5**, 251 (1966).

(5) R. W. Sidwell, J. H. Huffman, G. P. Khare, L. B. Allen, J. T. Witkowski, and R. K. Robins, *Science*, **177**, 705 (1972).

(6) E. Fanland, W. Kampe, M. Thiel, K. Dietmann, and W. Juhran, German Patent 2,034,785 (Jan 20, 1972); *Chem. Abstr.*, **76**, 113494b (1972).

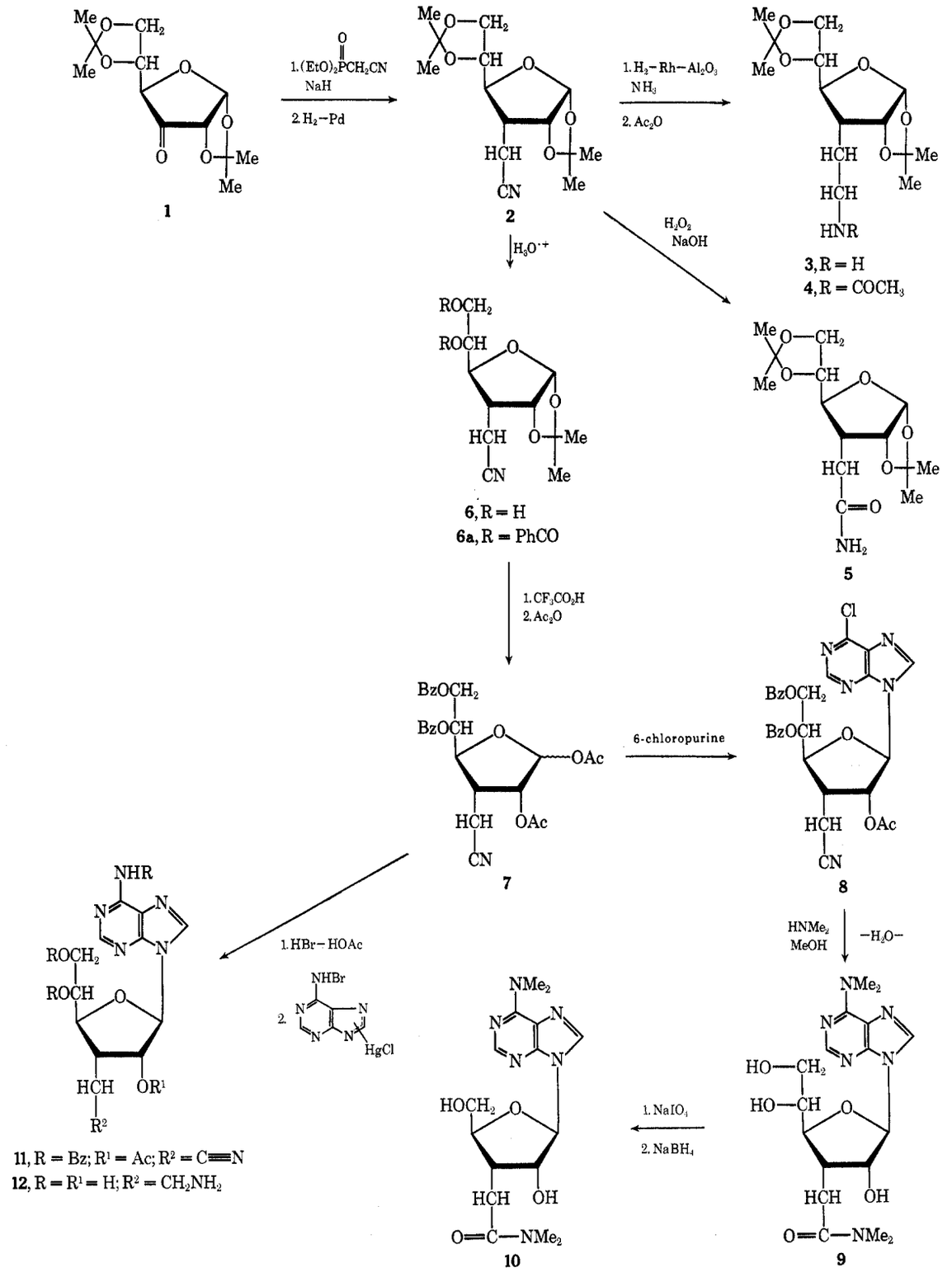
(7) M. J. Robins, L. N. Simon, M. G. Stout, G. A. Ivanovics, M. P. Schweizer, R. J. Rouseau, and R. K. Robins, *J. Amer. Chem. Soc.*, **93**, 1474 (1971).

(8) M. Kawana, R. J. Rousseau, and R. K. Robins, *J. Org. Chem.*, **37**, 288 (1972).

(9) A. Rosenthal, M. Sprinzl, and D. A. Baker, *Tetrahedron Lett.*, 4233 (1970).

(10) (a) P. J. Beynon, P. M. Collins, and W. G. Overend, *Proc. Chem. Soc.*, 342 (1964); (b) K. Onodera, S. Hirano, and N. Kashimura, *J. Amer. Chem. Soc.*, **87**, 4651 (1965); (c) K. Onodera, S. Hirano, and N. Kashimura, *Carbohyd. Res.*, **6**, 276 (1968); (d) K. N. Slessor and A. S. Tracey, *Can. J. Chem.*, **47**, 3989 (1969).

(11) A. Rosenthal and D. A. Baker, *Tetrahedron Lett.*, 397 (1969).



plings of less than 0.5 Hz whereas cis H_2–H_3 have couplings greater than 2.5 Hz,[12] the fact that H-2 of compound **2** exhibited a triplet at τ 5.18 having $J_{2,3}$ = 3.6 Hz (irradiation of the H-1 signal at τ 4.2 collapsed the H-2 signal to a doublet of J = 3.6 Hz) showed that H-2 and H-3 must be in the cis orientation and, therefore, compound **2** must have the allo configuration. The stereoselectivity of the reduction of the unsaturated sugars obtained in the Wittig reaction of **1** makes the synthesis of the key intermediate **2** very useful.

(12) R. J. Abraham, L. D. Hall, L. Hough, and K. A. McLauchlin, *J. Chem. Soc.*, 3699 (1962).

Because the primary objective of our research was to prepare structural analogs of puromycin,[4,13] we first converted **2** into the branched-chain amino sugar **3** by reduction over 5% rhodium on aluminum followed by acetylation to afford 3-*C*-(2′-acetamidoethyl)-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**4**) in 80% yield. When an attempt was made to utilize **4** in the synthesis of a branched-chain amino sugar nucleoside

(13) (a) L. V. Fisher, W. W. Lee, and L. Goodman, *J. Med. Chem.*, **13**, 775 (1970); (b) W. W. Lee, W. L. Tong, R. W. Blackford, and L. Goodman, *J. Org. Chem.*, **35**, 3808 (1960); (c) H. P. Albrecht and J. G. Moffatt, *Tetrahedron Lett.*, 1063 (1970).

by a known sequence of reactions[14] the synthesis was unsuccessful owing to the fact that, on deisopropylidenating **4**, the acetamido group participated and formed what was presumed to be a N-heterocyclic sugar.[15] Another course open to us appeared to be *via* the conversion of the cyanomethyl sugar into a carbamoylmethyl sugar. Hydrolysis of **2** with hydrogen peroxide in the presence of sodium hydroxide proceeded smoothly to afford crystalline 3-*C*-carbamoylmethyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**5**) in 70% yield. The latter compound also could not be directly utilized in nucleoside synthesis. This fact, coupled with the knowledge that the chemistry of nucleosides containing a carbamoyl group (as exemplified by the nucleoside antibiotic gougerotin[4,16]) has posed a problem of great complexity led us to direct our principal efforts towards the direct utilization of **2** in the synthesis of a structural analog of puromycin.

Selective hydrolysis of the 5,6-isopropylidene group of **2** was achieved with aqueous methanol containing sulfuric acid. The reaction was conducted at room temperature for 4 hr, giving the monoisopropylidene derivative **6** in almost quantitative yield. The reaction was monitored by thin layer chromatography (tlc) on silica gel and was stopped when **2** was consumed. It was essential to keep the reaction under careful surveillance because of the possibility of further hydrolysis. Compound **6** was converted into the crystalline 5,6-di-*O*-benzoate ester **6a** (which was purified by column chromatography) and its structure was confirmed by nmr spectroscopy. Acetolysis of the dibenzoate ester with an 80% solution of trifluoroacetic acid at room temperature for 0.75 hr (careful monitoring of reaction by tlc) removed the 1,2-*O*-isopropylidene group and did not hydrolyze the cyano group. The hydrolysis product obtained by use of trifluoroacetic acid was immediately acetylated with acetic anhydride and pyridine to afford crystalline 1,2-di-*O*-acetyl-5,6-di-*O*-benzoyl-3-*C*-cyanomethyl-3-deoxy-β-D-allofuranose (**7**) in 54% yield based on **6**. The β-anomeric configuration of **7** was assigned on the basis of the fact that H-1 exhibited a singlet in its nmr spectrum.[12] The β anomer **7** was condensed with 6-chloropurine by direct fusion at 160° without catalyst[17] to afford, after column chromatography on silica, the blocked nucleoside **8** as a solid foam in 69% yield. Treatment of the latter with 25% aqueous dimethylamine and methanol[13c] at room temperature for 4 hr afforded, after column chromatography on silica, an unblocked crystalline nucleoside **9** in 45% yield. This nucleoside exhibited a strong carbonyl absorption in its infrared spectrum at 6.30 μ but did not possess a cyano band. Its nmr spectrum clearly showed that deacylation was complete and that the compound **9** had four methyl groups (one NMe_2 from the expected substitution of the 6-chloro atom by the NMe_2). This evidence, coupled with the fact that the molecular weight of compound **9** was 394, strongly supported the unexpected result that the nucleoside now contained an *N*,*N*-dimethylcarbamoyl group in place of the cyano group. It is tentatively suggested that the C-2′ hydroxyl (after unblocking) might have participated[18] in forming an imine from the cyano group, and the imine was subsequently hydrolyzed to yield a five-membered cyclic lactone. The latter might be expected to undergo ready aminolysis with the dimethylamine to yield the unusual branched-chain nucleoside 6-*N*,*N*-dimethylamino-9-(3′-*C*-*N*,*N*-dimethylcarbamoylmethyl-3′-deoxy-β-D-allofuranosyl)purine (**9**). The assignment of β-anomeric configuration to **9** was based on the following: (1) ultraviolet (uv) absorption data of **9** substantiates the site of glycosylation[19] at N-9; (2) the trans rule[20] indicates that **9** has a β configuration; the allo nucleoside **9** exhibits a negative Cotton effect that is consistent with the proposals advanced[21,22] for purine β-D-nucleosides. Although the nmr measurement of **9** was of little value in confirming the β-anomeric configuration, the magnitude of $J_{1',2'} = 4$ Hz is consistent with the $J_{1',2'}$ coupling constant of other branched-chain β-allo nucleosides.[14,23]

Sodium metaperiodate oxidation of the allo nucleoside **9** yielded an aldehydo nucleoside that was immediately reduced with sodium borohydride to give, after column chromatography on silica, in 68% yield the expected ribo nucleoside **10**. Although the nmr spectrum was consistent with structure **10** (the nmr spectrum showed one primary and one secondary hydroxyl group and four methyl groups) the nucleoside failed to crystallize.

The cyanomethyl branched-chain sugar **7** was also used to prepare a nucleoside having a cyano group following a classical nucleoside synthesis.[24] Thus, treatment of **7** with anhydrous hydrogen bromide in dichloromethane readily afforded the bromo sugar (not characterized because of instability), which was immediately condensed with chloromercuri-6-benzamidopurine in anhydrous toluene under reflux conditions to afford, after silica column chromatography, 6-benzamido-9-(2′-*O*-acetyl-5′,6′-di-*O*-benzoyl-3′-*C*-cyanomethyl-3′-deoxy-β-D-allofuranosyl)purine (**11**) in 60% yield. Treatment of the latter with lithium aluminum hydride in tetrahydrofuran gave a mixture of compounds. The major component **12**, which was insoluble in water, was further purified by passage through a column of Dowex 1X resin. This component, isolated in 30% yield, gave a positive ninhydrin test and its nmr spectrum showed that the cyanomethyl group was reduced to an aminoethyl group. However, owing to complexing of the amino sugar nucleoside **12** with inorganic ions which could not be removed, its elemental analysis was not satisfactory.

Experimental Section

General Considerations.—Nmr spectra were obtained in chloroform-*d* solution (unless otherwise stated) with tetramethyl-

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(17) T. Sato, *Syn. Proc. Nucl. Acid Chem.*, **1**, 264 (1968).
(18) (a) P. W. Austin, J. C. Buchanan, and E. M. Oakes, *Chem. Commun.*, 374 (1965); (b) *ibid.*, 472 (1966); (c) H. B. Wood, Jr., and H. G. Fletcher, Jr., *J. Org. Chem.*, **26**, 1969 (1961).
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(20) B. R. Baker, Ciba Foundation Symposium, "Chemistry and Biology of Purines," Little, Brown and Co., Boston, Mass., 1957, p 120.
(21) T. R. Emerson, R. J. Swan, and T. L. V. Ulbricht, *Biochem. Biophys. Res. Commun.*, **22**, 505 (1966).
(22) T. Nishimura, B. Shimizu, and I. Iwai, *Biochim. Biophys. Acta*, **157**, 221 (1968).
(23) A. Rosenthal and M. Sprinzl, *Can. J. Chem.*, **47**, 4477 (1969).
(24) J. Davoll and B. A. Lowy, *J. Amer. Chem. Soc.*, **73**, 1650 (1951).

silane as the internal standard (set at τ 10) by using a Varian T-60 or Varian HA-100 spectrometer (peak multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet). Ir spectra were obtained with a Perkin-Elmer Model 457 spectrophotometer. Molecular weight was obtained by mass spectroscopy using an A.E.I.-M.S.9 spectrometer. All melting points (micro hot state) are corrected. Silica gel G was used for tlc and silica gel Grace (60–200 mesh, deactivated with 10% water) was used for column chromatography. Elemental analyses were performed by the microanalytical laboratory, University of British Columbia.

Wittig Reaction of 1,2:5,6-Di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (1) to Yield 3-*C*-Cyanomethyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (2).—To a suspension of sodium hydride (2.33 g) in anhydrous 1,2-dimethoxyethane (100 ml) was carefully added a solution of diethyl cyanomethylphosphonate (17.4 g) in 1,2-dimethoxyethane (100 ml). When the evolution of gas had ceased the mixture was filtered (all operations were performed in a drybox under a nitrogen atmosphere) and the solution was then cooled to 0°. To the cold solution of the carbanion a solution of the ketose **1** (16.9 g) in 1,2-dimethoxyethane (300 ml) was added with stirring and external cooling. The reaction was then allowed to warm to room temperature. After 4 hr the reaction mixture was removed from the drybox, diluted with 100 ml of water, and extracted with 3 × 250 ml of ether. The combined ether extracts were washed with water (3 × 20 ml), dried over sodium sulfate, filtered, and evaporated under reduced pressure to afford a syrup which appeared to be homogeneous as evidenced by tlc on silica gel G with 19:1 benzene–methanol (R_f 0.68). Hydrogenation of the syrup in ethanol over 10% palladium on charcoal gave 14.5 g (78%) of product **2** which was recrystallized from ether–petroleum ether (bp 35–60°): mp 109°; $[\alpha]^{22}D$ +91° (*c* 2, chloroform); ir 4.5 μ (C≡N); τ^{CDCl_3} 4.18 (d, $J_{1,2}$ = 3.6 Hz, H-1), 5.23 (t, $J_{2,3}$ = 3.6 Hz, H-2), 8–7.5 (m, H-3). Irradiation of the H-1 signal at τ 4.2 collapsed the H-2 signal to a doublet.

Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.30; H, 7.47; N, 4.94. Found: C, 59.26; H, 7.35; N, 4.81.

3-*C*-(2′-Acetamidoethyl)-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (4).—The branched-chain sugar **2** (1 g) dissolved in absolute ethanol (70 ml) saturated with ammonia was hydrogenated over 5% rhodium on alumina at room temperature and 60 psi for 20 hr. The catalyst was removed by filtration and the solvent was evaporated under diminished pressure. The resulting syrup was acetylated with a mixture of acetic anhydride (3.5 ml) and pyridine (3.5 ml) for 24 hr. The product was worked up in the usual way to afford 0.92 g of compound **4** (80%): ir 6.15 and 6.55 μ (C=O); τ^{CDCl_3} 5.26 (t, H-2), 4.23 (d, $J_{1,2}$ = 3 Hz, H-1), 3.20 (NH); $[\alpha]D$ 41° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{16}H_{27}NO_6$: C, 58.34; H, 8.20; N, 4.25. Found: C, 58.27; H, 8.44; N, 4.00.

3-*C*-Carbamoylmethyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (5).—To a solution of **2** (0.566 g) in ethanol (6 ml) was added hydrogen peroxide (0.8 ml) and 6 *N* sodium hydroxide[25] (0.8 ml). After the reaction mixture was left to stand at 50° for 6 hr, the solution was evaporated under reduced pressure to yield a syrup which was extracted with dichloromethane. The dichloromethane extract was evaporated under diminished pressure to yield a solid which was recrystallized from ether to yield 0.400 g (70%) of **5**: mp 138°; $[\alpha]^{21}D$ +86° (*c* 1.3, chloroform); ir 2.9 (NH_2), 6.1 μ (C=O); τ^{CDCl_3} 4.1 (NH_2), 4.23 (d, $J_{1,2}$ = 4 Hz, H-1), 5.27 (t, H-2).

Anal. Calcd for $C_{14}H_{23}NO_6$: C, 55.8; H, 7.69; N, 4.47. Found: C, 55.7; H, 7.91; N, 4.57.

3-*C*-Cyanomethyl-3-deoxy-1,2-*O*-isopropylidene-α-D-allofuranose (6).—To a solution of 6.5 g of **2** in 300 ml of methanol was added 30 ml of 1 *N* sulfuric acid. The reaction mixture was left stand at room temperature for 4 hr, then neutralized with solid sodium hydrogen carbonate, and extracted with chloroform (3 × 200 ml). The combined chloroform extracts were dried over sodium sulfate, filtered, and evaporated under diminished pressure to afford 5.5 g of **6** (quantitative yield): $[\alpha]^{25}D$ +99° (*c* 1.7, chloroform); ir 2280 cm^{-1} (C≡N); τ^{CDCl_3} 8.17 (s, 3 H), 8.33 (s, 3 H, isopropylidene).

Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.01; H, 7.21; N, 5.56.

(25) C. R. Noller, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 586.

5,6-Di-*O*-benzoyl-3-*C*-cyanomethyl-3-deoxy-1,2-*O*-isopropylidene-α-D-allofuranose (6a).—To a solution of 3-*C*-cyanomethyl-3-deoxy-1,2-*O*-isopropylidene-α-D-allofuranose (**2**) (60 g) in anhydrous benzene (30 ml) was added dropwise a mixture of benzoyl chloride (32 ml) and pyridine (4.5 ml). After standing for 14 hr at room temperature, the reaction mixture was filtered through a short column of grade II alumina (25 g) and the column was washed was washed with benzene (150 ml). Evaporation of the combined eluents gave **6a**, which was crystallized from ether–petroleum ether (bp 30–60°) to give 10.0 g (90%) of product: mp 71–72°; $[\alpha]^{24}D$ +48.2° (*c* 1.3, chloroform).

Anal. Calcd for $C_{25}H_{25}NO_7$: C, 66.60; H, 5.57; N, 3.10. Found: C, 66.33; H, 5.54; N, 2.95.

1,2-Di-*O*-acetyl-5,6-di-*O*-benzoyl-3-*C*-cyanomethyl-3-deoxy-β-D-allofuranose (7).—An amount of 8 g of **6a** was allowed to react with an 80% solution of trifluoroacetic acid (70 ml) for 0.75 hr, followed by neutralization with solid sodium hydrogen carbonate. The resulting mixture was extracted with methylene chloride. Evaporation of the combined methylene chloride extracts, after drying over sodium sulfate, gave 5.9 g of syrup. An aliquot of this syrup (5 g) was acetylated with acetic anhydride (20 ml) and pyridine (20 ml) and the product was worked up in the usual way to yield 5.4 g (54% yield based on **6**) of product **7**. An analytical sample of **7** was prepared by chromatographing it on neutral alumina using an 8:1 mixture of dichloromethane–ether as developer. The product, crystallized from ether, had mp 110°; $[\alpha]^{23}D$ −31° (*c* 2, chloroform); ir (KBr) 4.48 μ (C≡N); τ^{CDCl_3} 3.77 (s, H-1).

Anal. Calcd for $C_{26}H_{25}NO_9$: C, 63.02; H, 5.08; N, 2.81. Found: C, 63.00; H, 4.97; N, 2.65.

An attempted acetolysis[14] of the dibenzoate ester **6a** gave a complex mixture of products; the major component did not possess nitrogen.

6-Chloro-9-(2′-*O*-acetyl-5′,6′-di-*O*-benzoyl-3′-*C*-cyanomethyl-3′-deoxy-β-D-allofuranosyl)purine (8).—A thoroughly dried, finely powdered mixture of 1 g (2.02 mmol) of 1,2-di-*O*-acetyl-5,6-di-*O*-benzoyl-3-*C*-cyanomethyl-3-deoxy-β-D-allofuranose and 0.350 g (2.27 mmol) of anhydrous 6-chloropurine was heated in an oil bath at 160° at 30 Torr for 5 min followed by further heating at 160° at 1 Torr for 40 min. The melt was extracted with 50 ml of dichloromethane and the extract was then filtered. Evaporation of the filtrate gave 1.24 g of syrup, which was chromatographed on a silica column (70 g) using 1:1 benzene–ethyl acetate as developer. The faster moving component (0.150 g) was starting material, whereas the second fraction (0.700 g, 69% yield) was the blocked nucleoside **8**. This nucleoside was a solid foam which could not be crystallized: ir 4.5 μ (C≡N); $[\alpha]^{22}D$ −13° (*c* 1.7, $CHCl_3$); τ^{CDCl_3} 7.2 (d, CH_2CN), 6.6–6.4 (m, H-3′), 3.9 (d, $J_{1',2'}$ = 2 Hz, H-1′), 1.3 and 1.76 (s, H-2 and H-8).

Anal. Calcd for $C_{29}H_{24}N_5O_7Cl$: C, 59.19; H, 4.10; N, 11.87. Found: C, 59.46; H, 4.35; N, 11.47.

6-*N*,*N*-Dimethylamino-9-(3′-*C*-*N*,*N*-dimethylcarbamoylmethyl-3′-deoxy-β-D-allofuranosyl)purine (9).—To a solution of 20 ml of methanol and 10 ml of aqueous 25% dimethylamine was added 0.450 g of the blocked nucleoside **8** and the mixture was left to stand at room temperature for 4 hr. After removal of the solvent under diminished pressure, the residue was partitioned between water (20 ml) and dichloromethane (10 ml). The dichloromethane layer was washed with water (10 ml). The combined aqueous extracts were evaporated under diminished pressure to yield a syrup. This syrup was chromatographed on a column of silica (12 g) using 9:1 dichloromethane–methanol as developer to afford 0.160 g (45% yield) of the unblocked nucleoside **9**. An analytical sample of **9** was prepared by rechromatographing **9** on silica using water as developer. The nucleoside **9** was crystallized from ethanol–ether: mp 178–179°; ir 6.30 μ (C=O); λ_{max} (MeOH) 275 mμ (ε 20,000); CD max (MeOH) 275 mμ (θ −11,000); $[\alpha]^{23}D$ −66° (*c* 1.8, methanol); τ^{D_2O} 4.76 (t, H-2′), 3.74 (d, $J_{1',2'}$ = 4 Hz, H-1′), 1.56, 1.74 (s, H-2 and H-8); $\tau^{DMSO\text{-}d_6}$ 5.38 (t, primary OH), 4.23 and 4.50 (d, due to secondary OH's) (these signals disappear on addition of D_2O); τ^{CDCl_3} 7.10 and 6.95 (two methyls), 6.57 (singlet, equal to two methyl groups); mol wt (mass spectroscopy) 394.

Anal. Calcd for $C_{17}H_{26}O_5N_6$: C, 51.79; H, 6.64; N, 21.31. Found: C, 51.69; H, 6.71; N, 21.28.

Metaperiodate Oxidation and Reduction of 9 to Yield 6-*N*,*N*-Dimethylamino-9-(3′-*C*-*N*,*N*-dimethylcarbamoylmethyl-3′-deoxy-β-D-ribofuranosyl)purine (10).—To a solution of the allo

nucleoside **9** (0.275 g, 0.7 mmol) in 21 ml of water and 14 ml of ethanol was added with stirring 0.5 ml of saturated sodium hydrogen carbonate and a 5% aqueous solution of sodium metaperiodate (0.150 g, 0.7 mmol). The reaction mixture was left standing at room temperature in the dark for 2.5 hr. To the resulting solution was added with stirring sodium borohydride (0.212 g) and the mixture was stirred for 3 hr. Excess sodium borohydride was decomposed by addition of glacial acetid acid. The reaction mixture was evaporated under reduced pressure and the residue was treated with 3 × 5 ml of methanol followed by evaporation. The residue was extracted with dichloromethane and filtered, and the filtrate was evaporated to a syrup. Chromatography of this residue on silica (32 g) with 92:8 dichloromethane–methanol gave 0.170 g (68%) of a nucleoside **10**. This product appeared to be homogeneous by paper chromatography with 40:19:11 *n*-butyl alcohol–ethanol–water (R_f 0.68) or by tlc on silica with 9:1 dichloromethane–methanol (R_f 0.42): $[\alpha]^{25}D$ −35° (*c* 1.37, water); ir 3.2 (OH), 6.5 μ (C=O); uv λ_{max} 275 mμ (ε 14,300, water); τ^{CDCl_3} 7.10 and 6.97 (s, NMe_2), 6.55 (s, equal to 6 H of NMe_2), 4.5 (two OH groups), 4.07 (d, $J_{1',2'}$ = 3 Hz, H-1'), 1.82 (H-2 and H-8).

Anal. Calcd for $C_{16}H_{24}N_6O_4 \cdot {}^1/_2H_2O$: C, 51.30; H, 6.68; N, 23.06. Found: C, 50.86; H, 6.43; N, 22.40.

The analysis varied depending on the temperature at which the sample was dried under vacuum. The compound lost dimethylamine on heating.

6-Benzamido-9-(2'-*O*-acetyl-5',6'-di-*O*-benzoyl-3'-*C*-cyanomethyl-3'-deoxy-β-D-allofuranosyl)purine (11).—A solution of 1 g of 1,2-*O*-acetyl-5,6-di-*O*-benzoyl-3-cyanomethyl-3-deoxy-β-D-allofuranose (**7**) in dichloromethane (50 ml) kept at 0° was kept saturated with anhydrous hydrogen bromide for 15 min and the flask was then lightly stoppered and kept at 0° for 1 hr and finally at room temperature for 15 min. The solvents were removed under diminished pressure and two portions of anhydrous toluene were then added and removed under reduced pressure to yield a syrup. This syrup, dissolved in anhydrous toluene (40 ml), was immediately added to a thoroughly dried mixture (by distilling, at atmospheric pressure, anhydrous toluene from it) of 0.950 g (2.0 mmol) of chloromercuri-6-benzamidopurine, Celite (0.300 g) in anhydrous toluene (30 ml). The mixture was heated to the reflux temperature and refluxing was continued for 0.75 hr. The hot mixture was filtered and the filtrate was then evaporated under reduced pressure. The residue was extracted with dichloromethane (120 ml), and the extract was washed with two 20-ml portions of 30% KI and two 20-ml portions of water. Concentration of the dried ($MgSO_4$) dichloromethane layer gave a residue which was chromatographed on a silica column (60 g) using 1:1 benzene–ethyl acetate as developer to give 0.900 g (60%) of purified **11**: ir 4.50 μ (C≡N); τ^{CDCl_3} (100 MHz) 7.26 (d, CH_2CN), 0.8 (NH); $[\alpha]^{22}D$ −37° (*c* 1.5, $CHCl_3$).

Anal. Calcd for $C_{36}H_{30}N_6O_8$: C, 64.07; H, 4.45; N, 12.47. Found: C, 63.76; H, 4.72; N, 12.08.

9-(3'-*C*-Aminoethyl-3'-deoxy-β-D-allofuranosyl)adenine (12).—To a suspension of lithium aluminum hydride (210 mg, 5.5 mmol) in tetrahydrofuran (150 ml) was added dropwise a solution of 6-benzamido-9-(2'-*O*-acetyl-5',6'-di-*O*-benzoyl-3'-*C*-cyanomethyl-3'-deoxy-β-D-allofuranosyl)purine (**11**) (826 mg, 1.23 mmol) in THF. After the reaction mixture was left stand at room temperature for 0.5 hr and then refluxed for 2 hr, the excess reducing reagent was destroyed by the slow addition of water (10 ml), ethanol (10 ml), and 5 *N* ammonium hydroxide (10 ml). The resulting precipitate was removed by filtration and washed with ethanol (50 ml). The residue, obtained by evaporation of the combined filtrate and washings, was partitioned between dichloromethane (10 ml) and water (7.5 ml). Examination of the dichloromethane extract showed that it contained no nucleoside nor any substance giving a positive test with ninhydrin. The water extract was evaporated to dryness and the remaining material (700 mg) was taken up in ethanol and left to stand at 0° overnight. From this solution was obtained 200 mg of crystalline product having an ultraviolet spectrum similar to that of adenosine. The ultraviolet spectrum of the mother liquor indicated that it contained a negligible amount of nucleoside.

The above crystalline material was dissolved in 2% acetic acid (2 ml) and chromatographed on 5 ml of Dowex 50W-X2 (NH_4^+ form) resin. The column was first washed with 100 ml of water and then with 5% ammonium hydroxide to afford, after crystallization of the main component from methanol, a homogeneous nucleoside **12** (0.080 g, 30% yield): mp 170–171°; uv λ_{max} 261 mμ (ε 15,000, H_2O); τ^{DMSO-d_6} 1.66, 1.82 (2 s, 2 H, H-2, H-8), 2.70 (b, 2 H, NH_2), 4.10 (d, 1 H, H-1'), 4.2–4.6 (b, 2 H, NH_2), 5.28 (t, 1 H, H-2'); $[\alpha]^{25}D$ −59° (*c* 1, H_2O).

Anal. Calcd for $C_{13}H_{20}N_6O_4$: C, 48.14; H, 6.18; N, 25.91. Found: C, 44.45; H, 5.41; N, 21.69. The sample contained some inorganic material which could not be removed by use of resins.

Registry No.—**2**, 30694-90-7; **4**, 37108-14-8; **5**, 37108-15-9; **6**, 37108-16-0; **6a**, 37108-17-1; **7**, 37406-75-0; **8**, 37108-18-2; **9**, 37108-19-3; **10**, 37108-20-6; **11**, 37108-21-7; **12**, 37108-22-8.

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