ethyl acetate (20:80) yielded 0.220 g of pure **23** as a homogenous syrup (40% total yield). This syrup crystallized from ethanol as small aggregates of white, fibrous needles (110 mg in two crops, mp 152–156°). The two crystalline forms obtained for product **23** had identical physical properties (uv, pmr, analysis, tlc) except for their ir spectra (KBr). It was found possible to convert one form (prisms) to the other (fibers) by redissolving crystals of the former in hot ethanol and seeding the solution with crystals of the latter. The ir spectrum was found to have changed accordingly: uv $\lambda_{max}^{pH\ 1}$ 290 mμ (ε 7300), $\lambda_{min}^{pH\ 1}$ 259 (4600), $\lambda_{max}^{pH\ 11}$ 297 (6400), $\lambda_{min}^{pH\ 11}$ 264 (5200); pmr (DMSO-d_6) δ 1.27 (3, t, CH_3), 3.20–4.55 (7, m, H-2′, H-3′, H-4′, H-5′, and $COCH_2$), 4.60–5.40 (3, two doublets and one triplet, all exchangeable in D_2O, sugar OH's), 5.63 (1, d, H-1′), 5.97 (1, s, H-5), 6.61 and 7.54 (2, two AB doublets, CH=CH), 11.49 (1, broad singlet, NH), $J_{1',2'}$ = 5.0 Hz, J_{trans} = 16.0 Hz.

Anal. Calcd for $C_{14}H_{18}N_2O_8$: C, 49.12; H, 5.30; N, 8.18. Found: C, 49.01; H, 5.30; N, 8.09.

Registry No.—**2**, 36807-59-7; **3**, 13345-12-5; *cis*-**4**, 36807-60-0; *trans*-**4**, 36807-61-1; **5**, 22724-20-5; **5** phenylhydrazone, 36803-37-9; **7**, 18592-13-7; **8**, 36803-39-1; **9**, 36803-40-4; **10**, 15043-03-5; **11**, 36803-42-6; **12**, 36803-43-7; **13**, 36812-98-3; **14**, 36803-44-8; **15**, 36803-45-9; **20**, 36807-62-2; **21**, 36807-63-3; **23**, 36806-64-4.

Acknowledgment.—The authors are deeply grateful to Drs. H. Vorbrüggen and U. Niedballa of Schering AG, Berlin, for a generous gift of some of the 6-methyluridine used in this study. We are also indebted to Dr. B. H. Rizkalla of our laboratory for helpful discussions and to Mr. Marvin Olsen for recording the pmr spectra.

Interconversions of Hexofuranosyl Nucleosides. IV. Synthesis of Nucleosides Derived from 6-Deoxy-L-glucose[1]

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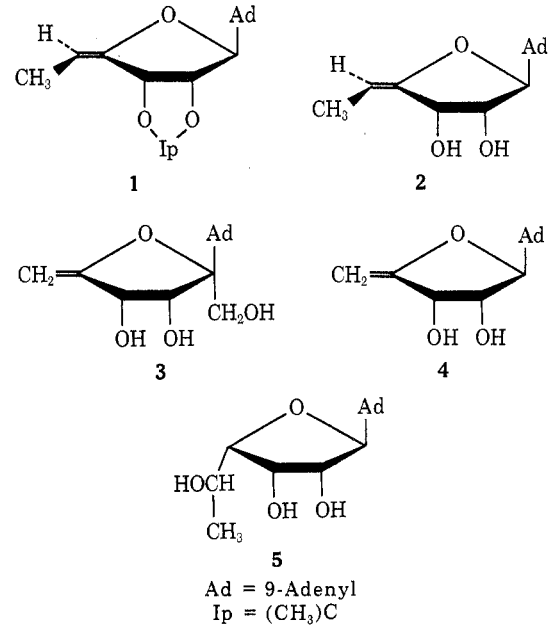
Acetolysis of 6-deoxy-1,5-di-*O*-acetyl-2,3-*O*-isopropylidene-L-mannofuranose (**6**) in 10:1 acetic acid–acetic anhydride followed by reaction of the crude product with 6-benzamidochloromercuripurine and titanium tetrachloride in refluxing 1,2-dichloroethane, gave 9-(6-deoxy-β-L-glucofuranosyl)adenine (**8**) and 9-(6-deoxy-α-L-mannopyranosyl)adenine (**7**) in a ratio of 4:1, after removal of blocking groups. Similarly, acetolysis of 6-deoxy-2,3-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-L-mannofuranose under the same conditions, followed by formation of the blocked nucleoside, afforded crystalline 9-(6-deoxy-2,3-di-*O*-acetyl-5-*O*-*p*-toluenesulfonyl-β-L-glucofuranosyl)adenine (**9**) and not 9-(6-deoxy-2,3-di-*O*-acetyl-5-*O*-*p*-toluenesulfonyl-α-L-mannofuranosyl)adenine, as had been previously reported. Acetolysis of **6**, removal of the blocking groups with base, and acetylation of the free sugars gave the crystalline anomeric 6-deoxy-1,2,3,4-tetra-*O*-acetyl-L-glucopyranoses (**11** and **12**) in good yield. 6-Deoxy-L-glucose was prepared in 62% yield from the β anomer **11**. Both **11** and the α anomer **12** were converted to 6-deoxy-2,3,4-tri-*O*-acetyl-α-L-glucopyranosyl bromide (**14**) by reaction with hydrogen bromide in acetic acid. The nucleoside, 9-(6-deoxy-β-L-glucopyranosyl)adenine, was prepared by reaction of **14** with 6-benzamidochloromercuripurine in boiling xylene followed by removal of the blocking groups with sodium methoxide.

In the previous article in this series[2] the synthesis of 9-(5,6-dideoxy-2,3-*O*-isopropylidene-β-D-*erythro*-hex-4-enofuranosyl)adenine (**1**) (Chart I) was described. The deblocked nucleoside **2** was of interest because of its structural relationship to the nucleoside antibiotic, decoyinine (**3**), and to a biologically active analog of **3**, 9-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenine (**4**).[3] However, removal of the isopropylidene group of **1** under the various acidic conditions attempted resulted in a complete degradation of the nucleoside because of its acid-unstable enol ether structure. The same problem arose in the preparation of **3** and **4**, but this was solved with use of the more acid-labile ethoxymethylidene blocking group in place of the isopropylidene group.[3] Therefore, a decision was made to prepare an alkoxymethylidene derivative of **2** with the expectation that this blocking group could be removed under conditions that would not hydrolyze the *N*-glycosyl bond.[4] To do this it was necessary to prepare alkoxymethylidene derivatives of 9-(6-deoxy-α-L-mannofuranosyl)adenine (**5**); therefore, a large quantity of **5** was required. Two routes leading to **5** have been reported,[5,6] but neither one is straightforward,

CHART I



Ad = 9-Adenyl
Ip = $(CH_3)C$

(1) This work was supported, in part, by Grant No. T-442 from the American Cancer Society.

(2) L. M. Lerner, *J. Org. Chem.*, **37**, 477 (1972).

(3) J. R. McCarthy, R. K. Robins, and M. J. Robins, *J. Amer. Chem. Soc.*, **90**, 4993 (1968).

(4) C. A. Dekker and L. Goodman in "The Carbohydrates," Vol. IIA, W. Pigman and D. Horton, Ed., Academic Press, New York, N. Y., 1970, p 1.

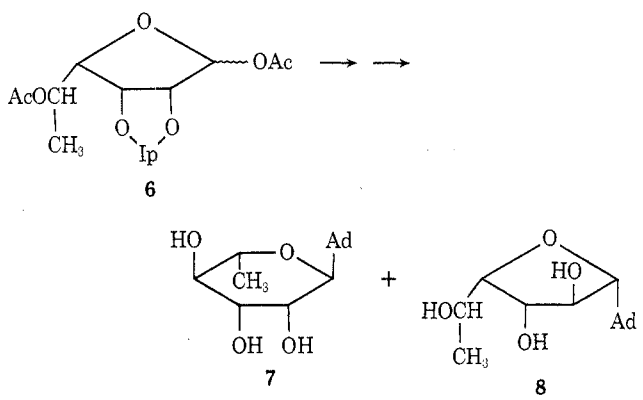
(5) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 966 (1957).

(6) L. M. Lerner and Y. Y. Cheng, *Carbohyd. Res.*, **14**, 297 (1970).

gives high yields, or can be speedily accomplished. Therefore, an attempt was made to prepare **5** from 6-deoxy-1,5-di-*O*-acetyl-2,3-*O*-isopropylidene-L-mannofuranose[6] (**6**) by acetolysis to form the impure tetraacetate, immediate formation of the blocked nucleoside, and subsequent removal of the blocking groups. A small amount of 9-(6-deoxy-α-L-mannopyranosyl)-adenine[7] (**7**) was also expected from this reaction sequence, but separation of **5** from **7** was not expected to present a serious problem.

Acetolysis of **6** gave a syrup which was coupled with 6-benzamidochloromercuripurine by the titanium tetrachloride method.[8] Removal of the blocking groups with sodium methoxide in methanol, separation of the nucleosides from unreacted sugars *via* their picrates,[7] and chromatography on an anion exchange column[9] afforded **7** and a nucleoside which was definitely not **5** in a ratio of about 1:4 (Chart II). This

CHART II



compound was identified as 9-(6-deoxy-β-L-glucofuranosyl)adenine (**8**), the enantiomer of which was first reported by Reist, *et al.*[10] Evidence for this identification is presented in Table I.

TABLE I

COMPARISON OF PHYSICAL PROPERTIES OF THE ENANTIOMERIC FORMS OF 9-(6-DEOXY-β-GLUCOFURANOSYL)ADENINE

Property	D form[a]	L form
Mp, °C	118–118.5	119.5–121
$[\alpha]_D$	−59.9°	+61.6°
Analysis	$C_{11}H_{15}N_5O_4 \cdot C_2H_5OH$	$C_{11}H_{15}N_5O_4 \cdot C_2H_5OH$
IO_4^- uptake	0.9 mole equiv/96 hr	0.81 mole equiv/96 hr 0.90 mole equiv/144 hr
Picrate mp, °C	204–208 dec	207–209 dec

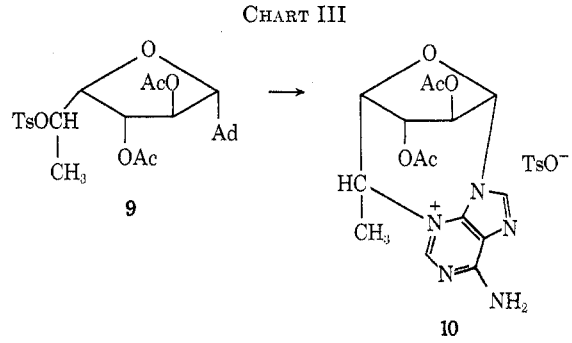
[a] Reference 10.

In addition, the infrared spectrum of **8** had the peaks reported for the D form and the ultraviolet spectrum indicated substitution at N-9 of the purine, a point which was not recorded for the D nucleoside.

The reason for the isolation of **8** instead of **5** is now understandable on the basis of some recent developments concerning epimerization at C-2 of carbohydrates. It has been reported[11,12] that acetolysis of aldofuranoses and their derivatives, which have cis hydroxyls at C-2 and C-3, under conditions quite similar to that described in this paper, resulted in epimerization at C-2. Some of this work had been based upon an older report by Jerkeman,[13] and two mechanisms[11,13] have been suggested to account for this phenomenon, both of which require a furanose ring and three adjacent hydroxyl groups with the two ring hydroxyls in a cis relationship. In the earlier paper,[13] it was suggested from chromatographic data that the only products were furanose acetates, but in the present work the isolation of **7** would indicate otherwise. It is important to note that in agreement with the previous reports and the mechanisms proposed for the acetolysis reaction, epimerization at C-2 only occurred with the furanose ring and not with the pyranose ring. During acetolysis an exchange of acetate groups occurred which allowed a portion of the furanose ring to rearrange to the pyranose form, and this portion of material was not converted into the L-gluco isomer. The 1:4 ratio of **7**:**8** should not be construed as being a real indication of the ratio of L-manno to L-gluco isomers because the sugars may have reacted to a different extent with the nitrogenous base.

Because of the nature of the reaction products isolated after acetolysis of **6** and formation of the nucleosides, a reexamination of the structure of a closely related product previously reported from this laboratory was felt to be necessary. Crystalline 9-(6-deoxy-2,3-di-*O*-acetyl-5-*O*-*p*-toluenesulfonyl-α-L-mannofuranosyl)-adenine was reported to be the product of a series of reactions which entailed acetolysis of 6-deoxy-2,3-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-L-mannofuranose under the same conditions reported herein.[2] It appeared to be a good possibility that this nucleoside derivative was really 9-(6-deoxy-2,3-di-*O*-acetyl-5-*O*-*p*-toluenesulfonyl-β-L-glucofuranosyl)adenine (**9**) (Chart III).[14] Evidence for this structure was obtained by

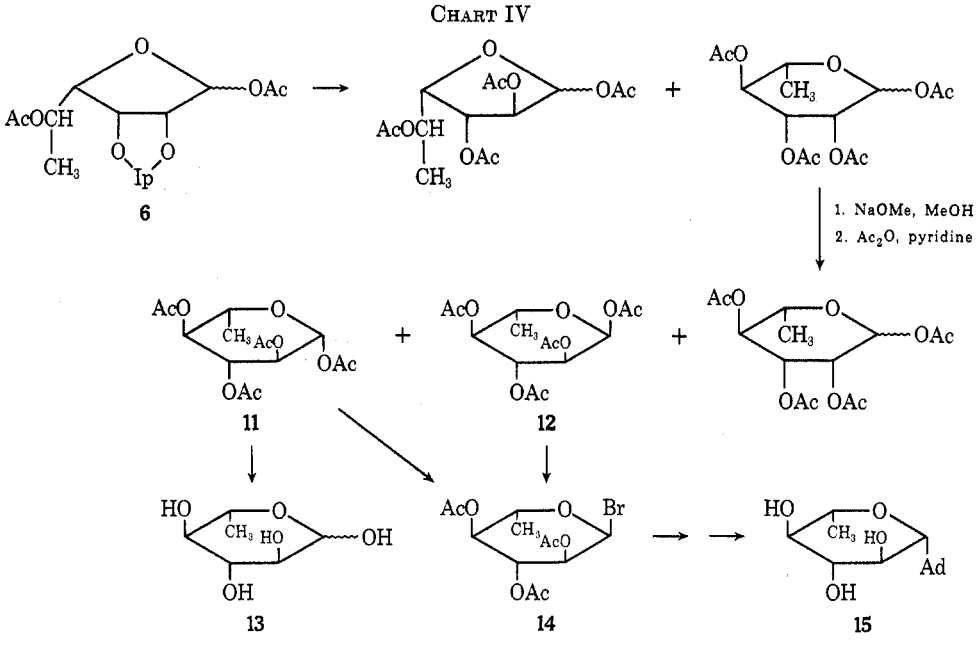
CHART III



formation of cyclonucleoside **10** in either boiling *N*,*N*-dimethylformamide or dioxane. The cyclonucleoside did not crystallize but it did show an expected ultraviolet maximum at 272 mμ and tosylate anion peaks at 1010 and 681 cm^{-1} in the infrared. Such a structure as **10** could not have formed unless the adenine ring and

(7) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 959 (1957).
(8) B. R. Baker, R. E. Schaub, J. P. Joseph, and J. H. Williams, *J. Amer. Chem. Soc.*, **77**, 12 (1955); J. Prokop and D. H. Murray, *J. Pharm. Sci.*, **54**, 359 (1965).
(9) C. A. Dekker, *J. Amer. Chem. Soc.*, **87**, 4027 (1965).
(10) E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Org. Chem.*, **23**, 1753 (1958).
(11) W. Sowa, *Can. J. Chem.*, **49**, 3292 (1971).
(12) G. J. F. Chittenden, *Carbohyd. Res.*, **22**, 491 (1972).
(13) P. Jerkeman, *Acta Chem. Scand.*, **17**, 2769 (1963).
(14) The author is indebted to Dr. Derek Ball for bringing the possibility of this to his attention. This information was also instrumental in the positive identification of **8**.

CHART IV



6 11 12 13 14 15

C-5′ were on the same side of the furanose ring. However, such evidence does not prove that the configuration of the sugar moiety is L-gluco, although it would be expected that the main product resulting from reaction of the sugar derivative with the mercuric chloride salt of the base would have a configuration at the anomeric carbon atom that is trans to the hydroxyl at C-2′.[15] Because **9** could not be converted to **8** without extensive degradation[2] and it was not feasible to prepare **9** from **8**, 100-MHz nuclear magnetic resonance spectroscopy was used[16] in order to gain further information in support of the structure of **9**, especially as concerned the relative configurations of C-2′ and C-3′. Salient features of the spectrum are shown in Table II.

TABLE II

NUCLEAR MAGNETIC RESONANCE DATA FOR 9-(6-DEOXY-2,3-DI-*O*-ACETYL-5-*O*-*p*-TOLUENESULFONYL-β-L-GLUCOFURANOSYL)ADENINE (**9**)[a]

Position, τ	Intensity	Multiplicity	Assignment
1.78	1	Singlet	H-2
1.84	1	Singlet	H-8
2.25	2	Doublet	Tosyl protons ortho to sulfonate
2.61	2	Doublet	Tosyl protons ortho to methyl
2.70	2	Singlet	NH_2
3.89	1	Broad singlet	H-1′
4.24	1	Broad singlet	H-2′
4.64	1	Doublet (distorted)	H-3′
4.96	1	Multiplet	H-5′
5.65	1	Multiplet	H-4′
7.62	3	Singlet	Tosyl methyl
7.89, 7.94	6	Two singlets	Acetate methyls
8.73	3	Doublet	C-6′ methyl

[a] Obtained in DMSO-d_6 using tetramethylsilane as reference.

The nmr spectrum appeared to support the structure of **9**. The trans relationship of the H-1′ and H-2′ protons is supported by the singlets at τ 3.89 and 4.24. The broadening of the peaks may be due to long-range coupling and it is of interest to note that in a double resonance experiment, in which the peak due to H-4′ was irradiated, the broad singlet due to H-1′ broke into a doublet. The peak at τ 4.64 for H-3′ gave a doublet due to the expected coupling of H-3′ with H-4′ and supports the trans relationship of H-2′ and H-3′.[17] The assignments of the multiplets at τ 4.96 and 5.65 were made after double-resonance experiments in which irradiation at τ 5.65 caused the doublet due to H-3′ to collapse to a singlet and irradiation at τ 4.96 caused the doublet at τ 8.73 (C-6′ methyl) to collapse to a singlet.

Further proof of the identity of the sugar in the present experiments as 6-deoxy-L-glucose (**13**) resulted in the development of a very simple and practical preparation of this rare sugar (Chart IV). After acetolysis of **6**, the acetyl groups were removed under mild basic conditions, which resulted in a rearrangement of the ring structure to the pyranose form. The pyranoses (a mixture of **13** and 6-deoxy-L-mannose) were acetylated with acetic anhydride in pyridine and the anomeric tetraacetates **11** and **12** were fractionally crystallized. These compounds do not seem to have been previously reported, although their D enantiomers are known.[18,19] Both **11** and **12** were converted into 6-deoxy-2,3,4-tri-*O*-acetyl-α-L-glucopyranosyl bromide (**14**), and although the physical data for **14** were similar to those of the D form,[20] the compound was too unstable to get a reliable elemental analysis. Removal of the acetyl groups of **11** with methanolic sodium methoxide resulted in a 62% yield of **13**.

Condensation of **14** with 6-benzamidochloromercuripurine by the procedure of Davoll and Lowy[21] and removal of the blocking groups afforded a 55% yield of

(15) B. R. Baker, in Ciba Foundation Symposium, "Chemistry and Biology of Purines," G. E. W. Wolstenholme and C. M. O'Connor, Ed., Little, Brown and Co., Boston, Mass., 1957, p 120.

(16) Nmr spectra were obtained by Dr. Harry Agahigian of the Baron Consulting Co., Orange, Conn.

(17) J. D. Stevens and H. G. Fletcher, Jr., *J. Org. Chem.*, **33**, 1799 (1968).

(18) W. Schuepp and E. Hardegger, *Helv. Chim. Acta*, **53**, 1336 (1970).

(19) E. Hardegger and R. M. Montavon, *ibid.*, **29**, 1199 (1946).

(20) J. Compton, *J. Amer. Chem. Soc.*, **60**, 395 (1938).

(21) J. Davoll and B. A. Lowy, *ibid.*, **73**, 1650 (1951).

9-(6-deoxy-β-L-glucopyranosyl)adenine (**15**). Preparation of **15** directly from a crude syrupy mixture containing **11** and **12** using the titanium tetrachloride method of coupling did not offer any advantages, since purification of the product necessitated the use of chromatography.

Proof of structure of **15** was supported by an ultraviolet maximum at 260 mμ, indicating that the sugar was bonded to adenine at N-9. The compound consumed 1.8 molar equiv of periodate, which supported the pyranose ring. In order to ascertain the configuration at the anomeric carbon atom, a polarimetric investigation of the dialdehyde product **17** obtained after periodate oxidation was made. 9-(6-Deoxy-β-L-galactopyranosyl)adenine[22] (**16**) and **7** were used as reference compounds and the results are shown in Table III.

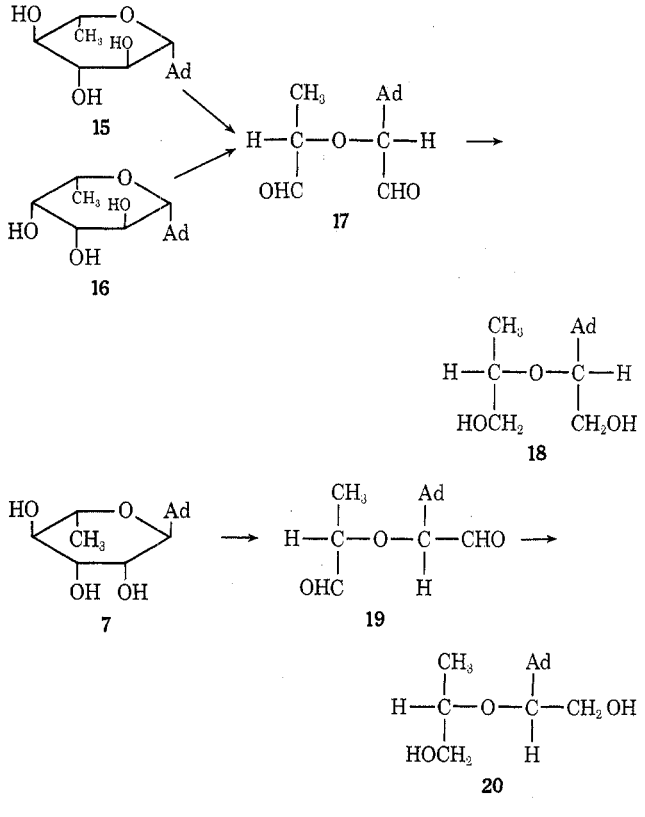
TABLE III
POLARIMETRIC STUDIES WITH NUCLEOSIDES

Nucleoside	$[\alpha]_D$ after IO_4^- oxidation[a]	$[\alpha]_D$ after $NaBH_4$ reduction[a]
15	−5°	−50°
16	−7°	−46° (−54°)[b]
7	−5°	+74° (+81°)[b]

[a] Based upon the calculated dry weight of the dialdehyde or dialcohol product. [b] Values in parentheses are for the pure crystalline dialcohols, ref 22.

It was expected that **15** and **16** would give the same dialdehyde **17**, whereas **7** would give the diasteromeric dialdehyde **19** (Chart V). However, the specific rotations were too close to each other and too near zero to be of any use in structure determination. Therefore, in a separate experiment, the dialdehydes were reduced with sodium borohydride to the known dialcohols[22] **18** and **20** and their specific rotations were determined. The results indicated that **15** had the β-L configuration.

CHART V



Experimental Section[23]

9-(6-Deoxy-β-L-glucofuranosyl)adenine[24] (**8**).—To an ice-cold mixture containing 10.9 g of 6-deoxy-1,5-di-*O*-acetyl-2,3-*O*-isopropylidene-L-mannofuranose[6] (**6**), 224 ml of glacial acetic acid, and 22.4 ml of acetic anhydride was added, dropwise, 12.5 ml of concentrated sulfuric acid. After 48 hr at room temperature the reaction mixture was poured into 500 g of ice, and this was stirred vigorously until all of the ice had melted. Chloroform (100 ml) was added to the stirring mixture, the layers were separated, and the aqueous layer was extracted two additional times with 100-ml portions of chloroform. The chloroform extracts were combined and washed with cold water (five 300-ml portions), saturated sodium bicarbonate (two 300-ml portions), and once again with water. The chloroform solution was dried and evaporated, and traces of acetic acid were removed by evaporation of toluene, leaving an oil which weighed 8.4 g.

The oil (8.3 g, 25 mmol) was dissolved in 1200 ml of 1,2-dichloroethane to which 14.2 g (30 mmol) of 6-benzamidochloromercuripurine and 14.2 g of Celite-545 were added. A portion of the solvent (200 ml) was distilled, 3.3 ml (30 mmol) of titanium tetrachloride in 200 ml of 1,2-dichloroethane was added, and the mixture was refluxed for 22 hr.[8] The mixture was cooled, 500 ml of saturated sodium bicarbonate was added, and vigorous stirring was continued for 2 hr. The mixture was filtered through a pad of Celite-545, the filter cake was washed with 250 ml of warm 1,2-dichloroethane, the organic layer was separated, and the solvent was evaporated. The residue was dissolved in 200 ml of chloroform and washed with 30% aqueous potassium iodide (two 150-ml portions) and water (200 ml), and dried. Evaporation gave 12.1 g of a foam which was dissolved in 150 ml of methanol, treated with 10 ml of 1 *N* methanolic sodium methoxide, and heated at reflux for 1 hr. This solution was evaporated to dryness, dissolved in 100 ml of water, brought to neutrality with acetic acid, and washed with chloroform (three 50-ml portions). The aqueous layer was evaporated, leaving a red-colored residue which was dissolved in 50 ml of warm methanol and treated with 140 ml of 10% methanolic picric acid. A yellow precipitate formed immediately and the flask was chilled for 2 hr. The filtered product was washed with cold methanol and ether, giving 7.1 g.

The picrate was suspended in 1 l. of stirring hot water, the yellow color was discharged by addition of Bio-Rad AG1-X8 (CO_3^{2-}) resin, and stirring was continued for an additional 1.5 hr.[7] Filtration and evaporation of the water left a white foam which was redissolved in a small amount of water and placed on top of a column (31 × 2.4 cm) of Bio-Rad AG1-X2 (OH, 200–400 mesh) resin.[9] Elution of the column was carried out with 30% aqueous methanol and 10-ml fractions were collected and monitored by ultraviolet absorption at 254 mμ. Fractions 35–65 were combined and evaporated to dryness, and the product (550 mg, 8%) was crystallized from ethanol. This product was identified as 9-(6-deoxy-α-L-mannopyranosyl)adenine (**7**), mp 214–216°, $[\alpha]^{23}D$ −61° (*c* 1.1, H_2O). This compound did not depress the melting point upon admixture with an authentic sample[25] of **7**, the infrared spectra were identical, as also were the mobilities upon paper chromatography in two solvent systems.

Fractions 205–800 were pooled and evaporated, and crystallization occurred during this step to give 2.12 g (30%), which was recrystallized from ethanol to afford 1.94 g of **8** in three crops: mp 119.5–121°; $[\alpha]^{22}D$ +61.6° (*c* 0.813, H_2O); uv max (0.1 *N* HCl) 258 mμ (ε 14,500), (H_2O) 259 (14,450), (0.1 *N*

(22) L. M. Lerner and R. R. Rossi, *Biochemistry*, **11**, 2772 (1972).

(23) General methods and instrumentation are described in the first paper of this series: L. M. Lerner, *J. Org. Chem.*, **37**, 470 (1972). Moist organic solutions were dried over anhydrous magnesium sulfate and evaporations were performed under reduced pressure at bath temperatures between 40 and 50°.

(24) In a preliminary experiment, Dr. Davaluri R. Rao prepared this compound during an attempted preparation of **5**.

(25) A sample of **7** was prepared by Dr. Ralph R. Rossi following the procedure in ref 7.

NaOH) 259 (15,400). Periodate consumption is reported in Table I.

Anal. Calcd for $C_{11}H_{15}N_5O_4 \cdot C_2H_5OH$: C, 47.70; H, 6.47; N, 21.40. Found: C, 47.03; H, 6.10; N, 21.83.

A crystalline picrate, prepared by mixing several milligrams of **8** in water with a saturated aqueous solution of picric acid, had mp 207–209° dec.

Cyclonucleoside 10 from 9-(6-deoxy-2,3-di-*O*-acetyl-5-*O*-*p*-toluenesulfonyl-β-L-glucofuranosyl)adenine (9).—A solution containing 50 mg of **9** in 3 ml of *N*,*N*-dimethylformamide was heated at reflux for 1 hr. The solvent was evaporated but the syrupy product failed to crystallize: λ_{max}^{MeOH} 272 mμ; ir (film, NaCl) 1010 and 681 cm^{-1} (tosylate anion). The syrup was also soluble in cold water. Tlc[26] in 5:1 chloroform–methanol gave R_f 0.05; **9** had R_f 0.54.

Anomers of 6-Deoxy-1,2,3,4-tetra-*O*-acetyl-L-glucopyranose (11 and 12).—Compound **6** (35 g) was treated with 735 ml of acetic acid, 73.5 ml of acetic anhydride, and 41 ml of concentrated sulfuric acid as described for the preparation of **8**. The syrup (25.4 g) which was obtained was dissolved in 280 ml of methanol, treated with 20 ml of 1 *N* methanolic sodium methoxide, and allowed to stand at room temperature for 40 min. The solution was brought to neutrality with Dowex 50 (H^+) resin, the resin was removed by filtration and washed thoroughly with methanol, and the methanol was evaporated. A thin syrup remained which formed a hard gum (13.3 g) upon evaporation (three times) with acetone. The entire gum was dissolved in 100 ml of dry pyridine (heat required) and chilled in an ice bath, and 110 ml of cold acetic anhydride was added in small portions over a period of 20 min. After 1 hr at 0°, the solution was kept at room temperature for 23 hr. The mixture was chilled in ice again and 120 ml of ice-cold ethanol was added. The solution was stirred for 30 min and then for 1 hr at room temperature, whereupon it was evaporated to a thin yellow syrup. This was dissolved in 150 ml of chloroform and washed with cold 10% aqueous sulfuric acid (100 ml), cold water (200 ml), saturated sodium bicarbonate (150 ml), and again with water (200 ml). After being dried, the chloroform was evaporated and the syrup was dissolved in warm ethanol. Large prismatic rods were slowly deposited over 3 days to afford 5.85 g of 6-deoxy-1,2,3,4-tetra-*O*-acetyl-β-L-glucopyranose (**11**), mp 148–149°. One recrystallization from ethanol raised the melting point to 149–149.5°, $[\alpha]^{23}D$ −21.6° (*c* 1.15, $CHCl_3$) [reported[18] for the D form, mp 146°, $[\alpha]D$ +21.5° (*c* 1, $CHCl_3$)].

Anal. Calcd for $C_{14}H_{20}O_9$: C, 50.60; H, 6.07. Found: C, 50.51; H, 6.07.

The mother liquor was concentrated somewhat by boiling and stored at room temperature. Large needles were deposited which closely resembled **11**, 0.71 g, mp 110–122°. 6-Deoxy-1,2,3,4-tetra-*O*-acetyl-α-L-glucopyranose (**12**) was isolated in pure form by recrystallization from ethanol to yield 334 mg, mp 122–124.5°, $[\alpha]^{23}D$ −104° (*c* 1.01, $CHCl_3$) [reported[19] for the D form, mp 117°, $[\alpha]D$ +122° (*c* 1.3, $CHCl_3$)].

Anal. Calcd for $C_{14}H_{20}O_9$: C, 50.60; H, 6.07. Found: C, 50.69; H, 6.05.

Additional concentration of the mother liquor by boiling yielded 4.1 g of crystals, mp 97–103°. Careful recrystallization from ethanol using seeds of **11** or **12** could effect a partial separation of the anomers. One recrystallization of the bulk product gave clumps of crystals melting at 110–120° and other clumps melting at 137–142°. No further crops of crystals of **11** and **12** could be isolated. Presumably the remaining 12 g of syrup, $[\alpha]^{25}D$ −50° (*c* 1.35, $CHCl_3$), was an anomeric mixture of peracetylated 6-deoxy-L-mannopyranose.

6-Deoxy-L-glucose (13).—In 19 ml of warm methanol was dissolved 1 g of **11**, the solution was chilled in an ice bath, and 1 ml of 1 *N* methanolic sodium methoxide was added. The solution was kept at room temperature for 1.5 hr and neutralized with Dowex 50 (H^+) resin, the resin was removed by filtration, and the methanolic solution was concentrated by evaporation to approximately 15 ml. The solution was treated with activated charcoal and the methanol was evaporated. A small amount of warm acetone was added and the clear, colorless syrup was rubbed with a glass rod until crystallization occurred. After standing for several hours, the crystals (166 mg) were filtered off and two more crops (139 mg) were obtained (305 mg, 62%), mp 142–143°, $[\alpha]^{22}D$ −29.8° (3 hr, final; *c* 2.01, H_2O) [lit.[27] mp 142–144°, $[\alpha]^{20}D$ −29.9 (3 hr, final; *c* 2, H_2O)].

6-Deoxy-2,3,4-tri-*O*-acetyl-α-L-glucopyranosyl Bromide (14). From 11.—To 3 g of **11** was added 14 ml of a 30–32% solution of hydrogen bromide in acetic acid (Eastman). The flask was stoppered and shaken for 15 min, by which time the compound had dissolved. Almost immediately a mass of white crystals began to form. After 1 hr, 20 ml of chloroform was added which dissolved the crystals. The solution was diluted further with 80 ml of chloroform, washed with ice–water (three 150-ml portions), and dried. The chloroform was evaporated, leaving a white solid which was recrystallized from benzene in three crops as large, colorless needles, 2.49 g (78%), mp 151–153° $[\alpha]^{24}D$ −255° (*c* 1.12, $CHCl_3$) [reported[20] for the D form mp 150–152°, $[\alpha]D$ +247° (*c* 3.89, $CHCl_3$)]. Preparations of the bromide were unstable even in a desiccator in the freezer and would decompose within 48 hr. The analysis was, therefore, quite poor.

From 12.—A mixture of 334 mg of **12** and 2.5 ml of hydrogen bromide in acetic acid (30–32%, Eastman) was allowed to react and worked up as described above. A yield of 168 mg of **14** was obtained which was identical in all respects with the compound prepared from **11**.

9-(6-Deoxy-β-L-glucopyranosyl)adenine (15). From 14.—A mixture of 2.7 g (5.7 mmol) of 6-benzamidochloromercuripurine, 2.7 g of Celite-545, and 200 ml of dry xylene was prepared and 30 ml of the solvent was distilled to remove traces of moisture. To this hot solution was added 2.0 g (5.7 mmol) of freshly prepared **14** and the mixture was heated at reflux for 3 hr.[21] The mixture was filtered while still hot and the filter cake was washed with 100 ml of warm chloroform. The solvents were evaporated, the residue was dissolved in 100 ml of chloroform, and the solution was filtered. The chloroform solution was washed with 30% aqueous potassium iodide (two 100-ml portions) and water (100 ml), and dried. Evaporation gave 4.4 g of a light orange oil, which was dissolved in 100 ml of methanol, and 9.5 ml of 1 *N* methanolic sodium methoxide was added. The solution was heated at reflux for 1 hr, the methanol was evaporated, and the residue was dissolved in 100 ml of water. Acetic acid was used to adjust to neutral pH, and the solution was washed with chloroform (three 25-ml portions) and evaporated to dryness. The residue was dissolved in 18 ml of methanol, and 50 ml of 10% methanolic picric acid was added. The flask was chilled in an ice bath for 1 hr and the picrate (2.03 g) was isolated by filtration and washed with cold methanol and ethyl ether.

The entire amount of picrate was dissolved in 300 ml of hot water, the yellow color was discharged with Bio-Rad AG1-X8 (CO_3^{2-}) resin, and stirring was continued for 1 hr.[7] The filtered solution was evaporated, whereupon crystallization occurred. The flask was chilled until crystallization appeared to be complete, affording 0.89 g (55%). Recrystallization from aqueous ethanol gave clusters of rosettes on the walls of the flask. **15** (0.72 g) was deposited in two crops: mp 290–294° dec; $[\alpha]^{23}D$ +21° (*c* 1.26, H_2O); uv max (0.1 *N* HCl) 257 mμ (ε 14,640), (H_2O) 259 (14,940), (0.1 *N* NaOH) 259 (15,250). The nucleoside consumed 1.81 mol of periodate per mol of nucleoside in less than 24 hr.

Anal. Calcd for $C_{11}H_{15}N_5O_4$: C, 46.96; H, 5.38; N, 24.90. Found: C, 46.89; H, 5.46; N, 24.98.

From 11 and 12.—From 13.7 g of **6** was prepared 13.4 g of a thick syrup containing **11** and **12** as described above. A portion of this (8.3 g) was treated with 14.2 g of 6-benzamidochloromercuripurine, 14.2 g of Celite-545, 3.3 ml of titanium tetrachloride, and 1200 ml of 1,2-dichloroethane as described for the preparation of **8**. A brown gum weighing 10.4 g was isolated which was dissolved in 150 ml of methanol and treated with 20 ml of 1 *N* methanolic sodium methoxide. After 45 min at reflux, the solution was evaporated, and the residue was dissolved in 100 ml of water and neutralized with acetic acid. The solution was washed with chloroform and the water was evaporated. A picrate (4.14 g) was prepared as described above, this was treated with the carbonate resin in 600 ml of hot water, and the water was evaporated. The product would not crystallize at this stage and so it was chromatographed on a column (40 × 2 cm) of Bio-Rad AG1-X2 (OH, 200–400 mesh) resin[9] which was packed with water. The product was eluted with 30% aqueous methanol, giving 1.29 g of slightly off-white crystals from ethanol, mp 287–291° dec. Recrystallization from aque-

(26) Tlc was performed on Brinkman F_{254} plates of 0.25-mm thickness.

(27) E. Zissis, N. K. Richtmyer, and C. S. Hudson, *J. Amer. Chem. Soc.*, **73**, 4714 (1951).

ous ethanol gave clusters of rosettes, mp 291–293° dec, identical with **15** prepared above.

Periodate Uptake.—Periodate uptake was determined spectrophotometrically at 300 mμ by the procedure developed for nucleosides by Rammler and Rabinowitz.[28]

Polarimetric Studies.—The procedure used here was similar to that used previously for the determination of anomeric configuration of a number of hexopyranosyl nucleosides,[29] except that the rotations of the dialdehydes and the dialcohols were determined in separate experiments.

Dialdehydes.—Between 10 and 13 mg of each nucleoside was weighed into a 2-ml volumetric flask and dissolved in 0.75 ml of water (heated, if necessary), and 0.5 ml of 0.25 *M* sodium metaperiodate was added at room temperature. The reaction was allowed to proceed in the dark for 3 days, the volume was adjusted to 2 ml with water, and the rotations were determined. The results are shown in Table III.

Dialcohols.—The exact same procedure was used here as described above except that after the 3 days, 60 mg of sodium borohydride was added, and the reaction was allowed to proceed for 45 min. The excess borohydride was destroyed by careful addition of 0.4 ml of 20% acetic acid. When effervescence ceased (1–2 hr), the volume was adjusted to 2 ml and the rotation was determined.

(28) D. H. Rammler and J. C. Rabinowitz, *Anal. Biochem.*, **4**, 116 (1962).
(29) L. M. Lerner and P. Kohn, *J. Med. Chem.*, **7**, 655 (1964).

Registry No.—**7**, 36807-77-9; **8**, 36807-78-0; **8** picrate, 36807-79-1; **9**, 36807-80-4; **11**, 36807-81-5; **12**, 36807-82-6; **13**, 35867-45-9; **14**, 36807-84-8; **15**, 36807-85-9.

Branched-Chain Glycosyl α-Amino Acids. I. Stereospecific Synthesis of 2-L-(3-Deoxy-1,2-*O*-isopropylidene-α-D-allofuranos-3-yl)glycine, an Analog of the Polyoxin Sugar Moiety

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Stereospecific hydroxylation of the hitherto described 3-*C*-*trans*-(methoxycarbonylmethylene)-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose (**2**) with osmium tetroxide or potassium permanganate in pyridine yielded 3-*C*-[*S*-hydroxy(methoxycarbonyl)methyl]-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**6**) in high yield. Selective acetylation of **6** using acetic anhydride and pyridine gave 3-*C*-[*S*-acetoxy(methoxycarbonyl)methyl]-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**7**) in 73% yield which was stereoselectively dehydrated with thionyl chloride in pyridine to afford 3-*C*-*trans*-1′-*O*-acetyl-1′-methoxycarbonylmethylene-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-ribofuranose (**8**). Stereospecific catalytic reduction of **8** afforded 3-*C*-[*R*-acetoxy(methoxycarbonyl)methyl]-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**10**). Tosylation of deacetylated **10** yielded the tosylate **12**, which was then transformed into an azide. Reduction of the latter compound afforded methyl 2-L-(3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranos-3-yl)glycinate (**13**). Basic hydrolysis of **13** yielded 2-L-(3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranos-3-yl)glycine (**15**). Selective hydrolysis of **15** afforded 2-L-(3-deoxy-1,2-*O*-isopropylidene-α-D-allofuranos-3-yl)glycine (**16**). The ORD spectra of the branched-chain α-amino and α-hydroxy acid sugars are described.

The structurally novel amino acid sugar 5-amino-5-deoxy-D-allofuranuronic acid is a component of the polyoxin complex of antifungal agents.[1] The elucidation of structures of the polyoxins has been recently described.[1] Subsequently, the sugar component[2] and the nucleoside moiety of the polyoxins have been synthesized.[3,4] The sugar moiety of the polyoxins might be regarded as being composed of a two-carbon α-L-amino acid moiety attached to C-4 of the sugar. We report herein a stereospecific synthesis of an analog of the sugar moiety of the polyoxins in which the two-carbon α-L-amino acid moiety is attached to C-3 of a hexofuranose having essentially the same stereochemistry as the sugar of the polyoxin. In essence, the objective of the research described herein was to replace stereospecifically with inversion the C-3 hydroxyl of D-glucofuranose by a two-carbon α-L (*S*)[5] amino acid to yield a branched-chain sugar having the allo configuration. Such a sugar could then be readily degraded by periodate oxidation followed by sodium borohydride reduction to afford a branched-chain sugar possessing the D-ribo constitution.

The key intermediate in the synthesis of the branched-chain sugar was 3-*C*-*trans*-(methoxycarbonylmethylene)-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose (**2**), previously described[6] but not obtained in crystalline form. Compound **2** was prepared from the readily available 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**1**).[7] When the condensation of the ketose **1** and phosphonoacetic acid trimethyl ester in the presence of potassium *tert*-butoxide was allowed to take place at room temperature, the major component of the reaction products was a mixture of trans- and cis-unsaturated ribo sugars **2** and **3**. A minor component (about 6%) consisted of a mixture of trans- and cis-unsaturated sugars **4** which was tentatively believed to have the xylo configuration. The ribo-unsaturated sugars **2** and **3** were readily separated from the epimeric mixture of unsaturated sugars **4** by column chromatography on silica gel. Fractional crystallization of the mixture of trans- and cis-unsaturated sugars **2** and **3** from hexane afforded pure crystalline ribo trans-unsaturated sugar **2** in about 40% yield. Although the mixture of xylo

(1) K. Isono, K. Asahi, and S. Suzuki, *J. Amer. Chem. Soc.*, **91**, 7490 (1969), and references cited therein.
(2) T. Naka, T. Hashizumo, and M. Nishimura, *Tetrahedron Lett.*, 95 (1971).
(3) N. P. Damodaran, G. H. Jones, and J. G. Moffatt, *J. Amer. Chem. Soc.*, **93**, 3812 (1971).
(4) H. Ohrui, H. Kuzuhara, and S. Emoto, *Tetrahedron Lett.*, 4267 (1971).
(5) R. S. Cahn and C. K. Ingold, *J. Chem. Soc.*, 612 (1951); R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956); E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962.
(6) A. Rosenthal and L. Nguyen, *J. Org. Chem.*, **34**, 1029 (1969).
(7) (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).