Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.36; H, 4.76; N, 9.53.

1-(3-Methoxy-4-benzyloxybenzyl)-7-methoxyisoquinoline Methiodide (XVII).—The nitrile XV, 11.0 g (0.038 mol), was dissolved in 100 ml of DMF at 0° and was treated under N_2 with a threefold excess of NaH. After 10 min, a twofold excess of 4-benzyloxy-3-methoxybenzyl chloride in 50 ml of DMF was added. The mixture was stirred overnight, excess EtOH was added to destroy remaining NaH, and the mixture was allowed to stir for an additional 24 hr. Benzene and water were added and the benzene layer was separated and washed with water and then with 6 *M* HCl. The acidic layer was made basic with NaOH and extracted with $CHCl_3$. The organic extracts were combined, dried, and evaporated to yield 10.8 g (68%) of 1-(3-methoxy-4-benzyloxybenzyl)-7-methoxyisoquinoline (XVI) as a crude brown oil. To this oil was added 50 ml of iodomethane and 50 ml of MeOH and the solution was heated at reflux for 6 hr. The solvent was then removed *in vacuo* to leave a yellow solid, which was recrystallized from ethanol to give 9 g (60%) of 1-(3-methoxy-4-benzyloxybenzyl)-7-methoxyisoquinoline methiodide (XVII), mp 201°.

Anal. Calcd for $C_{26}H_{26}NO_3I$: C, 59.30; H, 4.97; N, 2.67. Found: C, 58.95; H, 4.98; N, 2.35.

(±)-2,9-Dimethoxy-3-hydroxypavinane (VII).—XVII (5 g) was dried and pulverized and then added to a slurry of 1 g of $LiAlH_4$ in anhydrous ether. The mixture was stirred for 3 hr at room temperature and the excess hydride was decomposed by addition of wet ether followed by a saturated solution of sodium potassium tartrate. The ether layer was separated and evaporated to yield 2.0 g (55%) of the crude 1,2-dihydroisoquinoline as a yellow oil. To this was then added 35 ml of 7:3 HCOOH–H_3PO_4 and the solution was heated at reflux for 18 hr. The solution was diluted with water and washed with $CHCl_3$. The aqueous layer was made basic and extracted with $CHCl_3$. The extracts were combined, dried, and evaporated to a crude oil which was 65% VII by nmr and tlc. Column chromatography on Florisil with benzene as eluting solvent yielded pure (±)-2,9-dimethoxy-3-hydroxypavinane (VII), mp 162°, whose ir, nmr, uv, and mass spectra, and tlc R_f values were identical with those of the natural alkaloid.

Registry No.—VII, 41498-94-6; (±)-VII, 41498-95-7; IX, 41498-25-3; IX hydrochloride, 41498-26-4; X, 41498-27-5; XI, 41498-28-6; XII, 41498-29-7; XII picrate, 41498-30-0; XII hydrochloride, 41498-31-1; XIV, 39989-39-4; XV, 41498-33-3; XVI, 41498-34-4; XVII, 41498-35-5; *N*-(3,4-dimethoxyphenethyl)-2-(4-methoxyphenyl)acetamide, 4078-65-3; 1-(4-methoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline, 41498-37-7.

Interconversions of Hexofuranosyl Nucleosides. V. Synthesis and Reexamination of the Structure of 9-(6-Deoxy-α-L-mannofuranosyl)adenine[1]

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9-(6-Deoxy-α-L-mannofuranosyl)adenine (**3**) has been prepared by several synthetic procedures and completely structure proofed. It was concluded that the substance previously reported to be **3** really could not have been, based upon the differences in physical properties and the present structure proof. The most successful synthesis required conversion of 6-deoxy-1,5-di-*O*-benzoyl-2,3-*O*-isopropylidene-L-mannofuranose into 6-deoxy-1,2,3,5-tetra-*O*-benzoyl-L-mannofuranose in two steps, conversion of this into the glycosyl chloride with ethereal hydrogen chloride, and condensation of the latter with 6-benzamidochloromercuripurine in hot xylene. Removal of the blocking groups with sodium methoxide and purification *via* a picrate gave an 18% yield of **3**. Other coupling procedures, such as the titanium tetrachloride method, gave rather complex, colored mixtures, which required extensive column chromatography to purify **3**, and consequently lower yields. Attempts to prepare **3** following acetolysis of 6-deoxy-1,5-di-*O*-acetyl-2,3-*O*-isopropylidene-L-mannofuranose (**4**) resulted in the isolation of 9-(6-deoxy-β-L-glucofuranosyl)adenine (**5**) and 9-(6-deoxy-β-L-mannopyranosyl)adenine (**6**) in addition to **3**. Considerable yields of **5** occurred even under acetolysis reaction conditions that are reportedly not supposed to cause epimerization at C-2. Acetolysis of **4** in 1:1 acetic acid–acetic anhydride with 3% sulfuric acid, followed by nucleoside formation by the titanium tetrachloride procedure, afforded **5**, **3**, and **6** in a ratio of 1.5:2.2:1.0 and acetolysis of **4** in 3:7 acetic acid–acetic anhydride with 5% sulfuric acid changed this ratio to 0.1:1.5:1.0.

The synthesis of hexofuranosyl nucleosides has been a subject of investigation by the author for a number of years.[2-5] Such studies have received occassional impetus from reports in the literature concerning the biological or enzymatic activity of compounds like these.[6] The purpose of the current investigations was to improve upon the synthesis of hexofuranosyl nucleosides by causing the inversion of configuration at one or more hydroxyl groups of the preformed nucleosides, thereby precluding the necessity of preparing rare sugars to be used in *de novo* synthesis of such compounds.[3]

In the previous two articles,[4,5] reasons were presented for the synthesis of 9-(5,6-dideoxy-β-D-*erythro*-hex-4-enofuranosyl)adenine (**1**) (Chart I). Because of the difficulties encountered in the removal of the isopropylidene blocking group of **2** without complete degradation of the nucleoside, it was thought to be desirable to prepare 9-(6-deoxy-α-L-mannofuranosyl)adenine (**3**, 9-α-L-rhamnofuranosyladenine) in large quantity and, starting from this source, to prepare a derivative of **3** having a blocking group at the 2′,3′ position which could be more easily removed after the 4′,5′ double bond was formed. In an attempt to prepare **3** from 6-deoxy-1,5-di-*O*-acetyl-2,3-*O*-isopropylidene-L-mannofuranose (**4**), the latter compound was subjected to acetolysis conditions which are now known to cause epimerization at C-2, and, as a result, two nucleosides were formed from the uncharacterized syrup upon condensation with 6-benzamidochloromercuripurine. The main product was 9-(6-deoxy-β-L-glucofuranosyl)adenine (**5**) and the other was 9-(6-deoxy-α-L-mannopyranosyl)adenine (**6**).[5] Conditions were sought for the acetolysis of **4** not accompanied by epimerization and

(1) The present work was supported by Grant No. CA13802 from the National Cancer Institute, National Institutes of Health.

(2) (a) L. M. Lerner and P. Kohn, *J. Org. Chem.*, **31**, 339 (1966); (b) P. Kohn, R. H. Samaritano, and L. M. Lerner, *ibid.*, **31**, 1503 (1966); (c) L. M. Lerner, B. D. Kohn, and P. Kohn, *ibid.*, **33**, 1780 (1968); (d) ref 3–5.

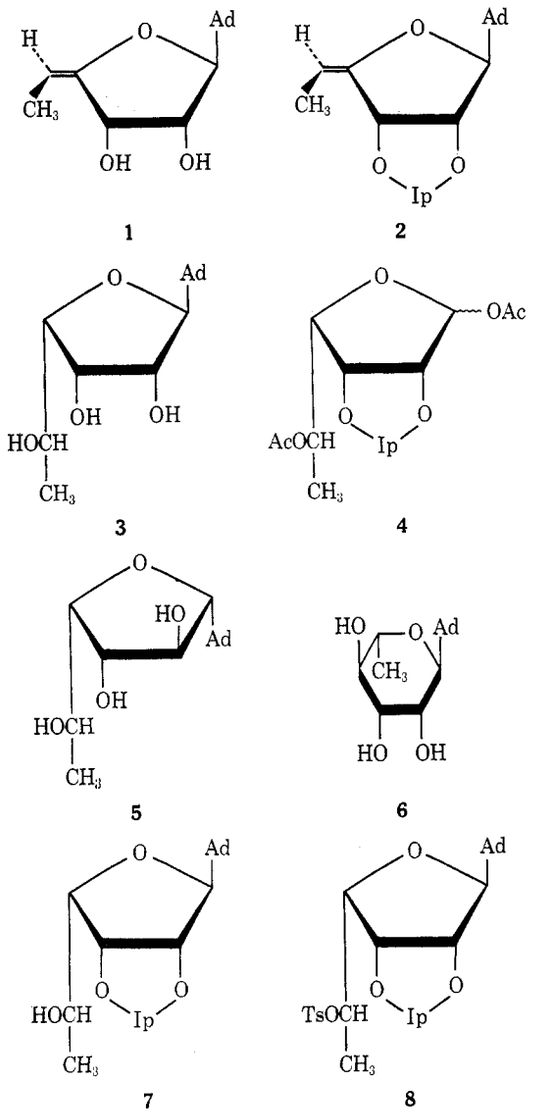
(3) L. M. Lerner, *J. Org. Chem.*, **37**, 470 (1972); **37**, 473 (1972).

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

(5) L. M. Lerner, *J. Org. Chem.*, **37**, 4386 (1972).

(6) For examples, see A. Hampton, P. J. Harper, and T. Sasaki, *Biochemistry*, **11**, 4736 (1972); J. F. Henderson, A. R. P. Paterson, I. C. Caldwell, B. Paul, M. C. Chan, and K. F. Lau, *Cancer Chemother. Rep.*, [2] **3**, 71 (1972); I. C. Caldwell and J. F. Henderson, *ibid.*, **2**, 237 (1971); and J. F. Henderson, J. F. Gadd, R. E. A. Palser, and M. Hori, *Can. J. Biochem.*, **48**, 573 (1970).

CHART I



Ad = adenyl, Ip = $C(CH_3)_2$

the products of nucleoside synthesis were separated by chromatography on an anion-exchange resin column.[7] When this was done, a new peak arose from the column which had not previously been observed. This substance crystallized from water as a monohydrate, and, later, a sample was crystallized from ethanol in an anhydrous form. Although this substance had physical properties unlike that reported earlier,[8] it is now evident that it is, indeed, 9-(6-deoxy-α-L-mannofuranosyl)-adenine (**3**) and some doubt must now be cast upon the identity of the previously reported material.[9] The purpose of this article is to (a) present evidence for the structure of **3**, (b) report the results obtained when the synthesis of Baker and Hewson[8] was repeated, (c) discuss other procedures used for the synthesis of **3**, and (d) report on the results obtained when **4** was subjected to acetolysis under different conditions.

Baker and Hewson[8] reported that **3** had a melting point of 132–135° and a specific rotation of −18° after crystallization from a mixture of ethanol and methyl ethyl ketone. The compound gave an elemental analysis which indicated to these workers that the ketone and some water were firmly bound to the crystals, and the ir spectrum confirmed the presence of a carbonyl group. However, very little evidence identifying the compound as **3** was actually presented. The nucleoside upon which the following structural evidence is presented was obtained from any of the procedures described below for its synthesis, or from the acetolysis studies. The monohydrate prismatic crystals were chosen only because they had crystallized first and the structural studies were already in motion when the anhydrous crystals were obtained from ethanol. The latter were shown to be readily recrystallized from water to form the monohydrate, which has a double melting point of 155 and 196°. The specific rotation of −72° was the first indication that this substance was really different from that reported previously and, since there was no reason to believe that a change at the C-6′ position from a hydroxyl group to a hydrogen would affect the value of the optical rotation to any great extent, it appeared that this substance may actually be the "real" **3**. Table I shows a comparison of the optical rotations of some hexofuranosyl nucleosides which differ only at C-6′ and which gave the first clue to the identity of **3**.

TABLE I

OPTICAL ROTATIONS OF SOME HEXOFURANOSYL NUCLEOSIDES

Hexofuranose confign	[α]D, degree 6′-CH_3	[α]D, degree 6′-CH_2OH
β-D-allo	−74[a]	−57[b]
β-D-gluco	−60[c]	−58[d]
α-L-talo	−35[e]	−32[b,f]
α-L-manno	−72 (−18[h])	−75[f,g]

[a] E. J. Reist, L. Goodman, R. R. Spencer, and B. R. Baker, *J. Amer. Chem. Soc.*, **80**, 3962 (1958). [b] Reference 2b. [c] E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Org. Chem.*, **23**, 1753 (1958). [d] E. J. Reist, R. R. Spencer, and B. R. Baker, *ibid.*, **23**, 1958 (1958). [e] E. J. Reist, L. Goodman, and B. R. Baker, *J. Amer. Chem. Soc.*, **80**, 5775 (1958). [f] The number reported is the absolute value, with a change of sign to conform to the expected value for the unknown enantiomer. [g] Reference 2a. [h] Reference 8.

The uv spectrum of **3** had a maximum at 260 nm, suggesting that the substitution was at N-9 of the purine. The nucleoside consumed 1 mol equiv of periodate in <10 min which was evidence that the ring was in a furanose form and that the hydroxyl groups at C-2′ and C-3′ were oriented cis to each other. Hydrolysis of **3** in hot acid afforded crystalline adenine, which was identified by melting point, ir spectroscopy, and paper chromatography, and a sugar which did not crystallize. The sugar was identified as 6-deoxy-L-mannose (L-rhamnose) by paper chromatography and by conversion into a phenylosazone. Since 6-deoxy-L-glucose yields the same osazone, chromatographic systems were used which would separate the two sugars. It was fairly obvious at this point that the compound was a 9-(6-deoxy-L-mannofuranosyl)adenine, but the anomeric configuration still had to be solved.

(7) C. A. Dekker, *J. Amer. Chem. Soc.*, **87**, 4027 (1965).

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

(9) L. M. Lerner and Y. Y. Cheng, *Carbohyd. Res.*, **14**, 297 (1970), reported a small yield of a substance, obtained by acid hydrolysis of a crude sample of **7** whose physical properties were somewhat close to those of the previously reported compound[8] and it was assumed to be the same. Unfortunately, this particular sample has been exhausted, but other samples obtained from similar experiments have now been found to be identical with nucleoside **3** as crystallized from ethanol.

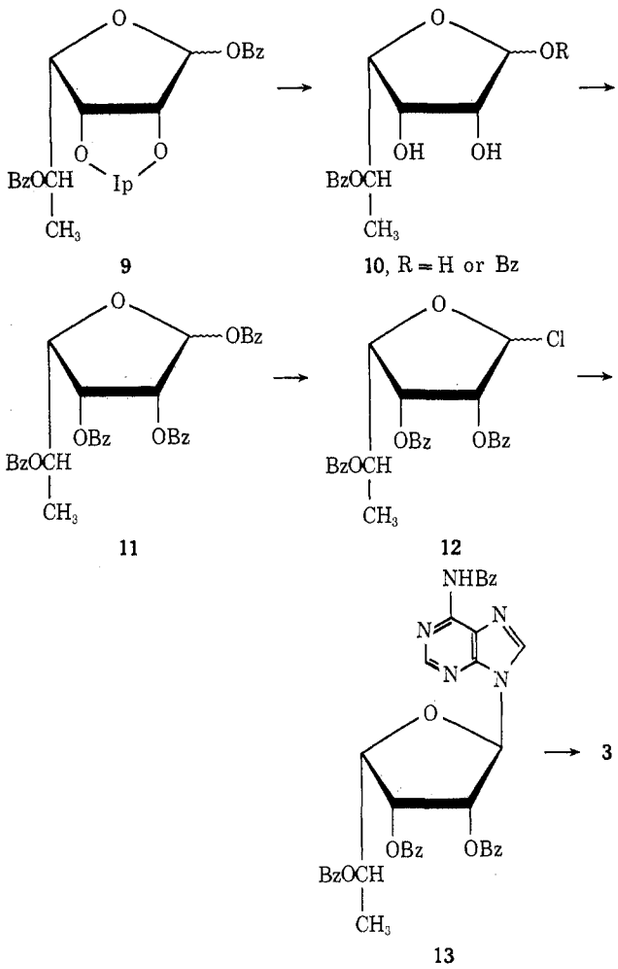
Baker and Hewson[8] never proved the anomeric configuration of their nucleoside, but instead they used the argument that the major product obtained from the condensation of a heavy metal salt of a purine and a glycosyl halide would have a configuration in which the purine was situated trans to the hydroxyl group at C-2′.[10] To determine the anomeric configuration of **3**, the nmr spectrum of two compounds related to **3** were examined. Previously, 9-(6-deoxy-2,3-*O*-isopropylidene-α-L-mannofuranosyl)adenine (**7**)[4,9] and 9-(6-deoxy-2,3-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-α-L-mannofuranosyl)adenine (**8**)[4] were prepared and their structural relationship was shown by detosylation of **8** to **7**. Furthermore, the anomeric configuration of compound **2**, which was obtained from **8** by elimination of a molecule of *p*-toluenesulfonic acid, was shown to be α by nmr spectroscopy.[4] This would imply that **3** also had an α configuration if the structural relationship of these molecules could be confirmed. Therefore, a pure sample of **7**, obtained from the previous work,[4] was carefully treated with 9:1 trifluoroacetic acid–water to remove the isopropylidene group, and this resulted in the crystallization of **3**, first in its anhydrous form, then as a monohydrate after recrystallization from water. A sample of nucleoside **3**, obtained in the present work, was treated with acetone, using *p*-toluenesulfonic acid as a catalyst, and a good yield of **7** was obtained. In addition, the nmr spectrum of **7** revealed a singlet at τ 3.95, which is consistent with a trans orientation of H-1′ and H-2′. These data established the structure of **3** as 9-(6-deoxy-α-L-mannofuranosyl)adenine.

In their original work, Baker and Hewson[8] prepared what they believed to have the structure of **3** by two different routes. In the first of these,[8] what was believed to be 6-chloro-9-(6-deoxy-2,3,5-tri-*O*-benzoyl-α-L-mannofuranosyl)purine[11] was treated with hot methanolic ammonia and, in the second,[8] the reactions illustrated in Scheme I were used. The route shown has now been carefully reinvestigated and found to give **3** in an overall yield of 18%, having all of the properties associated with the compound described in the present paper. Comments concerning the individual reactions from **9** → **3** are presented in the Experimental Section.

In an effort to improve the synthesis of **3**, changes in the various steps illustrated in Scheme I were considered and these are described in detail in the Experimental Section. It is somewhat ironic that the best synthesis of **3** was accomplished by coupling the intermediate chloride **12** with 6-benzamidochloromercurpurine under the conditions originally described by Baker and Hewson.[8] The procedure was especially advantageous because the products were much cleaner and **3** could be crystallized without the necessity of extensive and time-consuming column chromatography.

At the outset of this investigation, it was hoped that **3** would be obtainable by the general scheme used previously[5] in which 6-deoxy-1,5-di-*O*-acetyl-2,3-*O*-isopropylidene-L-mannofuranose (**4**) was subjected to acetolysis and the products, consisting mainly of peracetylated 6-deoxy-L-mannofuranose, could then be coupled directly to the base by the titanium tetrachloride procedure. Reports in the literature indicated that the extent of epimerization occurring at C-2 was related to the relative concentrations of acetic acid to acetic anhydride and that a mixture of 1:1 acetic acid–acetic anhydride containing about 3% concentrated sulfuric acid did not cause epimerization,[12,13] or, at least if it did, only trace amounts of the epimerized product could be observed.[14] Most studies concerned with isomerizations occurring as a result of treatment of sugars with acetolysis mixtures have examined the identity of sugars obtained after hydrolysis of the acetate groups and have used paper chromatographic techniques.[14-16] However, the present author was interested primarily in a good, rapid preparation of **3**, and so a number of acetolysis studies were carried out with the products being immediately converted to adenine nucleosides and the identity and distribution of the nucleosides were determined. This study was greatly aided by the highly reproducible technique of column chromatography on an anion-exchange column worked out by Dekker.[7] It is important to realize that the different sugar acetates may have reacted to a different

SCHEME I



(10) 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.

(11) B. R. Baker, K. Hewson, H. J. Thomas, and J. A. Johnson, *J. Org. Chem.*, **22**, 954 (1957).

(12) E. J. Reist, D. E. Gueffroy, and L. Goodman, *J. Amer. Chem. Soc.*, **86**, 5658 (1964).

(13) J. A. Montgomery, K. Hewson, A. G. Laseter, and M. C. Thorpe, *J. Amer. Chem. Soc.*, **94**, 7176 (1972).

(14) W. Sowa, *Can. J. Chem.*, **49**, 3292 (1971).

(15) P. Jerkeman, *Acta Chem. Scand.*, **17**, 2769 (1963).

(16) G. J. G. Chittenden, *Carbohyd. Res.*, **22**, 491 (1972).

extent with the nitrogenous base and that the yields reported for the nucleosides may not be representative of the true ratio of 6-deoxy-L-mannose to 6-deoxy-L-glucose or, for that matter, of 6-deoxy-L-mannofuranose to pyranose tetraacetates, resulting from the acetolysis mixtures. The ratio of nucleosides obtained are shown in Table II in comparison with the amount of 9-(6-deoxy-L-mannopyranosyl)adenine (**6**) found. Although the yields of **3** were generally lower than desirable and it was necessary to purify the products by chromatography, the results shown are quite interesting, especially in regard to **5**. The data clearly show a trend in which the degree of C-2 epimerization decreased considerably as the concentration of acetic acid was reduced, verifying an observation noted previously.[14] A change in the concentration of sulfuric acid did not seem to significantly change the results and is also in agreement with previous conclusions.[14] What is striking here is that, under conditions which are not supposed to give epimerization, namely, 1:1 acetic acid–acetic anhydride, a considerable amount of **5** was isolated after nucleoside formation. Even when the concentration of acetic acid was reduced further, such as with 3:7 acetic acid–acetic anhydride, **5** could still be isolated and crystallized. Furthermore, these results indicate that it cannot be assumed that epimerization has not occurred in any acetolysis mixtures, unless for some unexplained reason these results are peculiar only to 6-deoxy-L-mannose. It should be recalled that this isomerization only seems to occur in those cases where the sugar is in the furanose ring form and the hydroxyl groups in the ring are oriented in a cis relationship.[5,14,15] In a similar manner, Chittenden[16] has rexamined the acetolysis conditions used by Guthrie and Smith[17] (3:4 acetic acid–acetic anhydride) for the preparation of D-ribofuranose tetraacetate and found a ratio of D-ribose to D-arabinose of 6:1. In a recent communication, Montgomery, *et al.*,[13] claimed that a 1:1 mixture of acetic acid–acetic anhydride did not cause epimerization of ethyl 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*ribo*-heptofuranuronate, but that the acid-catalyzed fusion with a purine did, resulting in a mixture of nucleosides. Moreover, in a footnote, they called attention to an experiment in which the usual method of glycosyl chloride formation with ethereal hydrogen chloride also was responsible for epimerization in one case. In agreement with these authors, it is also suggested here that nucleosides and other deivatives of sugars obtained after exposure of their precursors to *any* acid conditions be scrutinized carefully and their structures unequivocally proved.

(17) R. D. Guthrie and S. C. Smith, *Chem. Ind. (London)*, 547 (1968).

TABLE II

NUCLEOSIDES OBTAINED AFTER ACETOLYSIS OF 6-DEOXY-1,5-DI-*O*-ACETYL-2,3-*O*-ISOPROPYLIDENE-L-MANNOFURANOSE (**4**)[a]

	Ratio		
Nucleoside	10:1[b-d]	1:1[b,e]	3:7[b,d]
6	1.0	1.0	1.0
3	Not detected	2.2	1.5
5	3.9	1.5	0.1

[a] Results are reported as comparisons of the yield of nucleoside to **6**. [b] Ratio of acetic acid:acetic anhydride. [c] Reference 5. [d] 5% sulfuric acid. [e] 3% sulfuric acid.

Experimental Section[18]

All of the structural information reported below was obtained using the monohydrate crystals of **3**. Because of the repetitive nature of many of the experiments with regard to the isolation and characterization of the nucleosides **3**, **5**, and **6**, the phrase "identical in every respect" is used to indicate that the compounds isolated were identical by melting point, mixture melting point, ir, and paper chromatography in solvents A, B, and C. In most cases, the optical rotation was also checked and found to agree within experimental limitations.

Paper chromatography was run on 24-in.-long Whatman No. 1 sheets for 18–24 hr by a descending technique. The solvents used were (A) 5% aqueous disodium hydrogen phosphate, (B) 86:14 1-butanol–water, (C) 5:1:2 1-butanol–acetic acid–water, (D) 8:2:1 ethyl acetate–pyridine–water, (E) 2:1:2 ethyl acetate–pyridine–water, (F) 40:11:19 1-butanol–ethanol–water, and (G) 1:5:3:3 benzene–1-butanol–pyridine–water. The expression R_{Ad} refers to the ratio of the distance the nucleoside migrated to the distance which adenine migrated. Chromatographic data for the nucleosides **3**, **5**, **6**, and **7** are presented in Table III.

TABLE III

R_{Ad} VALUES FOR ADENINE NUCLEOSIDES

	R_{Ad}		
Compd	A[a]	B[a]	C[a]
3	1.66	0.72	0.89
5	1.47	1.20	1.15
6	1.39	0.39	0.71
7	1.59	2.29	1.59

[a] Solvent.

Periodate Uptake.—The consumption of periodate was determined by a spectrophotometric procedure as described by Rammler and Rabinowitz.[19] **3** consumed 0.96 mol equiv of periodate in <10 min and this amount remained unchanged after 6 and 24 hr.

Composition of 3.—A sample of **3** (59 mg) was dissolved in 4 ml of 0.1 *N* sulfuric acid and heated at reflux for 2 hr. The solution was cooled to room temperature, adjusted to pH 7 with dilute ammonium hydroxide, and concentrated by evaporation to approximately 1.5–2.0 ml, whereupon crystals began forming. The crystals were redissolved by heating the flask on a steam bath and the flask was kept in a refrigerator for several hours. Filtration of the crystals produced 16 mg of adenine, identified by its high melting point, >320° (slow decomposition), ir spectrum, which was identical with that of authentic adenine, and paper chromatography in solvent systems A, B, and C.

The mother liquor was passed through an Amberlite MB-3 column (8 × 1 cm) and the column was washed with water. Evaporation of the water resulted in a gum which was used for paper chromatography and its mobility was compared against that of samples of authentic 6-deoxy-L-mannose (Pfanstiehl) and 6-deoxy-L-glucose.[5] The chromatograms were sprayed with aniline oxalate reagent and heated at 110° for 10 min.[20] The results are reported in Table IV as R_g values, which represent

TABLE IV

PAPER CHROMATOGRAPHIC DATA FOR 6-DEOXYHEXOSES

	R_g		
Solvent	L-Rhamnose	6-Deoxy-L-glucose	Hydrolysis product
B	3.92	3.57	4.04
D	3.60	3.03	3.55
E	2.00	1.89	2.05
F	1.92	1.92	1.92
G	2.00	1.92	2.01

(18) General methods and instrumentation used in these investigations have been described.[3] Moist organic solutions were dried over anhydrous magnesium sulfate. Evaporations were performed under reduced pressure at bath temperatures between 40–45°, unless stated otherwise.

(19) D. H. Rammler and J. C. Rabinowitz, *Anal. Biochem.*, **4**, 116 (1962).

(20) S. M. Partridge, *Biochem. Soc. Symp.* (Cambridge, Engl.), **3**, 52 (1949).

the ratio of the distances that the sugars migrated to the distance that D-glucose migrated.

The phenylosazone of the sugar (~0.03 g) was prepared by mixing 0.06 g of phenylhydrazine hydrochloride, 0.09 g of anhydrous sodium acetate, and 2 ml of water, and this mixture was heated on a steam bath for 15 min. The turbid solution slowly crystallized: mp 178–180°. An authentic sample of 6-deoxy-L-mannose, when treated in the same manner, gave crystals, mp 176–178° (lit.[21] mp 178–179°). The ir spectra of the two samples were identical and there was no depression of melting point when the samples were mixed.

9-(6-Deoxy-2,3-*O*-isopropylidene-α-L-mannofuranosyl)adenine (7).—To 100 mg of **3** monohydrate suspended in 30 ml of acetone was added 3 ml of 2,2-dimethoxypropane and 0.64 g of *p*-toluenesulfonic acid monohydrate. The nucleoside went into solution after a few minutes and the mixture was stirred for 3 hr at room temperature, protected from moisture. The yellow mixture was poured into a stirring solution of 1 g of sodium bicarbonate in 10 ml of water. The precipitate was removed by filtration and washed well with acetone. The solvents were evaporated, leaving a white residue, which was triturated with 50 ml of chloroform. The solid portion was filtered off and the chloroform was evaporated. The residue was dissolved in 3 ml of boiling methanol, 4 ml of hot water was slowly added, and the solution was put aside. Crystals formed slowly during the next 3 days to give 88 mg (81%) of **7**: mp 226–229° (lit.[4,9] mp 225–228°); $[\alpha]^{27}D$ −26.1° (c 0.64, methanol) {an optical rotation obtained on a previously prepared sample[5] was found to be $[\alpha]^{25}D$ −25.5° (*c* 0.54, methanol)}; nmr τ 1.75, 2.12 (both s, 1 proton each, H-2, H-8), 3.27 (s, 2, NH_2), 3.95 (s, 1, H-1′), 4.4–4.8 (m, 2, H-2′, H-3′), 5.78–5.85 (broad unresolved m, 2, H-4′, H-5′), 8.41 (d, 3, C-6′ CH_3), 8.67, 8.73 (both s, 6, *gem*-dimethyl).

9-(6-Deoxy-L-mannofuranosyl)adenine (3). Method A.—To 222 mg of **7**, obtained during a previous study,[4] was added 3 ml of 9:1 trifluoroacetic acid–water.[22] The nucleoside derivative dissolved after stirring for ~5 min, the solution was kept at room temperature for an additional 7 min, and the solvents were evaporated *in vacuo* at 35°. The residue was dissolved in 20 ml of water, the pH was adjusted to neutrality with Bio-Rad AG1-X2 (OH^-) resin, and the resin was filtered off. The residue obtained after evaporation was triturated with hot ethanol and some insoluble material was removed by filtration. The solution was concentrated to about 1–2 ml and allowed to crystallize at room temperature. A second crop of crystals was obtained in a similar manner to give a total of 55 mg (30%), mp 118–124 and 194–196°, identical in every respect with the anhydrous form of **3** prepared in method D. The first crop of crystals was recrystallized from water to give **3** as the monohydrate, mp 157 and 192–196°, identical in every respect with **3** prepared by method B.

Method B.—The procedure for this synthesis was the one described by Baker and Hewson.[8] The instructions were carefully adhered to, except that a smaller amount of 6-deoxy-1,5-di-*O*-benzoyl-2,3-*O*-isopropylidene-L-mannofuranose (**9**, 5.65 g) was used. **9** was treated with refluxing 70% aqueous acetic acid for 3 hr and the products were partitioned between water and 1:1 ethyl acetate–benzene. The organic soluble substance (**10**) was benzoylated to give **11**, 4.63 g of which was converted to chloride **12** and coupled with 6-benzamidochloromercuripurine in refluxing xylene. When the blocking groups of **13** were removed with sodium methoxide and the product was isolated *via* the picrate, an attempt was made to crystallize the product from ethanol and methyl ethyl ketone, as described earlier.[8] Only a portion of the substance separated and this had mp 145–157° and a second melting point above 170°; $[\alpha]^{26}D$ −63° (*c* 0.57, H_2O). The material was all recombined, dissolved in hot water, and allowed to stand for several days. Prismatic crystals of **3** formed: 301 mg; mp 155–156.5°, slowly crystallizing again above 160°, and melting at 195–196°; $[\alpha]^{23}D$ −72.3° (*c* 0.65, H_2O); uv $\lambda_{max}^{pH\ 1}$ 257 (ε 14,900), $\lambda_{max}^{H_2O}$ 260 (ε 14,900), $\lambda_{max}^{pH\ 13}$ 260 nm (ε 15,300).

Anal. Calcd for $C_{11}H_{15}N_5O_4 \cdot H_2O$: C, 44.14; H, 5.73; N, 23.40. Found: C, 44.15; H, 5.86; N, 23.41.

The mother liquor was chromatographed on a column (45 × 1 cm) of Bio-Rad AG1-X2 (OH^-, 200–400 mesh) using 30% aqueous methanol and 7-ml fractions were collected. Tubes 60–101 yielded another 89 mg of **3**, mp 155 and 197–198.5° (total yield 430 mg, 18%). Two other uv absorbing peaks were observed. The peak at tubes 6–24 afforded 43 mg of **6** from ethanol–water, identical in every respect with the authentic compound.[5] Tubes 48–55 contained only 8 mg of a substance that was not identified.

Method C.—**9**[8] (13.9 g) was dissolved in 120 ml of 9:1 trifluoroacetic acid–water and kept for 15 min at room temperature. The solvents were evaporated under reduced pressure at 35°, resulting in a slightly greenish syrup containing crystals, presumably benzoic acid formed by hydrolysis of the anomeric benzoate. The syrup was dissolved in 85 ml of 1:1 ethyl acetate–benzene, washed with 60 ml of water and twice with 50-ml portions of cold saturated sodium bicarbonate solution, and dried. The syrup obtained after evaporation of the solvents weighed 7.6 g: ir ν_{max} 3410 (strong OH), 1724 (C=O of benzoate), and 712 cm^{-1} (monosubstituted phenyl). The original water layer contained 0.8 g of a chloroform-soluble, benzene-insoluble substance, which was not 6-deoxy-L-mannose as determined by tlc on silica gel plates (HF, Merck) using 9:1 chloroform–methanol.

The syrup **10** (7.6 g) was dissolved in 100 ml of dry pyridine and the solution was chilled in an ice bath while 60 ml of acetic anhydride was slowly added. The reaction was allowed to proceed at room temperature for 21 hr and then poured into 400 ml of an ice–sodium bicarbonate mixture. This was stirred for 1 hr, the product was extracted with chloroform (150 ml), and the chloroform solution was washed with saturated sodium bicarbonate (2 × 200 ml) and water (200 ml) and dried. Evaporation of the chloroform and coevaporation with toluene three times gave 14.7 g of an amber-colored syrup. This material (14.1 g) was added to a mixture of 6-benzamidochloromercuripurine (18.7 g), Celite-545 (18.7 g), titanium tetrachloride (5.5 ml), and 1,2-dichloromethane (1250 ml) and the mixture was refluxed for 24 hr, cooled to room temperature, and stirred for 2 hr with 700 ml of saturated sodium bicarbonate solution. The mixture was filtered through a Celite pad and the filter cake was washed thoroughly with warm 1,2-dichloroethane (~200 ml). After evaporation, the syrup was dissolved in 250 ml of chloroform, washed with 30% aqueous potassium iodide solution (2 × 200 ml) and water (300 ml), and dried. Evaporation of the chloroform afforded a hard gum (14.8 g) which was dissolved in methanol and treated with 16 ml of 1 *N* methanolic sodium methoxide. The solution was refluxed for 1.25 hr, cooled to room temperature, and neutralized with acetic acid. The solvents were evaporated, the residue was partitioned between 175 ml of water and 75 ml of chloroform, and the aqueous layer was further washed with chloroform (3 × 35 ml). Filtration and evaporation gave a residue which was dissolved in 65 ml of methanol and 75 ml of 10% methanolic picric acid was added. The flask was placed in an ice bath for 2 hr and the yellow crystals were filtered off and washed with cold methanol, then cold water. The wet picrate was suspended in 800 ml of water and enough Bio-Rad AG1-X8 (CO_3^{2-}) resin was added in portions over 3 hr to the stirring mixture to discharge the yellow color. The water was evaporated and attempts to crystallize the orange product or to remove the yellow color with charcoal failed. Therefore, the material was dissolved in 20 ml of water and placed on a column (27 × 2 cm) of Bio-Rad AG1-X2 (OH^-, 200–400 mesh) resin and the column was eluted with 30% aqueous methanol. Ten-milliliter fractions were collected. The major peak in tubes 51–104 were pooled and the product was crystallized from water to give 0.751 g of **3**. An additional 0.033 g was obtained from the mother liquor (yield 7%), mp 153–155 and 195–197°. This substance was identical in every respect with **3** prepared by method B.

Method D.—The acetate (7.86 g), prepared by method C, was heated with 6-benzamidochloromercuripurine (10.4 g), Celite-545 (10.4 g), titanium tetrachloride (3.0 ml), and 1,2-dichloroethane (800 ml) at reflux and processed as described above to give 8.86 g of a light brown foam. This material was fractionated on a column (10 cm long × 8 cm wide) of silicic acid (Mallinckrodt, 100 mesh, activated at 130° for 16 hr). The column was prepared in chloroform and washed with 9:1 chloroform–ethyl acetate and 1050 ml collected to give 1.84 g of unreacted sugar derivatives. Elution of the column with 19:1 chloroform–methanol followed, the first 500 ml was discarded, and the next 900 ml contained 7.0 g of blocked nucleosidic material. The blocking groups were removed in a refluxing mixture of 200 ml of methanol and 12 ml of 1 *N* methanolic sodium methoxide. The methanol was evaporated and the residue was dissolved in 100 ml of water and neutralized with IR-120 (H^+) resin. After filtration, the aqueous solution was washed with chloroform (2 × 50 ml) and treated with

(21) Khr. Akhtardzhiev and D. Kolev, *Pharm. Zentralh.*, **100**, 14 (1961); *Chem. Abstr.*, **55**, 15829*i* (1961).

(22) J. E. Christensen and L. Goodman, *Carbohyd. Res.*, **7**, 510 (1969).

a little Norit A, and the water was evaporated. Since the resulting gum did not crystallize, it was purified on an anion-exchange column (29 × 2.4 cm) as described in method C and 10-ml fractions were collected. The main peak was at tubes 32–100, which yielded 1.3 g (23%). Recrystallization from ethanol gave 691 mg (12%), mp 121–123°, solidifying above 160° and melting again at 193–195°. The analytical sample was prepared by further recrystallization and required drying at 100° under high vacuum over P_2O_5: mp 121–124 and 194–196°; $[\alpha]^{25}D$ −76° (*c* 0.79, H_2O).

Anal. Calcd for $C_{11}H_{15}N_5O_4$: C, 46.96; H, 5.41; N, 24.90. Found: C, 46.88; H, 5.41; N, 25.11.

When a small sample of this substance was recrystallized from water, the crystals which formed (mp 157–159 and 196–198°) were identical in very respect with **3** monohydrate.

Tubes 4–20 afforded a tan powder which was rechromatographed on a column (43 × 1 cm) by the same procedure as above. The main uv-absorbing peak was isolated to give a substance (165 mg) which did not crystallize from most common solvents. It did, however, afford a white precipitate from ethanol–methyl ethyl ketone, mp 131–137°, and from acetone, mp 90–150°. It is interesting to note that Baker and Hewson reported[8] mp 132–135 and 50–135° for their compound from these same solvents, respectively. However, the optical rotation $[\alpha]^{25}D$ −40° (*c* 0.37, H_2O) differed greatly. Paper chromatography in solvent C showed this substance to have a mobility very different from that of **3** or **6**, but identical with that of **7** which it obviously was not. Uv showed λ_{max} 258 (pH 1), 259 (H_2O), and 259 nm (pH 11). Although isolated from several preparations, including some as performed in method C, this substance has not yet been identified.

Method E.—This procedure gave the poorest results and is of no synthetic use. Tetrabenzoate **11** (4.4 g) was dissolved in 10 ml of methylene chloride and treated with 23 ml of 32% hydrogen bromide in acetic acid (Eastman) at room temperature for 45 min. The mixture was poured into 50 ml of ice–water and the product was extracted with 50 ml of chloroform. The aqueous layer was extracted once more with 20 ml of chloroform, and the solutions were combined and washed three times with 50-ml portions of ice-cold water. The solvent was evaporated and small portions of toluene were coevaporated two times to eliminate traces of acetic acid. The halide was treated with 4.4 g of 6-benzamidochloromercuripurine as described in method B. All of the subsequent steps were as described in method B and the nucleoside was isolated *via* the picrate and chromatography on the anion-exchange column. The only major peak yielded 30 mg (1.4%) of **3** from ethanol, mp 118–120 and 196–197°, identical in every respect with the substance prepared by method D.

Acetolysis of 6-Deoxy-1,5-di-*O*-acetyl-2,3-isopropylidene-L-mannofuranose (4).[9]—The data reported in Table II for a 10:1 mixture of acetic acid–acetic anhydride was obtained earlier.[5] The 1:1 acetic acid–acetic anhydride mixtures contained 3% concentrated sulfuric acid and were run according to the directions of Reist, *et al.*[12] Acetolyses conducted in 3:7 acetic acid–acetic anhydride were run exactly as described for that above using 5% sulfuric acid, the concentration of acid that had been previously used in the 10:1 acetic acid–acetic anhydride mixtures. The syrups obtained were used directly for nucleoside synthesis.

Nucleosides Obtained after Coupling of Acetolysis Products. From 1:1 Acetic Acid–Acetic Anhydride.—The reaction mixture consisted of 3.4 g of the sugar acetate mixture, 5.8 g of 6-benzamidochloromercuripurine, 5.8 g of Celite-545, 1.7 ml of titanium tetrachloride, and 600 ml of 1,2-dichloroethane. After work-up, a pale yellow foam was obtained, 4.47 g. Removal of the ester groups with hot methanolic sodium methoxide and treatment with a little charcoal gave a syrup which was fractionated on a column (28 × 2.4 cm) of Bio-Rad AG1-X2 (OH^-, 200–400 mesh).[7] The column was packed with water and the sample was added dissolved in water. Development was carried out with 30% aqueous methanol and 9-ml fractions were collected. The contents of tubes 15–58 were pooled and the product was crystallized from ethanol–water to give 145 mg (5%) of **6**, mp 215–217°, identical in every respect with an authentic sample of **6**. The contents of tubes 144–250 were pooled and the product was crystallized from water to afford 323 mg (10.5%) of **3** in two crops, mp 156–158.5°, resolidifying above 165° and melting again at 198–200°. This compound was identical in every respect with **3** as reported in method B. Crystallization from ethanol of the nucleoside collected in tubes 277–440 afforded 208 mg (6%) of **5** in two crops, mp 119–122°, identical in every respect with an authentic sample.[6]

From 3:7 Acetic Acid–Acetic Anhydride.—The reaction mixture consisted of 3.2 g of the sugar acetate, 5.5 g of Celite-545, 1.5 ml of titanium tetrachloride, and 680 ml of 1,2-dichloroethane. The steps followed and the column chromatography were run exactly as described above. Tubes 21–37 yielded **6** (210 mg, 8%, mp 216–218.5°) and tubes 77–220 afforded **3** (305 mg, 11%, mp 157–160 and 197–200°). The eluent was changed to 60% aqueous methanol at tube 334 and the peak at tubes 355–397 yielded 27 mg (0.9%) of **5**, mp 118–121°. These nucleosides were identical with the previous preparations in every respect.

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Registry No.—**3**, 29847-43-6; **4**, 29847-40-3; **7**, 29847-42-5; **9**, 41507-10-2; 2,2-dimethoxypropane, 77-76-9; *p*-toluenesulfonic acid, 104-15-4.