of boron trifluoride ethyl etherate [1.32 g, freshly distilled at 44° (9 mm)] in 10 ml of tetrahydrofuran was added dropwise over a period of 15 min. After 2 hr, water was carefully added to destroy excess reagent and the solution was treated with 30% hydrogen peroxide while maintaining the pH at 9 with 3 *N* sodium hydroxide. This was stirred for 1.5 hr, the solvents were evaporated, and the residue was extracted with chloroform which was washed with water and dried. Evaporation left a syrup which crystallized slowly over the next 4 months. The syrup–crystal mixture was triturated with methanol to give 22 mg (5%) of crystals which were recrystallized from methanol. Tiny, colorless prisms weighing 6 mg were obtained: mp 220–220.5°; ir (KBr) 3320 (NH, OH), 1680, 1600, 1572 ($NH_2C{=}N$, purine ring), 1384–1364 (multiplet, *gem*-dimethyl), 1092, 1064 (COC, CO).

Anal. Calcd for $C_{14}H_{19}N_5O_4$: C, 52.33; H, 5.96; N, 21.80. Found: C, 52.04; H, 5.73; N, 21.90.

Enol Mesylate (8).—A mixture of 5.1 g of **3**, Dowex 1-X10 (acetate, 200–400 mesh) resin, and 200 ml of acetic anhydride was heated at reflux for 8 hr. The resin was removed by filtration and the filtrate was evaporated to a brown foam which was coevaporated five times with a mixture of ethanol and toluene. The foam (5.4 g) was dissolved in methanol and treated with 13 ml of 1 *N* methanolic sodium methoxide at reflux for 1 hr. After neutralization with Dowex 50 (H) resin and a Darco G-60 treatment, the methanol was removed by evaporation, leaving a tan foam which was dissolved in 0.1 *N* sulfuric acid and kept at room temperature for 6 days. The neutralization step was carried out as described above for **6**. The aqueous solution was washed with chloroform and evaporated, and the residue was dissolved in a minimum amount of 30% aqueous methanol. This was applied to the top of a column of Bio-Rad AG 1-X2 (OH, 200–400 mesh)[10] (30 × 2.3 cm), the column was eluted with the same solvent, and 12 ml fractions were collected. Fractions 136–225 represented the only major uv-absorbing component. The contents of these tubes were pooled and evaporated to dryness and crystallization was achieved from ethanol–water (644 mg, 16%). Two recrystallizations yielded 380 mg of feathery platelets: mp 160°; $[\alpha]^{27}D$ +143° (*c* 0.71, 1 *N* HCl); ir (KBr) 1702, 1643, 1618, 1575 ($CH{=}CH_2$ and purine ring), 1360, 1175 (sulfonate), and 885 cm^{-1} (*gem*-vinyl); Rad 1.58 in 5% aqueous disodium hydrogen phosphate and 0.57 in 86:14 *n*-butyl alcohol–water.

Anal. Calcd for $C_{12}H_{15}N_5O_6S$: C, 40.33; H, 4.23; N, 19.60; S, 8.97. Found: C, 40.31; H, 4.21; N, 19.56; S, 8.99.

Registry No.—**1**, 32659-04-4; **2**, 32659-05-5; **2** (picrate), 32829-93-9; **3**, 32659-06-6; **4**, 10279-88-6; **5**, 32659-07-7; **6**, 32829-95-1; **7**, 32659-08-8; **8**, 32829-96-2.

Interconversions of Hexofuranosyl Nucleosides. II. Preparation of 9-α-L-Idofuranosyladenine and 5′,6′-Unsaturated Derivatives[1]

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9-(2,3-Di-*O*-acetyl-5,6-di-*O*-*p*-toluenesulfonyl-β-D-glucofuranosyl)adenine (**3**) was prepared from 1,2-*O*-isopropylidene-5,6-di-*O*-*p*-toluenesulfonyl-α-D-glucofuranose (**1**) in a four-step synthesis. Inversion of configuration at C-5′ was not possible without extensive degradation and cyclonucleoside (**4**) formation. 9-(2,3-Di-*O*-acetyl-6-*O*-benzoyl-5-*p*-toluenesulfonyl-β-D-glucofuranosyl)adenine successfully underwent inversion to the L-idose nucleoside (**8**) but in too small of a yield to be of preparative value. Therefore, 9-α-L-idofuranosyladenine (**8**) was synthesized starting from 3,6-di-*O*-acetyl-5-*O*-benzoyl-1,2-*O*-isopropylidene-β-L-idofuranose (**9**) and proceeded by condensation of the acetate **10**, prepared by acetolysis of **9**, with 6-benzamidochloromercuripurine and titanium tetrachloride. An 5′,6′-olefinic blocked nucleoside **12** was prepared from **3** in hot sodium iodide-acetone or by a pathway starting from the known unsaturated sugar derivative, 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-glucofuranose. This derivative was converted in two steps to an acetate **15** which was coupled to adenine by the titanium tetrachloride method. Removal of the blocking groups of **12** gave 9-(5,6-dideoxy-β-D-*xylo*-hex-5-enofuranosyl)adenine, a noncrystalline, unstable compound.

The aims of the present investigation were set forth in the previous paper of this series.[2] 9-α-L-Idofuranosyladenine (**8**) appeared to be an interesting compound to prepare because of its structural relationship to 9-β-D-xylofuranosyladenine, a compound of biological interest because of its ability to inhibit growth of some forms of animal tumors.[3] It was of interest to see if epimerization of C-5′ of a preformed D-glucofuranosyl nucleoside derivative could be effected, thereby giving the nucleoside with the L-ido configuration. To do this it was necessary to prepare a derivative of 9-β-D-glucofuranosyladenine which had a group at C-5′ that could easily be displaced by an SN2 reaction or assisted by neighboring group participation. 9-(2,3-Di-*O*-acetyl-5,6-di-*O*-*p*-toluenesulfonyl-β-D-glucofuranosyl)adenine (**3**) seemed like such a compound.

The preparation of **3** started from 1,2-*O*-isopropylidene-5,6-di-*O*-*p*-toluenesulfonyl-α-D-glucofuranose[4] (**1**) and the route used is illustrated in Scheme I. Acetolysis of **1** converted it to tri-*O*-acetate **2**, which was immediately coupled, without further purification, with 6-benzamidochloromercuripurine using the titanium tetrachloride method of nucleoside synthesis.[5] The product of this condensation was treated with picric acid,[6] and a crystalline picrate of **3** was obtained in excellent yield. Removal of the picrate ion with an ion exchange resin[7] gave **3**.

Buss, *et al.*,[8] were able to convert 3-*O*-acetyl-1,2-*O*-isopropylidene-5,6-di-*O*-toluenesulfonyl-α-D-glucofuranose to 3-*O*-acetyl-5,6-di-*O*-benzoyl-1,2-*O*-isopropylidene-β-L-idofuranose in a yield of 50% using the hot sodium benzoate–dimethylformamide system first de-

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

(2) L. M. Lerner, *J. Org. Chem.*, **36**, 470 (1971).

(3) D. B. Ellis and G. A. LePage, *Cancer Res.*, **26**, 893 (1966).

(4) H. Ohle and E. Dickhauser, *Ber.*, **58**, 2593 (1925).

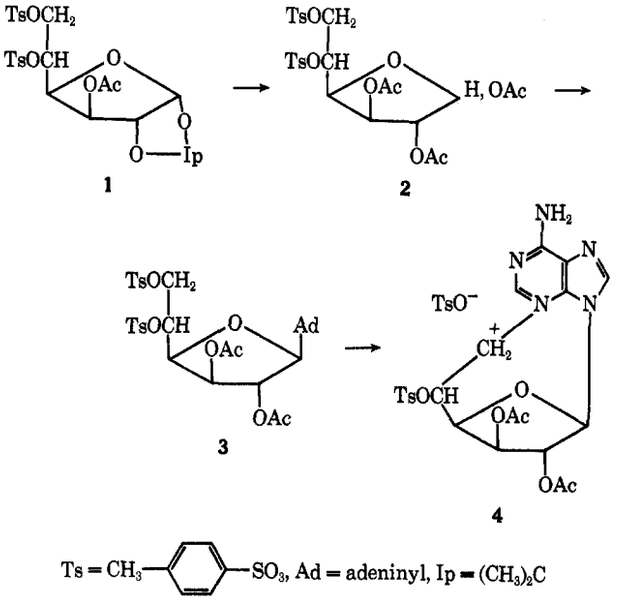
(5) B. R. Baker, R. E. Schaub, J. P. Joseph, and J. H. Williams, *J. Amer. Chem. Soc.*, **77**, 12 (1955); J. Prokop and D. H. Murray, *J. Pharm. Sci.*, **54**, 359 (1965).

(6) J. R. Parikh, M. E. Wolff, and A. Burger, *J. Amer. Chem. Soc.*, **79**, 2778 (1957).

(7) M. L. Wolfrom, A. B. Foster, P. McWain, W. von Bebenburg, and A. Thompson, *J. Org. Chem.*, **26**, 3095 (1961).

(8) D. H. Buss, L. D. Hall, and L. Hough, *J. Chem. Soc.*, 1616 (1965).

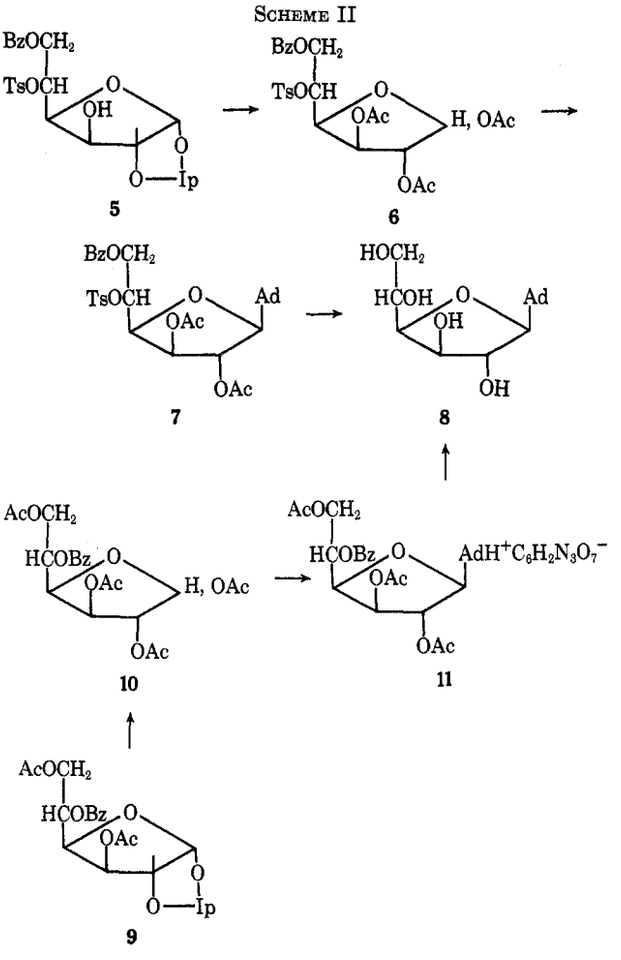
SCHEME I



scribed by Baker and his colleagues.[9] When **3** was allowed to react in a boiling mixture of sodium benzoate and moist *N*,*N*-dimethylformamide, extensive degradation ensued in minutes as the mixture became black. After work-up, hardly any organic-soluble material could be isolated from the organic phase and this appeared to consist of decomposed tarry residues. On the assumption that a cyclonucleoside had formed which had passed into the aqueous phase during work-up, confirmatory evidence was sought by scanning the water layer in the ultraviolet. Cyclonucleosides derived from adenine nucleosides are internal salts which are very water-soluble even when the hydroxyl groups are blocked with organic-soluble residues.[10] An absorption peak near λ_{max} 272 mμ confirmed this as a strong possibility. Therefore, a sample of **3** was heated at reflux alone in *N*,*N*-dimethylformamide and although the cyclonucleoside **4** would not crystallize, its structure was evident from the absorption maximum at 274 mμ and from two new bands at 1010 and 685 cm^{-1} in the infrared. This is believed to be the first report of an N-3,6′ cyclonucleoside and acts as a proof of the β configuration of **3**. Stereomodels confirmed that, if **3** had the α configuration, then it would not have been possible to form the cyclonucleoside. Problems such as cyclonucleoside formation during attempts to carry out reactions at the primary carbons of pentose nucleosides are not uncommon or unexpected.[11] Similarly, a substitution to yield the N-3,6′ cyclonucleoside (**4**) rather than the N-3,5′ cyclonucleoside would be expected due to the greater reactivity of the primary carbon.

Failure of the reaction pathway proposed above to give the desired product **8** prompted the investigation of another route starting from 6-*O*-benzoyl-1,2-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-α-D-glucofuranose[12] (**5**) and this is shown in Scheme II. Acetolysis of **5**

SCHEME II



gave **6**, which was coupled with 6-benzamidochloromercuripurine and this was converted to the picrate as described in the preparation of **3**. The blocked nucleoside obtained after removal of the picrate ion failed to crystallize, but was believed to be 9-(2,3-di-*O*-acetyl-6-*O*-benzoyl-5-*O*-*p*-toluenesulfonyl-β-D-glucofuranosyl)adenine (**7**). It was hoped that the use of a benzoyl group block at position 6′ would prevent the undesirable effect which occurred with compound **3**. Because Goodman had stated in a recent review article[13] that the exocyclic carbons of aldofuranose derivatives undergo displacement only by an SN2 mechanism and it was believed that the products of the reaction of acetate ion in acetic anhydride with 6-*O*-benzoyl-5-*O*-tosylhexofuranosyl derivatives were the inverted 5-*O*-acetate derivatives,[14,15] **7** was treated with Dowex 1 (acetate) in boiling acetic anhydride.[15] Some decomposition was evident and only a very small yield of **8** occurred after removal of the blocking groups. It is now known that the 6-benzoyloxy group participates in these reactions and the yields of C-5 inverted prod-

(9) E. J. Reist, L. Goodman, and B. R. Baker, *J. Amer. Chem. Soc.*, **80**, 5775 (1958).

(10) V. M. Clark, A. R. Todd, and J. Zussman, *J. Chem. Soc.*, 2952 (1951); W. Anderson, D. H. Hayes, A. M. Michelson, and A. R. Todd, *ibid.*, 1882 (1954).

(11) See, for example, W. Jahn, *Chem Ber.*, **98**, 1705 (1965); M. Hubert-Habart and L. Goodman, *Can. J. Chem.*, **48**, 1335 (1970); J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, **35**, 2319 (1970); and ref 10.

(12) J. Kovar, *Can. J. Chem.*, **48**, 2383 (1970).

(13) L. Goodman, *Advan. Carbohyd. Chem.*, **22**, 119 (1967).

(14) L. Vargha, *Chem. Ber.*, **87**, 1351 (1954); M. A. Miljkovic and E. A. Davidson, Abstract of Papers, 155th Meeting of the American Chemical Society, San Francisco, Calif., 1968, C-7.

(15) P. Perchemlides, T. Osawa, E. A. Davidson, and R. W. Jeanloz, *Carbohyd. Res.*, **3**, 463 (1967).

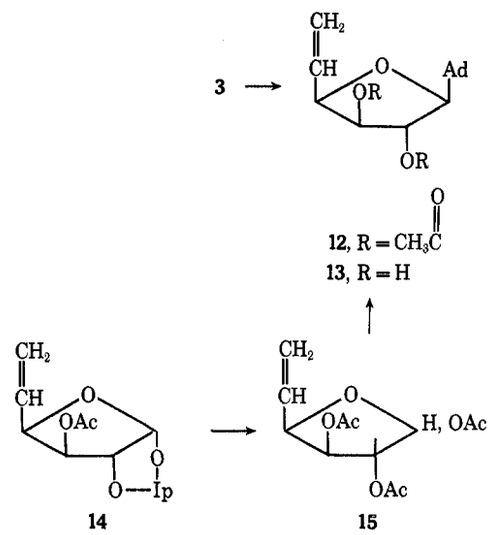
ucts are very high with sugar derivatives.[16] It is therefore not inconceivable that the nitrogen at N-3 of the purine ring was capable of competing with acetate ion in attacking the 6′ position as the benzoate migrated. This matter was not pursued further and a completely new synthesis of 9-α-L-idofuranosyladenine (**8**) was achieved as described below.

The decision to make **8** by condensation of L-idose derivatives with the base was due to recent publications of improved methods for their synthesis from D-glucose.[12,17] 3,6-Di-*O*-acetyl-5-*O*-benzoyl-1,2-*O*-isopropylidene-β-L-idofuranose[12,18] (**9**) was converted to tri-*O*-acetate **10**, which was coupled in the usual fashion with the base. The nucleoside was isolated *via* an intermediate picrate,[6,7] the blocking groups were removed, and the free nucleoside **8** crystallized and was found to be identical with the one prepared above from **5**. No attempts were made to deduce the configuration of C-1′ of **8**, but a strong argument can be made in favor of the α configuration from what is known about the ratio of β/α anomers obtained after nucleoside formation by the titanium tetrachloride method.[5,19,20]

Attention was drawn next to the preparation of a 5,6-olefinic nucleoside (**13**) which could be synthesized in a homologous manner to the preparation of a similar compound from the D-mannosyl nucleoside described in the preceding paper. Treatment of **3** with sodium iodide in acetone[2,21] gave 9-(5,6-dideoxy-2,3-di-*O*-acetyl-β-D-*xylo*-hex-5-enofuranosyl)adenine (**12**) in a 21% yield. It was noted that the competition from cyclonucleoside formation was not as evident in this reaction as in the formation of **4** in dimethylformamide. The stability of compound **3** in boiling acetone and dioxane was investigated and it was discovered that no change in λ_{max} from 259 mμ occurred, indicating that under these conditions no cyclonucleoside had formed. Considering the reactivity of most pentose nucleosides under such conditions,[10,11] the only explanation that can perhaps be offered here would be that the ring structure of cyclonucleoside **4** would be more difficult to form than that found in the pentose nucleosides. Formation of **4** is clearly a solvent effect for solutions in *N*,*N*-dimethylformamide and such a result as noted here would be quite typical for this dipolar aprotic solvent.[22]

It now became of interest to see if the 5,6-olefinic nucleoside **12** could be prepared directly from an unsaturated sugar. Although unsaturated nucleosides have been previously reported, these have usually been prepared from preformed nucleosides[23] or by condensation of a glycal[24] or 2-hydroxyglycal[25] with a nitrogenous base, which in the latter cases resulted in a double-bond migration. 5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-hex-5-enofuranose[26] was acetylated to give the 3-*O*-acetate **14** as an oil (Scheme III). The boiling point of

SCHEME III



14 was considerably different from that recorded for this compound when it was prepared by condensation of 3-*O*-acetyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose with methylenetriphenylphosphorane;[27] however, the optical rotations agreed well and the infrared spectrum showed the required bands supporting the structure. Acetolysis converted **14** to the tri-*O*-acetate **15**. Of the methods available to couple a sugar derivative to a nitrogenous base, the most desirable ones were either the fusion method[28] or the titanium tetrachloride method;[5] other procedures require previous formation of a glycosyl halide which is usually done with a hydrogen halide in an organic solvent, conditions which will result in addition of the hydrogen halide across the double bond of **15**. Condensation of **15** with 6-benzamidochloromercuripurine and titanium tetrachloride gave a 33% yield of a picrate, which was prepared from the crude product. Removal of the picrate ion gave **12**. The acetyl groups of **12** were removed with base to give 9-(5,6-dideoxy-β-D-*xylo*-hex-5-enofuranosyl)adenine (**13**) which was an unstable substance.

Although not entirely unexpected, it is quite obvious from these experiments that interconversions of preformed hexofuranosyl nucleosides at the exocyclic carbons will be fraught with difficulties when the purine ring is on the same side of the sugar ring as the ethylene glycol side chain. Reactions that would probably be the most successful are those which would proceed by an SN2 displacement at C-5′ and have a nonparticipating group at C-6′. The nature of the solvent and the temperature will likewise effect this to a great extent.

(16) R. C. Chalk, D. H. Ball, M. A. Lintner, and L. Long, Jr., *Chem. Commun.*, 245 (1970); M. Miljković, A. Jokić, and E. A. Davidson, *Carbohyd. Res.*, **17**, 155 (1971).
(17) M. A. Miljkovic and E. A. Davidson, *Carbohyd. Res.*, **13**, 444 (1970).
(18) Named in ref 12 as 3,5-di-*O*-acetyl-6-*O*-benzoyl-1,2-*O*-isopropylidene-β-L-idofuranose.
(19) D. H. Murray and J. Prokop, *J. Pharm. Sci.*, **56**, 865 (1967).
(20) B. R. Baker, in Ciba Foundation Symposium, "Chemistry and Biology of Purines," G. E. Wolstenholme and C. M. O'Connor, Ed., Little, Brown and Co., Boston, Mass., 1957, p. 120.
(21) J. K. N. Jones and J. L. Thompson, *Can. J. Chem.*, **35**, 955 (1957).
(22) A. J. Parker, *Advan. Org. Chem.*, **5**, 1 (1965).
(23) J. R. McCarthy, Jr., R. W. Robins, and M. J. Robins, *J. Amer. Chem. Soc.*, **90**, 4993 (1968); J. R. McCarthy, Jr., M. J. Robins, L. B. Townsend, and R. K. Robins, *ibid.*, **88**, 1549 (1966); J. P. Horowitz, J. Chua, M. A. Da Rooge, M. Noel, and I. L. Klundt, *J. Org. Chem.*, **31**, 205 (1966).
(24) W. A. Bowles and R. K. Robins, *J. Amer. Chem. Soc.*, **86**, 1252 (1964); E. E. Leutzinger, R. K. Robins, and L. B. Townsend, *Tetrahedron Lett.*, 4475 (1968).
(25) K. Onodera and T. Yajima, *Carbohyd. Res.*, **13**, 97 (1970).
(26) L. D. Hall, L. Hough, and R. A. Pritchard, *J. Chem. Soc.*, 1537 (1961).
(27) D. G. Lance and W. A. Szarek, *Carbohyd. Res.*, **10**, 306 (1969).
(28) M. J. Robins, W. A. Bowles, and R. K. Robins, *J. Amer. Chem. Soc.*, **86**, 1251 (1964), and references cited therein.

Experimental Section[29]

9-(2,3-Di-*O*-acetyl-5,6-di-*O*-*p*-toluenesulfonyl-β-D-glucofuranosyl)adenine (3).—1,2-*O*-Isopropylidene-5,6-di-*O*-*p*-toluenesulfonyl-α-D-glucofuranose[4] (1) (15.1 g, 28.5 mmol) was dissolved in a mixture of 385 ml of glacial acetic acid and 36 ml of acetic anhydride, and 21.6 ml of concentrated sulfuric acid was added dropwise. During this procedure the temperature of the reaction mixture was held between 10 and 20° by frequent immersion in an ice bath. The flask was stored overnight at room temperature and then the contents were poured into 1.1 l. of ice–water. A heavy, white gum formed, which was extracted with chloroform (*ca.* 215 ml) and washed with water, saturated sodium bicarbonate, and again with water, and dried. The chloroform was removed by evaporation and traces of acetic acid were azeotropically distilled using toluene. A clear, almost colorless syrup (2) weighing 14.7 g (83%) resulted: ir (film, NaCl) 1755 (C=O of acetate), 1594 (phenyl ring), 1363 and 1175 cm^{-1} (sulfonate). There was no band for a hydroxyl group.

From a mixture containing 2.44 g (4 mmol) of **2**, 2.4 g of 6-benzamidochloromercuripurine, 2.4 g of Celite-545, and 200 ml of 1,2-dichloroethane was distilled 25 ml of the solvent in order to remove traces of moisture. A solution of 0.55 ml of titanium tetrachloride in 10 ml of 1,2-dichloroethane was added and the mixture was stirred under reflux for 19 hr.[5] When the flask had cooled, 73 ml of saturated sodium bicarbonate solution was added and stirring was continued at room temperature for 2.5 hr. The precipitate was removed by filtration through a pad of Celite and the filter cake was washed three times with 20-ml portions of chloroform. The organic phase was separated and evaporated to dryness. The syrupy residue was dissolved in chloroform and washed three times with 45-ml portions of 30% aqueous potassium iodide and once with water. After the solution had been dried and evaporated, an orange gum remained which weighed 3.17 g. This was dissolved in warm absolute ethanol and 13 ml of 10% ethanolic picric acid was added and the solution was heated at reflux for a few minutes and then allowed to cool.[6] Crystallization yielded 2.94 g (80%) of the picrate of **3**, mp 139°. A portion of this was recrystallized from methanol to give tiny, spherical crystals, mp 141–143°.

Anal. Calcd for $C_{35}H_{34}N_8O_{18}S_2$: C, 45.75; H, 3.87; N, 12.19. Found: C, 46.14; H, 3.87; N, 11.80.

To a solution of 2.83 g (3.1 mmol) of the picrate in 145 ml of 75% aqueous acetone was added Bio-Rad AG1-X8 (CO_3^{-2}) resin and the solution was stirred until the yellow color of the picrate ion had been removed.[7] An orange-colored contaminant was removed with a Darco G-60 treatment and the clear, colorless solution was evaporated to dryness giving a white solid. This was recrystallized from chloroform–ethanol to produce 1.2 g (56%) of crystals: mp 187–187.5°; $[\alpha]^{26}D$ −36° (*c* 1.5, $CHCl_3$); uv λ_{max}^{MeOH} 259 mμ; ir (KBr) 3370 (NH), 1760, 1740 (C=O), 1650, 1598 (phenyl and purine ring), 1360 and 1174 (sulfonate), 1104, 1093, 1074, 1012 cm^{-1} (COC, CO); tlc in 5:1 chloroform–methanol, R_f 0.66.

Anal. Calcd for $C_{28}H_{31}N_5O_{11}S_2$: C, 50.49; H, 4.54; N, 10.16; S, 9.30. Found: C, 50.07; H, 4.48; N, 9.80; S, 8.93.

Conversion of 3 to Cyclonucleoside 4.—A solution of 100 mg of **3** in 3 ml of *N*,*N*-dimethylformamide was heated at reflux for 1 hr. The mixture turned a dark brown and the ultraviolet absorption maximum shifted to 275 mμ. The solvent was evaporated off, but all attempts to achieve crystallization failed. The solubility of **4** in water was confirmed: λ_{max}^{MeOH} 274 mμ; ir (film, NaCl) 1010 and 685 cm^{-1} (tosylate anion). Another band expected near 1210 cm^{-1} was obscured by a broad plateau, tlc in 5:1 chloroform–methanol, R_f 0.09.

9-α-L-Idofuranosyladenine (8). From 9.—3,6-Di-*O*-acetyl-5-*O*-benzoyl-1,2-*O*-isopropylidene-β-L-idofuranose[12] (9) (4.9 g, 12 mmol) was dissolved in a mixture containing 58 ml of glacial acetic acid and 6.6 ml of acetic anhydride. The addition of sulfuric acid (2.8 ml) and the work-up were carried out as described above for **2**. The syrup was added to a mixture of 7.1 g of 6-benzamidochloromercuripurine, 7.1 g of Celite-545, titanium tetrachloride (1.7 ml), and a final volume of 550 ml of 1,2-dichloroethane. The reaction and work-up followed the procedure described for the preparation of **3**. A picrate was prepared by reaction of a solution of the completely blocked nucleoside in 30 ml of ethanol with 28 ml of 10% ethanolic picric acid at reflux for 0.5 hr. Yellow crystals (4.56 g, 50%) were deposited upon chilling. Recrystallization from acetone–ethanol (Darco treatment) gave colonies of crystals: 2.86 g; mp 188°; $[\alpha]^{26}D$ +38° (*c* 1.1, $CHCl_3$); ir (KBr) 1748, 1738 sh (C=O), 1694 (protonated adenine ring), 1610, 1582 (phenyl and purine rings), 1550 (NO_2), 1362 (*gem*-dimethyl), 1313 (NO_2), 1098–1050 (broad CO), 710 cm^{-1} (monosubstituted phenyl).

Anal. Calcd for $C_{30}H_{28}N_8O_{16}$: C, 47.62; H, 3.73; N, 14.81. Found: C, 46.82; H, 3.94; N, 14.42.

A solution of the picrate (2.73 g) in 200 ml of 80% aqueous acetone was stirred with Bio-Rad AG1-X8 (CO_3^{-2}) resin until the solution was colorless, whereupon the resin was filtered off and the solvents were removed by evaporation. Coevaporation with ethanol to dry the product left a white foam (1.84 g) which did not crystallize from common solvents. Finally a solution of this in 50 ml of methanol was treated with 6 ml of 1 *N* methanolic sodium methoxide and refluxed for 1 hr. IR-120 (H^+) ion exchange resin was used to neutralize the solution. After removal of the resin, the methanolic solution was concentrated by boiling, whereupon crystallization began and was allowed to proceed at room temperature, affording 668 mg, mp 227°. A second crop of crystals from the mother liquor gave 96 mg: mp 226° (total yield 71%) (recrystallization raised the melting point to 228–228.5°); $[\alpha]^{26}D$ −39° (*c* 1.0, 1 *N* HCl); uv max (0.1 *N* HCl) 257.5 mμ (ε 13,800), (H_2O) 257 (14,000), (0.1 *N* NaOH) 260 (14,300); Rad 1.47 (5% aqueous disodium hydrogen phosphate), 0.43 (86:14 *n*-butyl alcohol–water).

Anal. Calcd for $C_{11}H_{15}N_5O_5$: C, 44.45; H, 5.09; N, 23.56. Found: C, 44.44; H, 5.09; N, 23.52.

From 5.—6-*O*-Benzoyl-1,2-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-α-D-glucofuranose[12] (4.13 g, 8.6 mmol) was converted to the tri-*O*-acetate **6** as described above for the preparation of **2**, yielding 5.1 g of a hard, white foam. This was coupled with 6-benzamidochloromercuripurine (5.4 g), Celite-545 (5.4 g), titanium tetrachloride (1.3 ml), and 1,2-dichloroethane (450 ml) as previously described. The picrate was prepared by boiling a 60-ml solution of the product with 23 ml of 10% ethanolic picric acid, yielding 3.29 g of yellow crystals which were probably contaminated slightly with picric acid, mp 133–136°.

Anal. Calcd for $C_{35}H_{32}N_8O_{17}S$: C, 48.37; H, 3.71; N, 12.90. Found: C, 48.14; H, 3.75; N, 14.16.

The picrate ion was removed as described above giving a yellow foam (2.17 g) of 9-(2,3,6-tri-*O*-acetyl-5-*O*-benzoyl-β-D-glucofuranosyl)adenine, which was contaminated by two trace components which moved slower than the main product on tlc in 95:5 ethyl acetate–methanol: R_f 0.35; ir (film, NaCl) 3320 (NH), 1725 (broad C=O), 1642, 1598 (phenyl and purine ring), 1368, 1175 (sulfonate), 1108–1048 (plateau CO), 712 (monosubstituted phenyl).

The foam was dissolved in 65 ml of acetic anhydride and treated at reflux with 40 ml of Dowex 1-X8 (acetate) resin for 10 hr.[15] The reaction mixture darkened rather quickly and was nearly black by the end of the reflux time. The resin was removed by filtration and the solution was evaporated to dryness. The blocking groups were removed in methanolic sodium methoxide and a picrate was prepared,[30] yield 305 mg, mp 191–195°, resolidifying as needles which melted at 242–244° dec. The free nucleoside was regenerated[30] with an anion exchange resin in hot water and was crystallized from methanol giving 94 mg, mp 226.5–228°. This substance was identical with compound **8** as prepared from **9** in every respect.

9-(5,6-Dideoxy-2,3-di-*O*-acetyl-β-D-*xylo*-hex-5-enofuranosyl)adenine (12). From 3.—A solution of 1.36 g of **3**, 3.5 g of sodium iodide, and 50 ml of acetone was heated at 100° in a stainless steel bomb for 15 hr.[2,21] The mixture was diluted with chloroform and washed with 400 ml of one-half saturated sodium bicarbonate solution containing 9 g of sodium thiosulfate and water, and dried. The chloroform was evaporated on a steam bath, whereupon crystallization occurred. Two recrystallizations from ethanol gave 147 mg (19%) of colorless platelets: mp 202.5–203° with softening of the crystals between 195 and 201°; $[\alpha]^{23}D$ +22.5° (*c* 1.12, $CHCl_3$); uv max (EtOH) 259 mμ; ir (KBr) 3240 (NH), 3080 (CH=CH_2), 1745 (C=O of acetate), 1678, 1602, 1574 (purine ring), 1090, 1058, 1045 (CO), 988 (CH=CH_2); nmr ($CDCl_3$) 1.61, 1.84 (both s, H-2 and H-8),

(29) General methods and instrumentation are given in the preceding paper.[2] Tlc was performed on precoated silica gel F_{254} plates prepared by E. Merck A.G., Darmstadt. Paper chromatography was done on Whatman No. 1 paper. Rad (adenine) = 1.00.

(30) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 959 (1957).

3.68 (d, $J_{1,2}$ = 2.4 Hz, H-1'),[31] 4–4.8 (m, CH=CH_2 and unresolved H-2', H-3'), 5.1 (m, H-4'), 7.81, 7.90 (both s, CH_3); tlc in 95:5 ethyl acetate–methanol, R_f 0.31.

Anal. Calcd for $C_{15}H_{17}N_5O_5$: C, 51.87; H, 4.93; N, 20.16. Found: C, 51.51; H, 5.01; N, 19.77.

From 14.—To a solution of 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose[26] (4.75 g) in 50 ml of dry pyridine was added 16 ml of acetic anhydride while the mixture was stirred and chilled in an ice bath. After remaining at this temperature for 1 hr, the mixture was kept at room temperature for 24 hr. The solution was evaporated to a small volume diluted with 100 ml of chloroform, and washed with water (100 ml), saturated sodium bicarbonate (two 100-ml portions), and water (100 ml), and dried. Evaporation gave an oil from which traces of pyridine were removed by coevaporation of toluene. Distillation gave 2.4 g (41%) of an unstable oil (**14**): bp 67–70° (0.15 mm); $[\alpha]^{24}D$ −12° (*c* 4, $CHCl_3$); ir (film, NaCl) 1745 (C=O), 1648 (C=C), 1414 (=CH_2), 1375 (*gem*-dimethyl), 994 cm^{-1} (-CH=CH_2) [lit.[27] bp 154–157° (0.7 mm), $[\alpha]D$ −13° (*c* 1, $CHCl_3$)].

Compound **14** (2.4 g) was converted to tri-*O*-acetate **15** in a solution of glacial acetic acid (51 ml), acetic anhydride (6.8 ml), and concentrated sulfuric acid (3.5 ml) as described above for the preparation of **2**. A yellow syrup weighing 2.52 g resulted.

The coupling reaction was performed by previously described methods. The reaction mixture consisted of 2.52 g (9.3 mmol) of **15**, 5.44 g (11.5 mmol) of 6-benzamidochloromercuripurine, 5.4 g of Celite-545, 0.7 ml of titanium tetrachloride, and 200 ml of 1,2-dichloroethane. The syrupy residue obtained was dissolved in 20 ml of warm ethanol, 22 ml of 10% ethanolic picric acid was added, and the mixture was boiled under reflux until crystals began to appear after 5 min. The picrate was allowed to crystallize at room temperature, then chilled in an ice bath to give upon filtration 1.54 g of crystals. The mother liquor deposited an additional 0.32 g (total yield 33%). Recrystallization from acetone–ethanol gave 1.2 g of tiny crystals (picrate of **12**): mp 210–214° dec; ir (KBr) 1752 (C=O), 1694 (protonated adenine ring), 1608, 1568 (purine ring), 1548, 1314 (NO_2), 1077–1042 cm^{-1} (broad CO).

Anal. Calcd for $C_{21}H_{20}N_8O_{12}$: C, 43.76; H, 3.50; N, 19.44. Found: C, 43.41; H, 3.76; N, 19.26.

(31) The low coupling constant is indicative of a *trans* relationship between C-1' and C-2' and represents additional support for the configurational assignment.

The picrate (1.06 g) was dissolved in 150 ml of 80% aqueous acetone and the yellow color was discharged with Bio-Rad AG1-X8 (CO_3^{-2}) resin. The resin was filtered off, the solvents were removed by evaporation, and the product was crystallized from ethanol in two crops to give 344 mg (54%); mp 198–201° Recrystallization produced 248 mg of colorless platelets of **12**, mp 201–203°. The mixture melting point with **12** prepared from **3** gave no depression, the ir spectra were identical, and the compounds migrated the same on tlc plates.

9-(5,6-Dideoxy-β-D-*xylo*-hex-5-enofuranosyl)adenine (13).—To a solution of 207 mg of **12** in 25 ml of methanol was added 1.5 ml of 1 *N* methanolic sodium methoxide and the mixture was boiled under reflux for 50 min.[32] The dark solution was cooled to room temperature, brought to neutrality with Dowex 50 (H^+) resin, and evaporated to dryness. The brown residue was dissolved in water, treated with activated charcoal (heat), and evaporated again. The compound failed to crystallize but could be obtained as a hard, gray foam by evaporation of acetone to give 63 mg (40%) of **13**. This substance was very hygroscopic and slowly decomposed upon storage in a desiccator at room temperature. It was homogeneous on paper chromatograms: Rad 1.25 (5% aqueous disodium hydrogen phosphate) and 1.40 (86:14 *n*-butyl alcohol–water); uv max (0.1 *N* HCl) 257 and (H_2O or 0.1 *N* NaOH) 259 mμ.

Anal. Calcd for $C_{11}H_{13}N_5O_3$: C, 50.18; H, 4.98; N, 26.60. Found: C, 50.14; H, 5.25; N, 25.26.

A picrate prepared from **13** in methanol[30] had mp 209–211° dec on recrystallization. This material was very light sensitive.

Anal. Calcd for $C_{17}H_{16}N_8O_{10}$: C, 41.47; H, 3.28; N, 22.76. Found: C, 41.46; H, 3.30; N, 22.14.

Registry No.—**2**, 32653-56-8; **3**, 32653-57-9; **3** (picrate), 32653-58-0; **4**, 32653-59-1; **7** (picrate), 32781-70-7; **8**, 32653-60-4; **11** (picrate), 32653-67-1; **12**, 32653-61-5; **12** (picrate), 32653-62-6; **13**, 32653-63-7; **13** (picrate), 32653-64-8; **14**, 17225-57-9.

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(32) It is better to run this reaction overnight at room temperature to prevent degradation of the product.

Interconversions of Hexofuranosyl Nucleosides. III. Synthesis of a 4',5'-Unsaturated Hexofuranosyl Nucleoside[1]

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6-Deoxy-2,3-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-L-mannofuranose (**1**) was converted to the α-L-chloride (**2**) by reaction with thionyl chloride in pyridine. Compound **2** was coupled with 6-benzamidopurine and 9-(6-deoxy-2,3-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-α-L-mannofuranosyl)adenine (**4**) was isolated *via* its picrate **3**. Proof of the structure of **4** was obtained by removal of the tosyl group, which gave the known isopropylidene nucleoside **5**. When **4** was allowed to react with sodium benzoate in boiling *N*,*N*-dimethylformamide, the unsaturated nucleosides, 9-(5,6-dideoxy-2,3-*O*-isopropylidene-β-D-*erythro*-hex-4-enofuranosyl)adenine (**6**) and 9-(5,6-dideoxy-α-L-*lyxo*-hex-5-enofuranosyl)adenine (**7**), were unexpectedly isolated. The yield of **6** was 35% and could be raised to 54% by reaction of **4** with potassium *tert*-butoxide in hot *N*,*N*-dimethylformamide. The nucleosidic bond of **6** was extremely acid labile and attempts to remove the isopropylidene group resulted in immediate degradation and release of adenine. Interest in the unsaturated free nucleoside **10** is due to its structural relationship to the nucleoside antibiotic, decoyinine. Another nucleoside derivative, 9-(6-deoxy-2,3-di-*O*-acetyl-5-*O*-*p*-toluenesulfonyl-α-L-mannofuranosyl)adenine (**13**), was prepared as a potentially useful starting material toward the synthesis of **10**. Reaction of **1** under acetolysis conditions gave the triacetate **12** which was condensed with 6-benzamidochloromercuripurine by the titanium tetrachloride method. Removal of the *N*-benzoyl group gave **13**, whose chemical properties did not favor its transformation to **10**.

It was shown in the preceding two papers[2,3] that the transformation of a hexofuranosyl nucleoside into its 5' epimer was dependent to a great extent upon the configuration of the exocyclic group at C-4' relative to the configuration of the purine ring at C-1'. When they were both on the same side of the furan ring of the sugar, it became difficult to achieve a successful epimerization

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(2) L. M. Lerner, *J. Org. Chem.*, **37**, 470 (1972).

(3) L. M. Lerner, *ibid.*, **37**, 473 (1972).