Synthesis of Aldofuranosyl Nucleosides[1]

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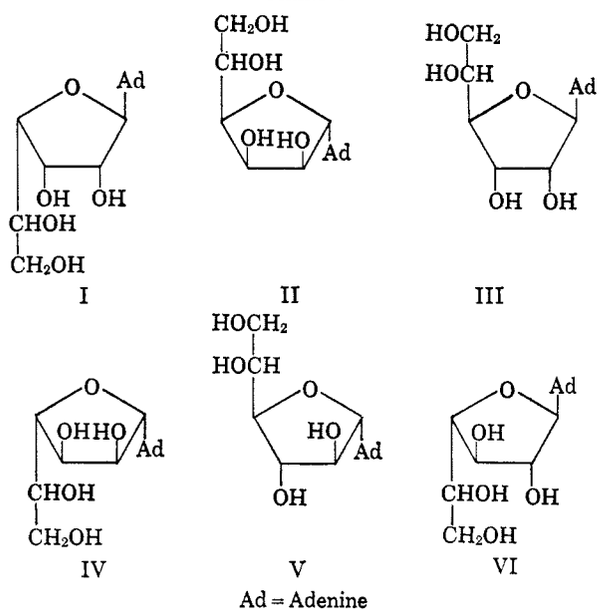
Penta-O-acylhexofuranoses, prepared *via* the reduction of tetra-O-acylaldono-γ-lactones with disiamylborane, were converted to the corresponding chloro sugars and coupled with 6-benzamidochloromercuripurine. The nucleosides prepared in this manner were 9-β-D-gulofuranosyladenine, 9-β-L-gulofuranosyladenine, 9-β-D-allofuranosyladenine, 9-α-D-talofuranosyladenine, 9-α-D-altrofuranosyladenine, and 9-β-D-galactofuranosyladenine. The synthesis of 9-β-D-*glycero*-D-*gulo*-heptofuranosyladenine from D-*glycero*-D-*gulo*-heptono-γ-lactone is also described.

Considerable interest exists in the preparation of hexofuranosyl nucleosides, primarily because of the structural similarity of these substances to the naturally occurring ribose nucleosides. The presence of a furanose ring in the latter compounds is an obvious feature of the molecules which would be desirable to retain in preparing analogs which might act as metabolic inhibitors and possess antiviral or antitumor properties. A principal difference, then, between hexofuranosyl nucleosides and ribose nucleosides is the presence at C-4′ of an ethylene glycol group, rather than a hydroxymethyl group.

Although it is relatively easy to obtain furanose derivatives of pentoses, there has until recently been no generally applicable method for preparing furanose derivatives of aldohexoses. A number of such nucleosides have, however, been prepared, but special methods have been required to obtain the furanose structure, and each method has been applicable to only a limited number of carbohydrates. Nucleosides prepared by these methods include 9-β-D-glucofuranosyladenine, 9-β-D-galactofuranosyladenine, and nucleosides of these hexoses containing bases other than adenine.[2] The furanose ring structure was achieved *via* partial demercaptylation of the dithioacetals. Baker and his associates, using isopropylidene derivatives to obtain the furanose ring, prepared 9-β-D-glucofuranosyladenine[3] and furanosyl nucleosides of a number of 6-deoxy hexoses.[4] Recently Lerner and Kohn reported on the synthesis of 9-D-mannofuranosyladenine[5] prepared *via* 2,3,5,6-di-O-isopropylidene-D-mannofuranose. In each situation, the pathways utilized were of limited applicability, in part due to a lack of knowledge of the chemistry of aldohexoses other than glucose, galactose, and mannose. However, in a recent report from this laboratory[6] we described a more generally applicable means of obtaining furanose derivatives of aldohexoses, which exploited the presence of the furan ring in γ-lactones, many of which are readily obtainable. The reaction route consisted of acylating the free hydroxyl groups of hexono-γ-lactones and reducing the products to the corresponding tetra-O-acylhexofuranoses with bis(2-butyl-3-methyl)borane (di-*sec*-isoamylborane; disiamylborane). The present paper describes the synthesis of 9-β-D-gulofuranosyladenine (I) (Chart I),

CHART I



9-β-L-gulofuranosyladenine (II), 9-β-D-allofuranosyladenine (III), 9-α-D-talofuranosyladenine (IV), 9-α-D-altrofuranosyladenine (V), and 9-β-D-galactofuranosyladenine (VI) from the corresponding pentaacylhexofuranoses.[6] This series of compounds will not only permit the evaluation of the biological effect of the difference in the group at C-4′, but also of the effect of changes in the configuration of other hydroxyl groups of the hexose. A similar series of pyranosyl nucleosides was recently reported.[7]

In addition there is described the synthesis of a heptofuranosyl nucleoside, 9-β-D-*glycero*-D-*gulo*-heptofuranosyladenine (VII) (Chart II) prepared *via* reduction of the penta-O-benzoyl-γ-lactone with disiamylborane. It is of interest to note that reduction of acylated lactones to hemiacetals with this reagent has now been successfully carried out with a considerable number of hexono-γ-lactones, both acetylated and benzoylated, an heptono-γ-lactone, and a benzolated δ-lactone (2,3,4,6-tetra-O-benzoyl-D-glucono-δ-lactone, unpublished), indicating a quite broad scope of the reaction.

(1) (a) Taken in part from the Ph.D. thesis of L. M. Lerner; (b) presented at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept, 1964; (c) supported in part by Training Grant No. GM-471 from the Division of General Medical Sciences of the U. S. Public Health Service and by Grant P-161 from the American Cancer Society.

(2) M. L. Wolfrom, P. McWain, R. Pagnucco, and A. Thompson, *J. Org. Chem.*, **29**, 454 (1964); M. L. Wolfrom and P. McWain, *ibid.*, **30**, 1099 (1965).

(3) E. J. Reist, R. R. Spencer, and B. R. Baker, *ibid.*, **23**, 1958 (1958).

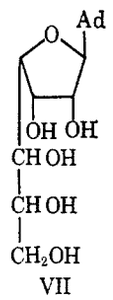
(4) E. J. Reist, L. Goodman, R. R. Spencer, and B. R. Baker, *J. Am. Chem. Soc.*, **80**, 3962 (1958); E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Org. Chem.*, **23**, 1757 (1958); E. J. Reist, R. R. Spencer, and B. R. Baker, *ibid.*, **23**, 1753 (1958); E. J. Reist, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **80**, 5775 (1958); B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 966 (1957).

(5) L. M. Lerner and P. Kohn, *ibid.*, **31**, 339 (1966).

(6) P. Kohn, R. H. Samaritano, and L. M. Lerner, *J. Am. Chem. Soc.*, **87**, 5475 (1965).

(7) L. M. Lerner and P. Kohn, *J. Med. Chem.*, **7**, 655 (1964).

CHART II



VII

The preparation of the requisite penta-O-acylhexofuranoses was described earlier.[6] Each of these compounds was converted to the O-acylglycosylchloride by reaction with hydrogen chloride in ethyl ether or methylene chloride at 0°.[8] The halogenoses, which were not crystallized, were immediately coupled with 6-benzamidochloromercuripurine in refluxing xylene by the method of Davoll and Lowy.[9] The crude products obtained from this condensation were treated with methanolic sodium methoxide to remove the blocking acyl groups and the nucleosides were ultimately extracted into water. The adenine nucleosides derived from D-talofuranose and D-gulofuranose crystallized directly from water and water–ethanol, respectively. All of the other compounds required purification *via* corresponding picrate derivatives[10] before they could be crystallized from ethanol–water.

9-β-D-Galactofuranosyladenine was synthesized from β-D-galactofuranose pentaacetate, prepared from the γ-lactone *via* the disiamylborane reduction procedure.[6] The nucleoside was identical with that prepared by Wolfrom, *et al.*,[2,11] from the 1-thioglycoside.

The presence of a furanose ring in the nucleosides was confirmed by periodate cleavage. In each case nearly 1 mole of formaldehyde was obtained/mole of nucleoside oxidized (Table I).[12]

TABLE I

PERIODATE OXIDATION OF NUCLEOSIDES

Nucleoside	Mole of HCHO/mole of nucleoside
9-β-D-Gulofuranosyladenine	0.95
9-β-L-Gulofuranosyladenine	0.96
9-β-D-Allofuranosyladenine	0.94
9-α-D-Talofuranosyladenine	0.97
9-α-D-Altrofuranosyladenine	0.95

The anomeric configuration of each nucleoside was assigned on the basis of the directive effect of the ester at C-2 of the sugar, in accord with the *trans* rule.[13] The comparison of the molecular rotations of the nucleosides with those of known α- and β-furanose glycosides further supports the assigned configuration.

(8) J. Davoll, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 967 (1948); B. R. Baker and R. E. Schaub, *J. Am. Chem. Soc.*, **77**, 5900 (1955).

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

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

(11) The authors are grateful to Dr. M. L. Wolfrom for providing a sample of this substance.

(12) J. R. Dyer, *Methods Biochem. Analy.*, **3**, 111 (1956).

(13) 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.

Experimental Section[14]

Melting points were obtained on a Kofler micro hot stage and correspond to corrected values. Optical rotations were determined in 100-mm. semimicro tubes using a Rudolph polarimeter, Model 70. Ultraviolet spectra were obtained in a Perkin-Elmer 202 spectrophotometer and the molar extinction coefficients (ε) were determined on a Gilford multiple sample recorder utilizing the optical system of a Beckman DU spectrophotometer. Infrared spectra were taken on a Perkin-Elmer Infracord spectrophotometer. Paper chromatograms of nucleosides were run in 5% aqueous disodium hydrogen phosphate (solvent A) without the organic phase[15] and in 1-butanol–acetic acid–water (4:1:5 v/v), organic phase (solvent B) by a descending technique on Whatman No. 1 paper. Spots were located with a Mineralight lamp which produced ultraviolet radiation at 254 mμ. The expression R_{ad} refers to the ratio of the distance the nucleoside migrated to the distance which adenine migrated. All yields of nucleosides reported are over-all yields from the acylaldofuranoses.

9-β-D-Gulofuranosyladenine (I).—1-O-Acetyl-2,3,5,6-tetra-O-benzoyl-D-gulofuranose[6] (4.5 g, 7.1 mmoles) was suspended in 125 ml of anhydrous ethyl ether at 0°. Dry hydrogen chloride was passed in until the ether was saturated. During this period the starting material completely dissolved. Acetyl chloride (5 ml) was added to keep the system dry and the flask was tightly sealed and stored at 3° for 6 days.[8] Evaporation of the solvent *in vacuo* (20°) followed by distillation from (3 × 25 ml) benzene (23°) to remove traces of acetic acid and hydrogen chloride left a clear syrup assumed to contain primarily tetra-O-benzoyl-D-gulofuranosyl chloride.

The halogenose was dissolved in 50 ml of dry xylene and added to an azeotropically dried mixture of 6-benzamidochloromercuripurine[9] (3.4 g, 7.1 mmoles), Celite-535 (3.4 g), cadmium carbonate (1 g), and 150 ml of dry xylene. The mixture was refluxed for 4 hr and filtered. Xylene was evaporated *in vacuo* (50°), and the residue was taken up in chloroform. The chloroform solution was washed with 30% potassium iodide solution and with water. After drying over magnesium sulfate, the solvent was removed by evaporation leaving a syrup (6.9 g) which was dissolved in 105 ml of absolute methanol containing 6 ml of 1 *N* methanolic sodium methoxide. The reaction mixture was heated under reflux for 2 hr to effect deacylation, neutralized with glacial acetic acid, and the solvent was removed by evaporation under reduced pressure. The residue obtained was partitioned between 75 ml each of water and chloroform. The chloroform layer was extracted twice with water, the aqueous extracts were combined, and the solution was filtered through a pad of Norit A and Celite-535. The solution was concentrated *in vacuo* (50°) to a small volume and a small amount of ethanol was added. Crystallization occurred, giving 150 mg (6% yield) of product, mp 223–226°. Recrystallization from water–ethanol gave 133 mg of fluffy white needles: mp 229–230°; $[\alpha]^{19}D$ −56.2° (*c* 2.03, 1 *N* HCl); R_{ad} 1.43 (solvent A), 0.42 (solvent B); ultraviolet and infrared spectra $\lambda_{max}^{H_2O}$ 259 mμ (ε 14,400), λ_{max}^{KBr} (μ) 2.85 (OH, NH), 6.05, 6.25, 6.7 (NH and purine ring), 9.1, 9.25–9.45, 9.7 (C–O–C, C–O–H).

Anal. Calcd for $C_{11}H_{15}N_5O_5$: C, 44.45; H, 5.09; N, 23.56. Found: C, 44.20; H, 5.19; N, 23.50.

9-β-L-Gulofuranosyladenine (II).—1-O-Acetyl-2,3,5,6-tetra-O-benzoyl-L-gulofuranose[6] (26.6 g 41.7 mmoles) was treated with 730 ml of saturated ethereal hydrogen chloride as described above. The syrup obtained was coupled with chloromercuri-6-benzamidopurine[9] (19.7 g, 41.7 mmoles). After removal of the blocking groups with methanolic sodium methoxide, a dark syrup was obtained which would not crystallize. A picrate derivative was prepared from boiling water; 10.6 g (48%) of the nucleoside picrate product was obtained. This compound sublimed between 190–220°, forming needles on the cover slip which decomposed between 220–280°. From the picrate, 9-β-L-gulofuranosyladenine was prepared as previously described.[10] A yield of 1.3 g (10%) was obtained. The product was dissolved in hot absolute ethanol to which enough water was added to cause solution. On cooling, the analytical sample was obtained: mp 230–231°; $[\alpha]^{22}D$ + 54.6° (*c* 2.05, 1 *N* HCl); R_{ad} 1.43 (sol-

(14) Elemental analyses were determined at the Spang Microanalytical Laboratory, Ann Arbor, Mich., or at the Midwest Microlab, Inc., Indianapolis, Ind.

(15) C. E. Carter, *J. Am. Chem. Soc.*, **72**, 1466 (1950).

vent A), 0.44 (solvent B); ultraviolet and infrared spectra $\lambda_{max}^{H_2O}$ 259 mμ (ε 14,500), λ_{max}^{KBr} (μ) 2.85 (OH, NH), 6.05, 6.25, 6.7 (NH and purine ring), 9.1, 9.7 (C–O–C, C–O–H).

Anal. Calcd for $C_{11}H_{15}N_5O_5$: C, 44.45; H, 5.09; N, 23.56. Found: C, 44.24; H, 5.34; N, 23.13.

9-β-D-Allopyranosyladenine (III).—2,3,5,6-Tetra-O-benzoyl-1-O-*p*-nitrobenzoyl-D-allofuranose[6] (21 g, 28.2 mmoles) was converted to the chloride in the manner described above except that methylene chloride was the solvent of choice. *p*-Nitrobenzoic acid was removed by filtration through a sintered glass funnel. The syrup obtained after evaporation of the solvent was condensed with 13.4 g (28.2 mmoles) of 6-benzamidochloromercuripurine.[9] After the work-up a syrup containing a white precipitate was obtained. Crystallization of this material from absolute methanol–chloroform yielded 8 g of the starting material 2,3,5,6-tetra-O-benzoyl-1-O-*p*-nitrobenzoyl-D-allofuranose. The mother liquor was concentrated to a syrup, the blocking groups were removed, and the nucleoside was purified *via* the picrate.[10] The picrate was crystallized from boiling water to yield 16.3 g (18%): mp 195–225° dec, $[\alpha]^{23}D$ −23.4° (*c* 2.77, dimethylformamide). The nucleoside was prepared from the picrate[10] to give an aqueous solution from which the water was removed by evaporation *in vacuo* (40°). A white residue was obtained which was crystallized from warm ethanol–water, 0.49 g (9.5% yield). Recrystallization from hot water gave 0.45 g of tiny needles which started decomposing at 241°. Progressive decomposition was observed as the temperature increased and melting occurred at 262–264°; $[\alpha]^{22}D$ −57.2° (*c* 3.67, 1 *N* HCl); R_{ad} 1.39 (solvent A), 0.57 (solvent B); ultraviolet and infrared spectra $\lambda_{max}^{H_2O}$ 259 mμ (ε 13,600), λ_{max}^{KBr} (μ) 2.8–3.0 (OH, NH), 6.05, 6.20, 6.75 (NH and purine ring), 9.0, 9.25, 9.65 (C–O–C, C–O–H).

Anal. Calcd for $C_{11}H_{15}N_5O_5$: C, 44.45; H, 5.09; N, 23.56. Found: C, 44.64; H, 5.26; N, 23.29.

9-α-D-Talofuranosyladenine (IV).—A syrup of 2,3,5,6-tetra-O-benzoyl-D-talofuranose[6] (5 g, 8.3 mmoles) was acetylated with acetic anhydride in pyridine. The syrupy product was converted to the chloride[8] and the latter was condensed with 6-benzamidochloromercuripurine[9] (3.94 g). 9-α-D-Talofuranosyladenine (0.56 g, 23% yield) crystallized from a concentrated aqueous solution after remaining in the refrigerator overnight. Recrystallization from water afforded beautiful clusters of large needles: mp 242.5–243.5°; $[\alpha]^{24}D$ +31.7° (*c* 3.44, 1 *N* HCl); R_{ad} 1.49 (solvent A), 0.63 (solvent B); ultraviolet and infrared spectra $\lambda_{max}^{H_2O}$ 257 mμ (ε 14,400), λ_{max}^{KBr} (μ) 2.85–3.0 (OH, NH), 6.05, 6.20, 6.8 (NH and purine ring), 8.95, 9.4 (C–O–C, C–O–H).

Anal. Calcd for $C_{11}H_{15}N_5O_5$: C, 44.45; H, 5.09; N, 23.56. Found: C, 44.29; H, 5.14; N, 23.52.

9-α-D-Altrofuranosyladenine (V).—2,3,5,6-Tetra-O-benzoyl-D-altrofuranose[6] (32.6 g, 54.7 mmoles), in the form of a syrup, was treated with 38 g of *p*-nitrobenzoyl chloride in pyridine. The syrupy pentaacyl derivative obtained was converted to the chloride[8] and the latter was coupled with 30 g of 6-benzamidochloromercuripurine.[9] The picrate was prepared after removal of the blocking groups. Recrystallization from boiling water gave 3.2 g (11%): mp 205–225° dec, $[\alpha]^{23}D$ +67.1° (*c* 3.28, dimethylformamide).

Anal. Calcd. for $C_{17}H_{18}N_8O_{12}$: C, 38.79; H, 3.45; N, 21.29. Found: C, 38.52; H, 3.44; N, 21.40.

9-α-D-Altrofuranosyladenine was regenerated from the picrate[10] and the white residue obtained after evaporation of the water was dissolved in ethanol–water and chilled. Crystals formed very slowly and 870 mg (5.3% yield) of the product was obtained. Recrystallization from ethanol–water gave 520 mg of pure white needles: mp 235.5–236°; $[\alpha]^{21}D$ + 69.1° (*c* 3.40, 1 *N* HCl); R_{ad} 1.39 (solvent A), 0.58 (solvent B); ultraviolet and infrared spectra $\lambda_{max}^{H_2O}$ 260 mμ (ε 14,500), λ_{max}^{KBr} (μ) 2.95 (OH, NH) 6.05, 6.25, 6.8 (NH and purine ring), 9.2, 9.4, 9.6 (C–O–C, C–O–H).

Anal. Calcd for $C_{11}H_{15}N_5O_5$: C, 44.45; H, 5.09; N, 23.56. Found: C, 44.66; H, 5.21; N, 23.69.

9-β-D-Galactofuranosyladenine (VI).—β-D-Galactofuranose pentaacetate[6] (2.0 g, 5.2 mmoles) was converted to the chloride[8] and the halogenose was coupled with 2.9 g of 6-benzamidochloromercuripurine.[9] The blocking groups were removed with methanolic sodium methoxide and the picrate was prepared[10] to afford 880 mg (32% yield), mp 204–206° dec, of product. The nucleoside was regenerated[10] and the water was removed by evaporation. The nucleoside crystallized from the syrup after standing at room temperature for 1 hr. The crystalline mass was triturated with cold 30% aqueous ethanol and filtered to give 0.33 g. (21%) of the product, mp 219–222°. Recrystallization from ethanol–water afforded the pure nucleoside, mp 226–227°. Admixture with an authentic sample[11] of 9-β-D-galactofuranosyladenine gave no depression of the melting point. The infrared and ultraviolet spectra and the mobility in solvent A (R_{ad} 1.52) of the two substances were identical.

2,3,5,6,7-Penta-O-benzoyl-D-*glycero*-D-*gulo*-heptono-γ-lactone (VIII).—D-*Glycero*-D-*gulo*-heptono-γ-lactone (10 g., 48.1 mmoles; Pfanstiehl Laboratories) was benzoylated according to the method of Levene and Meyer.[16] A thin syrup was obtained which was triturated twice with petroleum ether (bp 30–60°), chilled in the deep freeze, and the petroleum ether was decanted from the hardened syrup. After warming to room temperature the syrup was dissolved in hot absolute ethanol from which the product crystallized. Recrystallization from absolute ethanol–chloroform (8:2) gave 27.7 g. (79%) of very large needles. A sample recrystallized for analytical studies afforded tiny feathery needles: mp 152.5–153.5°; $[\alpha]^{21}D$ −38.9° (*c* 4.70, $CHCl_3$); infrared spectrum λ_{max}^{film} (μ) 5.55 (γ-lactone), 5.80 (benzoate carbonyl).

Anal. Calcd for $C_{42}H_{32}O_{12}$: C, 69.23; H, 4.43. Found: C, 69.02; H, 4.30.

2,3,5,6,7-Penta-O-benzoyl-D-*glycero*-D-*gulo*-heptofuranose (IX).—An amount of 23 g (31.5 mmoles) of VIII was dissolved in 40 ml of tetrahydrofuran and this solution was added dropwise to a solution of 126 mmoles of disiamylborane in 88 ml of tetrahydrofuran.[6,17] The reaction mixture was allowed to stand at room temperature under a nitrogen atmosphere for 16 hr, and 10 ml of water was slowly added. The borinic acid by-product was oxidized with 20 ml of hydrogen peroxide at 0° and pH 7–8, maintained with 3 *N* sodium hydroxide. The tetrahydrofuran was evaporated *in vacuo* (40°), the product was extracted with chloroform, and the chloroform solution was dried over magnesium sulfate. The solution was diluted to 500 ml with dry chloroform. Aliquots were removed for the determination of the yield by first deesterifying the product with methanolic sodium methoxide and then determining the amount of reducing sugar by the anthrone test, using a standard of D-*glycero*-D-*gulo*-heptofuranose (General Biochemicals, Chagrin Falls, Ohio). The yield according to this method was 72%. The product has not been crystallized.

2,3,5,6,7-Penta-O-benzoyl-1-O-*p*-nitrobenzoyl-D-*glycero*-D-*gulo*-heptofuranose (X).—A syrup containing IX (0.74 g) was dissolved in 20 ml of pyridine, cooled in an ice bath, and 550 mg of *p*-nitrobenzoyl chloride was added with swirling. The flask was stored at room temperature for 18 hr and then poured into a mixture of saturated sodium bicarbonate and ice. A gum formed which was dissolved in 25 ml of chloroform. The aqueous solution was extracted with two 25-ml portions of chloroform. The chloroform extracts were combined and washed twice with fresh saturated sodium bicarbonate followed by two washings with water. The solution was dried over magnesium sulfate and the chloroform was removed *in vacuo*. Toluene was added and removed three times. The syrup that remained was dissolved in methanol–chloroform and chilled in the refrigerator. The product, which gummed out, partially crystallized after 7 months. The gum was triturated with methanol–chloroform, some seed crystals were removed, and the flask was warmed gently to dissolve the gum. The warm solution was treated with Norit A and cooled. Seeds were added to effect crystallization. A yield of 153 mg of crude product was obtained. Recrystallization from methanol–chloroform gave 129 mg of a white product: mp 136–137.5°, $[\alpha]^{24}D$ −55.3° (*c* 3.80, $CHCl_3$).

Anal. Calcd for $C_{49}H_{37}NO_{15}$: C, 66.89; H, 4.24; N, 1.59. Found: C, 66.89; H, 4.35; N, 1.51.

9-β-D-*glycero*-D-*gulo*-heptofuranosyladenine (VII).—A syrup of IX (27.2 g) was acetylated with acetic anhydride in pyridine. The syrupy product was treated with saturated ethereal hydrogen chloride[8] and the halogenose was obtained as a light brown foam. This was condensed with 17.9 g of chloromercuri-6-benzamidopurine in the usual manner.[9] The blocking groups were removed in methanolic sodium methoxide and a dark syrup was obtained which was converted to a picrate derivative in the usual

(16) P. A. Levene and G. M. Meyer, *J. Biol. Chem.*, **76**, 513 (1928).

(17) Recently, disiamylborane obtained from Alfa Inorganics, Inc., Beverly, Mass., has been used to reduce several benzoylated γ-lactones, with satisfactory results. It appears that the tedium of preparing this reagent, as described in ref 6, can be eliminated by use of the commercial product.

manner.[10] The yield of picrate was 5.22 g (25%), which melted at 155.5–157.5°, resolidified, and then began to sublime at 175°. Needles which decomposed between 182 and 230° formed on the cover slip: $[\alpha]^{19}D$ −27.3 (*c* 3.11, dimethylformamide).

The nucleoside was regenerated from the picrate[10] and the product was crystallized from ethanol–water by chilling (1.65 g, 13.5% yield). The nucleoside was recrystallized to give 1.33 g of analytical material: mp 231.5–232.5°; $[\alpha]^{25}D$ −47.8° (*c* 3.66, 1 *N* HCl); R_{ad} 1.50 (solvent A), 0.37 (solvent B); ultraviolet and infrared spectra $\lambda_{max}^{H_2O}$ 260 mμ (ε 14,300), λ_{max}^{KBr} (μ) 2.9 (OH, NH), 6.2, 6.4, 6.8 (NH and purine ring), 9.15, 9.3, 9.5–9.6 (C–O–C, C–O–H).

Anal. Calcd for $C_{12}H_{17}N_5O_6$: C, 44.03; H, 5.25; N, 21.40. Found: C, 43.88; H, 5.27; N, 21.58.

Neighboring-Group Participation. The Preparation of Dithiopentose Sugars *via* a Thioacylonium Ion Intermediate[1]

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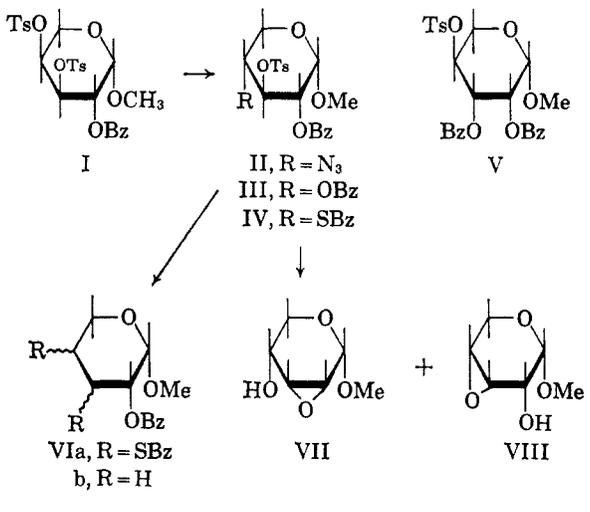
The reaction of methyl 2-O-benzoyl-3,4-di-O-(*p*-tolylsulfonyl)-β-L-arabinopyranoside (I) with sodium benzoate in N,N-dimethylformamide (DMF) selectively displaced the 4-tosylate of I to give methyl 2,4-di-O-benzoyl-3-O-(*p*-tolylsulfonyl)-α-D-xylopyranoside (III). Treatment of I with potassium thiolbenzoate in DMF resulted in the displacement of both tosylates to give methyl 2-O-benzoyl-3,4-di-S-benzoyl-3,4-dithio-β-L-lyxopyranoside (XIII) as indicated by nmr data. Presumably an intramolecular displacement of the tosylate group of methyl 2-O-benzoyl-4-S-benzoyl-4-thio-3-O-(*p*-tolylsulfonyl)-α-D-xylopyranoside (IV) by the 4-thiolbenzoate gave a thioacylonium ion (IX). Attack of this ion (IX) by a second thiolbenzoate ion gave, after a thionobenzoate → thiolbenzoate rearrangement, the observed product, XIII.

There has been considerable interest in recent years in the preparation of 4- and 5-substituted sugars in order to obtain sugar furanosides and pyranosides which contain a ring heteroatom other than oxygen. In our laboratories, the 4-substituted furanosides were of particular interest, since they could be incorporated into nucleosides which can be regarded as analogs of the components of the nucleic acids. Thus, the synthesis of 4′-thioadenosine[2] was described starting from L-lyxose.

In work designed to synthesize 4-amino-4-deoxy-D-ribosides, the precursors of nitrogen analogs of the naturally occurring nucleosides, methyl 2-O-benzoyl-3,4-di-O-(*p*-tolylsulfonyl)-β-L-arabinopyranoside (I) was prepared. It was observed that the 4-tosylate of I could be selectively displaced by sodium azide in DMF to give methyl 4-azido-2-O-benzoyl-4-deoxy-3-O-(*p*-tolylsulfonyl)-α-D-xylopyranoside[3] (II) (Scheme I). This was easily converted into methyl 4-acetamido-4-deoxy-D-ribopyranoside in four steps. That the selective displacement of the 4-tosylate of I could be effected by nucleophiles other than azide was demonstrated by the treatment of I with sodium benzoate in DMF. A 39% yield of crystalline methyl 2,4-di-O-benzoyl-3-O-(*p*-tolylsulfonyl)-α-D-xylopyranoside (III) was obtained. Treatment of III with methanolic sodium methoxide gave an epoxide which gave a satisfactory analysis but which could be resolved into two components on thin layer chromatography, indicating a mixture probably of methyl 2,3-anhydro-α-D-ribopyranoside (VII) and methyl 3,4-anhydro-α-D-ribopyranoside (VIII). On standing, one of the epoxides crystallized. Recrystallization gave an epoxide whose properties were in good agreement with those of methyl 2,3-anhydro-α-D-ribopyranoside as described by Vargha and Kuszmann.[4] If the displacement product had been the 4-tosyl lyxoside V rather than the 3-tosyl xyloside III, only one epoxide could have been formed, and that would be the 3,4-epoxide VIII. The formation of two epoxides, together with the positive identification of the 2,3-epoxide VII, requires the 3-tosyl xyloside III as the starting material.

SCHEME I



With the successful selective displacement of the 4-tosylate of I by both a nitrogen nucleophile and oxygen nucleophile, it was of interest to examine the behavior of I towards a sulfur nucleophile such as thiolbenzoate, since this would offer a more convenient route towards the synthesis of 4-thiopentose sugars. When the ditosylate I was treated with potassium thiolbenzoate in DMF at 100°, a crystalline product was obtained which proved to be a dithiolbenzoate (VIa) of unknown configuration rather than the expected methyl 2-O-benzoyl-4-S-benzoyl-4-thio-3-O-(*p*-tolylsulfonyl)-α-D-xylopyranoside (IV). If the reaction temperature was lowered, a mixture of dithiolbenzoate VI and starting material (I) was obtained. There was never any detectable amount of the monothiolbenzoate IV.

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(3) E. J. Reist, D. E. Gueffroy, and L. Goodman, *ibid.*, **87**, 677 (1965).

(4) L. Vargha and J. Kuszmann, *Chem. Ber.*, **96**, 411 (1963).