Acyclic Sugar Nucleoside Analogs. III[1,2]

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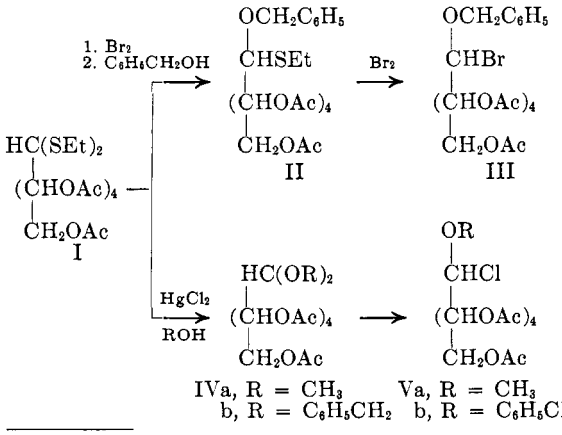
Penta-*O*-acetyl-D-galactose diethyl dithioacetal (I) has been converted into the acyclic nucleoside analogs, 1-(9-adenyl)-1-*O*-benzyl-1-deoxy-D-galactose aldehydrol (XI) and 1-deoxy-1-*O*-methyl-1-(1-thyminyl)-D-galactose aldehydrol (X). Compound I was treated with bromine to give the 1-bromo-1-*S*-ethyl derivative which was treated with benzyl alcohol containing silver carbonate to form the 1-*O*-benzyl-1-*S*-ethyl derivative. Displacement of the ethylthio group with bromine, followed by coupling of the resultant 1-bromo compound with 6-benzamido-9-chloromercuripurine (VIa), gave the acetylated derivative which was deacylated (through the picrate) to give 1-(9-adenyl)-1-*O*-benzyl-1-deoxy-D-galactose aldehydrol (XI). I was also converted into the dibenzyl acetal derivative (IVb) by treatment with mercuric chloride and cadmium carbonate in benzyl alcohol. The dibenzyl acetal was transformed into the 1-*O*-benzyl-1-chloro derivative (Vb) with acetyl chloride. Vb gave XI on coupling with 6-acetamido-9-chloromercuripurine (VIb) followed by deacetylation. The known 1-chloro-1-*O*-methyl derivative Va was treated with dithyminylmercury to give, after deacetylation, 1-deoxy-1-*O*-methyl-1-(1-thyminyl)-D-galactose aldehydrol (X). Attempts to convert the carbohydrate moiety of XI into the cyclic (furanosyl or pyranosyl) form by catalytic hydrogenolysis were unsuccessful.

This laboratory has long been interested in acyclic derivatives of the sugars. In previous communications[1,3] we have described acyclic sugar nucleoside analogs which could be considered as derived from the aldehydrol (hydrate) form of *aldehydo*-D-galactose (and D-glucose) pentaacetate. Similar derivatives of 2-amino-2-deoxy-D-glucose have been reported.[4] It was desirable to prepare an acyclic nucleoside analog containing a benzyloxy group attached to the aldehydrol carbon wherein cleavage of the 1-*O*-benzyl group by hydrogenolysis might yield a nucleoside with the sugar moiety in the cyclic (furanosyl or pyranosyl) form. Such an acyclic nucleoside analog (XI) was prepared from penta-*O*-acetyl-D-galactose diethyl dithioacetal (I) by two routes. In the one case the acetylated dithioacetal I was converted into penta-*O*-acetyl-D-galactose *O*-benzyl *S*-ethyl monothioacetal (II) by reaction with bromine in ether[5] followed by treatment of the bromo derivative thus formed with silver carbonate in benzyl alcohol. The acetylated II was then treated again with bromine in ether to give penta-*O*-acetyl-1-*O*-benzyl-1-bromo-1-deoxy-D-galactose aldehydrol (III) which was condensed with 6-benzamido-9-chloromercuripurine (VIa)[6] to give crude penta-*O*-acetyl-1-[9-(6-benzamidopurinyl)]-1-*O*-benzyl-1-deoxy-D-galactose aldehydrol which was not characterized but was *N*-debenzoylated by picrate formation and removal of the picrate anion with an ion-exchange resin. Complete deacetylation of this material was then effected with *n*-butylamine to give the crystalline 1-(9-adenyl)-1-*O*-benzyl-1-deoxy-D-galactose aldehydrol (XI).



In the second case I was converted to the fully acetylated dibenzyl acetal (IVb) by treatment with mercuric chloride in benzyl alcohol containing cadmium carbonate[7]; IVb was obtained in crystalline form after deacetylation with methanolic sodium methoxide and reacetylation with pyridine in acetic anhydride. Crystalline IVb was then converted with acetyl chloride, in the presence of boron trifluoride–etherate, into the 1-*O*-benzyl-1-chloro intermediate which was condensed with 6-acetamido-9-chloromercuripurine (VIb)[8] to give 1-[9-(6-acetamidopurinyl)]-penta-*O*-acetyl-1-*O*-benzyl-1-deoxy-D-galactose aldehydrol (VIIb) as a glass. The glass was then deacetylated with methanolic sodium methoxide and the resulting material was purified through the picrate to give crystalline 1-(9-adenyl)-1-*O*-benzyl-1-deoxy-D-galactose aldehydrol (XI). Both procedures might be expected to produce two anomeric nucleosides since reaction occurred at the optically active C-1 site but only one form was isolated. Thin layer chromatography indicated the possible presence of another form in very minor amounts.

When hydrogenolysis of the 1-*O*-benzyl group of XI was effected with a palladium catalyst under mild conditions, only starting material could be recovered. Under more stringent conditions, paper chromatography of the reaction products showed the presence of D-galactose and adenine and a spot corresponding to galactitol. Conditions were not found under which cleavage of the benzyl group took place without cleavage of the adenine moiety.

We include herein the first acyclic sugar pyrimidine nucleoside analog, 1-deoxy-1-*O*-methyl-1-(1-thyminyl)-D-galactose aldehydrol (X). Penta-*O*-acetyl-1-chloro-

(1) Previous communication in this series: M. L. Wolfrom, P. McWain, and A. Thompson, *J. Org. Chem.*, **27**, 3549 (1962).

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

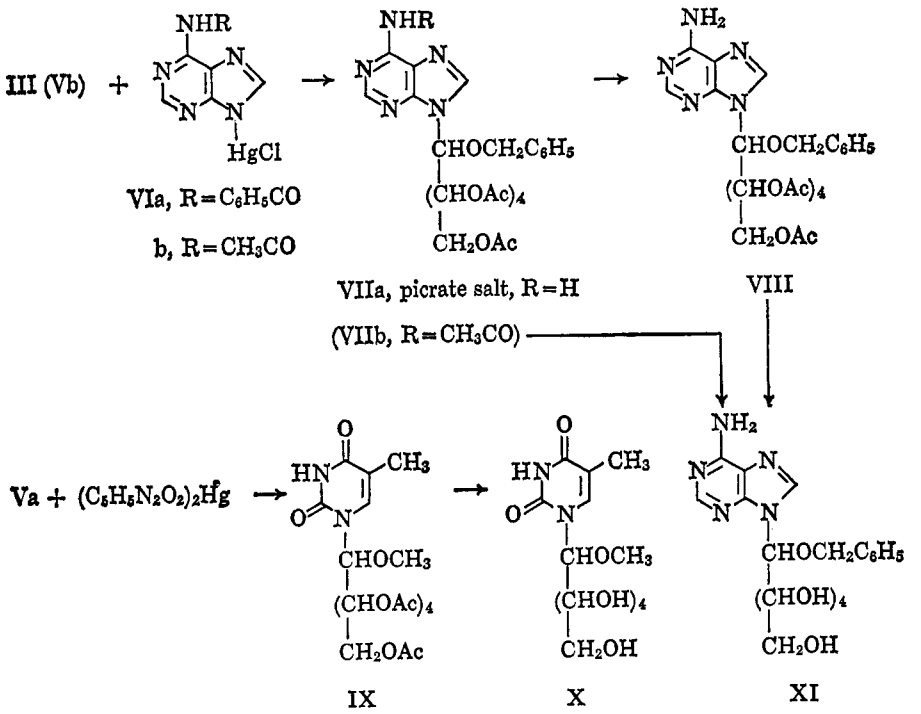
(4) M. L. Wolfrom, H. G. Garg, and D. Horton, *ibid.*, **29**, 3280 (1964); **30**, 1096 (1965).

(5) F. Weygand, H. Ziemann, and H. J. Bestmann, *Ber.*, **91**, 2534 (1958).

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

(7) M. L. Wolfrom, L. J. Tanghe, R. W. George, and S. W. W aisbrot, *ibid.*, **60**, 132 (1938).

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



1-deoxy-1-*O*-methyl-D-galactose aldehydrol (Va) had been prepared previously[9] and was condensed with dithyminyl mercury[10] to give sirupy penta-*O*-acetyl-1-deoxy-1-*O*-methyl-1-(1-thyminyl)-D-galactose aldehydrol (IX). Crude IX was then deacetylated in boiling methanolic *n*-butylamine to give X in crystalline form.

Experimental

Penta-*O*-acetyl-1-*O*-benzyl-1-deoxy-1-ethylthio-D-galactose Aldehydrol (II).—Penta-*O*-acetyl-1-bromo-1,1-dideoxy-1-ethylthio-D-galactose aldehydrol was prepared from penta-*O*-acetyl-D-galactose diethyl dithioacetal[11] (I) by the method of Weygand and co-workers.[5] This bromide (23.5 g.) was dissolved in 200 ml. of dry benzyl alcohol. Silver carbonate (31.0 g.) was added, and the mixture was stirred for 24 hr. in the absence of light. The salts were then removed by filtration, the filter cake was washed with hot ethanol, and the washings and filtrate were combined and taken to dryness under diminished pressure. The residue was extracted with excess hot ethanol, filtered, and placed in the refrigerator. The long needles which deposited were filtered and recrystallized from ethanol: yield 16.8 g. (68%); m.p. 117–18°, $[\alpha]^{21}D$ −8.0° (*c* 6, chloroform); absorption spectra data,[12] λ_{max}^{KBr} 3.32–3.50 (CH, aromatic), 5.72 (acetate carbonyl), 6.23, 6.69 (phenyl), 9.17–9.77 (C–O–C), 12.93, 13.20, 14.19 μ (aromatic); X-ray powder diffraction data,[13] 11.63 m, 9.94 s (1), 7.50 vw, 7.08 vw, 6.15 s (2), 5.90 m, 5.34 s(3), 4.90 m, 4.35 m (broad), 3.97 m, 3.71 m, 3.58 w, 3.36 w,

Anal. Calcd. for $C_{25}H_{32}O_{11}S$: C, 55.34; H, 6.23; S, 5.92. Found: C, 55.20; H, 6.50; S, 5.95.

D-Galactose Dibenzyl Acetal.—Penta-*O*-acetyl-D-galactose diethyl dithioacetal[11] (I, 15 g.) in 80 ml. of dry benzyl alcohol containing 60 g. of cadmium carbonate was heated to 80° with stirring. A solution of 60 g. of mercuric chloride in 150 ml. of hot (80°) benzyl alcohol was added to the stirred solution in one portion. The temperature and stirring were maintained for 4.5 hr. The mixture was then cooled to room temperature, filtered, and washed with 30% aqueous potassium iodide solution and then with water. Solvent removal from the dried (magnesium sulfate) benzyl alcohol solution by distillation under diminished pressure (1–3 mm.) led to a sirup which failed to crystallize. This sirup was deacetylated in ethanolic sodium methoxide. D-Galactose dibenzyl acetal crystallized from the deacetylation mixture within 24 hr. Pure material was obtained by two recrystallizations from ethanol: yield 7 g. (66%); m.p. 157–159°; $[\alpha]^{22}D$ +18.0° (*c* 2.4, *N*,*N*-dimethylformamide); absorption spectra data,[12] λ_{max}^{KBr} 2.82, 2.98–3.18 (O–H), 3.41 (CH), 6.23, 6.70 (phenyl), 8.9–9.8 (C–O–C, C–O–H), 13.59, 14.27 μ (monosubstituted phenyl); X-ray powder diffraction data,[13] 9.21 w, 7.03 vw, 6.46 m, 5.47 vw, 5.01 m (1), 4.85 w, 4.58 m, 4.37 m (2), 4.02 m (3), 3.87 m, 3.44 m.

Anal. Calcd. for $C_{20}H_{26}O_7$: C, 63.47; H, 6.93. Found: C, 63.58; H, 6.23.

Penta-*O*-acetyl-D-galactose Dibenzyl Acetal (IVb).—D-Galactose dibenzyl acetal (6 g.) in 50 ml. of dry pyridine containing 12 g. of acetic anhydride was maintained at room temperature for 24 hr. The mixture was then poured into 500 ml. of iced water. The water was decanted from the sirup which formed and fresh water was added to wash the sirup. The water was again decanted. The sirup crystallized on scratching the glass container. Pure material was obtained on recrystallization from methanol–water: yield 7 g. (64%); m.p. 79–81°; $[\alpha]^{20}D$ +9° (*c* 3.4, chloroform); absorption spectra data,[12] λ_{max}^{KBr} 3.45 (CH), 5.74 (acetate carbonyl), 6.23, 6.70 (phenyl), 9.4–9.8 (C–O–C), 13.4–13.6 μ (monosubstituted phenyl); X-ray powder diffraction data,[13] 14.26 s, 11.33 m, 8.19 vw, 7.03 vs (1), 6.11 m, 5.72 vw, 5.04 s (2), 4.82 m, 4.53 s (3), 4.23 m.

Anal. Calcd. for $C_{30}H_{36}O_{12}$: C, 61.23; H, 6.17. Found: C, 61.58; H, 6.13.

Penta-*O*-acetyl-1-*O*-benzyl-1-bromo-1-deoxy-D-galactose Aldehydrol (III).—Five grams of II was dissolved with stirring in 50 ml. of dry ether. To this stirred solution was added dropwise a solution of 1.5 g. of bromine in 20 ml. of dry ether. After the addition had proceeded for 15–20 min., a white precipitate appeared in the mixture. After completion of the bromine addition, the stirring was continued for 45 min. Excess bromine was removed by the addition of cyclohexene and, after the addition of petroleum ether (b.p. 65–100°), the solution was placed at 5° for crystallization: yield 4.9 g. (94%); m.p. 112–13; $[\alpha]^{21}D$ +73.6° (*c* 1.53, chloroform). This product was unstable and decomposed readily on exposure to air.

Anal. Calcd. for $C_{23}H_{29}BrO_{11}$: C, 49.20; H, 5.20; Br, 14.23. Found: C, 49.43; H, 5.26; Br, 14.82.

(9) M. L. Wolfrom and D. I. Weisblat, *J. Am. Chem. Soc.*, **62**, 878 (1940).

(10) J. J. Fox, N. Yung, J. Davoll, and G. B. Brown, *ibid.*, **78**, 2117 (1956).

(11) M. L. Wolfrom, *ibid.*, **52**, 2464 (1930).

(12) All infrared spectral data were obtained on a Perkin-Elmer Model 137B Infracord spectrophotometer, Perkin Elmer Corp., Norwalk, Conn. Structural assignments were based on analogous assignments by K. Nakanishi, "Infrared Absorption Spectroscopy, Practical," Holden-Day, Inc., San Francisco, Calif., 1963. The ultraviolet absorption analyses were made on a Cary recording spectrophotometer, Model 15, Applied Physics Corp., Pasadena, Calif.

(13) Interplanar spacing, Å., Cu Kα radiation. Relative intensity, estimated visually: s, strong; m, medium; w, weak; v, very; three strongest lines numbered (1, strongest).

Penta-*O*-acetyl-1-*O*-benzyl-1-chloro-1-deoxy-D-galactose Aldehydrol (Vb).—Penta-*O*-acetyl-D-galactose dibenzyl acetal (IVb, 1.5 g.) was dissolved in 2 ml. of freshly distilled acetyl chloride and 5 drops of boron trifluoride–etherate was added. The solution was placed in the refrigerator. After 2 hr. another 5 drops of boron trifluoride–etherate was added and the solution was allowed to stand at 5° overnight. The initial crystallization was aided by the addition of 20 ml. of a ether–petroleum ether (b.p. 30–60°) mixture (1:1). Recrystallization was effected from chloroform–ether; yield 0.5 g., m.p. 115–118°. The compound crystallized with 0.5 mole of ether and attempts to remove the ether caused extensive decomposition. The substance was unstable and an accurate optical polarization was not obtainable.

Anal. Calcd. for $2C_{23}H_{29}ClO_{11}\cdot C_4H_{10}O$: C, 54.23; H, 6.19; Cl, 6.40. Found: C, 54.39; H, 6.09; Cl, 6.40.

Penta-*O*-acetyl-1-(9-adenyl picrate)-1-*O*-benzyl-1-deoxy-D-galactose Aldehydrol (VIIa).—A mixture of 2.0 g. of Celite,[14] 1.7 g. of cadmium carbonate, and 5. 3 g. of 6-benzamido-9-chloromercuripurine[6] in 400 ml. of toluene was dried by azeotropic distillation. The solution was cooled to 60–70° and a solution of 4.8 g. of III in azeotropically dried toluene was then added. The mixture was refluxed with stirring for 4 hr. The hot solution was filtered and the filter cake extracted with hot chloroform (300 ml.). The filtrate and chloroform extracts were combined and concentrated to a glass under diminished pressure. The residual glass was extracted with 300 ml. of warm chloroform and the extract was filtered. The filtrate was washed with a 30% aqueous potassium iodide solution and water and dried (magnesium sulfate). The dried solution was concentrated to a glass under diminished pressure and the glass was dissolved in 75 ml. of methanol. Thin layer chromatography[15] of this solution showed two spots under ultraviolet light: a large spot at R_f 0.24 and a minor one at R_f 0.55. The material in the minor spot could not be obtained in pure form.

To the above methanol solution was added 14 ml. of a 10% methanolic picric acid solution, and the mixture was refluxed for 1 hr. A yellow solid precipitated from the hot solution. The solution was kept at 5° to complete precipitation and the yellow picrate was removed by filtration: yield 3.5 g. (52% based on III); m.p. 174–175° (from methanol); $[\alpha]^{20}D$ −40° (*c* 3.4, chloroform); X-ray powder diffraction data,[13] 10.28 w, 8.67 m (1), 7.63 m, (3), 6.19 m, 5.61 w, 5.16 w, 4.62 w, 4.31 m, 3.97 m, 3.69 m (2), 3.15 m.

Anal. Calcd. for $C_{34}H_{36}N_8O_{18}$: C, 46.00; H, 4.18; N, 13.25. Found: C, 46.26; H, 4.43; N, 13.11.

Penta-*O*-acetyl-1-(9-adenyl)-1-*O*-benzyl-1-deoxy-D-galactose Aldehydrol (VIII).—The above picrate (3.5 g.) was dissolved, with stirring, in aqueous acetone and sufficient Dowex-1 (CO_3^{2-} form)[16] was added to attain a colorless solution. The resin was then removed by filtration, and the filtrate was allowed to concentrate by evaporation at room temperature until crystals appeared. The mixture was kept at 5° to complete crystallization: yield 1.4 g. (54.9%); m.p. 225–226°; $[\alpha]^{21}D$ −7.4° (*c* 2.6, chloroform); absorption spectra data,[12] $\lambda_{max}^{H_2O}$ 259 mμ, λ_{max}^{KBr} 3.01, 3.16 (OH, NH), 3.41 (CH), 5.69 (ester carbonyl), 5.97, 6.10 (purine), 6.23 (phenyl), 9.16–9.30, 9.58 (C–O–C, C–O–H), 13.19, 14.27 μ (aromatic); X-ray powder diffraction data,[13] 14.49 m. 9.72 vw, 7.08 s (1), 6.42 w, 5.75 w, 5.04 m (2), 4.72 m (3), 4.48 w, 3.87 w, 3.48 w, 3.27 w, 2.98 w.

Anal. Calcd. for $C_{25}H_{33}N_5O_6$: C, 54.63; H, 5.43; N, 11.37. Found: C, 54.46; H, 5.53; N, 11.65.

1-(9-Adenyl)-1-*O*-benzyl-1-deoxy-D-galactose Aldehydrol (XI).—An amount of 1.4 g. of VIII was dissolved in a solution of 1:1 methanol–tetrahydrofuran and 1 ml. of *n*-butylamine was added. The solution was refluxed for 6 hr. It was then concentrated under diminished pressure to near one-half volume and placed in the refrigerator to effect crystallization: yield 0.71 g. (54.6%). Thin layer chromatography[17] of the product before recrystallization revealed two components, R_f 0.57 (minor) and 0.63. The minor component, which was absent after three recrystallizations from methanol–water, could not be obtained in sufficient amount for characterization.

After three recrystallizations from methanol–water, XI moved as a single spot on thin layer chromatography[17]: m.p. 212.5–213.5°; $[\alpha]^{21}D$ −13° (*c* 2.1, dimethyl sulfoxide); absorption spectra data,[12] $\lambda_{max}^{H_2O}$ 261 mμ, λ_{max}^{KBr} 2.92–3.17 (OH, NH), 3.42 (CH) 6.09, 6.23, 6.35, 6.72 (purine, phenyl), 9.22–9.66 (C–O–C, C–O–H), 13.29–13.40, 13.71 (aromatic); X-ray powder diffraction data,[13] 11.19 m, 8.59 m, 6.19 w, 5.61 vs (1), 4.67 vs (3), 4.42 m, 4.21 m, 4.06 m, 3.65 vs (2), 3.45 vw, 3.36 s, 3.21 m, 2.97 m, 2.89 vw, 2.81 m.

Anal. Calcd. for $C_{18}H_{23}N_5O_6$: C, 53.31; H, 5.72; N, 17.27. Found: C, 53.52; H, 5.92; N, 17.37.

Substance XI was first obtained by another route starting from Vb. A mixture of 10 g. of 6-acetamido-9-chloromercuripurine (VIb),[8] 20 g. of cadmium carbonate, and 300 ml. of toluene was dried by azeotropic distillation. To the dried mixture Vb, freshly prepared from 15 g. of penta-*O*-acetyl-D-galactose dibenzyl acetal (IVb), was added. The mixture was refluxed with efficient stirring for 4 hr. The hot solution was filtered through a bed of Celite,[14] the filter cake was extracted with chloroform, and the filtrate and extracts were combined and evaporated to dryness under diminished pressure. The residue was extracted with 500 ml. of chloroform, filtered, washed with 30% aqueous potassium iodide solution and water, and then dried (magnesium sulfate). The dried solution was concentrated to a glass under reduced pressure, and the residue was dissolved in 250 ml. of boiling methanol. Enough sodium methoxide was added to maintain alkalinity and the mixture was refluxed for 45 min. The hot solution was filtered, and the filtrate was concentrated to dryness under reduced pressure. The glassy residue was extracted with three 150-ml. portions of hot water and filtered, and the filtrate was concentrated to 60 ml. under diminished pressure. After standing at 0°, the solution deposited a small amount of microcrystalline material which was removed by filtration. Methanolic picric acid (60 ml. of a 10% solution) was added, and the mixture was allowed to stand at room temperature for 48 hr. A yellow picrate deposited and was removed by filtration: total yield 10 g. After recrystallization from methanol, with considerable loss, the picrate melted at 135°, resolidified, and melted again with decomposition above 220°. Removal of the picrate anion in the manner described above resulted in a yield of 1.2 g. of compound XI that was identical in all respects with the previously prepared compound XI.

Hydrogenolysis of 1-(9-Adenyl)-1-*O*-benzyl-1-deoxy-D-galactose Aldehydrol (XI).—An amount of 45 mg. of XI was dissolved in 40 ml. of methanol and 10 mg. of 10% palladium-on-charcoal catalyst was added. The suspension was shaken in a Parr hydrogenation apparatus under 42 p.s.i. of hydrogen for 24 hr. The suspension was filtered and the filtrate was chromatographed on paper.[18] By comparison with authentic samples, adenine, D-galactose, and galactitol were found in the filtrate. No spots were found corresponding to the desired 9-β-D-galactofuranosyladenine[19] or 9-β-D-galactopyranosyladenine.[3] When the same hydrogenolysis conditions were used with shorter reaction times (2–4 hr.), only unreacted starting material could be detected. Use of water as solvent or 5% palladium-on-charcoal catalyst with various pressures (20–48 p.s.i.) of hydrogen produced no detectable changes in the kinds of products obtained.

1-Deoxy-1-*O*-methyl-1-(1-thyminyl)-D-galactose Aldehydrol (X).—A mixture of 5.6 g. of dithyminylmercury,[10] 6.0 g. of cadmium carbonate, 4.0 g. of Celite,[14] and 400 ml. of xylene was azeotropically dried by distillation of 150 ml. of the xylene. The cooled suspension was treated with 8 g. of Va[9] and refluxed for 4 hr. with stirring. The mixture was filtered hot, the filtrate was evaporated to a sirup, and the hot chloroform soluble material

(14) A silicious filter aid, Johns-Manville Co., New York, N. Y.

(15) Thin layer plates (50 × 200 mm.) of silica gel G (0.25 mm.) (E. Merck, Darmstadt, Germany) utilizing a solution of benzene–ethyl acetate–methanol (9.0:0.5:0.5 v./v.) as developer. Indication of spots was by ultraviolet light and concentrated sulfuric acid spray.

(16) An anion-exchange resin produced by the Dow Chemical Co., Midland, Mich.

(17) Chromatography was on Avicel (technical grade) (microcrystalline cellulose produced by the FMC Corp., American Viscose Division, Marcus Hook, Pa.) plates (0.25 mm. thick, 50 × 200 mm.) following the procedure of M. L. Wolfrom, D. L. Patin, and R. M. de Lederkremer [*Chem. Ind.* (London), 1065 (1964); *J. Chromatog.*, **17**, 488 (1965)]. The developer was a solution of 1-butanol–ethanol–water (40:11:19). Location of spots was by ultraviolet light and with a spray of a solution consisting of 1 part of a solution of 1% potassium permanganate in 2% sodium carbonate and 4 parts of a solution of 2% sodium periodate.

(18) Descending chromatography on Whatman No. 1 paper with 1-butanol–ethanol–water (40:11:19 v./v.) with indication by ultraviolet light and by sodium metaperiodate and ammoniacal silver nitrate sprays according to L. Hough and J. K. N. Jones ("Methods in Carbohydrate Chemistry," Vol. I, R. L. Whistler and M. L. Wolfrom, Ed., Academic Press Inc., New York, N. Y., 1963, p. 28).

(19) M. L. Wolfrom, P. McWain, R. Pagnucco, and A. Thompson, *J. Org. Chem.*, **29**, 454 (1964).

was extracted from the sirup and the filter cake. The combined chloroform extracts were washed with 30% potassium iodide solution and water and then dried (sodium sulfate). Evaporation under reduced pressure gave a sirup (IX) which failed to crystallize: yield 4.2 g. The sirupy product (4.0 g.) was dissolved in 60 ml. of absolute methanol containing 5 ml. of *n*-butylamine. The mixture was refluxed for 4 hr., then evaporated to an oil. The oil was distributed between chloroform and water, and the water layer was washed with chloroform. The aqueous extract was decolorized (carbon) and evaporated to a sirup: yield 3.77 g. Crystallization from methanol followed by recrystallization from aqueous methanol gave analytically pure X: m.p. 201–204°; $[\alpha]^{24}D$ +77° (*c* 0.51, water); absorption spectra data,[12] $\lambda_{max}^{H_2O}$ 269 mμ, λ_{max}^{KBr} 2.90 (OH), 5.80 (CO), 6.80 (C=N), 7.30 (methyl hydrogen), 9.15, 9.55, 9.70 (C–OH); X-ray powder diffraction data,[13] 13.10 vs (1,1,1), 9.46 w, 8.42 vs (1,1,1), 6.35 m, 5.99 m, 5.25 m, 5.00 s, 4.66 m, 4.40 s, 4.17 s, 3.68 vs (1,1,1), 3.52 w, 3.31 m, 3.21 m, 3.11 vw, 2.95 w.

Anal. Calcd. for $C_{12}H_{20}N_2O_8$: C, 45.13; H, 6.00; N, 8.78; OCH_3, 9.72. Found: C, 44.89; H, 6.73; N, 8.72; OCH_3, 9.49.

Nucleosides. XXVII. 3′-Amino-3′-deoxyhexopyranosyl Nucleosides. II. Synthesis of 1-(3′-Amino-3′-deoxy-β-D-glucopyranosyl)pyrimidines and Related Compounds[1,2]

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A simple synthesis of the 3′-nitro-3′-deoxy derivative IV of 1-β-D-glucopyranosyluracil was achieved by treatment of uridine with metaperiodate followed by condensation with nitromethane. Reduction of IV yielded the 3′-amino analog V whose structure was rigidly proved by chemical and n.m.r. studies. The 3′-aminogluco nucleoside V was converted to 1-β-D-allopyranosyluracil (XIII) and to 1-(3′-amino-3′-deoxy-β-D-glucopyranosyl)-cytosine (XVII). Degradative studies with V, proceeding *via* a 5,6-dihydro nucleoside VII, yielded anomers of the known methyl-3-acetamido-3-deoxy-2,4,6-tri-*O*-acetyl-D-glucosides.

The past decade has witnessed the discovery of several 3-amino-3-deoxy sugars as antibiotics.[3] Nucleosides containing 3-amino-3-deoxy-D-ribose have also been found in nature,[4–6] some of which have since been synthesized chemically,[7] and have exhibited interesting biological properties.[8]

Nucleosides containing the 3-amino-3-deoxy*hexose* moiety have not as yet been isolated from natural sources.[9–11] The only recorded chemical synthesis of nucleosides containing a 3-aminohexosyl moiety is that reported by Baker, *et al.*,[12] who condensed suitably protected 3-aminohexoses (of the allosyl and altrosyl configuration) with the mercuri salts of certain purine derivatives.

This paper deals with a facile synthesis and a study of the chemical properties of 3′-amino-3′-deoxyhexosylpyrimidines which should have wide application in the nucleoside area. Preliminary communications on this subject have appeared.[2,13]

Baer and Fischer[14] showed that dialdehydes derived from aldopento- and aldohexopyranosides could be condensed with nitromethane to yield 3-nitro-3-deoxypyranosides, which, upon reduction, yielded glycosides of 3-amino sugars. Their procedure was adapted to 1-β-D-ribofuranosyluracil (uridine)[15] (see Scheme I).

Uridine (I) was oxidized with sodium metaperiodate to the dialdehyde II which was condensed with nitromethane in ethanol in the presence of sodium methoxide to yield the insoluble sodium salt of the *aci*-nitro nucleoside III. Neutralization of III was achieved under anhydrous conditions (to prevent the Nef reaction)[16,17] and gave a mixture of several isomers.[18] Neutralization under aqueous conditions, however, proceeded smoothly and a crystalline product (IV) was easily obtained in *ca.* 60% over-all yield from I. Hydrogenation of IV with Raney nickel under pressure[19] yielded the nucleoside V. The ultraviolet absorption spectrum of V resembled that of a 1-glycopyranosyluracil.[20] Compound V consumed 2 moles of periodate per mole, consistent with a hexopyranosyl structure and gave a positive ninhydrin test. The strong infrared absorption at ~6.4 μ[21] found in IV (due to the nitro group) was totally absent in V. The elemental

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(2) Paper I: K. A. Watanabe and Jack J. Fox, *Chem. Pharm. Bull.* (Tokyo), **12**, 975 (1964); Abstracts, 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1964, p. 5D.

(3) For review articles, see A. B. Foster and D. Horton, *Adv. Carbohydrate Chem.*, **14**, 432 (1959); J. D. Dutcher, *ibid.*, **18**, 259 (1963).

(4) C. W. Waller, P. W. Fryth, B. L. Hutchings, and J. H. Williams, *J. Am. Chem. Soc.*, **75**, 2025 (1953).

(5) N. N. Gerber and H. A. Lechevalier, *J. Org. Chem.*, **27**, 1731 (1962).

(6) N. M. Kredich and A. J. Guarino, *J. Biol. Chem.*, **236**, 3300 (1961).

(7) See (a) B. R. Baker, R. E. Schaub, J. P. Joseph, and J. H. Williams, *J. Am. Chem. Soc.*, **77**, 12 (1955), for the synthesis of puromycin; (b) B. R. Baker, R. E. Schaub, and H. M. Kissman, *ibid.*, **77**, 5911 (1955), for the synthesis of 3′-amino-3′-deoxyadenosine.

(8) See (a) M. A. Darken, *Pharmacol. Rev.*, **16**, 223 (1964), for puromycin; (b) ref. 5, for 3′-amino-3′-deoxyadenosine; (c) A. J. Guarino, M. L. Ibershof, and R. Swain, *Biochim. Biophys. Acta*, **72**, 62 (1963), for homocitrullylaminoadenosine.

(9) Gougerotin, an antibiotic from *Streptomyces gougerottii*, was originally reported to have a 3-amino-3-deoxyallose structure in the molecule.[10] This was corrected to the 4-amino-4-deoxygalactose structure.[11]

(10) H. Iwasaki, *Yakugaku Zasshi*, **82**, 1387, 1393 (1962).

(11) J. J. Fox, Y. Kuwada, K. A. Watanabe, T. Ueda, and E. B. Whipple, *Antimicrobial Agents Chemotherapy*, in press.

(12) B. R. Baker, J. P. Joseph, and R. E. Schaub, U. S. Patent 2,852,505 (Sept. 16, 1958); *Chem. Abstr.*, **53**, 8175*d* (1959).

(13) A brief communication by F. W. Lichtenthaler, H. P. Albrecht, and G. Olfermann [*Angew. Chem.*, **77**, 131 (1965)] has very recently appeared which also deals with the application of the nitromethane procedure to nucleosides. These authors were regretfully unaware of our previous paper[2] in this series (personal communication from Dr. F. W. Lichtenthaler).

(14) H. H. Baer and H. O. L. Fischer, *J. Am. Chem. Soc.*, **81**, 5184 (1959).

(15) Adaptation of this procedure to purine nucleosides will be reported in another paper in this series: *J. Heterocylic Chem.*, in press

(16) N. Kornblum and G. E. Graham, *J. Am. Chem. Soc.*, **73**, 4041 (1953).

(17) H. H. Baer and H. O. L. Fischer, *ibid.*, **81**, 5184 (1959).

(18) K. A. Watanabe, H. A. Friedman, J. Beránek, and J. J. Fox, unpublished experiments.

(19) A. C. Richardson and K. A. McLauchlan, *J. Chem. Soc.*, 2499 (1962).

(20) J. J. Fox and D. Shugar, *Biochim. Biophys. Acta*, **9**, 369 (1952).

(21) T. Urbanski, *Bull. soc. chim. France*, 1475 (1961).