Anal. Calcd for $C_{12}H_{16}N_4O_8 \cdot 2H_2O$: C, 41.38; H, 5.79; N, 16.09. Found: C, 41.88; H, 5.47; N, 16.27.

The water of crystallization was lost on drying at 100° on P_4O_{10} under reduced pressure for 3 hr.

A mixture melting point with an authentic sample[6] of 7-β-D-xylopyranosyltheophylline showed no depression, and the infrared spectrum was identical with that of the authentic sample.

7-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-glucopyranosyl)theophylline.—2,3,4,6-Tetra-*O*-acetyl-D-glucopyranose (10 g), theophylline (5.7 g), and P_4O_{10} (10 g) were dissolved in 300 ml of DMF as described above. The mixture was allowed to stand at 60–70° under vigorous stirring for 20 hr. The reaction product was repeatedly extracted with chloroform and the combined extracts were concentrated to a syrup. This was crystallized from hot ethanol and recrystallized from the same solvent: yield 7.0 g (48%); mp 145–146°; $[\alpha]^{20}D$ −14.5° (*c* 1.0, $CHCl_3$); ν_{max}^{KBr} 1760, 1710, 1680, 1620, 1550, 785, 765, and 755 cm^{-1}, no OH absorption; nmr (in $CDCl_3$), δ 2.00 [$CH_3C(=O)OR$, 12 H], 3.41 and 3.58 (CH_3N-1 and -3, 6 H), and 6.20 (HC-1′, 1 H), $J_{1',2'}$ = 9.0 cps; R_f 0.82.

Anal. Calcd for $C_{21}H_{26}N_4O_{11}$: C, 49.41; H, 5.13; N, 10.98. Found: C, 49.20; H, 5.38; N, 10.95

A mixture melting point with an authentic sample[6] of 7-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)theophylline showed no depression, and the infrared spectrum was identical with that of the authentic sample.

Deacetylation of the product was carried out in methanol saturated with ammonia to produce 7-β-D-glucopyranosyltheophylline: mp 261°; $[\alpha]^{13}D$ −2.9°[7] (*c* 1.0, water); $\lambda_{max}^{H_2O}$ 273 mμ, $\lambda_{min}^{H_2O}$ 244 mμ.

9-β-D-Glucopyranosyladenine.—2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranose (3.6 g), 6-benzamidopurine (2.4 g), and P_4O_{10} (2.0 g) were dissolved in 35 ml of DMF. After the mixture was allowed to stand 75 hr at 50–60° under stirring, DMF was evaporated from the reaction mixture under reduced pressure below 60°. The residue was dissolved in 500 ml of methanol saturated with ammonia and a precipitate produced was immediately removed by filtration. The filtrate was allowed to stand at room temperature overnight, and then concentrated to a syrup. This was dissolved in water and subjected to column chromatography with the use of an IR-120 (H^+ form) column (4.5 × 30 cm). The column was thoroughly washed with water and eluted with 2 *N* NH_4OH. The fractions which showed positive ultraviolet absorption were collected and concentrated to a syrup. 9-β-D-Glucopyranosyladenine was isolated by crystallization from a mixture of water, ethanol, and ether, and recrystallization was carried out from the same solvent: yield 0.3 g (9.8%); mp 198–200°; $[\alpha]^{21}D$ −9° (*c* 1.0, water); $\lambda_{max}^{H_2O}$ 259 mμ, $\lambda_{min}^{H_2O}$ 225 mμ; ν_{max}^{KBr} 3200–3470, 1640, 800, and 730 cm^{-1}.

Anal. Calcd for $C_{11}H_{15}N_5O_5 \cdot 0.5H_2O$: C, 43.13; H, 5.27; N, 22.86. Found: C, 43.11; H, 5.27; N, 23.33.

The water of crystallization was lost on drying at 100° on P_4O_{10} under reduced pressure for 3 hr.

A mixture melting point with an authentic sample[8] of 9-β-D-glucopyranosyladenine showed no depression, and the infrared spectrum was identical with that of the authentic sample.

9-β-D-Ribopyranosyladenine.—2,3,4-Tri-*O*-acetyl-D-ribopyranose (1.2 g), 6-benzamidopurine (1.2 g), and P_4O_{10} (1 g) were dissolved in DMF (15 ml) as described above. The mixture was allowed to stand at 70–75° for 50 hr. The reaction product, which was obtained by extraction with $CHCl_3$ as described in the preparation of 7-β-D-xylopyranosyltheophylline, was purified with the use of a Dowex-50 (H^+ form) column as described in the preparation of 9-β-D-glucopyranosyladenine. Crystallization and recrystallization were carried out from hot water: yield 0.1 g (6.0%); mp 242–243°; $[\alpha]^{21}D$ −37° (*c* 1.0, water) [lit. mp 237,[9] 254°[10,11]; $[\alpha]D$ −38,[9,11] −37°[10] (water)]; $\lambda_{max}^{H_2O}$ 258 mμ, $\lambda_{min}^{H_2O}$ 227 mμ; $R_{adenine}$ 0.54; ν_{max}^{KBr} 3200–3300 and 1640 cm^{-1}.

Anal. Calcd for $C_{10}H_{13}N_5O_4 \cdot H_2O$: C, 42.10; H, 5.30; N, 24.55. Found: C, 42.03; H, 5.34; N, 23.64.

The water of crystallization was lost on drying at 100° on P_4O_{10} under reduced pressure for 3 hr.

(6) K. Onodera, S. Hirano, and H. Fukumi, *Agr. Biol. Chem.* (Tokyo)' **28**, 173 (1964).

(7) The specific rotation is in good agreement with those reported: $[\alpha]D$ −2.33° (water) [E. Fischer and B. Helferich, *Ber.*, **47**, 210 (1914)] and $[\alpha]^{19}D$ −3.56° (*c* 1.49, water) [T. Hashizume and H. Iwamura, *Tetrahedron Letters*, 3095 (1965)], but this is different from those reported in our previous papers: $[\alpha]^{19}D$ +39.09° (*c* 0.92, water) [K. Onodera and H. Fukumi, *Agr. Biol. Chem.* (Tokyo), **27**, 864 (1963)] and $[\alpha]^{14}D$ +38° (*c* 0.9, water).[6] The positive value of the specific rotation obtained previously might be taken with the anomeric mixture of 7-D-glucopyranosyltheophylline. This is under investigation by preparing the α-D anomer.

(8) K. Onodera and H. Fukumi, *Agr. Biol. Chem.* (Tokyo), **27**, 864 (1963).

(9) M. Viscontini and S. Huwyler, *Helv. Chim. Acta*, **43**, 782 (1960).

(10) J. Davoll and B. A. Lowy, *J. Am. Chem. Soc.*, **74**, 1563 (1952).

(11) J. Baddiley, G. W. Kenner, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 657 (1944).

Hydroxylation of Ethyl 2,3-Didehydro-2,3-dideoxy-α-D-glucopyranoside

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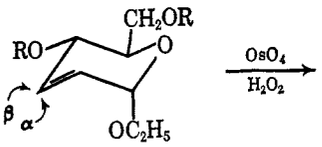
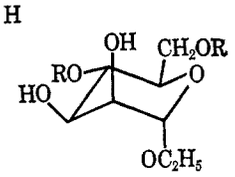
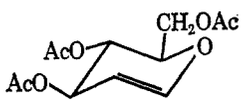
Two recent papers[2,3] have reported different syntheses of D-allose and its derivatives. While successful in their two approaches, these references still served to illustrate that difficulties remain in synthesizing that hexose. This paper reports a brief study of the stereochemical course of the osmium tetroxide catalyzed hydroxylation of unsaturated sugar derivatives[4] Ia and b, readily obtained from triacetyl glucal. Thus, it will be noted that attack of the *cis* hydroxylating



Ia, R = Ac
b, R = H





III

IIa, R = Ac
b, R = H

agent on the α face of I would yield the *allo* configuration while attack on the β face would yield the *manno* configuration. One might anticipate predominant reagent attack on the β face because of the increased steric requirements to α attack imparted by the α-ethoxy group at C-1 of I. Triacetyl glucal (III) has been shown to undergo stereoselective hydroxylation with osmium tetroxide, however, *via* α attack to yield the *gluco* configuration in great predominance.[5a] Galactal also suffers α hydroxylation affording D-galactose exclusively.[5b] No 2,3-dehydro sugars appear

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(2) N. A. Hughes and P. R. H. Speakman, *J. Chem. Soc.*, 2236 (1965).

(3) B. R. Baker and D. H. Buss, *J. Org. Chem.*, **30**, 2304 (1965).

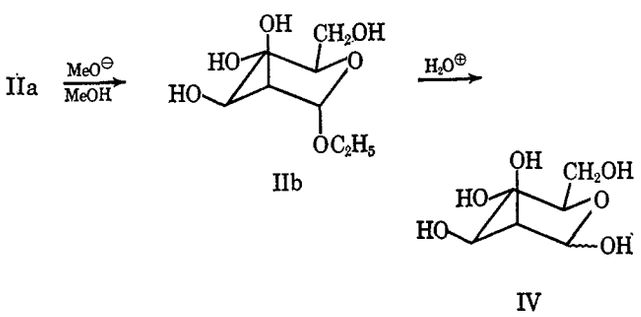
(4) S. Laland, W. G. Overend and M. Stacey, *J. Chem. Soc.*, 738 (1950); M. Bergmann, *Ann.*, **443**, 223 (1925).

(5) (a) R. G. Hockett, A. C. Sapp, and J. R. Millman, *J. Am. Chem. Soc.*, **63**, 2051 (1941); (b) R. C. Hockett and S. R. Millman, *ibid.*, **63**, 2587 (1941). (c) Osmium tetroxide–hydrogen peroxide hydroxylations of carbohydrates have been reviewed by G. J. Moody, *Advan. Carbohydrate Chem.*, **19**, 172 (1964).

to have been subjected to osmium tetroxide hydroxylation.[5c] The event of selective α attack in this present case would have afforded a synthetic route to allose conveniently adaptable to relatively large scale.

Reaction of Ia at room temperature with hydrogen peroxide and osmium tetroxide afforded a crystalline product, IIa, in 57% yield. The *manno* configuration of IIa (β attack) was assigned on the basis of the following data. The molecular rotation of IIa was 11,800 in fair agreement with that of methyl α-mannoside, 15,300, but widely different from that of methyl α-alloside, 27,500.

The anomeric proton of IIa was seen at τ 5.12[6a] as a somewhat broadened (width at half-height = 2.7 cps) singlet.[6b] Since low H_1–H_2 J values would be expected from both the *manno* and *allo* configurations, the observed low J value was considered as consistent with but not diagnostic for structure IIa. While synthetic mixtures of D-allose[2] and D-mannose resisted separation by paper and thin layer chromatography in a wide variety of systems, vapor chromatography of their respective trimethylsilyl derivatives[7] was successful. Thus, the 4- and 6-acetyl groups of IIa were removed by treatment with catalytic methoxide in



methanol and the product, without characterization, was further converted to the free sugar by aqueous acid treatment. A portion of this product was converted to its corresponding silyl ether and, on vapor chromatography, was shown to be identical with authentic mannose. The remainder of the free sugar sample was converted to mannose osazone, identical with an authentic sample. The mother liquors from the preparation of crystalline IIa were subjected to the same saponification–hydrolysis treatment. The saponification product, on vapor chromatography, showed that allose, if it were formed, was formed to the extent of about 4% in the hydroxylation reaction of Ia.

Removal of the acetyl groups of Ia did not significantly alter the stereochemistry of the hydroxylation reaction. Thus, the reaction of Ib was studied and vapor chromatography indicated almost exclusive formation of the *manno* configuration. A peak with the retention time of D-allose comprised about 4% of the total hydrolyzed product

Experimental Section

Melting points are uncorrected. Thin layer chromatography was performed on silica gel H in the following systems: A, chloroform–acetone (1:7); B, 1-butanol–water–ethanol–ammonium hydroxide (5:1.4:3:1.3). Sulfuric acid spray was used to locate spots. Vapor phase chromatography was done on a column packed with 15% ethylene glycol succinate on Chromosorb W at temperatures of 160 and 181°.

Ethyl 4,6-Di-O-acetyl-α-D-mannopyranoside (IIa).—A solution of 5.0 g (0.019 mole) of Ia[4] in 50 ml of dried *t*-butyl alcohol was treated at room temperature with 0.040 g of osmium tetroxide and 3 ml of anhydrous hydrogen peroxide in *t*-butyl alcohol.[8] Additional hydrogen peroxide was added as needed. The reaction course was followed by thin layer chromatography (system A) and was complete after 4.5 days. The product (II) had R_f 0.60 (starting Ia, R_f 0.75). The solvent was distilled *in vacuo* and the product was crystallized and recrystallized from ethyl ether. The total yield of several crops was 3.2 g (57%): mp 108–109°; $[\alpha]^{27}D$ +40.5° (*c* 1, ethanol); nmr ($CDCl_3$), τ 8.78 (3 H, triplet, J = 7 cps), 7.9 (6 H, two singlets), 6.6–4.2 (10 H, multiplets), and 5.12 (1 H, broadened singlet). *Anal.* Calcd for $C_{12}H_{20}O_8$: C, 49.31; H, 6.90. Found: C, 49.46; H, 6.99.

Hydrolysis of IIa.—A solution of 1.15 g of diacetate IIa in 50 ml of methanol was stirred at room temperature with added sodium methoxide (pH ~8). After 2 hr the reaction was complete according to thin layer chromatography (system B). After neutralization with ammonium chloride, the solvent was evaporated and the resulting oil (IIb) was dissolved in 50 ml of 0.5 *N* hydrochloric acid and warmed at steam bath temperatures for 48 hr. After neutralization with Dowex-1 (hydroxide form), the water was evaporated, affording a gum (IV).

Vpc.—A small portion of the above gum (IV) was converted to its trimethyl silyl ether.[7] Vapor phase chromatography yielded two peaks at relative retention times of 1.00 (major) and 1.83 (minor). Authentic mannose afforded the same peaks. A minor (less than 10%) impurity in IV was ethyl glycoside IIb (relative retention time 0.81).

Mannose Osazone.—By standard procedure the remainder of IV was converted to 250 mg of mannose osazone. After recrystallization from pyridine–water, the product had mp 203°; the mixture melting point with an authentic sample was undepressed.

The mother liquors from the crystallizations of IIa were subjected to sodium methoxide saponification followed by acid hydrolysis for 24 hr. A portion of the resulting gum was converted to its trimethyl silyl derivative[7] and analyzed by vapor phase chromatography. The following peaks (relative retention time, per cent of total) were observed: mannose (1.00 and 1.8, 40%), ethyl α-mannopyranoside IIb (0.8, 31%), allose (1.4, 11%), and unknowns (1.2 and 1.7, 8 and 9%, respectively). Since these mother liquors comprised only 43% of the reaction product, the over-all yield of allose in the reaction of Ia with osmium tetroxide was of the order of 4%. If both unknown peaks were also due to compounds of the *allo* configuration, the total yield would then be of the order of 12%.

Hydroxylation of Ib.—A solution of 5.0 g of Ib in 100 ml of *t*-butyl alcohol was treated at room temperature with 0.060 g of osmium tetroxide and 2 ml of anhydrous hydrogen peroxide in *t*-butyl alcohol. Additional hydrogen peroxide was added as needed over a 2-day period. After removal of solvents *in vacuo*, the yellow oily residue was extracted repeatedly with ether. The resulting ether solution yielded a clear oil on evaporation. A portion was then treated with 0.5 *N* hydrochloric acid for 24 hr at steam-bath temperatures. Neutralization with Dowex-1 (hydroxide form) and evaporation afforded a gum. Preparation of the trimethylsilyl derivative[7] and vapor phase chromatography showed the following peaks (relative retention time, per cent of total): mannose (1.0 and 1.8, 55%), ethyl α-mannopyranoside IIb (0.8, about 35%), allose (1.4, about 4%), and unknown (1.6, about 4%). If the unknown were of the *allo* configuration, the total yield of allose would then be of the order of 8–10%.

Acknowledgment.—The financial support of the U. S. Public Health Service, Grant CA 03772, is gratefully acknowledged for a portion of this work.

(6) (a) The equatorial anomeric proton of an α-mannoside would be expected to occur roughly 0.2 ppm upfield (*cf.* ref 6b) from that of methyl α-D-glucopyranoside (τ 4.87): B. Capon and D. Thacker, *Proc. Chem. Soc.*, 369 (1964). (b) Similar results have been observed for other anomeric protons which suffer diequatorial splitting: *e.g.*, R. U. Lemieux and J. D. Stevens, *Can. J. Chem.*, **43**, 2059 (1965).

(7) C. L. Sweeley, R. Bently, M. Makita, and W. Wells, *J. Am. Chem. Soc.*, **85**, 2497 (1963).

(8) Prepared by the method described in A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed, John Wiley and Sons, Inc., New York, N. Y., 1956, p 895.