Acyl Derivatives of Aldoses. II. Derivatives of D-*glycero*-D-*galacto*-Heptose and D-Galactose

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The α and β anomers of hexa-*O*-benzoyl-D-*glycero*-D-*galacto*-heptose and the penta-*O*-benzoyl-β-D-galactose have been prepared for the first time. Anomerization of the α anomer of these benzoyl derivatives by fusion with zinc chloride and benzoic acid led to a mixture of anomers in which the 1–5 *trans* anomer widely predominates. A similar behavior of the benzoyl derivatives of D-*glycero*-D-*galacto*-heptose and the configurationally related hexose has been shown; but the molecular rotations of the corresponding derivatives differ considerably.

In the first paper of this series,[1] we have reported the preparation of the anomeric forms of the benzoates of D-*glycero*-D-*gulo*-heptose and the acetates and benzoates of D-*glycero*-L-*manno*-heptose. We describe, now, the preparation and properties of the anomeric hexa-*O*-benzoates of D-*glycero*-D-*galacto*-heptose and the β anomer of penta-*O*-benzoyl-D-galactose.

D-*glycero*-D-*galacto*-Heptose was prepared by Montgomery and Hudson,[2] by the classical method with sodium amalgam in 38–44% yield. We have obtained the sugar in 72% yield by reduction of the D-*glycero*-D-*galacto*-heptonolactone with sodium amalgam in a buffer of sodium acid oxalate adapting the procedure used by Frush and Isbell,[3] for the preparation of L-glucose.

Montgomery and Hudson[4] prepared hexa-*O*-acetyl-D-*glycero*-β-D-*galacto*-heptose by acetylation of D-*glycero*-D-*galacto*-heptose with acetic anhydride and sodium acetate. We have obtained this hexa-*O*-acetate in a higher yield, by acetylation of the sugar with acetic anhydride in pyridine.

A comparison of the behavior of the D-*glycero*-D-*galacto*-heptose with that of the configurationally related D-galactose shows good agreement. By benzoylation of D-*glycero*-D-*galacto*-heptose with benzoyl chloride in pyridine at 0° we have obtained hexa-*O*-benzoyl-D-*glycero*-α-D-*galacto*-heptose, m.p. 95–97° $[\alpha]^{20}\text{D}$ +82.9° (chloroform). Wolfrom and Christman[5] and Deferrari and Deulofeu[6] under similar reaction conditions obtained the penta-*O*-benzoyl-α-D-galactose. We have obtained the β anomer hitherto unreported by a procedure similar to that reported by Hudson and co-workers[7] for the preparation of penta-*O*-benzoyl-β-D-glucopyranose, which consists in heating the sugar in pyridine prior to benzoylation. Such a procedure led to a mixture of the anomeric penta-*O*-benzoates of D-galactose from which we isolated by fractional crystallization the pure β anomer, m.p. 169–170°, $[\alpha]^{20}\text{D}$ +53.5° (chloroform). This method applied to D-*glycero*-D-*galacto*-heptose gave a crude product, $[\alpha]^{16}\text{D}$ +58.6° (chloroform) corresponding to 61% of the α anomer and 39% of the β anomer. By chromatography on alumina of this mixture we could separate the hexa-*O*-benzoyl-D-*glycero*-β-D-*galacto*-heptose as needles, m.p. 115–116°, $[\alpha]^{21}\text{D}$ +21.1° (chloroform). The α anomer isolated by chromatography showed the same melting point and specific rotation as the previously mentioned hexa-*O*-benzoyl-D-*glycero*-α-D-*galacto*-heptose prepared by benzoylation of the sugar with benzoyl chloride in pyridine at 0°.

According to Hudson and Monroe[8] the molecular rotations of the corresponding derivatives of D-*glycero*-D-*galacto*-heptose and D-galactose should be similar; examination of Table I shows that these values for the anomeric penta-*O*-benzoates of D-galactose differ considerably from the values for the corresponding derivatives of the heptose. Montgomery and Hudson[2] have also found disagreement between the values for some derivatives of these two related sugars.

We have calculated the 2A values for the anomeric benzoyl derivatives listed in Table I. These data show disagreement with Hudson's first isorotation rule.

We anomerized hexa-*O*-benzoyl-D-*glycero*-α-D-*galacto*-heptose and penta-*O*-benzoyl-α-D-galactose by fusion with zinc chloride and benzoic acid in adaptation of the procedure used by Hudson and co-workers[7] for the anomerization of penta-*O*-benzoyl-β-D-glucopyranose. Both of the α anomers gave by anomerization a mixture containing only about 10% of the β anomer, calculated on the basis of the observed rotations of the crude products isolated. For the identification of both of the anomers in the mixture we adapted the technique of thin-layer chromatography on silicic acid–starch. We chromatographed the crude product of anomerization simultaneously with the pure α and β anomers. The mixture was resolved in two spots with R_f

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[1] J. O. Deferrari and R. M. de Lederkremer, *J. Org. Chem.*, **27**, 2558 (1962).

[2] E. Montgomery and C. S. Hudson, *J. Am. Chem. Soc.*, **64**, 247 (1942).

[3] H. L. Frush and H. S. Isbell, *J. Res. Natl. Bur. Standards*, **54**, 267 (1955).

[4] E. Montgomery and C. S. Hudson, *J. Am. Chem. Soc.*, **56**, 2463 (1934).

[5] M. L. Wolfrom and C. Christman, *ibid.*, **58**, 39 (1936).

[6] J. O. Deferrari and V. Deulofeu, *J. Org. Chem.*, **17**, 1097 (1952).

[7] R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, *J. Am. Chem. Soc.*, **72**, 2200 (1950).

TABLE I

2A VALUES FOR COMPLETELY O-BENZOYLATED SUGARS

	Specific rotation		Molecular rotation		
Benzoate of	α anomer $[\alpha]_D$	β anomer $[\alpha]_D$	α anomer $[M\alpha]_D$	β anomer $[M\beta]_D$	2A $[M\alpha]_D - [M\beta]_D$
D-Glucose	+136.8[a]	+24.2[a]	95,760	16,940	78,820
D-Mannose	−18.6[a]	−82.0[a]	−13,020	−57,400	44,380
D-Galactose	+187.1[b]	+53.5	131,000	37,450	93,550
D-*glycero*-D-*galacto*-Heptose	+82.9	+21.1	69,300	17,600	51,700
D-*glycero*-D-*gulo*-Heptose	+72.8[c]	−3.3[c]	60,750	−2,750	63,500
D-*glycero*-L-*manno*-Heptose	+96.9[c]	+31.2[c]	80,940	26,040	54,900

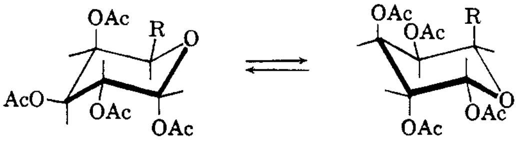
[a] Ref. 7. [b] Ref. 5. [c] Ref. 1.

values coincident with those for the pure anomers. In this case, too, the related benzoyl derivatives of D-*glycero*-D-*galacto*-heptose and D-galactose have shown a similar behavior, because both of the α anomers gave a higher R_f value than the corresponding β anomer under similar conditions. The details of this technique applied to the resolution and identification of anomeric acyl derivatives will be given in a future communication.

On the other hand, the α anomer which predominates in the crude anomerization mixture of either the hexa-O-benzoyl-D-*glycero*-α-D-*galacto*-heptose ($I_a \rightleftarrows I_b$) or the penta-O-benzoyl-α-D-galactose ($II_a \rightleftarrows II_b$) shows the 1-5 *trans* configuration. We can conclude as Bonner[9] pointed out for the acetates of aldohexoses, and Hassel and Ottar[10] for the acylglycosyl halides, that the anomer predominating at equilibrium is that whose two chair conformations may be so related.

$$C_{1\,ax}\ C_{5\,eq} \rightleftarrows C_{1\,eq}\ C_{5\,ax}$$

This is also true for the acetyl derivatives of these two related sugars. Montgomery and Hudson[4] anomerized hexa-O-acetyl-D-*glycero*-D-*galacto*-heptose and obtained a mixture in which the α anomer widely predominates. Bonner[9] reported a similar behavior for the penta-O-acetates of D-galactose.



Ia. R = CHOAc—CH$_2$OAc
IIa. R = CH$_2$OAc
Ib. R = CHOAc—CH$_2$OAc
IIb. R = CH$_2$OAc
Ac = CO—CH$_3$ or CO—C$_6$H$_5$

Experimental

D-*glycero*-D-*galacto*-Heptose.—D-*galacto*-Heptonolactone (20 g.), prepared by a procedure similar to that reported by Fisher and Passmore,[11] was dissolved in 1 l. of ice water and sodium acid oxalate (180 g.) was added. The mixture was stirred vigorously and 5% sodium amalgam pellets (500 g.) were added at one time. After 4 hr. of stirring at ice bath temperature, the mercury was separated and the solution neutralized with 1 *N* sodium hydroxide in the presence of phenolphthalein indicator. The crystalline sodium oxalate was filtered and washed with hot methanol. The solution was concentrated *in vacuo* until crystallization of more sodium oxalate and treated with five volumes of hot methanol; after cooling the precipitated salts were separated and washed with methanol. The solution was again evaporated *in vacuo* to a volume of about 100 ml., and another crop of crystals was filtered. The filtrate was evaporated *in vacuo* to a sirup which was dissolved in water and deionized by passage through Amberlite IR 120 and De Acidite E, respectively. The deionized solution was evaporated at a temperature less than 60° to a sirup, which was dissolved in 50 ml. of boiling methanol. On cooling, 12.38 g. of needles, m.p. 143–145°, was obtained. Recrystallization from 10 parts of 10:1 ethanol–water gave D-*glycero*-D-*galacto*-heptose m.p. 145° $[\alpha]^{20}{}_D$ +120.5° after 5 min. → +68.7° after 24 hr. (c 2, water). Montgomery and Hudson[2] observed for the anhydrous D-*glycero*-α-D-*galacto*-heptose a melting point of 145° and a mutarotation in water from +124° (extrapolated) to +69.0° (c 4, water).

Hexa-O-acetyl-D-*glycero*-α-D-*galacto*-heptose.—D-*glycero*-D-*galacto*-Heptose (4 g.) was added to a mixture of acetic anhydride (48 ml.) and pyridine (40 ml.). After 24 hr., in the shaking-machine, the sugar had dissolved. It was then poured into ice water and allowed to stand overnight whereupon it crystallized yielding 7.2 g. of product. Recrystallization from 50% ethanol gave 6.4 g. (72.8%) of hexa-O-acetyl-D-*glycero*-α-D-*galacto*-heptose as long prisms, m.p. 106–107° $[\alpha]^{25}{}_D$ +35.0° (c 1.2, chloroform). Montgomery and Hudson[4] cite m.p. 107°, $[\alpha]^{20}{}_D$ +34.1° (c 1.30, chloroform).

Hexa-O-benzoyl-D-*glycero*-α-D-*galacto*-heptose.—D-*glycero*-D-*galacto*-Heptose (2.100 g.) was suspended in pyridine (20 ml.) at 0°. Benzoyl chloride (10 ml.) was added slowly with stirring. After 24 hr., in the shaking-machine at room temperature the mixture was heated for 30 min. on a water bath at 60°. It was cooled and poured into ice water (300 ml.), and then allowed to stand overnight. The resulting oil was extracted with chloroform, the extract washed with 2 *N* sulfuric acid, water, saturated sodium bicarbonate solution, water, and finally dried over anhydrous sodium sulfate. The chloroform was removed by evaporation *in vacuo* and the resulting oil, soaked in methanol, became friable after 48 hr. It was filtered and washed with cold methanol. There resulted 7.9 g. (94%) of crude product which was dissolved in boiling ethanol; by cooling there was obtained 6.800 g. of amorphous product, m.p. 95–97° $[\alpha]^{20}{}_D$ +81.9° (c 2.5, chloroform). This solid could not be induced to crystallize even after purification by chromatography on alumina. After this treatment pure hexa-O-benzoyl-D-*glycero*-α-D-*galacto*-heptose resulted, having m.p. 95–97° $[\alpha]^{20}{}_D$ +82.9° (c 1.5, chloroform). These properties remained unchanged after further purification from ethanol.

Anal. Calcd. for $C_{49}H_{38}O_{13}$: C, 70.48; H, 4.60; Found: C, 70.77; H, 4.73.

Hexa-O-benzoyl-D-*glycero*-β-D-*galacto*-heptose.—D-*glycero*-D-*galacto*-Heptose (2.100 g.) in dry pyridine (20 ml.) was heated on a water bath at 100° for 30 min. While cooling the mixture at 0°, benzoyl chloride (10 ml.) was added

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[8] C. S. Hudson and K. P. Monroe, *J. Am. Chem. Soc.*, **46**, 979 (1924).

[9] W. Bonner, *ibid.*, **81**, 1448 (1959).

[10] O. Hassel and B. Ottar, *Acta Chem. Scand.*, **1**, 929 (1947).

[11] E. Fisher and F. Passmore, *Chem. Ber.*, **23**, 2226 (1890).

slowly with stirring. The reaction flask was heated for 1 hr. at 60°; 1 ml. of water was added to the cooled contents and 10 min. later it was poured into 200 ml. of ice water. After 1 hr. the water was decanted and the oil was washed with cold water, then with water at 60° and finally with saturated sodium bicarbonate solution and again with water. After this treatment the product became friable. There resulted 8.0 g. (96%) of material $(\alpha)^{16}\text{D}$ +58.6° (c 2.1, chloroform). This optical rotation corresponds to a mixture containing 3.14 g. (39.2%) of the β anomer. The separation was effected by flowing chromatography on Woelm acid alumina (activity I). Three grams of the mixture dissolved in 10 ml. of benzene was placed on a column (400 × 20 mm.) of alumina previously wetted with benzene. Elution was first carried out with benzene collecting thirty-five fractions of 40 ml. of eluate each; evaporation of fractions 1 to 30 afforded 1.400 g. of hexa-*O*-benzoyl-D-*glycero*-α-D-*galacto*-heptose, $[\alpha]^{16}\text{D}$ +79.8° (c 1.0, chloroform). Purification from isopropyl alcohol gave the pure α anomer; $(\alpha)^{16}\text{D}$ +82.2° (c, 1.0; chloroform). Eluting with a mixture of ethyl ether and benzene 1:9 gave twenty fractions of 40 ml. each; evaporation to dryness yielded 0.900 g. of hexa-*O*-benzyol-D-*glycero*-β-D-*galacto*-heptose, needles, m.p. 115–116° $(\alpha)^{21}\text{D}$ +21.1° (c 0.9, chloroform); further recrystallization failed to change these values.

Anal. Calcd. for $C_{49}H_{38}O_{13}$: C, 70.48; H, 4.60; Found: C, 70.83; H, 5.00.

Anomerization of Hexa-*O*-benzoyl-D-*glycero*-α-D-*galacto*-heptose.—Anhydrous zinc chloride (0.200 g.) was fused in a lightly corked glass tube and at a temperature of 130°, hexa-*O*-benzoyl-D-*glycero*-α-D-*galacto*-heptose (1 g.) and benzoic acid (1 g.) were added. After 30 min. of heating in an oil bath at 130–140°, the reaction flask was cooled and the mixture was dissolved in pyridine, filtered, and the dark solution was poured into water. The oil obtained solidified after washing with water and finally with cold methanol. The solid material was filtered, dissolved in methanol–acetone (5:1), decolorized by filtration through Norit and the filtrate, evaporated to dryness yielded 0.850 g. of material, $[\alpha]^{20}\text{D}$ +76.09° (c 1.2, chloroform). This optical rotation corresponds to a mixture containing 0.093 g. (10.9 %) of the β anomer. The identification of both of the anomers in the mixture was effected by thin-layer chromatography on silicic acid–starch with benzene as eluent. The crude product of anomerization was chromatographed simultaneously with the pure α and β anomers. The mixture was resolved into two spots with R_f values of 0.26 and 0.0, coincident with those for the α and β anomers, respectively. The spots were visible after spraying with the silver nitrate–ammonia–sodium methylate reagent, recommended by Cadenas and Deferrari,[12] and heating the plates for 10 min. at 105°

Penta-*O*-benzoyl-β-D-galactopyranose.—D-Galactose (2 g.) in dry pyridine (30 ml.) was heated on a boiling water bath for 1 hr. and on cooling, benzoyl chloride (8 ml.) was added slowly with stirring. The reaction flask was heated for 90 min. at 60°; after cooling 1 ml. of water was added and 10 min. later an additional 10 ml. of water; the mixture was then poured into 200 ml. of ice water. After standing overnight, the water was decanted and the resulting gum washed several times with water, and finally it was covered with methanol, wherein it crystallized after standing overnight. There resulted 7.030 g. (91.3%) of crude product $[\alpha]^{20}\text{D}$ + 103.8° (c 1.0, chloroform). This optical rotation corresponds to a mixture containing 4.38 g. (62.3%) β anomer and 2.650 g. (37.7 %) α anomer. After three fractional recrystallizations of this material from methanol–acetone 5:1 pure penta-*O*-benzoyl-β-D-galactopyranose resulted, as needles of m.p. 169–170° $[\alpha]^{20}\text{D}$ + 53.5° (c 0.8, chloroform).

Anal. Calcd. for $C_{41}H_{32}O_{11}$: C, 70.28; H, 4.57; Found: C, 70.37; H, 4.66.

Anomerization of Penta-*O*-benzoyl-α-D-galactopyranose.—Penta-*O*-benzoyl-α-D-galactose[6] (5 g.) was added to a mixture of anhydrous zinc chloride (0.500 g.) and benzoic acid (5 g.) heated at 130° in an oil bath. After 1 hr. at this temperature the mixture was cooled and dissolved in pyridine (20 ml.), filtered, and the filtrate poured into 100 ml. of ice water. The oil was extracted with chloroform and the extract was washed with 2 *N* sulfuric acid, water, cold sodium bicarbonate solution, again with water, and finally dried over anhydrous sodium sulfate. Solvent removal yielded 4.200 g. of material $(\alpha)^{20}\text{D}$ + 176.8° (c 1.55, chloroform). This optical rotation corresponds to a mixture with 0.320 g. (7.6 %) of the β anomer. The identification of both of the anomers in the mixture was effected by thin-layer chromatography as described for the anomerization mixture of hexa-*O*-benzoyl-D-*glycero*-α-D-galacto-heptose. The α and β anomers showed R_f values of 0.52 and 0.0, respectively.

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[12] R. Cadenas and J. O. Deferrari, *The Analyst*, **86**, 132 (1961).

Olefinic Structures from Acetylated Phenylhydrazones of Sugars

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The acetylated forms of the acyclic phenylhydrazones of D-glucose, D-mannose, and D-galactose readily eliminate acetic acid to yield a tetraacetoxy-1-phenylazo-*trans*-1-hexene (IV) whose structure was established by NMR spectra data and by chemical evidence. The optical rotatory dispersion of IV exhibits a complex Cotton effect.

Attempts in this laboratory some years ago to prepare penta-*O*-acetyl-*aldehydo*-D-glucose phenylhydrazone (III) by treating *aldehydo*-D-glucose pentaacetate (I) with phenylhydrazine resulted in a crystalline reaction product (IV) in which a molecule of acetic acid had been lost. The compound was isomeric with a substance described by Wolfrom and Blair[2] and obtained by the acetylation of D-mannose phenylhydrazone but was at first thought to be different from it. The difference was resolved when the crystals were found to be dimorphous but indeed identical in chemical composition. The same substance was also obtained by the mild acetylation of D-glucose "β"-phenyl-

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[1] Research Associate (A. T.) and Fellow (D. R. L.) of the Corn Industries Research Foundation.

[2] M. L. Wolfrom and M. Grace Blair, *J. Am. Chem. Soc.*, **68**, 2110 (1946).