Acyl Derivatives of Aldoses. I. Derivatives of D-*glycero*-D-*gulo*-Heptose and D-*glycero*-L-*manno*-Heptose

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Received January 15, 1962

The α and β anomers of hexa-*O*-benzoyl-D-*glycero*-D-*gulo*-heptose, hexa-*O*-acetyl-D-*glycero*-L-*manno*-heptose, and hexa-*O*-benzoyl-D-*glycero*-L-*manno*-heptose have been prepared for the first time. Anomerization of the β anomer of these acyl derivatives led in each case to a mixture in which the anomer with a 1–5 *trans* configuration predominates.

The preparation of these acyl derivatives was incidental to the research of ammonolysis of acyl derivatives of heptoses which is the subject of a future publication.

The free sugars we needed were prepared by two methods of reduction of lactones. For the preparation of D-*glycero*-D-*gulo*-heptose we used the procedure reported by M. L. Wolfrom and H. Wood[1] for the reduction of D-*glycero*-D-*gulo*-heptonolactone with sodium borohydride and we obtained a similar yield (66.7%).

We have prepared D-*glycero*-L-*manno*-heptose in 75% yield by reduction of D-*glycero*-L-*manno*-heptonolactone with sodium amalgam in a buffer of sodium acid oxalate, in adaptation of the procedure reported by Frush and Isbell[2] for the preparation of L-glucose. D-*glycero*-L-*manno*-Heptose was obtained by Hann, Merrill, and Hudson[3] by the classical method with sodium amalgam, in 50% yield of crude product.

The *aldehydo* acetate of D-*glycero*-L-*manno*-heptose prepared by Hann and Hudson[4] appears to be the only acetate reported of this sugar. We undertook the preparation of the anomeric hexa-*O*-acetates of the pyranoid form of D-*glycero*-L-*manno*-heptose by acetylating the sugar with acetic anhydride in pyridine. Thus, we obtained largely the hexa-*O*-acetyl-D-*glycero*-β-L-*manno*-heptose $[\alpha]^{27}D$ −26.3° (chloroform) and from the alcoholic mother liquors we obtained the α anomer $[\alpha]^{26}D$ +61.3° (chloroform) by fractional crystallization.

The difference, 2A, between the molecular rotations of this α-β pair is 40,425 which is in agreement with the values reported for other such pairs. For example, Montgomery and Hudson[5] found a 2A value of 40,000 for the hexa-*O*-acetates of D-*glycero*-D-*galacto*-heptose.

We confirmed that this and all the other pairs of acyl derivatives we prepared were anomers by anomerizing one of them and isolating the other from the mixture of anomers obtained.

We anomerized the benzoates of the aldoheptoses by fusion of the appropriate anomer with zinc chloride and benzoic acid in adaptation of the procedure used by Ness, Fletcher, and Hudson[6] for the anomerization of penta-*O*-benzoyl-β-D-glucopyranose. The acyl derivatives we prepared were assumed to be pyranoid, as this is the cyclic form usually obtained on esterification of sugars.

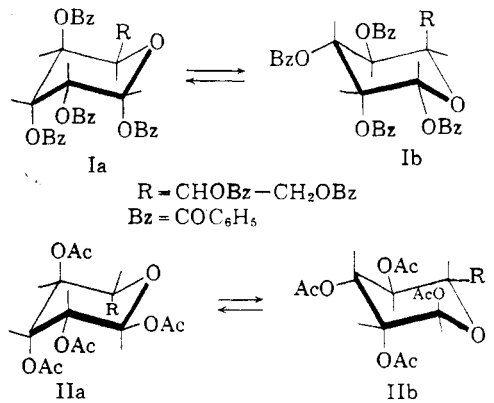
From the observed rotations of the anomerization mixtures or from the relative yield of anomers actually isolated we can conclude, as O. Hassel and B. Ottar[7] pointed out for the acylglycosyl halides, and Bonner[8] for the acetates of aldohexoses, that the anomer predominating at equilibrium in the case of the anomerization of acyl aldoheptoses is that whose two chair conformations may be so related

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

and the anomer less abundant is that whose two chair forms can be represented by

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

The conformations $I_a \rightleftarrows I_b$ for the α anomer of hexa-*O*-benzoyl-D-*glycero*-D-*gulo*-heptose, which is the more abundant at equilibrium show the 1–5 *trans* configuration.



(1) M. L. Wolfrom and H. Wood, *J. Am. Chem. Soc.*, **73**, 2933 1951).

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

(3) R. M. Hann, A. T. Merrill, and C. S. Hudson, *J. Am. Chem. Soc.*, **57**, 2100 (1935).

(4) R. M. Hann and C. S. Hudson, *ibid.*, **59**, 1899 (1937).

(5) E. Montgomery and C. S. Hudson, *ibid.*, **56**, 2463 (1934).

(6) R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **72**, 2200 (1950).

(7) O. Hassel and B. Ottar, *Acta Chim. Scand.*, **1**, 929 (1947).

(8) W. Bonner, *J. Am. Chem. Soc.*, **81**, 1448 (1959).

By benzoylation of D-*glycero*-D-*gulo*-heptose with benzoyl chloride in pyridine we have obtained the hexa-*O*-benzoyl-D-*glycero*-β-D-*gulo*-heptose $[\alpha]^{23}D$ −3.3° (chloroform). We could not obtain the α anomer by heating the free sugar in pyridine prior to benzoylation, because the equilibrium of the mutarotation of D-*glycero*-D-*gulo*-heptose is strongly shifted towards the β anomer.[9] When we subjected the hexa-*O*-benzoyl-D-*glycero*-β-D-*gulo*-heptose to the anomerizing conditions described below we obtained a mixture containing 66% of hexa-*O*-benzoyl-D-*glycero*-α-D-*gulo*-heptose (Ia ⇄ Ib). By chromatography on alumina we separated from the crude mixture the pure α anomer $[\alpha]^{24}D$ +72.8° (chloroform).

By benzoylation of D-*glycero*-L-*manno*-heptose we obtained a mixture of both of the anomers with a larger proportion of the β anomer.

By chromatography on alumina we separated hexa-*O*-benzoyl-D-*glycero*-β-L-*manno*-heptose $[\alpha]^{20}D$ +31.2° (chloroform) from hexa-*O*-benzoyl-D-*glycero*-α-L-*manno*-heptose $[\alpha]^{20}D$ +96.9° (chloroform).

In the case of the hexa-*O*-acetyl and hexa-*O*-benzoyl derivatives of D-*glycero*-L-*manno*-heptose the β anomer (II_a ⇄ II_b), also with a 1–5 *trans* configuration predominates in the mixture of anomerization; this is related to the greater stability of this anomer as Hassel and Ottar[7] explained for the acylglycosil halides.

Experimental

Chromatograms were made with the flowing method using Woelm acid alumina (pH 4.5; activity I).

Hexa-*O*-benzoyl-D-*glycero*-β-D-*gulo*-heptose.—(a). D-*glycero*-β-D-*gulo*-Heptose, m.p. 191–192°, $[\alpha]^{25}D$ −21.3° (c 0.53, water), was prepared by the procedure reported by Wolfrom and Wood[1] who give the same melting point and $[\alpha]^{22}D$ −20.0° (c 3.5, water). D-*glycero*-β-D-*gulo*-Heptose (8.400 g.) was suspended in dry pyridine (20 ml.) and while cooling in ice, benzoyl chloride (45 ml.) was added slowly with stirring. After 24 hr. in the shaking-machine the reaction flask was heated for 20 min. at 60°. It was cooled and then poured into 800 ml. of ice water. The gummy precipitate was extracted with chloroform and the extract washed with 2 *N* sulfuric acid, water, saturated sodium bicarbonate solution, water, and finally dried over anhydrous sodium sulfate. The chloroform extract diluted with an equal volume of methanol was decolorized with Norit and evaporated *in vacuo*. The residue washed with cold methanol and soaked in methanol, crystallized after 2 days. There resulted 27.3 g. (81.7 %) of crude product, m.p. 113–115°. Two recrystallizations from methanol–acetone (5:1) and one from ethanol gave the pure hexa-*O*-benzoyl-D-*glycero*-β-D-*gulo*-heptose, needles, m.p. 125–127°, $[\alpha]^{23}D$ −3.3° (c 0.45, chloroform). Subsequent recrystallization did not change the specific rotation.

When the hexa-*O*-benzoyl-D-*glycero*-β-D-*gulo*-heptose crystallized from an ethanolic solution by slow evaporation of the solvent at room temperature it was obtained as prisms of m.p. 115–116° with the same specific rotation.

Anal. Calcd. for $C_{49}H_{38}O_{13}$: C, 70.48; H, 4.60. Found: C, 70.34; H, 4.57.

(9) C. S. Hudson and E. Yanovsky, *J. Am. Chem. Soc.*, **59**, 1033 (1937).

Hexa-*O*-benzoyl-D-*glycero*-β-D-*gulo*-heptose.—(b). D-*glycero*-D-*gulo*-Heptose (8.400g.) in dry pyridine (100 ml.) was heated on a boiling water bath for 1 hr. Cooling the mixture at 0°, benzoyl chloride (45 ml.) was added slowly with stirring. It was then heated for 1 hr. at 60°; after cooling, 5 ml. of water was added and 5 min. later, 50 ml. more. The mixture was then poured into 1 l. of ice water; the oil obtained was allowed to stand overnight at room temperature after which it became friable. The water was decanted and the solid treated twice with 200-ml. portions of methanol. On standing in methanol it crystallized after 24 hr. yielding 29.05 g. (87%) of crude product. Recrystallization from absolute alcohol yielded 22.200 g. of hexa-*O*-benzoyl-D-*glycero*-β-D-*gulo*-heptose as needles, m.p. 124–126°, $[\alpha]^{25}D$ −2.6° (c 1.36, chloroform). By slow evaporation of the methanolic liquors at room temperature, there was obtained 1.360 g. of the benzoate, prisms, m.p. 115–116°, $[\alpha]^{27}D$ −3.5° (c 0.85, chloroform).

Hexa-*O*-benzoyl-D-*glycero*-α-D-*gulo*-heptose by Anomerization of Hexa-*O*-benzoyl-D-*glycero*-β-D-*gulo*-heptose.—Anhydrous zinc chloride (1 g.) was fused in a lightly corked glass tube and, at a temperature of 140°, benzoic acid (10 g.) and hexa-*O*-benzoyl-D-*glycero*-β-D-*gulo*-heptose (10 g.) was added. The contents was heated for 1 hr. in an oil bath at 130°. The resulting reddish brown mixture was dissolved in pyridine, filtered, and the filtrate poured into 200 ml. of ice water. The oil obtained was washed several times with water, then with saturated sodium bicarbonate solution and finally with water, after which it became a friable solid. There resulted 8.525 g. of material $[\alpha]^{20}D$ +47.0° (c 1.6, chloroform). This optical rotation corresponds to a mixture containing 5.62 g. (66%) α anomer. The separation of the pure hexa-*O*-benzoyl-D-*glycero*-α-D-*gulo*-heptose was effected by chromatography on alumina. A 0.400-g. sample of the mixture dissolved in 4 ml. benzene were placed on a column (210 × 20 mm.) of alumina previously wetted with benzene. Elution was carried out with benzene and forty-five fractions of 30 ml. each were collected. Fractions 5–15 afforded by evaporation 0.100 g. of hexa-*O*-benzoyl-D-*glycero*-β-D-*gulo*-heptose, m.p. 124–126°, $[\alpha]^{20}D$ −3.5° (c 1.2, chloroform). Fraction 16–20 gave 0.050 g. of a mixture $[\alpha]^{20}D$ +43.6° (c 0.55, chloroform). Evaporation to dryness of fractions 21–42 yielded 0.180 g. of amorphous solid. Purification from isopropyl alcohol gave hexa-*O*-benzoyl-D-*glycero*-α-D-*gulo*-heptose, m.p. 86–88°, $[\alpha]^{24}D$ +72.8 (c 0.96, chloroform). Further purification from isopropyl alcohol did not change these properties.

Anal. Calcd. for $C_{49}H_{38}O_{13}$: C, 70.48; H, 4.60. Found: C, 70.35; H, 4.53.

D-*glycero*-L-*manno*-Heptose.—D-*glycero*-L-*manno*-Heptonolactone (20 g.), prepared by the procedure reported by Hann, Merrill, and Hudson,[4] was dissolved in water (200 ml.). Enough slush ice, to make 1 l. total volume and sodium acid oxalate (200 g.) were added. While cooling in an ice bath, 5% sodium amalgam pellets (500 g.) were added at one time. After 3 hr. of stirring at 0–5° the mercury was separated and the reaction mixture was neutralized with 1 *N* sodium hydroxide solution to phenolphthalein. The crystalline sodium oxalate was separated by filtration and washed with hot methanol. The solution was concentrated under reduced pressure until crystallization of sodium salts and treated with 5 volumes of methanol. The precipitated salts were removed by filtration and washed with methanol. The solution was again evaporated *in vacuo* at a temperature less than 50° to 50 ml. and again treated with 5 volumes of methanol. The precipitated salts were separated and the filtrate was concentrated *in vacuo* to a sirup which was dissolved in water and deionized by passage through Amberlite IR 120 and De Acidite E, respectively. The effluent and washings were concentrated *in vacuo* to a sirup which was treated with 5 volumes of methanol. The resulting gummy precipitate was extracted several times with cold methanol; after this treatment a residue of 0.300 g. of D-*glycero*-L-*manno*-heptitol, m.p. 183–185°, was obtained. Recrystal-

lization from 70% ethanol afforded pure D-*glycero*-L-*manno*-heptitol, m.p. 186–187°. Pierce[10] reported m.p. 187° for the enantiomorph, D-*glycero*-D-*galacto*-heptitol. Slow evaporation at room temperature of the methanolic liquors yielded 16.40 g. (75%) of D-*glycero*-L-*manno*-heptose monohydrate, m.p. 83–84°. The substance showed mutarotation from $[\alpha]^{27}D$ −26.0° (after 3 min.) to $[\alpha]^{27}D$ −14.0° (at equilibrium) (c 1, water) expressed as a measurement of the anhydrous sugar. The water content was determined by drying to constant weight at 110° *in vacuo*.

Anal. Calcd. For $C_7H_{14}O_7 \cdot H_2O$: H_2O, 8.57. Found: H_2O, 8.17.

Hudson and co-workers[8] reported m.p. 77–78° $[\alpha]^{20}D$ −26° → −15.3° (at equilibrium, water) J. Sowden and D. B. Strobach obtained m.p. 83–85° and $[\alpha]^{20}D$ −13.7° (c 4, water) at equilibrium.

Hexa-*O*-acetyl-D-*glycero*-β-L-*manno*-heptose.—D-*glycero*-L-*manno*-Heptose (5 g.) was added to a mixture of pyridine (60 ml.) and acetic anhydride (60 ml.); it was shaken for 2 hr. until the solid had dissolved and allowed to stand 24 hr. at room temperature. It was then poured into 500 ml. of ice water; the gummy precipitate that separated crystallized after washing twice with cold water, yielding 8.10 g. (77%), m.p. 125–128°. Three recrystallizations from ethanol afforded pure hexa-*O*-acetyl-D-*glycero*-β-L-*manno*-heptose, prismatic needles, m.p. 131–132° $[\alpha]^{27}D$ −26.3° (c 0.42, chloroform). Further recrystallization did not change its properties.

Anal. Calcd. for $C_{19}H_{26}O_{13}$: C, 49.33; H, 5.63. Found: C, 49.40; H, 5.72.

Hexa-*O*-acetyl-D-*glycero*-α-L-*manno*-heptose.—The ethanolic mother liquors from the recrystallization of hexa-*O*-acetyl-D-*glycero*-β-L-*manno*-heptose yielded on evaporation a crystalline residue, which was successively extracted with ether. The insoluble portion was recrystallized twice from 50% ethanol. There resulted 0.150 g. of hexagonal prisms, m.p. 142–143° $[\alpha]^{26}D$ +61.3° (c 0.85, chloroform),

Anal. Calcd. for $C_{19}H_{26}O_{13}$: C, 49.33; H, 5.63. Found: C, 49.41; H, 5.62.

Anomerization of Hexa-*O*-acetyl-D-*glycero*-β-L-*manno*-heptose.—Hexa-*O*-acetyl-D-*glycero*-β-L-*manno*-heptose (2 g.) was heated for 30 min. with a mixture of zinc chloride (0.500 g.) in glacial acetic acid (3 ml.) and acetic anhydride (8 ml.). It was then poured into 200 ml. of ice water and after washing several times with water it crystallized, yielding 1.450 g. of the β anomer, m.p. 131–132°. The mother liquors were extracted with chloroform and the extract washed with sodium bicarbonate solution, with water, and finally dried with anhydrous sodium sulfate. The solvent was evaporated *in vacuo* to a sirup, treated with methanol, and again evaporated to dryness. There resulted 0.090 g. of crystalline product $[\alpha]^{25}D$ +14.6° (c 1.3, chloroform), this rotation corresponds to a mixture containing 0.042 g. of α anomer. The material was washed with ether and recrystallized twice from 50% ethanol yielding 0.020 g. of hexa-*O*-acetyl-D-*glycero*-α-L-*manno*-heptose, m.p. 142–143°, $[\alpha]^{20}D$ +61.0° (c 1.0, chloroform).

(10) G. Pierce, *J. Biol. Chem.*, **23**, 327 (1915).

Hexa-*O*-benzoyl-D-*glycero*-α-L-*manno*-heptose and Hexa-*O*-benzoyl-D-*glycero*-β-L-*manno*-heptose.—D-*glycero*-L-*manno* Heptose (3.150 g.) was suspended in pyridine (30 ml.), and while cooling at 0°, benzoyl chloride (15 ml.) was added slowly with stirring. After 20 hr. in the shaking-machine the reaction flask was heated for 20 min. at 60°, cooled and poured into 400 ml. of ice slush; the oil obtained was extracted with chloroform, the extract washed with 2 *N* sulfuric acid, water, saturated sodium bicarbonate solution, and again with water. After drying with anhydrous sodium sulfate the solution was diluted with an equal volume of methanol and decolorized by filtration through Norit. The solution was evaporated *in vacuo* and the residue dissolved in boiling ethanol; on cooling, 10 g. (80%) of material $[\alpha]^{20}D$ +51.1° (c 1.2, chloroform) was obtained. The separation of both of the anomers was effected by flowing chromatography on alumina. Three grams of the mixture dissolved in 10 ml. of benzene was placed on a column of alumina previously wetted with benzene. Eluting with a mixture of ethyl ether and benzene (5:95) thirty fractions of 40 ml. each were collected; evaporation to dryness yielded 1.800 g. of crystalline product. Recrystallization from ethanol afforded pure hexa-*O*-benzoyl-D-*glycero*-β-L-*manno*-heptose, prisms, m.p. 99–100° $[\alpha]^{20}D$ +30.8. These properties remained unchanged after further recrystallization.

Anal. Calcd. for $C_{49}H_{38}O_{13}$: C, 70.48; H, 4.60. Found: C, 70.54; H, 4.69.

Eluting with a mixture of ethyl ether–benzene (10:90), eighteen fractions of 40 ml. each were collected. The last 14 fractions gave on evaporation 0.800 g. of hexa-*O*-benzoyl-D-*glycero*-α-L-*manno*-heptose, needles, m.p. 173–175° $[\alpha]^{20}D$ +94.8° (c 0.30, chloroform). Recrystallization from ethanol afforded the pure compound m.p. 174–175° $[\alpha]^{20}D$ +96.9° (c 0.3, chloroform).

Anal. Calcd. for $C_{49}H_{38}O_{13}$: C, 70.78; H, 4.60. Found: C, 70.44; H, 4.63.

Anomerization of Hexa-*O*-benzoyl-D-*glycero*-β-L-*manno*-heptose.—To a mixture of freshly fused zinc chloride (0.150 g.) and benzoic acid (1 g.) at 130°, hexa-*O*-benzoyl-D-*glycero*-β-L-*manno*-heptose (1 g.) was added. The mixture was heated for 50 min. in an oil bath at 110°, cooled, dissolved in pyridine (10 ml.), and filtered. The solution was poured into water (50 ml.). The resulting oil was washed with water, bicarbonate solution, and again with water. The amorphous material was dissolved in boiling methanol– acetone (5:1) and decolorized with Norit. On cooling the filtrate, it crystallized, yielding 0.125 g. of hexa-*O*-benzoyl-D-*glycero*-β-L-*manno*-heptose, m.p. 98–100°, $[\alpha]^{20}D$ +30.7° (c 1.26, chloroform). The alcoholic mother liquors evaporated to dryness afforded 0.630 g. of material $[\alpha]^{20}D$ +45.6° (c 1.1, chloroform). This optical rotation corresponds to a mixture containing 0.140 g. (21.9 %) α anomer.

A 0.400-g. sample of the mixture was chromatographed on alumina; with a mixture of ethyl ether and benzene (5:95), 0.280 g. of hexa-*O*-benzoyl-D-*glycero*-β-L-*manno*-heptose m.p. 98–100° was eluted. With a mixture of ether and benzene (1:9), 0.070 g. of crystalline material, m.p. 168–170°, was eluted. Recrystallization from ethanol, gave the pure hexa-*O*-benzoyl-D-*glycero*-α-L-*manno*-heptose, m.p. 173–174° $[\alpha]^{20}D$ +96.2° (c 0.3, chloroform).