THE BROMINOLYSIS OF CARBOHYDRATE IODIDES

II. A SYNTHETIC ROUTE TO 2,5-ANHYDROSUGARS[1]

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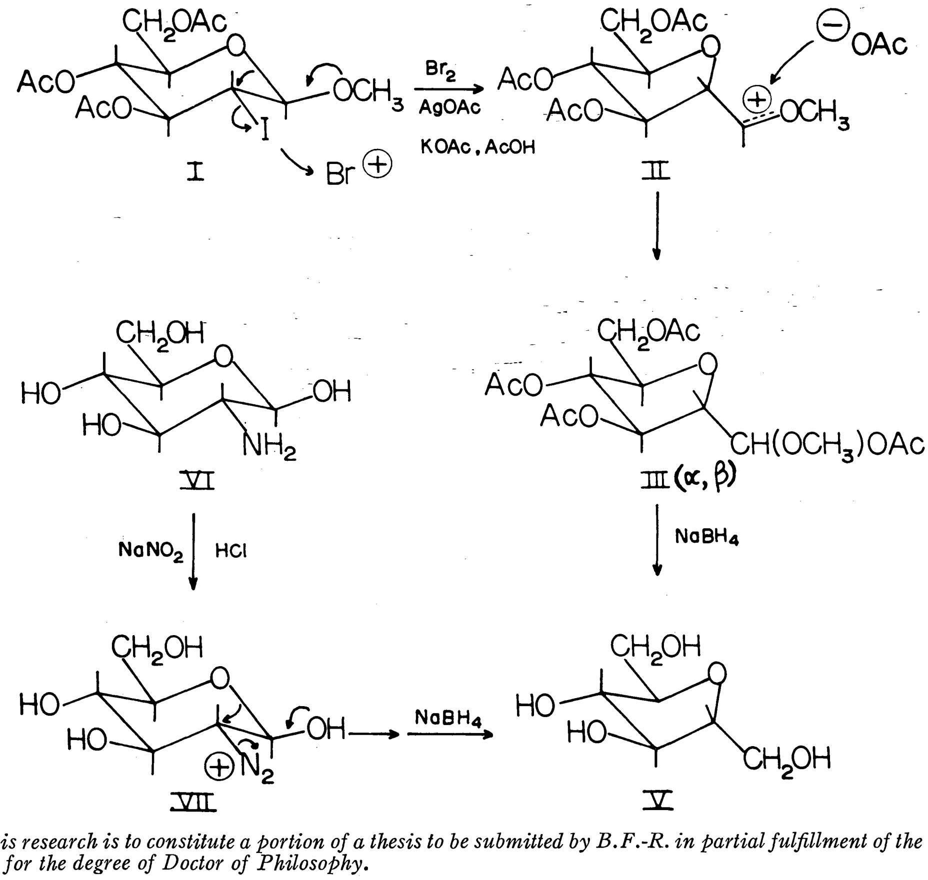
ABSTRACT

Reaction of methyl 2-deoxy-2-iodo-β-D-glucopyranoside triacetate with a 20-fold excess of bromine and a 10-fold excess of silver acetate in a 10% solution of potassium acetate in acetic acid gave a near-quantitative yield of an equimolar mixture of the anomeric forms of 1,3,4,6-tetra-*O*-acetyl-2,5-anhydro-1-methoxy-D-mannose. Treatment of the mixture with methanolic hydrogen chloride gave the dimethylacetal of 2,5-anhydro-D-mannose (chitose).

In the first paper in this series (1), the halogenolysis of alkyl iodides was reviewed and the products formed on the brominolysis in the presence of silver acetate of methyl 6-deoxy-6-iodo-α-D-glucopyranoside triacetate and methyl 2-deoxy-2-iodo-α-D-mannopyranoside triacetate were described. This communication reports the formation of 1,3,4,6-tetra-*O*-acetyl-2,5-anhydro-1-methoxy-D-mannose on the brominolysis of methyl 2-deoxy-2-iodo-β-D-glucopyranoside triacetate (I).



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[1] *This research is to constitute a portion of a thesis to be submitted by B.F.-R. in partial fulfillment of the requirements for the degree of Doctor of Philosophy.*

Brominolysis of I in 10% potassium acetate in acetic acid containing silver acetate led to the formation in quantitative yield of an about equimolar mixture of two compounds. The compounds were separated by column partition chromatography using dimethyl sulphoxide on silicic acid as static phase (2). Nuclear magnetic resonance (NMR) spectroscopy clearly required the compounds to be diastereoisomers differing only in configuration at the anomeric center. The more dextrorotatory compound (IIIα) was assigned the α-configuration and the other (IIIβ) the β-configuration following the original basis for naming anomeric compounds derived from D-sugars (3). Except for the spacings of doublets arising from the anomeric hydrogen, the NMR spectra of the two compounds were virtually identical and required the presence of four acetyl groups per methoxyl group. For IIIα, the doublet was at 5.90 p.p.m. with a spacing of 5.0 c.p.s. In the case of IIIβ, the doublet was at 5.91 p.p.m. with a spacing of 5.8 c.p.s. Since both IIIα and IIIβ underwent profound and rapid degradation on attempted deacetylation with base, the compounds were deacetylated under reductive conditions using sodium borohydride. Although several compounds were formed, the main product of the reaction was a substance identified as 2,5-anhydro-D-mannitol (V) by direct comparison with a sample prepared by borohydride reduction of 2,5-anhydro-D-mannose obtained by nitrous acid deamination of D-glucosamine (VI) (4, 5). It was therefore clear that the brominolysis of I proceeded with participation of the ring-oxygen as is established for the deamination of D-glucosamine (6). The fact that about equimolar amounts of IIIα and IIIβ were formed indicates that the oxocarbonium ion II was a discrete reaction intermediate. This course of reaction further illustrates that the brominolyses of iodides proceed by way of highly reactive intermediates (1) which possess properties very similar to the diazonium salts (VII) formed as intermediates in the nitrous acid deaminations of primary amines (7).

The great ease for the formation of hydroxymethylfurfuraldehyde and related compounds on treatment of 2,5-anhydro-D-mannose with bases or aqueous acid is well known (8–10). It is of interest in this regard that treatment of the mixture of IIIα and IIIβ with methanolic hydrogen chloride readily gave the dimethyl acetal (IV). This type of compound is stable to bases and may prove useful as intermediates in the preparation of 2,5-anhydrosugars (11–13).

EXPERIMENTAL

The melting points, nuclear magnetic resonance spectra, and paper chromatograms were established as described in the previous paper of this series (1). The methyl 2-deoxy-2-iodo-β-D-glucopyranoside triacetate (I) was prepared by iodomethoxylation of D-glucal triacetate (14).

1,3,4,6-Tetra-O-acetyl-2,5-anhydro-1-methoxy-α- and -β-D-mannose (IIIα and IIIβ)

Methyl 2-deoxy-2-iodo-β-D-glucopyranoside triacetate (I), m.p. 94–95° (14), 3.24 g (7.5 mmoles), was dissolved in 150 ml of a 10% solution of potassium acetate in acetic acid which contained 24.0 g (150 mmoles) of bromine. In separate experiments, titration for iodate in the reaction mixture showed that the brominolysis of the iodine was extremely slow (10% reaction in 1 week). However, on the addition of 12.5 g (75 mmoles) of silver acetate, reaction in the dark as shown by the appearance of iodate was complete in 6 hours at room temperature. After a 7-hour reaction time, 150 ml of a 25% aqueous solution of sodium acetate was added and the bromine was reduced by the addition of formic acid. The product was isolated by filtration to remove precipitated solids followed by extraction with chloroform and evaporation in the usual manner (1). The dried colorless syrupy product, 2.48 g, was found by chromatography on dimethyl sulphoxide impregnated paper (15), using Skellysolve B as the developing phase, to contain two components. This composition was substantiated by a comparison of the NMR spectrum of the mixture with those of the two components obtained by preparative chromatography on a column of silicic acid impregnated with dimethyl sulphoxide (2) using a 15% mixture of diisopropyl ether in Skellysolve B as developing phase. The mixture, 853 mg, was added to 2.5 cm × 27.5 cm column and the first pure component (IIIβ), 261 mg, $[\alpha]_D$ +46.3° (c, 2.26 in chloroform) was isolated in the 1500 to 1600 ml fraction of eluate. The next 75 ml provided 350 mg of a mixture of the two components. Compound (IIIα), 161 mg, $[\alpha]_D$ +49.4° (c, 2.7 in chloroform) was obtained in the following 80 ml of eluate. Both the pure compounds gave NMR spectra with sharp signals for four acetoxy groups and one methoxy group at 2.12 and 3.51 p.p.m., respectively. The spectra were almost identical in the range 4.0 to 5.7 p.p.m. and could readily be assigned to the presence in both compounds of two methylenic hydrogens of an acetoxymethyl group (4.26 p.p.m.), two hydrogens on secondary carbons bonded to ring-oxygen (4.0–4.4 p.p.m.) and two hydrogens bonded to secondary carbons each substituted by acetoxy groups (5.37 and 5.14 p.p.m.). In addition, both compounds gave a doublet of intensity 1 at low field. For compound IIIβ, the doublet was at 5.91 p.p.m. and had a spacing of 5.8 c.p.s. In the other compound (IIIα) the doublet center was at 5.90 p.p.m. and the spacing was 5.0 c.p.s. The relative intensities of these doublets in the spectrum of the mixture required IIIβ and IIIα to be present in about equal amounts.

2,5-Anhydro-D-mannose Dimethyl Acetal (IV)

On reacting the mixture of IIIα and IIIβ (0.410 g) formed in the brominolysis reaction with 15 ml of 2% methanolic hydrogen chloride for 7 hours, followed by isolation in the usual manner, the material was converted to a single substance, $R_f = 0.67$, which produced a strong color reaction with *p*-anisidine hydrochloride on paper chromatograms. The compound rapidly consumed 1 mole of periodate per mole in agreement with the assumption that the substance is the dimethylacetal (IV) of 2,5-anhydro-D-mannose (chitose). The compound was acetylated with acetic anhydride in pyridine and the product, $[\alpha]_D$ +41.7° (*c*, 1.39 in chloroform), produced signals in its NMR spectrum for acetoxy- and methoxy-group hydrogens of intensities in the ratio 3:2. A sharp doublet of intensity 1 was present at 3.54 p.p.m. with a spacing of 5.5 c.p.s.

2,5-Anhydro-D-Mannitol (V)

A. From D-*glucosamine*.—A sample of D-chitose was prepared according to the directions prescribed by Bera, Foster, and Stacey (5) starting from D-glucosamine hydrochloride. Reduction of the product with sodium borohydride as described below for the alternate preparation led to the isolation of a substance which on analysis by paper chromatography showed the presence of at least six components using the periodate–permanganate spray reagent. The main component, $R_f = 0.66$, was isolated by chromatography on a cellulose column using *n*-butanol as developing phase. The substance was acetylated using pyridine and acetic anhydride and isolated in the usual manner. The clear syrupy product was dissolved in chloroform and the solution was passed through a short column of silicic acid and the column was washed with chloroform. The chloroform was removed *in vacuo* to leave a syrup, $[\alpha]_D$ +27.3° (*c*, 4.2 in chloroform). The NMR spectrum showed three sharp signals at 4.83 (3- and 4-hydrogens), 5.75, and 1.88 (acetyl hydrogens) p.p.m. of relative intensities 2:6:12 as expected for tetra-*O*-acetyl-2,5-anhydro-D-mannitol should the signals for the six hydrogens at the 1-, 2-, 5-, and 6-positions show no chemical shift and occur at 5.75 p.p.m.

B. From the mixture of IIIα and IIIβ.—The mixture of IIIα and IIIβ from the brominolysis reaction, 4.10 g, was treated with an excess of sodium borohydride, 10 g, in aqueous methanol at room temperature for 7 hours. An excess of acetic acid was then added and the solution was reduced to dryness. Methanol was distilled several times from the residue to remove the boric acid. The product was dissolved in water and the sodium ion was removed by sulphonic acid resin in the acid form. Paper chromatographic examination of the residue obtained on evaporation *in vacuo* showed the presence of at least six components with the main zone at $R_f = 0.66$. The R_f values and relative intensities of the zones were the same as those observed above on chromatography of the product from the borohydride reduction of D-chitose. The main component was isolated on a cellulose column and acetylated and purified as described above. The product $[\alpha]_D$ +26.4° (*c*, 3.9 in chloroform) had the same NMR and infrared spectra as the above described tetra-*O*-acetyl-2,5-anhydro-D-mannitol.

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