Aminosugars and Related Compounds

Part V.* 2-Amino-1:6-Anhydro-2-Deoxy- β -D-altropyranose hydrochloride**

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Treatment of methyl 2:3-anhydro-4:6-*O*-benzylidene- α -D-allopyranoside (IV) with methanolic ammonia (followed by acetylation) yields, as the major product, methyl 2-acetamido-4:6-*O*-benzylidene-2-deoxy- α -D-altropyranoside monohydrate (II) the structure of which is proved. Graded and total acidic hydrolysis of the latter compound yields respectively methyl 2-acetamido-2-deoxy- α -D-altropyranoside and 2-amino-1:6-anhydro-2-deoxy- β -D-altropyranose hydrochloride. The latter compound serves to characterise the parent aminosugar.

Until 1945 the only aminosugars which had been isolated from natural sources were 2-amino-2-deoxy-D-glucose¹ and 2-amino-2-deoxy-D-galactose². Since then a number of other naturally occurring aminosugars have been recognized † and interest in their synthesis has been stimulated ††. In addition to these aminosugars a number of *N*-methylamino¹⁵ and *N,N*-dimethylamino sugars¹⁶ are now known. This paper describes work aimed at the synthesis of 2-amino-2-deoxy-D-altrose.

An obvious starting point for a synthesis of 2-amino-2-deoxy-D-altrose is the compound methyl 2-acetamido-3-*O*-acetyl-4:6-*O*-benzylidene-2-deoxy- α -D-altropyranoside (I) reported by Peat and Wiggins¹⁷ to be the major product of the action of methanolic ammonia (followed by acetylation) on methyl 2:3-

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† Muramic acid³, 3-amino-3-deoxy-D-ribose⁴, 2-amino-2-deoxy-D-fucose⁵, 2-amino-2-deoxy-D-gulose⁶, 2-amino-2-deoxy-D-talose⁷ and 2-amino-2-deoxy-D-mannose⁸.†† The following D-aminosugars have been synthesized: 2-amino-2-deoxy-D-allose⁹, 2-amino-2-deoxy-D-galactose¹⁰, 2-amino-2-deoxy-D-glucose¹¹, 2-amino-2-deoxy-D-gulose¹², 2-amino-2-deoxy-D-mannose¹³ and 2-amino-2-deoxy-D-talose¹⁴, usually isolated as the hydrochloride or *N*-acetate.

anhydro-4:6-*O*-benzylidene- α -D-allopyranoside (IV). Whilst the minor product of this reaction, methyl 3-acetamido-2-*O*-acetyl-4:6-*O*-benzylidene-3-deoxy- α -D-glucopyranoside, was studied in detail¹⁷ the major product apparently was not further examined.

Reinvestigation of this reaction gave methyl 3-acetamido-2-*O*-acetyl-4:6-*O*-benzylidene-3-deoxy- α -D-glucopyranoside in 4.2 % yield with physical constants (m. p. 271°, $[\alpha]_D +44.1^\circ$ in chloroform) in good agreement with those reported¹⁷ (m. p. 270°, $[\alpha]_D +44.6^\circ$ in chloroform) by Peat and Wiggins. The major product *A* (45.7 %) of the reaction was initially assumed to be methyl 2-acetamido-3-*O*-acetyl-4:6-*O*-benzylidene-2-deoxy- α -D-altropyranoside(I) although the physical constants (m. p. 188°, $[M]_D +218^\circ$ in chloroform) were slightly different from those (m. p. 184°, $[M]_D +179^\circ$ in chloroform) reported¹⁷ for this compound. However, failure to release acetate ions by treatment of compound *A* with alkali suggested the absence of *O*-acetyl groups and this was proved by the fact that the infra-red spectrum of compound *A* showed strong absorptions (1 541 and 1 651 cm^{-1}) characteristic¹⁸ of *N*-acetyl groups but no absorption in the region 1 725—1 749 cm^{-1} characteristic¹⁸ of *O*-acetyl groups. The identity of Peat and Wiggins' compound, of which a specimen survived in the chemical collection of the University of Birmingham Chemistry Department, was confirmed when its infra-red spectrum was found to contain strong absorptions at 1 531 and 1 649 cm^{-1} (*N*-acetyl) and at 1 729 cm^{-1} (*O*-acetyl) and on Zemplén deacetylation it gave compound *A*. The latter compound is thus shown to be methyl 2-acetamido-4:6-*O*-benzylidene-2-deoxy- α -D-altropyranoside (II) (isolated as a monohydrate). The infra-red spectra of a series of sugar derivatives containing *O*-acetyl and/or *N*-acetyl groups revealed the range 1 726—1 748 cm^{-1} for *O*-acetyl absorptions and the ranges 1 531—1 555 and 1 634—1 665 cm^{-1} for *N*-acetyl absorptions.

The absence of an *O*-acetyl group from compound *A* is surprising, especially since the minor product isolated from the same reaction mixture was *O*-acetylated. Attempts to *O*-acetylate compound *A* with pyridine and acetic anhydride or acetyl chloride were unsuccessful. The *O*-acetyl group in methyl 2-acetamido-3-*O*-acetyl-4:6-*O*-benzylidene-2-deoxy- α -D-altropyranoside (the product anticipated on *O*-acetylation of compound *A*) was not abnormally labile in that recrystallization could be effected without change under the usual conditions. Since Peat and Wiggins¹⁷ did not give full experimental details further comparison is not possible.

Other evidence was accumulated which substantiated the structure of compound *A*. The presence of a free hydroxyl group was confirmed on treatment of compound *A* with toluene-*p*-sulphonyl chloride in pyridine when methyl 2-acetamido-4:6-*O*-benzylidene-2-deoxy-3-*O*-toluene-*p*-sulphonyl- α -D-altropyranoside (III) was obtained in good yield.

Graded acidic hydrolysis of compound *A* removed the benzylidene residue and yielded methyl 2-acetamido-2-deoxy- α -D-altropyranoside. The ready consumption of approximately one mole of metaperiodate by this latter compound under the usual conditions¹⁹ indicates the presence of a vicinal glycol group and confirms the location of the acetamido residue at *C*₂ in compound *A*. Assuming normal cleavage of the epoxide ring in methyl 2:3-anhydro-4:6-*O*-benzylidene- α -D-allopyranoside under the action of methanolic ammonia

to give diaxial substituents (Fürst-Platner rule ²⁰) then compound *A* and the compounds subsequently derived from it must have the D-altrose configuration. The presence of vicinal *cis*-hydroxyl groups in methyl 2-acetamido-2-deoxy- α -D-altropyranoside is indicated by the more rapid consumption of oxidant than in the case of methyl 2-acetamido-2-deoxy-D-glucopyranoside which contains vicinal *trans*-hydroxyl groups.

Total acidic hydrolysis of methyl 2-acetamido-2-deoxy- α -D-altropyranoside or its 4:6-O-benzylidene derivative (II) yielded 2-amino-1:6-anhydro-2-deoxy- β -D-altropyranose hydrochloride (V) in low yield (28 % and 33 %, respectively). The highly crystalline nature of this compound recommends it for characterization of the parent aminosugar. That 2-amino-2-deoxy-D-altrose was also produced in the hydrolysis was indicated by the reducing power of the hydrolysate since the 1:6-anhydro compound itself is non-reducing. Examination of the hydrolysate by paper chromatography using the organic phase of a butanol-water-acetic acid (4:5:1) solvent system revealed only a single component. However with the *t*-butanol-water-acetic acid (2:1:1) solvent system ²¹ two components were observed which had R_F values and chemical properties similar to those of 2-amino-2-deoxy-D-gulose and 2-amino-1:6-anhydro-2-deoxy- β -D-gulopyranose ⁶. Attempts to isolate the 2-amino-2-deoxy-D-altrose failed to yield a crystalline product.

The formation of a mixture of the free amino sugar and its 1:6-anhydride on acidic hydrolysis of methyl 2-acetamido-2-deoxy- α -D-altropyranoside and its 4:6-O-benzylidene derivative (II) is not surprising since the action of acid on D-altrose is well known ²² to yield an equilibrium mixture of approximately equal proportions of D-altrose and 1:6-anhydro-D-altrose. The $[M]_D$ value -315° (water) of 2-amino-1:6-anhydro-2-deoxy- β -D-altropyranose hydrochloride is similar to those, -339° and -348° , respectively, of 3-amino-1:6-anhydro-3-deoxy- β -D-altropyranose hydrochloride ²³ and 1:6-anhydro- β -D-altropyranose ²².

Like 2-amino-1:6-anhydro-2-deoxy- β -D-gulopyranose hydrochloride ⁶, 2-amino-1:6-anhydro-2-deoxy- β -D-altropyranose hydrochloride readily consumed 2 moles of periodate.

EXPERIMENTAL

All m. p. s are uncorrected. Dry pyridine connotes pyridine which has been distilled repeatedly from phosphorus pentoxide.

Action of methanolic ammonia on methyl 2:3-anhydro-4:6-*O*-benzylidene- α -D-allopyranoside

Methyl 2:3-anhydro-4:6-*O*-benzylidene- α -D-allopyranoside [m. p. 198°, $[\alpha]_D +140.2^\circ$ (c, 1.0 in CHCl_3)] was prepared from methyl 4:6-*O*-benzylidene-2:3-di-*O*-toluene-*p*-sulphonyl- α -D-glucopyranoside by the method of Richtmyer and Hudson²⁴.

The alloside (5 g) was treated, in a Carius tube, with a cooled (0°) mixture of methanol (60 ml, dried over calcium oxide) and liquid ammonia (21 ml). The tube and contents were cooled in liquid air, the tube sealed and then heated at 140° for 3 days. After cooling in liquid air the tube was opened, the solvents were evaporated at 40° (bath)/14–16 mm, and the residue dried over phosphorus pentoxide *in vacuo*. Acetylation of the residue was effected by addition of dry pyridine (50 ml) and acetic anhydride (7.5 ml). After 12 h the mixture was evaporated at 30° (bath)/0.1 mm, the residue was washed with water then dissolved in chloroform (5 ml) and diluted with ether. On cooling (methanol-solid carbon dioxide mixture) methyl 3-acetamido-4:6-*O*-benzylidene-3-deoxy- α -D-glucopyranoside separated which after recrystallization from chloroform-ether afforded a product (0.3 g, 4.2 %) m. p. 271°, $[\alpha]_D +44.1^\circ$ (c, 1.0 in chloroform). (Peat and Wiggins¹⁷ record m. p. 270°, $[\alpha]_D +44.6^\circ$ for this compound). The infra-red spectrum (KBr disc) of this compound showed strong absorptions characteristic of *O*-acetyl (1726 cm^{-1}) and *N*-acetyl (1549 and 1634 cm^{-1}).

From the mother liquors a second product separated and after recrystallization from aqueous-methanol methyl 2-acetamido-4:6-*O*-benzylidene-2-deoxy- α -D-altropyranoside hydrate (2.8 g, 45.7 %) m. p. 188°, $[\alpha]_D +64^\circ$ (c, 1.0 in chloroform) was obtained. (Found: C 55.8; H 6.7; N 4.1. $\text{C}_{16}\text{H}_{20}\text{O}_8\text{N} \cdot \text{H}_2\text{O}$ requires C 56.3; H 6.7; N 4.1), $[\text{M}]_D +218^\circ$. The infra-red spectrum (KBr disc) showed strong absorptions characteristic of the *N*-acetyl group (1541 and 1651 cm^{-1}) but not for *O*-acetyl.

Attempted *O*-acetylation of the foregoing compound using dry pyridine and acetyl chloride or acetic anhydride was unsuccessful; starting material was recovered unchanged.

Methyl 2-acetamido-4:6-*O*-benzylidene-2-deoxy-3-*O*-toluene-*p*-sulphonyl- α -D-altropyranoside

A solution of methyl 2-acetamido-4:6-*O*-benzylidene-2-deoxy- α -D-altropyranoside (2 g) in dry pyridine (12 ml) was treated with toluene-*p*-sulphonyl chloride (3 g) at 30° for 48 h. On dilution of the reaction mixture with ice water and recrystallization of the precipitate from aqueous-acetone the product (1.4 g, 50 %) was obtained m. p. 174° (decomp.), $[\alpha]_D +62^\circ$ (c, 1.0 in acetone), $[\text{M}]_D +296^\circ$. (Found: C 58.0; H 5.6; N 3.0; S 7.2. $\text{C}_{22}\text{H}_{27}\text{O}_8\text{NS}$ requires C 57.8; H 5.7; N 2.9; S 6.8.)

Acidic hydrolysis of methyl 2-acetamido-4:6-*O*-benzylidene-2-deoxy- α -D-altropyranoside

(a) A solution of methyl 2-acetamido-4:6-*O*-benzylidene-2-deoxy- α -D-altropyranoside (1 g) in 2 *N* hydrochloric acid (10 ml) was boiled under reflux for 3.5 h. After two extractions with light petroleum (60–80°) the hydrolysate was neutralised with methyl di-*n*-octylamine²⁵ and then freeze dried. Dissolution of the syrupy residue in 2 *N* hydrochloric acid and dilution with acetone gave 2-amino-1:6-anhydro-2-deoxy- β -D-altropyranose hydrochloride (0.19 g, 33 % after recrystallization from the same solvent system) which was non-reducing towards Fehling's solution and had m. p. 350° (decomp.), $[\alpha]_D -160^\circ$ (c, 0.5 in water) $[\text{M}]_D -315^\circ$. (Found: C 35.7; H 6.0. $\text{C}_6\text{H}_{10}\text{O}_4\text{N} \cdot \text{HCl}$ requires C 36.4; H 6.1.)

The hydrolysate from which the foregoing compound was isolated was strongly reducing towards Fehling's solution. Examination of the neutralised hydrolysate by paper chromatography using the organic phase of a butanol-water-acetic acid (4:5:1) solvent system gave apparently a single spot which reacted strongly with ninhydrin, aniline hydrogen phthalate²⁶ and ammoniacal silver nitrate²⁷. However with a *t*-butanol-water-acetic acid (2:1:1) solvent system²¹ two spots were obtained with mobilities similar to those of 2-amino-2-deoxy-D-glucose and 2-amino-1:6-anhydro-2-deoxy-β-D-glucose*. In each case the faster moving component reacted with ninhydrin only and the slower moving component reacted with both ninhydrin and aniline hydrogen phthalate²⁸. Attempts to isolate the 2-amino-2-deoxy-D-altrose, presumed present in the hydrolysate, by preparative scale paper chromatography did not yield a crystalline product.

(b) A solution of the altroside (1 g) in 0.5 % methanolic hydrogen chloride (10 ml) was boiled under reflux for 2 h. After two extractions with light petroleum (60–80°) the solution was diluted with water and deacidified with methyl di-*n*-octylamine²⁵ and then evaporated at 30° (bath)/0.1 mm. Methyl 2-acetamido-2-deoxy-α-D-altropyranoside (0.672 g, 92.5 %) was obtained as a syrup showing $[\alpha]_D +16.3^\circ$ (c, 1.3 in water), $[M]_D +94^\circ$.

A solution of methyl 2-acetamido-2-deoxy-α-D-altropyranoside (0.0672 g) in water (5 ml) was treated with 0.25 M sodium metaperiodate solution (15 ml) and the volume rapidly adjusted to 50 ml. The consumption of oxidant was determined by the standard arsenite procedure on aliquots withdrawn at suitable time intervals. In a separate experiment methyl 2-acetamido-2-deoxy-α-D-glucopyranoside (0.0672 g) was oxidised under identical conditions. The consumption of oxidant (moles per mole) was as follows:

Time (h)	0.5	1.0	2.0	3.0	4.5
altroside	0.915	0.950	0.950	0.950	0.950
glucoside	0.710	0.915	0.950	0.994	0.994

A solution of methyl 2-acetamido-2-deoxy-α-D-altropyranoside (0.5 g) in 2 N-hydrochloric acid (10 ml) was boiled under reflux for 3 h. 2-Amino-1:6-anhydro-2-deoxy-β-D-altropyranose hydrochloride (0.118 g, 28 %), m. p. 350° (decomp.), $[\alpha]_D -160^\circ$ (c, 0.5 in water) was subsequently isolated as in the foregoing hydrolysis (a).

Periodate oxidation of 2-amino-1:6-anhydro-2-deoxy-β-D-altropyranose hydrochloride

The aminosugar derivative (25 mg) was subjected to periodate oxidation in a manner similar to that described earlier. The consumption of oxidant was as follows:

30 min. 1.85 moles; 1 h. 2.02 moles (final constant value).

Deacetylation of methyl 2-acetamido-3-O-acetyl-4:6-O-benzylidene-2-deoxy-α-D-altropyranoside

A solution of the altroside derivative¹⁷ (50 mg) in dry methanol (20 ml) was treated with a few mg of metallic sodium. After 12 h the solution was neutralised with carbon dioxide, evaporated and the residue recrystallized from aqueous methanol to yield a product m.p. 188° alone or in admixture with the methyl 2-acetamido-4:6-O-benzylidene-2-deoxy-α-D-altropyranoside hydrate described above.

The infra-red spectrum (KBr disc) of methyl 2-acetamido-3-O-acetyl-4:6-O-benzylidene 2-deoxy-α-D-altropyranoside showed strong absorptions characteristic of O-acetyl (1729 cm⁻¹) and N-acetyl (1531 and 1649 cm⁻¹).

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