126. *The Hydrolysis of Acetobromocellobiose: Isolation and Properties of Two New Cellobiose Hepta-acetates.*

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Hydrolysis of acetobromocellobiose under controlled conditions leads to two new acetates, 2,3,6,2′,3′,4′,6′- and 1,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-α-cellobiose. The latter is converted in aqueous pyridine into the former. With ethyl iodide and silver oxide both acetates give ethyl hepta-*O*-acetyl-β-cellobioside. The mechanism of this rearrangement is discussed, as well as the significance of the formation of 2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-α-cellobiose during preparation of 2-hydroxycellobial hepta-acetate.

Although 2-hydroxyglycal acetates have been known for 30 years,[1] the mechanism of their formation by the elimination of hydrobromic acid from acetobromo-sugars by diethylamine is still unknown. It would be expected that some *O*-acetyl-*NN*-diethyl-β-glycosylamine would be produced although this may not necessarily be an intermediate.[2] Although the corresponding *NN*-dimethylglycosylamine acetates are relatively stable,[3] the isolation of a *NN*-diethylglycosylamine intermediate has only been reported in one case,[4] namely, with acetobromoglucose, but it was even then not conclusively identified. We have examined the by-products from the preparation of 2-hydroxycellobial acetate, and have not been able to isolate a cellobiosylamine derivative. The isolation of minor products is difficult owing to considerable degradation but it was possible to isolate a new, nitrogen-free compound whose analysis corresponded to that of a hepta-*O*-acetyl disaccharide. Octa-*O*-acetylcellobiose and ethyl hepta-*O*-acetyl-β-cellobioside were also isolated in small yields. The octa-acetate no doubt was an impurity in the acetobromocellobiose, and the ethyl cellobioside must have arisen when unchanged acetobromocellobiose reacted with ethanol used for fractional crystallisation.

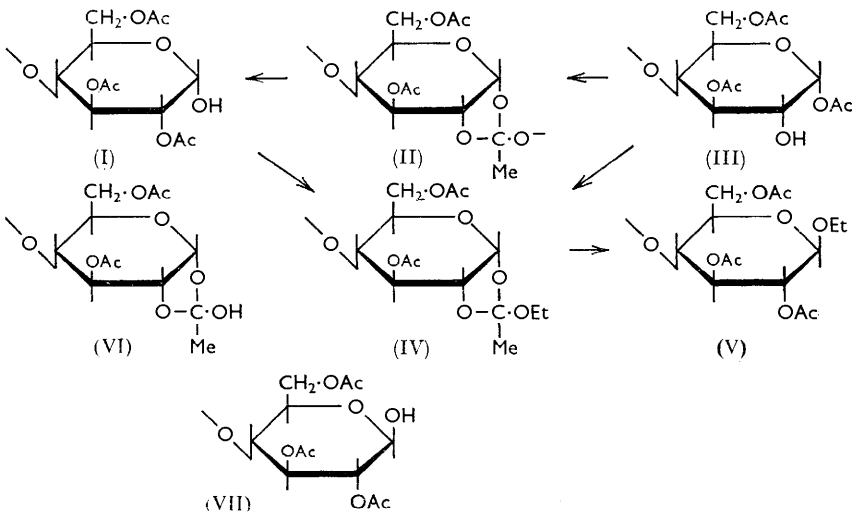
The hepta-acetate gave, on acetylation, a cellobiose octa-acetate, but its constants did not correspond to those of the known 2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-β-cellobiose. The high positive rotation of the new acetate, which also mutarotated, suggested that it is probably the α-form. On being fused, the acetate appeared to anomerise in a manner

[1] Maurer, *Ber.*, 1929, **62**, 332.
[2] Wolfrom and Husted, *J. Amer. Chem. Soc.*, 1937, **59**, 2559.
[3] Corbett and Kidd, *J.*, 1959, 1594, and references therein.
[4] Baker, *J.*, 1929, 1205.

similar to that observed with the corresponding glucose acetates [5] since the optical rotation decreased to $[\alpha]_D^{20}$ +14·1°. Hepta-*O*-acetyl-β-cellobiose behaved similarly, except that the rotation increased from a negative value to $[\alpha]_D^{20}$ +22·0°. The similarity of the melting points and of the rotations of the fused acetates indicated that they were mixtures of the same compounds. This was confirmed by examination of their infrared spectra. Therefore the new acetate is 2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-α-cellobiose. This acetate has also been obtained by hydrolysis of acetobromocellobiose in the presence of silver nitrate as described below.

Formation of hepta-*O*-acetyl-α-cellobiose during the reaction of diethylamine with acetobromocellobiose must be due to traces of water in the system. By analogy with the hydrolysis of acetobromo-sugars with silver nitrate and a limited amount of water,[5] the formation of the α-hepta-acetate must occur through an intermediate such as hepta-*O*-acetyl-*NN*-diethyl-β-cellobiosylamine. Several attempts have been made without success to prepare this derivative by the action of diethylamine upon acetobromocellobiose under various conditions. When diethylsodamide was used it was possible to isolate a small quantity of material having the correct elemental analysis for the cellobiosylamine derivative, but its reactions have not been examined.

In order to confirm the structure of the new acetate, a solution of acetobromocellobiose in tetrahydrofuran was hydrolysed with silver nitrate and a limited amount of water. From the products were isolated 2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-α- and -β-cellobiose and a third acetate. Unlike the other two acetates, the last did not mutarotate in solution.



Because of its positive rotation, its isomerisation to 2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-α-cellobiose (I) in aqueous pyridine, and its conversion into cellobiose octa-acetate on acetylation, it is considered to be 1,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-α-cellobiose (III). Similar compounds are known for D-ribose [6] and D-xylose,[7] and their structures have been proved by a study of their infrared spectra.

Ethylation of 1,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-α-cellobiose with ethyl iodide and silver oxide yielded, not the expected ethyl ether, but ethyl hepta-*O*-acetyl-β-cellobioside (V). This rearrangement further examples of which have recently been reported to occur during the methylation of 1,3,4-tri-*O*-acetyl-D-xylose [8] and 1,3,4,6-tetra-*O*-acetyl-α- and

[5] Georg, *Helv. Chim. Acta*, 1932, **15**, 924.
[6] Ness and Fletcher, *J. Amer. Chem. Soc.*, 1956, **78**, 4710.
[7] Antia, *ibid.*, 1958, **80**, 6138.
[8] Srivastava, *Chem. and Ind.*, 1959, 159.

-β-glucose,[8a] must occur through an orthoacid. The ion (II) which must be responsible for acyl migration in aqueous pyridine will not exist under the etherifying conditions, and the orthoester (IV) is a more feasible intermediate in the reaction. Breakdown of the ester (IV) would be by attack of the ethoxy-oxygen atom at the 1-β-position, to give the β-cellobioside (V). This reaction may or may not be preceded by ionisation of the ethoxy-group.

Rearrangement is not due to silver oxide alone, for a dioxan solution of the acetate is stable when refluxed with silver oxide. Under these conditions any rearrangement would be through the orthoacid intermediate (VI), and it has been shown that orthoacids themselves are unstable and, when formed, rearrange to the corresponding esters. Partial stabilisation of the ortho-structure is achieved by the presence of an alkyl halide which forms the orthoester, probably not *via* the acid itself.

If the above mechanism is correct, then ethylation of 2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-α-cellobiose (I) would also be expected to yield ethyl β-cellobioside acetate *via* the orthoester (IV). This was found to be the case. In contrast, the *trans*-arrangement of the 1- and the 2-group in 2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-β-cellobiose (VII) precludes the formation of an orthoester, and therefore ethylation should occur without inversion. Ethylation of the β-acetate did indeed give the expected ethyl β-cellobioside acetate.

The mechanism postulated above assumes that the intermediate orthoester is unstable. Lemieux and Brice [9] have been able to isolate a methyl orthoester of glucose closely related to the postulated intermediate in the above rearrangement, and have found it to be stable at room temperature. However, there is evidence that at elevated temperatures orthoesters undergo ionisation,[10] and this would explain the breakdown of the postulated orthoester intermediate during ethylation.

Experimental

Acetyl analyses were by alkaline hydrolysis and are consequently high.

2,3,6,2′,3′,4′,6′-*Hepta*-O-*acetyl*-α-*cellobiose*.—(a) *From acetobromocellobiose and diethylamine.* A solution of acetobromocellobiose (61·6 g.) in dry chloroform (250 ml.) and diethylamine (27·7 ml.) was kept at room temperature for 70 hr., and then further chloroform (300 ml.) was added. The solution was washed with water, dilute sulphuric acid, sodium hydrogen carbonate solution, and finally water. It was dried (Na_2SO_4), treated with charcoal, and concentrated under reduced pressure to a syrup which crystallised from ethanol to give hepta-*O*-acetyl-2-hydroxycellobial (12·4 g., 23%), m. p. 129—130° (Found: C, 50·3; H, 5·4. Calc. for $C_{26}H_{34}O_{17}$: C, 50·5; H, 5·5%).

The ethanol mother-liquors were concentrated to a syrup which partly crystallised. The residual syrup was dissolved in ether (300 ml.), and the crystals were fractionally crystallised from ethanol to give octa-*O*-acetyl-α-cellobiose, m. p. and mixed m. p. 226—228°, and ethyl hepta-*O*-acetyl-β-cellobioside, m. p. and mixed m. p. 190—191°.

The ether solution slowly deposited crystals which, after recrystallisation from ethanol–ether, had m. p. 217—218°, and $[\alpha]_D^{22}$ +35·0° (*c*, 4·0 in chloroform). They were 2,3,6,2′,3′,4′,6′-*hepta*-O-*acetyl*-α-*cellobiose* (Found: C, 49·0; H, 5·7. $C_{26}H_{36}O_{18}$ requires C, 49·1; H, 5·7%).

(b) *From acetobromocellobiose and silver nitrate.* A solution of acetobromocellobiose (5·0 g.) in tetrahydrofuran (47 ml.) containing water (0·12 ml.) was refluxed for 5 min. with "active" silver nitrate [5] (1·76 g.). Excess of calcium carbonate was then added, and the mixture refluxed for a further 30 min. The solution was filtered and on addition of ether deposited a very small quantity of crystals, m. p. 208—210°, which gave a positive nitrate test [11] and may be hepta-*O*-acetyl-α-cellobiose 1-nitrate. The filtrate was concentrated to a syrup which partly crystallised from ether, to give 1,3,6,2′,3′,4′,6′-*hepta*-O-*acetyl*-α-*cellobiose* (0·7 g.), m. p. 165—170°. After two recrystallisations from ethanol–ether and one from chloroform–ether, it had m. p. 178—180°, $[\alpha]_D^{19}$ +67·6° (constant; *c* 3·5 in chloroform) (Found: C, 48·8; H, 5·5; Ac, 49·1. $C_{26}H_{36}O_{18}$ requires C, 49·1; H, 5·7; Ac, 47·4%). The concentrated mother-liquors

[8a] Bonner, *J. Org. Chem.*, 1959, **24**, 1388.
[9] Lemieux and Brice, *Canad. J. Chem.*, 1955, **33**, 119.
[10] Isbell and Frush, *J. Res. Nat. Bur. Stand.*, 1949, **43**, 161.
[11] Königs and Knorr, *Ber.*, 1901, **34**, 926.

deposited needles (0·2 g.), m. p. 177—178°, which after three recrystallisations from chloroform–ether had m. p. 214—215°, undepressed on admixture with the above 2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-α-cellobiose, $[\alpha]_D^{19}$ +33·0° (*c* 1·9 in chloroform). Further concentration of the mother-liquors yielded 2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-β-cellobiose (0·06 g.), m. p. 203—204°, $[\alpha]_D^{18}$ −11·2° (*c* 1·3 in chloroform).

Hepta-O-*acetyl*-β-*cellobiose* 1-*Nitrate*.—A solution of acetobromocellobiose (0·5 g.) in dry dioxan (2 ml.) and dry ether (4 ml.) was refluxed for 2 hr. with dry, powdered silver nitrate (*ca.* 0·4 g.). The filtered solution was concentrated under reduced pressure to a syrup which from chloroform–ether gave needles of *hepta*-O-*acetyl*-β-*cellobiose* 1-*nitrate* which, after three recrystallisations, had m. p. 165°, $[\alpha]_D^{18}$ −11·7° (*c* 3·4 in chloroform) and gave a positive test for nitrate [11] (Found: C, 45·4; H, 5·1; N, 2·0. $C_{26}H_{35}O_{20}N$ requires C, 45·8; H, 5·2; N, 2·1%).

Reactions of 2,3,6,2′,3′,4′,6′-*Hepta*-O-*acetyl*-α-*cellobiose*.—(a) *Acetylation*. The hepta-acetate with acetic anhydride containing a small amount of perchloric acid gave octa-*O*-acetyl-α-cellobiose, m. p. and mixed m. p. 230—236°.

(b) *Anomerisation*. The hepta-acetate mutarotated in chloroform solution from $[\alpha]_D^{20}$ +33·3° to +25·0° (24 hr.) (*c* 4·8). Under similar conditions the β-hepta-acetate mutarotated from $[\alpha]_D^{20}$ −7·0° to +19·8° (*c* 3·5).

The α-hepta-acetate, when heated at 220° for 5 min., gave a glass which from chloroform–ether gave crystals, m. p. 189—193°, $[\alpha]_D^{20}$ +14·1° (*c* 1·9 in chloroform). Under similar conditions the β-hepta-acetate gave crystals, m. p. 212—216°, $[\alpha]_D^{20}$ +22·0° (*c* 1·0 in chloroform). The infrared spectra of the two products were identical.

(c) *Ethylation*. The α-hepta-acetate (*ca.* 30 mg.) in dioxan (4 ml.) was refluxed for 1 hr. with excess of ethyl iodide and silver oxide. After filtration, the solution was concentrated to a syrup which crystallised completely, to give ethyl hepta-*O*-acetyl-β-cellobioside, m. p. and mixed m. p. 183—185·5°, $[\alpha]_D^{23}$ −25·3° (*c* 4·3 in chloroform). Under similar conditions the β-hepta-acetate gave ethyl hepta-*O*-acetyl-β-cellobioside, m. p. and mixed m. p. 187—189°.

Reactions of 1,3,6,2′,3′,4′,6′-*Hepta*-O-*acetyl*-α-*cellobiose*.—(a) *Acetylation*. This hepta-acetate with acetic anhydride and perchloric acid gave octa-*O*-acetyl-α-cellobiose, m. p. and mixed m. p. 227—230°.

(b) *Acyl migration*. A solution of the acetate (30·5 mg.) in pyridine–water (10 : 2 by vol.; 5 ml.) was kept at room temperature for 30 hr. during which the optical rotation fell from $[\alpha]_D^{21}$ +52·5° to +26·2°. The solution was diluted with water; on cooling, a gelatinous mass separated. This was centrifuged off, dried, triturated with ether, and recrystallised from ethanol to give 2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-α-cellobiose, m. p. and mixed m. p. 190—192°, depressed on admixture with the β-form.

(c) *Ethylation*. In dioxan the acetate with ethyl iodide and silver oxide gave ethyl hepta-*O*-acetyl-β-cellobioside in high yield, m. p. and mixed m. p. 186—188°, $[\alpha]_D^{20}$ −25·9° (*c* 1·1 in chloroform).

Reaction of Diethylsodamide with Acetobromocellobiose.—Diethylsodamide was prepared by treating sodium wire with diethylamine under reflux, whereupon a gelatinous deposit was formed. To a suspension of this amide (*ca.* 0·16 g.) in diethylamine (40 ml.) was added a solution of acetobromocellobiose (1·0 g.) in chloroform (10 ml.). The mixture was refluxed for 3 hr., further chloroform was added, and the whole was filtered and concentrated under reduced pressure to a dark syrup which was crystallised from absolute ethanol. After three recrystallisations, the *product* (0·15 g.) had m. p. 185—187° (decomp.) (Found: C, 52·0; H, 6·5; N, 2·0. $C_{30}H_{45}O_{17}N$ requires C, 52·2; H, 6·6; N, 2·0%).

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