REDUCTION OF SECONDARY *p*-TOLUENESULFONYLOXY GROUPS WITH LITHIUM ALUMINUM HYDRIDE IN SUGAR SERIES. III.*

REDUCTION OF METHYL 4,6-O-BENZYLIDENE-2,3-DI-O-*p*-TOLUENESULFONYL-α-D-IDOPYRANOSIDE AND α-D-ALTROPYRANOSIDE

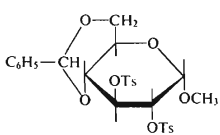
A. ZOBÁČOVÁ, V. HEŘMÁNKOVÁ and J. JARÝ

Laboratory of Monosaccharides,
Institute of Chemical Technology, Prague 6

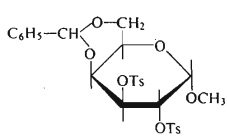
Received May 29th, 1970

Reduction of 4,6-O-Benzylidene-2,3-di-O-*p*-toluenesulfonyl-α-D-altropyranoside (*IVa*) leads to the corresponding 3-deoxy derivative *IVb* as the main product, while the stereoisomer of the *ido* configuration gave 2-deoxy compound *Vc*.

In our previous papers we followed the course of the reduction of stereoisomeric 2,3-ditosyl-4,6-benzalhexosides of *gluco* (*I*) (ref.[1]), *galacto* (*II*) (ref.[2]), and *manno* (*III*) (ref.[1]) configuration. We found that the course of the reduction is strongly influenced by the sterical arrangement of the whole molecule. With mannoside *III* with a *cis* arrangement of both tosyloxy groups, where neither the formation of oxides nor an intramolecular reduction to deoxy derivative can take place, the cleavage of O—S bonds took place exclusively, giving rise to corresponding hydroxy derivatives[1]. Glucoside *I* gave on intramolecular reduction the 3-deoxy derivative[1] in 45% yield, while in the case of the *galacto* configuration[2] the intramolecular reduction does not take place at all; with the α-anomer *II* only the cleavage of the O—S bonds



I



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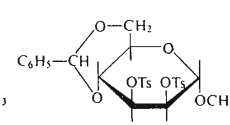


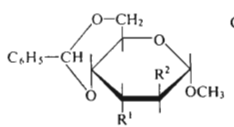
III

* Part II: This Journal *36*, 303 (1971).

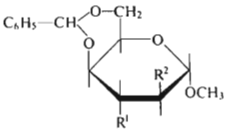
takes place, with the β-anomer the oxide formation and its reductive cleavage to corresponding 3-deoxyidoside prevails.

In order to be able to follow and to compare the course of this reaction in a series of stereoisomeric methyl-4,6-O-benzylidene-2,3-di-O-*p*-toluenesulfonyl-α-D-hexopyranosides we prepared and reduced the remaining two possible stereoisomers with a *trans*-configuration of both tosyloxy groups, in which reduction up to the deoxy derivative could be supposed, *i.e.* the altroside *IVa* and the idoside *Va*.

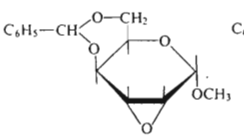
Ditosylaltroside *IVa* was prepared according to Robertson and Whitehead[3] from *allo*-epoxide. In order to prepare the as yet underscribed idoside *Va* we chose ditosyl galactoside *II* as starting material which we transformed according to Huber and Reichstein[4] (using methoxide) to a mixture of corresponding epoxides of *gulo* (*VI*) and *talo* (*VII*) configuration. In contrast to the results of the mentioned authors our own results were quite reproducible in a number of experiments. If the reaction mixture is refluxed in a sufficiently large flask (foaming), the reaction time can be shortened to 30–40 minutes. No starting galactoside could be found in the reaction mixture. Shortening of the reaction time diminishes the unwanted opening of the epoxides with methoxide. Both epoxides were present in the reaction mixture in an approximate 5 : 3 ratio, *i.e.* the isomer of the *gulo*-configuration slightly prevails.



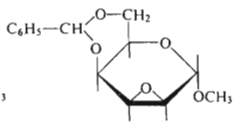
IVa; $R^1 = OTs$, $R^2 = OTs$
IVb; $R^1 = H$, $R^2 = OH$
IVc; $R^1 = OH$, $R^2 = H$
IVd; $R^1 = OH$, $R^2 = OH$



Va; $R^1 = OTs$, $R^2 = OTs$
Vb; $R^1 = OH$, $R^2 = OH$
Vc; $R^1 = OH$, $R^2 = H$
Vd; $R^1 = OH$, $R^2 = OCH_3$
Ve; $R^1 = OCH_3$, $R^2 = OH$
Vf; $R^1 = OH$, $R^2 = SC_6H_4CH_3$-*p*



VI



VII

Further, products of the opening of the epoxide ring with methanol, *i.e.* 2-O-methyl-idoside *Vd* and 3-O-methyl-idoside *Ve* in a 1 : 3 ratio, were also present. This mixture was separated chromatographically on alumina, leading to pure epoxides, or hydrolysed directly with boiling alkali hydroxide[5]. The products of hydrolysis were separated chromatographically to give the two unchanged methylidosides *Vd* and *Ve* in pure state, and also benzalidoside *Vb* as the main product. On tosylation the latter gave ditosylidoside *Va* in 90% yield.

The reduction was carried out in the usual manner[1], with lithium aluminum hydride in tetrahydrofuran, and the crude product was chromatographed on alumina. From ditosylaltroside *IVa* 3-deoxyaltroside *IVb* was thus obtained in up to 60% yield in addition to a small percentage of 2-deoxyaltroside *IVc*. As usual, small amounts of the starting compound *IVa* and of benzalaltroside *IVd* were also isolated. In contrast to this ditosylidoside *Va* gave 2-deoxyidoside *Vc* and 2-thioderivative *Vf* as the main products, accompanied by the starting compound *Va* and benzalidoside *Vb*. The presence of 2-*p*-tolylthioderivative *Vf* in the reaction mixture can be explained by the opening of the intermediarily formed *gulo*-epoxide *VI* by thiocresolate anion, similarly as in the case of the reduction of 4,6-O-benzylidene-2,3-di-O-*p*-toluenesulfonyl-β-D-galactopyranoside[2]. For comparison we prepared an authentic sample by reaction of *gulo*-epoxide *VI* with thiocresol, employing a method described in our previous communication[2]. On the basis of literature data[6] according to which *gulo*-epoxide *VI* opens under the influence of mercaptans exclusively at the position 2 we assigned the configuration *Vf* to our tolylthioderivative.

The first step in both reductions described in this paper evidently again consists in a stereoselective splitting off of one tosyl group (cleavage of the S—O-bond), in the case of altroside in the position 2, and in the case of idoside in the position 3. If comparing all four conformations studied at this point we see that both hexosides having both six-membered rings attached in *cis*-configuration (analogy to *cis*-decalin system), *i.e.* galactoside *II* and idoside *Va*, have a tendency to split off the tosyloxy group in the position 3 primarily, while hexosides with a *trans*-decalin system, *i.e.* glucoside *I* and altroside *IVa*, split off first the tosyl group in the position 2. The selectivity cannot be caused by differing axial equatorial positions of the corresponding tosyloxy groups, because in all instances they were *trans*-ditosyl derivatives in which both groups are equivalent, *i.e.* either both axial or both equatorial. The effect cannot be explained by an inductive effect spread along the chain either, because the compounds are stereoisomers. Hence, it depends evidently on the overall steric arrangement of the molecule. Analogous selective elimination of one of the two tosyloxy groups (cleavage of the O—S bond) takes place in these compounds in alkaline medium during the formation of epoxides. It is known from the literature, for example, that glucoside *I* affords anhydro derivative of *allo* configuration[7] only, and that altroside *IVa* gives anhydro derivative of *manno* configuration[3]; thus, in both cases the tosyloxy group in the position 2 is split off preferentially.

From α-galactoside *II* epoxides are formed less easily than in the case of other configurations, giving rise to a mixture of both isomers, *VI* and *VII*; however, from β-anomer the epoxide of talo configuration[5] is formed mainly, *i.e.* the tosyloxy group in the position 3 is split off preferentially. This is also the case with idoside *Va* from which on alkaline treatment we obtained a mixture of *gulo*-epoxide *VI* and *talo*-epoxide *VII* in 6 : 1 ratio. This means that the preferential cleavage of the group in the position 3 predominates.

The second step of the reduction consists in the transformation of the temporarily formed monotosyl derivative. This is partly transformed by further cleavage of the S—O-bond to dihydroxyderivative (*IVd*, *Vb*) in a manner taking place more or less in all presently investigated reductions, and it gives partly the deoxy derivative. However, in the case of *altro*- and *ido*-configuration it cannot be decided strictly whether this deoxy derivative is formed by intramolecular reduction as in the case of glucoside[1] or whether the reduction of the temporarily formed epoxide takes place as in β-galactoside[2], as both mechanisms would lead here to the same products. We consider it only probable that the reduction of altroside is intramolecular because neither an epoxide nor the products of its cleavage could be isolated from the reaction mixture. In contrast to this in the case of idoside *Va* a reduction of the temporarily formed epoxide could be involved because in this case the product formed by its opening, *Vf*, was isolated.

Finally, the observations made during the reductions of the tosyloxy groups in the positions 2 and 3, of the 4,6-benzalhexosides investigated up to the present time can be summarised. The reduction to a deoxy compound can take place in those instances where on the neighbouring carbon atom the suitable substituent is in *trans* position enabling either an intramolecular reduction or the formation of epoxides. The reduction is very sensitive to steric arrangement of the molecule. The α- and β-anomers of the same hexose give completely different results. Similarly small changes in configuration mean great differences in the yield of deoxy compound and even distinct changes in the reaction mechanism. The difference is especially striking in the case of the following pairs: *gluco* (45% of 3-deoxyderivative)–*galacto* (α – 0%, β – approx. 15–20% of 3-deoxy derivative), and *altro* (58% of 3-deoxy derivative)–*ido* (36% of 2-deoxy derivative), which differ from one another only by the configuration on the fourth carbon atom, while the configuration on both groups involved in the reaction is always identical. The change of configuration on the fourth carbon, meaning the change of the *trans*-fused six-membered rings to *cis*-fused ones (in analogy to *trans*- and *cis*-decalin), brings about in both cases a sharp drop of reactivity in the mentioned sense, or also a change in stereoselectivity (3-deoxy to 2-deoxy) and probably also the change of the reaction mechanism (intermolecular *versus* reduction of epoxide).

The influence of the axial or the equatorial position of the tosyloxy group is evident when comparing the pairs *altro* : *gluco* and *ido* : *galacto* which differ

only by configuration on carbons 2 and 3. When considering all hexosides in the usual C-1 conformation, then *altro* and *ido* have both tosyloxy groups in axial positions and *gluco* and *galacto* in equatorial positions which is less suitable for intramolecular reduction or for the formation of epoxides. The corresponding diaxial compound in both cases gave slightly higher yield of deoxy derivative than the corresponding diequatorial compound.

EXPERIMENTAL

Melting points were determined on a Kofler block and they are not corrected. Mixture melting points were determined in capillaries. Samples for analysis were dried *in vacuo* at room temperature for 8 hours. Solutions were evaporated on a vacuum rotatory evaporator at 40°C bath temperature. Reaction courses and the purity of products were controlled by thin-layer chromatography on alumina (Brockmann, activity II—III), using benzene with 0 to 20% of ethanol as eluent and iodine vapours for detection, or on silica gel fixed with gypsum, using benzene or chloroform with 0 to 20% ethanol for elution. Optical rotations were measured in a tube 2 dm long, using chloroform as solvent, at a concentration 1 ± 0·1, if not stated otherwise.

Methyl 4,6-O-Benzylidene-2,3-di-O-*p*-toluenesulfonyl-α-D-altropyranoside (*IVa*)

It was prepared by tosylation of methyl 4,6-O-benzylidene-α-D-altropyranoside[3] with a 100% excess of toluenesulfonyl chloride in a mixture of pyridine and chloroform. Yield of the product 80%, m.p. 181—182°C, $[\alpha]_D^{20}$ +46·5°C. Literature[3] gives m.p. 179°C, $[\alpha]_D^{15}$ +46·9° (chloroform).

Methyl 2,3-Anhydro-4,6-O-benzylidene-α-D-gulopyranoside (*VI*) and Methyl 2,3-Anhydro-4,6-O-benzylidene-α-D-talopyranoside (*VII*)

A. A hot solution of 10 g of ditosyl galactoside *II* in 75 ml of benzene was added to 2 g of sodium dissolved in 30 ml of methanol (500 ml flask) and the mixture was refluxed for 40 minutes. It was then decomposed with 80—100 ml water and methanol was evaporated under reduced pressure. The aqueous residue was extracted with 4 × 70 ml of benzene and the benzene extract was evaporated. The residue was chromatographed on 120 g of alumina, affording 1146 mg (25·7%) of *gulo*-epoxide *VI*, m.p. 176°C (lit.[4] gives m.p. 174—175°C), 500 mg (11·2%) of a mixture of both epoxides *VI* and *VII*, 696 mg (15·6%) of *talo*-epoxide *VII* containing small amounts of 3-methoxyidoside *Ve* which after crystallisation from ethanol gave pure *VII*, m.p. 238—240°C (lit.[4] gives m.p. 240 to 242°C), and 331 mg (6·6%) of a mixture of methoxy derivatives *Vd* and *Ve*.

B. To a solution of 460 mg of ditosylate *Va* in 30 ml of methanol 6 ml of a 2·7M sodium methoxide solution were added and the mixture was refluxed for 3 hours. After decomposition with water methanol was evaporated under reduced pressure. The aqueous residue was extracted with four 50 ml portions of benzene, the extract was evaporated and the residue chromatographed on 80 g of alumina. The following fractions were obtained: 137 mg (66·5%) of *gulo*-epoxide *VI*, m.p. 174—175°C; 25 mg (12·2%) of *talo*-epoxide *VII*, m.p. 238°C; 20 mg (8·5%) of 3-methoxyidoside *Ve*; 8 mg (3·5%) of a mixture of *Ve* and *Vd*.

Methyl 4,6-O-Benzylidene-α-D-idopyranoside (*Vb*)

A. On hydrolysis of 2 g of a mixture of pure epoxides *VI* and *VII* in a solution of 5 g potassium hydroxide in 80 ml of water at 100°C and crystallisation from methanol 1·48 g (69%) of chromatographically pure benzalidoside *Vb* were obtained, m.p. 147—149°C, $[\alpha]_D^{20}$ +49·1°. Literature[5] gives m.p. 148—149°C, $[\alpha]_D^{14}$ +49·2° (chloroform).

B. A mixture of 10 g of ditosyl galactoside *II*, 31 ml of 2·7M sodium methoxide, and 75 ml of benzene was refluxed for 1·5 hours, decomposed with water, and concentrated *in vacuo*. The residue was extracted with benzene and the extract was evaporated to dryness. The residue was hydrolysed in a solution of 9 g of potassium hydroxide in 120 ml of water at 100°C for 15 hours. The solution was neutralised (phenolphthalein) with carbon dioxide, evaporated to dryness, and the residue extracted with four 80 ml portions of hot chloroform. The extract was evaporated and the residue chromatographed on 100 g of alumina. Fractions: 630 mg (14·1%) of 3-methoxyidoside *Ve*, m.p. 132–133°C, $[\alpha]_D^{20}$ +66·8° (lit.[8] gives m.p. 134°C, $[\alpha]_D$ +66°, chloroform); 162 mg (3·6%) of a mixture of *Ve* and *Vd*; 198 mg (4·4%) of 2-methoxyidoside *Vd*, m.p. 174°C, $[\alpha]_D^{20}$ +73·8° (lit.[8] gives m.p. 176°C, $[\alpha]_D$ +76·7°, chloroform); 1 242 mg (26·1%) of benzalidoside *Vb*. The yields were calculated using the starting ditosyl derivative *II* as basis of calculation.

Methyl 4,6-O-Benzylidene-2,3-di-O-*p*-toluenesulfonyl-α-D-idopyranoside (*Va*)

A mixture of 1·7 g of benzalidoside *Vb*, 9 ml of pyridine, 6 g of toluenesulfonyl chloride, and 15 ml of chloroform was allowed to stand at 35–40°C. After decomposition with water and conventional working up 3·2 g (90%) of ditosyl derivative *Va* were isolated, m.p. 153–155°C, $[\alpha]_D^{20}$ +35·7°. For $C_{28}H_{30}O_{10}S_2$ (590·7) calculated: 56·93% C, 5·12% H, 10·86% S; found: 56·91% C, 4·96% H, 10·86% S.

Reduction of Methyl 4,6-O-Benzylidene-2,3-di-O-*p*-toluenesulfonyl-α-D-altropyranoside (*IVa*)

A. A suspension of 0·8 g of lithium aluminum hydride in 15 ml of tetrahydrofuran was refluxed for 1·5 hours, upon which a solution of 3 g ditosyl derivative *IVa* in 20 ml of tetrahydrofuran was added to it dropwise. The reaction mixture was refluxed 18 h (90–100°C bath temperature), decomposed with 10 ml of ethyl acetate and then with a solution of 20 g natrium potassium tartrate in 50 ml of water. The mixture was extracted four times with 100 ml portions of ether. The combined ethereal extracts were dried over magnesium sulfate, filtered and evaporated. The residue, 1·6 g, was chromatographed on a column of 130 g of alumina. Fractions: 54 mg of a mixture in which according to thin-layer chromatography ditosylate *IVa* and 2-deoxyaltroside *IVc* prevailed; 160 mg (11·8%) of 2-deoxyaltroside *IVc*, m.p. 115–118°C, 126°C, $[\alpha]_D^{20}$ +143° (lit.[9] gives m.p. 117–119°C, 126–128°C, $[\alpha]_D$ +151·9 ± 3°, chloroform); 193 mg of a mixture in which prevail both deoxy compounds *IVb* and *IVc*; 780 mg (58%) of 3-deoxyaltroside *IVb*, m.p. 110–111°C, $[\alpha]_D^{20}$ +95·6° (lit.[10] gives m.p. 111·5–113°C, $[\alpha]_D$ +95·5° in chloroform); 160 mg (11·2%) of benzalaltroside *IVd*, m.p. 169–170°C, mixture m.p. with an authentic specimen was undepressed.

B. On reduction of 3 g of ditosyl derivative *IVa* with 0·5 g of lithium aluminum hydride the following fractions are obtained: 289 mg of a mixture which contained mainly *IVa* and *IVc*; 228 mg of a mixture of compounds in which *IVb* predominated; 670 mg (49·6%) of *IVb*; 140 mg (10%) of *IVd*.

Reduction of Methyl 4,6-O-Benzylidene-2,3-di-O-*p*-toluenesulfonyl-α-D-idopyranoside (*Va*)

A. Reduction and the isolation of products was carried out in the same manner as in the preceding experiment. From 3 g of *Va* and 0·8 g of lithium aluminum hydride the following products were obtained: 7·3 mg of a mixture of *Va* and *Vc*; 490 mg (36%) of 2-deoxyidoside *Vc*, m.p. 77–78°C, 102–103°C, $[\alpha]_D^{20}$ +74° (lit.[6] gives m.p. 78–79°C, 103–104°C, $[\alpha]_D^{20}$ +77° in chloroform); 125 mg of a mixture of *Vc* and *Vf*; 334 mg (17%) of *Vf* which was identical with an authentic sample prepared by a known method[2] from *gulo*-epoxide *VI* and thiocresol, m.p.

95—97°C, $[\alpha]_D^{20}$ —45·8°. For $C_{21}H_{24}O_5S$ (388·5) calculated: 64·92% C, 6·23% H, 8·26% S; found: 65·34% C, 6·23% H, 8·55% C. Further 476 mg (33%) of benzalidoside *Vb*, m.p. 144—146°C were also isolated. Its mixture melting point was undepressed.

B. In a similar manner 2 g of *Va* and 0·34 g of lithium aluminum hydride gave: 33 mg of a mixture of *Va* and *Vc*; 257 mg (28·6%) of *Vc*; 134 mg of a mixture of *Vc* and *Vf*; 171 mf (13%) of *Vf*; 324 mg (33%) of *Vb*.

The analyses were carried out in the Department of Organic Analysis of the Central Laboratories, Institute of Chemical Technology, under the direction of Dr L. Helešic. For the preparation of the starting material we thank to Mr M. Sova.

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Translated by Ž. Procházka.