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REDUCTION OF SECONDARY *p*-TOLUENESULPHONYLOXY GROUPS WITH LITHIUM ALUMINIUM HYDRIDE IN SUGAR SERIES. II.* **

REDUCTION OF α- AND β-METHYL-4,6-O-BENZYLIDENE-2,3-DI-O-*p*-TOLUENESULPHONYL-D-GALACTOPYRANOSIDE

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In our previous work[1] we studied reduction of secondary toluenesulphonyloxy groups with lithium aluminium hydride. We have found that the secondary toluenesulphonyl group may be reduced to the deoxy stage provided there is a suitably located group which can form an alkoxyaluminium hydride and thus enable an intramolecular reduction. Such a group may be a neighbouring ester or hydroxy group, *trans* to the tosyloxy group which is reduced: this we demonstrated by several successful reductions of 2- and 3-tosyloxy groups in sugar derivatives of the *gluco* series. It was of interest to know to what extent this reduction is influenced by steric arrangement of the whole molecule and we decided therefore to study the reduction of stereoisomeric *galacto* compounds. In the *gluco* series[1] it was the 2,3-ditosyl derivative *Ia* which afforded the appropriate deoxy compound in highest yield and for this reason we chose for the reduction study the analogous ditosyl galactoside *IIa* which differs only in the configuration on $C_{(4)}$ and which might give either 3-deoxy or 2-deoxy derivative. We performed reduction of the tosyl derivative *IIa* under the same conditions as in the case of the glucoside *Ia* but from the reaction mixture we isolated, in addition to the starting ditosyl derivative *IIa*, only the 2-O-tosylgalactoside *IIb* and the benzal derivative *IIc*. As shown by thin-layer chromatography, in several chromato-

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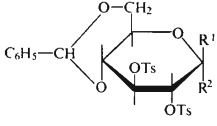
** Dedicated to the memory of Professor R. Lukeš (deceased 1960).

graphic fractions containing mainly 2-tosyl derivative *IIb*, small amount of a compound *A* was present. This compound (*A*), however, was obtained only as a mixture with the derivative *IIb*. We suppose that the compound *A* is probably one of the possible deoxy compounds rather than the isomeric 3-tosyl derivative *IId* because this mixture (*A* + *IIb*) has lower rotation and sulphur content. However, the total yield of this compound did not exceed 2—3% in several repeated experiments. Use of higher excess of lithium aluminium hydride resulted in higher yield of the benzalgalactoside *IIc* and lower yield of the derivatives *IIa* and *IIb*. Thus, in contrast to the *gluco* series, in reduction of the ditosylgalactoside *IIa* the S—O fission strongly predominates and the deoxy derivative, if any, arises in the amount of only 2—3%.

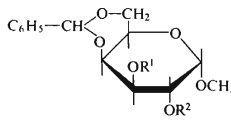
It is possible to draw an analogy between epoxide formation from the *trans*-ditosyl derivatives and their intramolecular reduction to deoxy compounds because both reactions have two common requirements: *a*) the preferential removal of one of the tosyl groups (fission of the S—O bond) which is the stereoselectivity determining step of the reaction, *b*) the *anti*-periplanar arrangement of substituents on $C_{(2)}$ and $C_{(3)}$. This crude analogy holds for both the α-glucoside *Ia* (45% of the deoxy product)[1] and for the α-galactoside *IIa* (2% deoxy): it is known that the galactoside *Ia* affords smoothly and stereospecifically the *allo*-epoxide[2] whereas reaction of the corresponding galacto derivative is both very sluggish and non-stereospecific[3]. The same analogy holds for the α- and β-anomers *Ia* and *Ib*; in this case the formation of epoxide[4] as well as of the deoxy-derivative from the β-anomer is more difficult[5] than from the α-anomer.

Having in mind the fact that in the *galacto* series epoxides are formed readily from the β-anomer[3,6,7], we reduced also the anomeric compound *IIIa*. This is indeed reduced to the deoxy compound but the reaction course differs from all cases hitherto studied.

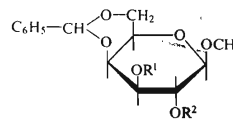
Instead of isolation of either 2- or 3-deoxygalactoside, which would be the likely products of intramolecular reduction, we obtained the 3-deoxyidoside *Va*. This compound could arise only



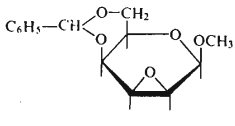
Ia, $R^1 = H$, $R^2 = OCH_3$
Ib, $R^1 = OCH_3$, $R^2 = H$



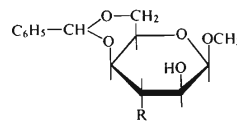
IIa, $R^1 = Ts$, $R^2 = Ts$
IIb, $R^1 = H$, $R^2 = Ts$
IIc, $R^1 = H$, $R^2 = H$
IId, $R^1 = Ts$, $R^2 = H$



IIIa, $R^1 = Ts$, $R^2 = Ts$
IIIb, $R^1 = H$, $R^2 = H$
IIIc, $R^1 = H$, $R^2 = Ts$



IV



Va, R = H
Vb, $R = CH_3C_6H_4S$

Ts = *p*-toluenesulphonyl

by reduction of the *talo*-epoxide *IV*, precursor of which is the 2-tosyl derivative *IIIc* which in turn can arise from the ditosyl derivative *IIIa* by preferential S—O fission of the $C_{(3)}$ tosyl group. In actual fact, both the compounds *IIIc* and *IV* were isolated from the reaction mixture. In addition to these compounds we obtained the benzalgalactoside *IIIb* and the starting ditosyl derivative *IIIa* in amounts which depended on the employed excess of hydride. We isolated also small amount of a compound, *B*, which contained sulphur, but had different melting point, rotation, R_F value and elemental analysis from the all likely tosyl derivatives. The infrared spectrum of this compound exhibited a free hydroxyl band, but characteristic absorptions of the sulfonate group at 1 200 cm^{-1} and 1 400 cm^{-1} were absent. We assumed that this compound is a product of opening of the *talo*-epoxide, present in the reaction mixture, with thiocresolate anion which arose by reduction of toluenesulphonyl group, and hence ascribed to this compound structure *Vb*. To verify this assumption, we prepared the authentic compound by reaction of the *talo*-epoxide *IV* with *p*-thiocresolate. We obtained in high yield a product which was identical with compound *B* isolated from the reduction. Opening of the epoxide *IV* may in principle afford two compounds, either 3-tolylthioidoside *Vb* or the isomeric 2-tolylthio derivative of the *galacto*-configuration. It is known, however, that nucleophilic reagents[6,7], including mercaptanes[8], attack the *talo*-epoxide *IV* exclusively on the carbon $C_{(3)}$ to give producs of the *ido*-configuration, in accord with Fürst-Plattner rule[9]: we therefore assign compound *B* the structure *Vb*.

As conclusion we may say that the reduction of tosyl derivatives with lithium aluminium hydride depends very sensitively on the steric arrangement of the whole molecule. Whereas reduction of the glucoside *Ia* results in preferential cleavage of the tosyl group on $C_{(2)}$, in the reduction of α- and β-galactoside *IIa* and *IIIa* cleavage on $C_{(3)}$ takes place, forming thus intermediates with one tosyloxy group. The monotosyl intermediate of the α-*gluco* series undergoes then an intramolecular reduction to give mainly the deoxy derivative[1]; the β-*galacto* derivative is transformed into the epoxide and products of its further reaction, and finally, the α-*galacto*-monotosylate gives only the dihydroxy derivative by further S—O cleavage.

EXPERIMENTAL

Melting points were determined on a Kofler block and are not corrected. Mixed melting points were determined in a capillary. Solutions were evaporated on a vacuum rotatory evaporator at 40°C (bath). Reactions were followed and purity of products was checked by thin-layer chromatography on alumina (grade II—III) using 0—20% ethanol–benzene as eluent, depending on the compound studied. Spots were detected with iodine. Unless otherwise stated, optical rotations were measured in 2 dm tube in chloroform solution ($c = 1 \pm 0{\cdot}1$).

Compounds Used

Methyl 4,6-O-*Benzylidene*-2,3-*di*-O-*p*-*toluenesulphonyl*-α-D-*galactopyranoside* (IIa) was prepared by tosylation of methyl 4,6-O-benzylidene-α-D-galactopyranoside[7] in 88% yield, m.p. 178—179°C, $[\alpha]_D^{23}$ +141°. The literature[7] states m.p. 182—183°C, $[\alpha]_D^{14}$ +137° (chloroform).

Methyl 4,6-O-*Benzylidene*-2,3-*di*-O-p-*toluenesulphonyl*-β-D-*galactopyranoside* (IIIa) was obtained by tosylation of methyl 4,6-O-benzylidene-β-D-galactopyranoside[7] in 89% yield, m.p. 180—181°C, $[\alpha]_D^{20}$ +29·8°. The literature[7] reports m.p. 171—172°C, $[\alpha]_D^{20}$ +39·7° (chloroform).

Reduction of Methyl 4,6-O-Benzylidene-2,3-di-O-*p*-toluenesulphonyl-α-D-galactopyranoside (*IIa*)

a) A suspension of lithium aluminium hydride (0·5 g) in tetrahydrofuran (15 ml) was heated under reflux 2 h. A solution of the tosyl derivative *IIa* (3 g) in tetrahydrofuran (25 ml) was added, the mixture was boiled for 18 h (bath temperature 90—100°C), then decomposed with ethyl

acetate (5 ml) and after 30 minutes an aqueous solution (40 ml) of sodium potassium tartrate (12 g) was added. The mixture was extracted four times with ether (100 ml), the combined ethereal extracts dried with magnesium sulphate and taken down. The residue (1·5 g) was chromatographed on an alumina column (120 g) and fractions analysed by thin-layer chromatography. The chromatography afforded: starting ditosyl derivative *IIa*, m.p. 178—179°C (476 mg, 15·9%), 2-tosylgalactoside *IIb*, m.p. 184—186°C, $[\alpha]_D^{20}$ +121·6° (672 mg, 30·3%); the literature[6] reports m.p. 179—180°C, $[\alpha]_D^{18}$ +117·8° (chloroform); a mixture of *IIb* with compound *A* (110 mg) (this mixture has $[\alpha]_D^{20}$ +111° and contains 5·83% S; for *IIb* calculated: 7·34% S), and benzalgalactoside *IIc*, m.p. 171—172°C, undepressed on admixture with an authentic specimen.

b) Reduction of the ditosylderivative *IIa* (3 g) with lithium aluminium hydride (0·8 g) gave a mixture of *IIa* and *IIb* (94 mg), *IIb* which contained traces of *A* (180 mg), and *IIc* (1 230 mg, 86%).

Reduction of the Methyl 4,6-O-Benzylidene-2,3-di-O-*p*-toluenesulphonyl-β-D-galactopyranoside (*IIIa*)

a) Reduction of the tosyl derivative *IIIa* (3 g) with lithium aluminium hydride (0·8 g) followed by the usual work-up procedure afforded: 40 mg (1·3 %) of the starting ditosylgalactoside *IIIa*, m.p. 180—182°C, $[\alpha]_D^{20}$ +30·3°; 124 mg (6·3%) of *Vb*, m.p. 120—121°C, $[\alpha]_D^{20}$ −9·1°. For $C_{21}H_{24}O_5S$ (388·5) calculated: 64·93% C, 6·23% H, 8·25% S; found: 66·01% C, 6·44% H, 8·20% S. The infrared spectrum exhibits a band at 3 540 cm^{-1} (hydroxyl) but no bands of the sulfo ester group (1 180 cm^{-1} and 1 380 cm^{-1}). Further, we isolated a mixture of *IV*, *Va* and *IIIc* (460 mg), separation and characterisation of which is described in experiment *b*), and the benzal derivative *IIIb* (510 mg, 35·6%), m.p. 204—206°C, $[\alpha]_D^{20}$ −34·3°, no depression in melting point on admixture with an authentic specimen.

b) Analogous reduction of the tosyl derivative *IIIa* (3 g) with 0·5 g of lithium aluminium hydride afforded: a mixture of *IIIa* and *Vb* (190 mg); 123 mg (4·1%) of *IIIa*; a mixture of *IIIa* and *IV* (46 mg); the *talo*-epoxide *IV* (100 mg, 7·4%), m.p. 245—246°C, $[\alpha]_D^{20}$ −143·5° (*c* 0·3, pyridine), the literature[7] gives m.p. 248°C, $[\alpha]_D^{17}$ −142° (*c* 0·4, pyridine); 180 mg (12·6%) of the benzalgalactoside *IIIb*; 746 mg of a mixture of *IV*, *Va* and *IIIc* from which the pure components were separated by further chromatography and crystallisation: *a*) 150 mg (11·1%) of the *talo*-epoxide *IV*; *b*) 190—260 mg (15—20%) of the 3-deoxyidoside *Va*, m.p. 143—144°C, $[\alpha]_D^{20}$ −100·3°, the literature[8] gives m.p. 145—146°C, $[\alpha]_D$ −104° (chloroform); *c*) 150 mg (6·7%) of the 2-tosylgalactoside *IIIc*, m.p. 164—165°C, $[\alpha]_D^{20}$ −53·2°, the literature[6] states m.p. 164—165°C, $[\alpha]_D^{17}$ −52·8° (chloroform).

Methyl 4,6-O-Benzylidene-3-deoxy-3-*p*-tolylthio-β-D-idopyranoside (*Vb*)

To a suspension of sodium hydride (164 mg) in tetrahydrofuran (5 ml) was added dropwise a solution of *p*-thiocresol (508 mg) (m.p. 43—44°C) in tetrahydrofuran (5 ml) followed by the *talo*-epoxide *IV* (167 mg) in tetrahydrofuran (15 ml). The reaction mixture was refluxed for 4 hours, then cooled, decomposed with water and extracted with ether (3 × 60 ml). The combined ethereal extracts were taken down, dried, and the residue was chromatographed on an alumina column (50 g), giving 230 mg (93%) of the thio derivative *Vb*, m.p. 120—121°C, $[\alpha]_D^{20}$ −9·6°. For $C_{21}H_{24}O_5S$ (388·5) calculated: 64·93% C, 6·23% H, 8·25% S; found: 64·88% C, 6·46% H, 8·55% S.

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ISOMERISATION VON NITROOLEFINEN

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Über die Isomerie ungesättigter Nitroverbindungen finden sich im Schrifttum nur verhältnismäßig wenige Angaben. Baskov und Mitarbeiter[1] beschrieben die Isomerisation von 3-Nitro-1-propen (*I*) zu *trans*- und *cis*-1-Nitro-1-propen (*II* und *III*) und die Einstellung eines Gleichgewichtes zwischen den Isomeren bei Einwirkung von Natriummethanolat in Spurenmengen während eines Jahres bei Raumtemperatur (Gleichgewichtszusammensetzung 23% *I*, 75% *II*, 2% *III*). Das Reaktionsgemisch wurde kernresonanzspektroskopisch analysiert. Bordwell und Garbisch[2] fanden im Gleichgewicht von 3-Nitro-1-buten und 2-Nitro-2-buten 87% konjugiertes und 13% nichtkonjugiertes Isomer. Die mit Triäthylamin katalysierte Reaktion, bei der sie aber bloß von 3-Nitro-1-buten ausgingen, verfolgten sie infrarotspektroskopisch. 3-Nitro-2-acetoxybutan ergab bei Einwirkung von Triäthylamin die gleiche Zusammensetzung des Gleichgewichtsgemisches[2]. Auch das Gleichgewicht zwischen 3-Nitro-2-methyl-1-propen und 1-Nitro-2-methyl-1-propen im Verhältnis von 81 : 19% ist zugunsten des konjugierten Isomeren verschoben[3,4]. Bei der Untersuchung der Kinetik dieser Gleichgewichtseinstellung fanden Hesse und Mitarbeiter[4], daß ΔH^0_{293} 1,5 kcal/mol beträgt und die Gleichgewichtslage nur unbedeutend von der Polarität des Lösungsmittels abhängt. Bourillot und Mitarbeiter[5] untersuchten die thermische Gleichgewichtseinstellung einer Reihe Nitroolefine und behaupten umgekehrt, daß bei dieser Isomerisation die Gleichgewichtslage stark vom angewandten Lösungsmittel abhängt.