REDUCTION OF SECONDARY *p*-TOLUENESULFONYLOXY GROUPS IN THE POSITION 5 OF HEXOFURANOSES WITH LITHIUM ALUMINUM HYDRIDE

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Reduction of 6-O-benzoyl-3-deoxy-1,2-O-isopropylidene-5-O-*p*-toluenesulfonyl-α-D-*ribo*-hexofuranose (*Ib*) with lithium aluminum hydride in ether gave 3,5-dideoxy-1,2-O-isopropylidene-α-D-*erythro*-hexofuranose (*IIb*, 75%) in addition to 3-deoxy-1,2-O-isopropylidene-α-D-*ribo*-hexofuranose (*IIc*) (17%); in a similar manner 6-deoxy-1,2-O-isopropylidene-5-O-*p*-toluenesulfonyl-α-D-glucofuranose (*Ic*) afforded corresponding 5-deoxy derivative *IIIb* (75%) together with diol *IIIa* (21%). In contrast to this only 3,6-dideoxy-1,2-O-isopropylidene-α-D-*ribo*-hexofuranose (*IIa*, 86%) was obtained from 3,6-dideoxy-1,2-O-isopropylidene-5-O-*p*-toluenesulfonyl-α-D-*ribo*-hexofuranose (*Id*). Hence, the mechanism of reduction of 5-*p*-toluenesulfonyloxy group in hexofuranoses is intramolecular, in this case with the participation of the group at $C_{(3)}$ or at $C_{(6)}$.

In our preceding papers[1-3] we investigated the reductions of secondary *p*-toluenesulfonyloxy groups in derivatives of hexopyranoses under the effect of lithium aluminum hydride. We found that this reaction may give a deoxy derivative if a suitable substituent is present in the *trans*-position of the vicinal carbon atom, and if this substituent participates in the reduction either by formation of an alkoxy aluminum hydride or by the formation of a temporarily generated epoxide. Which of the two mechanisms will prevail depends on the configuration of the given substance[3]. In all instances a substance was obtained as a by-product in which the original hydroxyl group with unchanged configuration was regenerated under the effect of lithium aluminum hydride, *i.e.* the common product of reduction of the secondary tosyloxy group in the sugar molecule. Independently, Japanese authors came to similar conclusions[4] – at least in the case of *gluco* configuration. In this paper we wanted to check whether similar rules also apply for the reduction of secondary tosyloxy groups in the side chain, *i.e.* in the position 5 of hexofuranoses.

In the literature[5] a single case of such a reduction has been described, when a corresponding 5-deoxy derivative, *i.e.* *xylo*-hexofuranose *IIIc* was obtained from 5-O-tosylfuranose *Ia*. The authors expressed the view that the hydroxyl group in the position 3 participates in the reduction; this group enables the intramolecular reduction of the 5-tosyloxy group by the formation of alkoxy aluminum hydride. Hence,

this would represent a case of a reduction affected by the substituent on a more remote carbon atom.

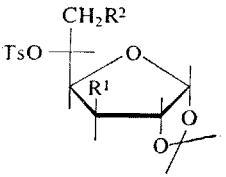
However, a further possibility of the explanation of the formation of 5-deoxy compound may also consist in the effect of the neighbouring group[1-3], as for example in this case of the benzoyloxy group at $C_{(6)}$. This group may be easily cleaved by hydride under formation of alkoxy aluminum hydride, and in view of the free rotation around the $C_{(5)}$—$C_{(6)}$ bond it may assume a position enabling intramolecular substitution with hydride anion. In view of the magnitude of the temporarily formed cycle this intramolecular reduction even would take place under more favourable conditions than if the aluminum were bound *via* the oxygen atom on $C_{(3)}$. Finally, the possibility of a direct S_N2 substitution of the 5-tosyloxy group without the influence of any further groups should also be taken into consideration, because the substituent is on an outer chain, which is sterically more accessible than the substituents in the cycle.

In order to decide which of the mentioned mechanisms leads to the formation of deoxy derivatives, we prepared and reduced several model compounds (*Ib, c, d*) in which always a single one or none of the substituents enabling an intramolecular interaction was present in the molecule, *i.e.* the substituents at $C_{(3)}$ and $C_{(6)}$.

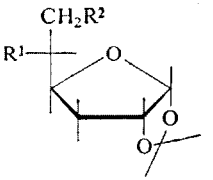
6-O-Benzoyl-3-deoxy-1,2-O-isopropylidene-5-O-*p*-toluenesulfonyl-α-D-*ribo*-hexafuranose (*Ib*) was prepared from 3-deoxy-1,2-O-isopropylidene-α-D-*ribo*-hexofuranose by benzoylation and subsequent tosylation[6]. The starting material for the preparation of 6-deoxy-1,2-O-isopropylidene-5-O-*p*-toluenesulfonyl-α-D-glucofuranose (*Ic*) was 1,2-O-isopropylidene-6-O-*p*-toluenesulfonyl-α-D-glucofuranose which was converted to the corresponding 6-deoxy derivative *IIIa* under the effect of sodium dihydro-bis(2-methoxyethoxy)aluminate (Synhydride) in benzene. The 6-deoxyglucofuranose *IIIa* obtained reacted with *p*-toluenesulfonyl chloride reluctantly. Therefore, pyridine alone was used as solvent instead of the common pyridine–chloroform mixture and the reaction mixture was heated up to 90–95°C. Under such conditions undesirable reactions also take place, so that we were unsuccessful in the preparation of monotosyl derivative *Ic* in a yield higher than 44%. Monotosyl derivative *Ic* has a correct analysis and an adequate IR spectrum. The position of the tosyl group follows from the reduction of this compound to 5-deoxy derivative with lithium aluminum hydride. This compound could not be formed from an isomeric compound with the tosyloxy group at $C_{(3)}$, which was also obtained from the mother liquors of *Ic* as a by-product.

The compound *Id* was prepared in two manners. For both of them 3-deoxy-1,2-O-isopropylidene-α-D-*ribo*-hexofuranose (*IIc*) served as starting material. From *IIc* 3-deoxy-1,2-O-isopropylidene-6-O-*p*-toluenesulfonyl-α-D-*ribo*-hexofuranose (*IIe*) was obtained by selective tosylation[7]. The latter compound was converted to corresponding 5,6-anhydro derivative[7,8] (*IV*) which was then submitted to reduction with Synhydride under formation of 3,6-dideoxy compound *IIa*. The reduction of 6-tosyl-

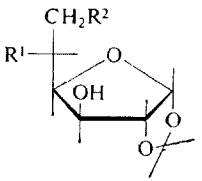
furanose *IIe* with Synhydride led to the same product directly. The subsequent tosylation of *IIa* to *Id* proceeded readily in contrast to the similar reaction of *IIIa* to *Ic*.



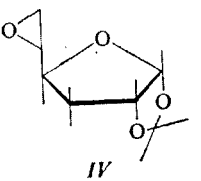
Ia; $R^1 = OH$, $R^2 = OCOC_6H_5$
Ib; $R^1 = H$, $R^2 = OCOC_6H_5$
Ic; $R^1 = OH$, $R^2 = H$
Id; $R^1 = H$, $R^2 = H$



IIa; $R^1 = OH$, $R^2 = H$
IIb; $R^1 = H$, $R^2 = OH$
IIc; $R^1 = OH$, $R^2 = OH$
IId; $R^1 = H$, $R^2 = H$
IIe; $R^1 = OH$, $R^2 = OTs$



IIIa; $R^1 = OH$, $R^2 = H$
IIIb; $R^1 = H$, $R^2 = H$
IIIc; $R^1 = H$, $R^2 = OH$



IV

Ts = *p*-$CH_3C_6H_4SO_2$

For the study of the reduction with lithium aluminum hydride we first chose the simplest case, *i.e.* 3,6-dideoxy-1,2-O-isopropylidene-5-O-*p*-toluenesulfonyl-α-D-*ribo*--hexofuranose (*Id*) where no substituent is present either at $C_{(3)}$ or $C_{(6)}$ and therefore no formation of epoxide or any other intramolecular reaction is possible. In addition to this the tosyloxy group at $C_{(5)}$ is sterically accessible, at least to the same degree as in compound *Ic*, and undoubtedly more than in compound *Ia* or *Ib*. Hence, if a direct S_N2 substitution of the 5-tosyloxy group takes place, it should take place preferentially in this case. However, after reduction of this substance 5-hydroxy compound *IIa* alone was isolated from the reaction mixture in 86% yield, but trideoxy derivative *IId* was not found at all. Compound *IIa* was identified by comparison with substances prepared by reduction of 6-tosyl derivative *IIe* and 5,6-anhydro compound *IV* with Synhydride. The meltig points, optical rotations, R_F values in various systems, and the mass spectra of all three compounds were identical. From these results it is evident that the accessible secondary tosyloxy group in the side chain of the sugar molecule does not undergo nucleophilic substitution under the conditions of lithium

aluminum hydride reduction in ether either; a reductive cleavage of the S—O but not C—O bond takes place only. Hence, one of the substituents at $C_{(3)}$ or $C_{(6)}$ participates in the formation of 5-deoxy compounds.

The reduction of 3-deoxyfuranose *Ib*, which carries the benzoyloxy group in the position 6, takes place smoothly up to 5-deoxy derivative *IIb* which was isolated chromatographically on silica gel in 75% yield in addition with 17% of diol *IIc*. Substance *IIb* has a satisfactory elemental analysis and it is not identical with the isomeric 3,6-dideoxy derivative *IIa* which is a potential product of this reduction. In the ^{1}H-NMR spectrum no signal characteristic of a C—CH_3 group (δ 1·20; *cf.*[8]) is present in the δ 1.5—1 p.p.m. region (in addition to two distinct singlets of the isopropylidene group at δ 1·47 or 1·27), which would indicate the alternative structure *IIa* or its configurational isomer. On the contrary, the triplet centered at δ 3·7 and $J_{5,6} \sim 6{\cdot}7$ Hz, corresponding to two protons, may be clearly assigned to the hydroxymethyl group of substance *IIb* the signal of which is split by the two protons of the methylene group on $C_{(5)}$. From this result it is evident that the formation of the 5-deoxy derivative is due to the benzoyloxy group at $C_{(6)}$ and that the reaction does not proceed *via* the epoxide stage, because no 6-deoxy derivative was found in the reaction mixture.

We tried to explain the effect of the substituent at $C_{(3)}$ by submitting 6-deoxy--1,2-O-isopropylidene-5-O-*p*-toluenesulfonylglucofuranose (*Ic*) to reduction. On reduction with lithium aluminum hydride in ether we obtained 5,6-dideoxy derivative *IIIb* in 75% yield, simultaneously with 21% of diol *IIIa*. Evidently the hydroxy group in the position 3 is responsible for the formation of 5-deoxy derivative in this case.

Hence, the reduction of 5-O-*p*-toluenesulfonyl-hexofuranoses with lithium aluminum hydride in ether may proceed smoothly up to the stage of 5-deoxy derivative if the molecule contains a group capable of formation of alkoxy aluminum hydride and thus enables intramolecular reduction. In contrast to the already described reductions of secondary *p*-toluenesulfonyloxy groups on the sugar ring[1-4,9] the reduction takes place in this case more easily, the formation of anhydro derivative was not observed, and the group participating in the reduction should not necessarily be a vicinal one. In agreement with the mentioned studies no direct S_N2 substitution of the tosyloxy group with hydride anion takes place in this case either, and unless an intramolecular assistance is possible the formation of deoxy derivative does not take place at all.

EXPERIMENTAL

The melting points were determined on a Kofler block and they are not corrected. The reaction course and the purity of the products were controlled by thin layer chromatography on alumina (according to Brockmann, act. III) in benzene with 0—20% of ethanol. The substances were detected using iodine vapours. When silica gel G thin layers were used the development was carried out with benzene or chloroform with 0—10% of ethanol, or with a mixture of ethyl acetate and

light petroleum in a 1 : 2 ratio. Detection was carried out by spraying with a 2% cerium sulfate solution in 10% H_2SO_4 and heating. The rotations were measured in a 2 dm tube using chloroform solutions in a $1 \pm 0{\cdot}1$ g/100 ml concentration. ^{1}H-NMR spectrum was measured on a Tesla BS 477 60 MHz instrument in deuteriochloroform, using hexamethyldisiloxan as internal standard. The mass spectra were measured on a G. C.-M. S. LKB 9000 apparatus, using direct inlet system, a temperature of 290°C and 70 eV. The IR spectra were measured on a Perkin Elmer 247 spectrophotometer.

6-O-Benzoyl-3-deoxy-1,2-O-isopropylidene-5-O-*p*-toluenesulfonyl-α-D-*ribo*-hexofuranose (*Ib*)

This substance was prepared by selective benzoylation and subsequent tosylation of 1,2-O-isopropylidene-3-deoxy-α-D-*ribo*-hexofuranose[6], m.p. 123—125°C, $[\alpha]_D^{20} + 16{\cdot}7°$.

3-Deoxy-1,2-O-isopropylidene-6-O-*p*-toluenesulfonyl-α-D-*ribo*-hexofuranose (*IIe*)

Pyridine (1·4 ml) was added to a solution of 990 mg of diol *IIc* and 1 100 mg of *p*-toluenesulfonyl chloride in 14 ml of chloroform cooled at −50°C. A precipitate was formed which disappeared after 1—2 hours standing. After 3 hours' standing in a cooling bath the mixture was allowed to stand at room temperature for 12 hours, then decomposed with water and the products were extracted with chloroform (4 × 100 ml). The combined chloroform extracts were filtered and evaporated. The syrupy residue (1 750 mg) was chromatographed on silica gel. Yield 1 210 mg (69%) of chromatographically pure tosyl derivative *IIe*, $[\alpha]_D^{25} -4{\cdot}8°$. It was a syrup which crystallized after several days standing and melted at 49—51°C; attempts at crystallization were unsuccessful, however. For $C_{16}H_{22}O_7S$ (358·4) calculated: 8·94% S; found: 8·60% S. In the literature[7] the substance is described as a crude oily intermediate only.

5,6-Anhydro-3-deoxy-1,2-O-isopropylidene-α-D-*ribo*-hexofuranose (*IV*)

This was prepared from 6-O-*p*-toluenesulfonyl derivative *IIe* on reaction with sodium methoxide in chloroform[7] in the form of a syrup, $[\alpha]_D^{21} -21{\cdot}9°$ (ethanol, *c* 1·5), in accordance with the literature[7].

3,6-Dideoxy-1,2-O-isopropylidene-α-D-*ribo*-hexofuranose (*IIa*)

A) Synhydride (1·3 ml of a 70% $NaH_2Al(OCH_2CH_2OCH_3)_2$ in benzene) was added to a solution of 300 mg of anhydro derivative *IV* in 5 ml of benzene and the mixture was allowed to react at room temperature for 30 minutes. After this period it did not contain any starting material according to thin-layer chromatography. The solution was put onto a silica gel column and eluted first with 1% ethanol in benzene. The elution gave 304 mg (94%) of 3,6-dideoxyfuranose *IIa*, identical with a substance described under *B*.

B) A mixture of 1 320 mg of tosyl derivative *IIe*, 3 ml of Synhydride and 30 ml of benzene was allowed to stand at room temperature for 1/2 hours, then decomposed with 10 ml of ethanol and filtered. The filtrate was evaporated and the residue chromatographed on silica gel. 3,6-Dideoxyfuranose *IIa* (600 mg; 88%) was obtained, with m.p. 37—40°C (without crystallization), $[\alpha]_D^{20} -26{\cdot}4°$. Mass spectrum (*m/e*): 189 (M + 1), 187 (M − 1), 173 (40%), 143 (50%), 113, 125, 131, no 157 (M − 31). The substance is identical with a product prepared as under *A*) and it differs from the isomeric 3,5-dideoxyfuranose *IIb*, in the mass spectrum mainly in different intensity of the ions 143 and 173.

3,6-Dideoxy-1,2-O-isopropylidene-5-O-*p*-toluenesulfonyl-α-D-*ribo*-hexofuranose (*Id*)

Pyridine (6 ml) was added to a solution of 850 mg of 3,6-dideoxyfuranose *IIa* and 3 g of *p*-toluenesulfonyl chloride in 50 ml of chloroform at −30°C and the mixture was allowed to stand at room temperature for 12 hours and at 40°C for 4 days. The reaction mixture did not contain any starting material after this period (according to thin-layer chromatographic analysis) and it was decomposed with 50 ml of water, extracted 4 times with 100 ml of chloroform and the extracts were combined, washed with water, filtered and evaporated *in vacuo*. The residue was chromatographed on alumina, affording 1 407 mg (91%) of tosyl derivative *Id*, syrup, $[\alpha]_D^{25}$ −8·5°. For $C_{16}H_{22}O_6S$ (342·4) calculated: 56·13% C, 6·48% H, 9·36% S; found: 56·44% C, 6·44% H, 9·32% S.

6-Deoxy-1,2-O-isopropylidene-α-D-glucofuranose (*IIIa*)

1,2-O-Isopropylidene-6-O-*p*-toluenesulfonyl-α-D-glucofuranose (5 g) was added over 30 minutes to a solution of 20 ml of Synhydride in 80 ml of benzene under cooling in a water bath. The mixture was stirred at room temperature for one hour and then decomposed gradually with 1·5 ml of water, 15 ml of ether, 1·5 ml of 15% aqueous sodium hydroxide solution, 4·5 ml of water and 30 ml of ether. The benzene solution was filtered and the insoluble material extracted with three 100 ml portions of hot benzene. Evaporation of the combined benzene fractions gave 3·7 g of a syrup from which 2·21 g (81·4%) of 6-deoxyglucofuranose *IIIa*, m.p. 91−92°C, $[\alpha]_D^{20}$ −24·3°, were obtained by chromatography on alumina. Literature[5,10] gives m.p. 87°C, $[\alpha]_D$ −27·5° or m.p. 92°C, $[\alpha]_D$ −26·3°, respectively.

6-Deoxy-1,2-O-isopropylidene-5-O-*p*-toluenesulfonyl-α-D-glucofuranose (*Ic*)

A solution of 1 g of 6-deoxy derivative *IIIa* and 1 g of *p*-toluenesulfonyl chloride in 11 ml of pyridine was heated at 90−100°C for 45 minutes (in a bath). After cooling the mixture was decomposed with ice, extracted six times with 30 ml of chloroform, and this was washed gradually with dilute hydrochloric acid, potassium hydrogen carbonate and water. After drying over magnesium sulfate the solution was filtered and evaporated. The residue was chromatographed on silica gel (chromatography on alumina with benzene led to decomposition). Yield 824 mg (44%) of 5-tosyl derivative *Ic*, m.p. 111−114°C (ethyl acetate–light petroleum), $[\alpha]_D^{20}$ +18·7°. For $C_{16}H_{22}O_7S$ (358·4) calculated: 53·62% C, 6·19% H, 8·94% S; found: 53·70% C, 6·23% H, 8·93% S. IR spectrum: 3 400 (OH), 1 360 and 1 190 (R—SO_2OR') cm^{-1}. From mother liquors isomeric 6 deoxy-1,2-O-isopropylidene-3-O-toluenesulfonyl-α-D-glucofuranose, m.p. 90°C, $[\alpha]_D^{20}$ −2·5° was obtained.

Reduction of 6-O-Benzoyl-3-deoxy-1,2-O-isopropylidene-5-O-*p*-toluenesulfonyl-α-D-*ribo*-hexofuranose (*Ib*) with Lithium Aluminum Hydride

A suspension of 0·6 g of lithium aluminum hydride in 20 ml of ether was refluxed for one hour and a suspension of 2·7 g of *Ib* in 120 ml of ether was added dropwise to it under stirring over 2 hours. The mixture was refluxed for 20 hours, then cooled and additioned with 8 ml of ethyl acetate. After another 45 minutes a solution of 20 g of sodium potassium tartrate in 40 ml of water was added to the mixture which was extracted with four 100 ml portions of ether. The combined ethereal extracts were dried over magnesium sulfate and evaporated at 30°C. The residue (1·6 g) was chromatographed on a silica gel column CH (70−200μ) in chloroform. From the fractions 580 mg (91·5%) of benzyl alcohol, 830 mg (75%) of 3,5-dideoxyfuranose *IIb*, (syrup, $[\alpha]_D^{20}$ −7·1°; ^{1}H-NMR spectrum (δ p.p.m.): 1·47 (s, 3 H) and 1·27 (s, 3 H) $C(CH_3)_2$, 3·71 (t, 2 H, J = 6·7 Hz); mass spectrum (*m/e*): 189 (M + 1), 187 (M − 1), 173 (63%), 143 (12%), 113, 125, 131), and 200 mg (17%) of diol *IIc*, which was identical with an authentic specimen[6] were obtained.

Reduction of 6-Deoxy-1,2-O-isopropylidene-5-O-*p*-toluenesulfonyl-α-D-glucofuranose (*Ic*) with Lithium Aluminum Hydride

The reduction was carried out in the same manner as in the preceding experiment. The crude product obtained from 540 mg *Ic* was chromatographed on silica gel in the system ethyl acetate–light petroleum (1 : 2) giving 213 mg (75%) of 5,6-dideoxyfuranose *IIIb*, m.p. 76–77°C, $[\alpha]_D^{20}$ −23·4°, (literature[11,5] gives m.p. 78–79°C, $[\alpha]_D^{20}$ −21·9° or m.p. 70–72°C, $[\alpha]_D^{20}$ −29°) and 65 mg (21%) of 6-deoxyglucofuranose *IIIa*, m.p. 91–92°C, $[\alpha]_D^{20}$ −24·3°, which was identical with an authentic sample.

Reduction of 3,6-Dideoxy-1,2-O-isopropylidene-5-O-*p*-toluenesulfonyl-α-D-*ribo*-hexofuranose (*Id*) with Lithium Aluminum Hydride

Under the same conditions as in the preceding two experiments 585 mg *Id* gave after conventional working up 277 mg (86·3%) of 3,6-dideoxy-1,2-O-isopropylidene-α-D-*ribo*-hexofuranose (*IIa*), m.p. 37–39°C, identical with a product obtained on reduction of anhydro derivative *IV* and reduction of tosyl derivative *IIe*.

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