SYNTHESES WITH ANHYDRO SUGARS. XIII.*
PREPARATION OF THE DEOXY DERIVATIVES OF THE 1,6-ANHYDRO-β-D-HEXOPYRANOSES BY CATALYTIC REDUCTION OF 1,6 : 2,3- AND 1,6 : 3,4-DIANHYDRO-β-D-HEXOPYRANOSES

T.Trnka and M.Černý

*Department of Organic Chemistry,
Charles University, Prague 2*

By catalytic reduction of 1,6 : 2,3- and 1,6 : 3,4-dianhydro-β-D-hexopyranoses on Raney nickel in ethanol at 40°C and under atmospheric pressure have been obtained the monodeoxy derivatives of the 1,6-anhydro-β-D-hexopyranoses in yields of about 80%. The reduction took place diaxially with high stereoselectivity except in the case of 1,6 : 2,3-dianhydro-β-D-mannopyranose and 1,6 : 2,3-dianhydro-β-D-talopyranose, where both isomeric monodeoxy derivatives were formed in comparable amounts. In all reductions the dideoxy derivatives of the 1,6-anhydro-β-D-hexo-pyranoses were formed as by-products in amounts of 6 to 20%.

One of the methods for preparing the deoxy derivatives of hexoses and pentoses consists in the reductive cleavage of the oxiran ring of sugar derivatives containing the hemi-acetal group in a protected form. The reduction is carried out either with complex hydrides or by catalytic hydrogenation. The latter method gives often other deoxy derivatives than the reduction with hydrides. With regard to preparative work, the catalytic reduction has several advantages: It is not necessary to work in an anhydrous medium, the course of the reaction can be followed very easily, and the reaction mixture is easier worked up. Prins[1] hydrogenated methyl 2,3-an-hydro-4,6-O-benzylidene-α-D-allopyranoside in methanol at 100—120°C and 120 kp/cm² in the presence of Raney nickel and isolated methyl 3-deoxy-α-D-*ribo*-hexopyranoside as the main product. Later it was found that in the reaction mixture are also present the 2-deoxy derivative and methyl 2,3-dideoxy-α-D-*erythro*-hexopyranoside[2,3]. By hydrogenation of methyl 2,3-an-hydro-4,6-O-benzylidene-α-D-mannopyranoside were obtained methyl 3-deoxy-α-D-*arabino*-hexo-pyranoside and the same dideoxy derivative[4]. Of the 3,4-anhydro derivatives of the hexoses were reduced both anomeric methyl 3,4-anhydro-D-galactopyranosides[2,3,5] giving always a mix-ture of the corresponding 3- and 4-deoxy derivatives in equal amounts.

As has been shown previously[6] and also in the present paper, it is possible to perform the cleavage of the oxiran ring on Raney nickel in ethanol at atmospheric pressure and at only gently elevated temperature. Under similar conditions the reduction of methyl 2,3-anhydro-β-D-*ribo*-pyranoside has also been described[7] giving exclusively the 3-deoxy derivative. In all mentioned cases Raney nickel has been proved to be the most suitable catalyst. From the literature[1,7−9]

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it is known that neither platinum nor palladium on charcoal are suitable catalysts for the reduction of the oxiran ring of sugar compounds.

In the present work we investigated the reduction of all isomeric 1,6-dianhydro-β-D-hexopyranoses on Raney nickel[10] T-1 in ethanol under atmospheric pressure at 40°C *i.e.* under mild reduction conditions so far not usually applied, where can be assumed a higher reduction selectivity.

The composition of the reaction mixtures gained after hydrogenation was determined by gas chromatography after the products had been converted into the acetates. Identification was carried out by gas chromatography, thin-layer chromatography, or, after isolation, on a silica gel column. The results are summarized in Table I and in the formula scheme. Interesting, though to a certain extent surprising, was the finding that in addition to the monodeoxy derivatives of the 1,6-anhydro-β-D-hexopyranoses produced in yields of approximately 80% was in all cases proved the presence of 6 to 20% of the corresponding dideoxy derivatives.
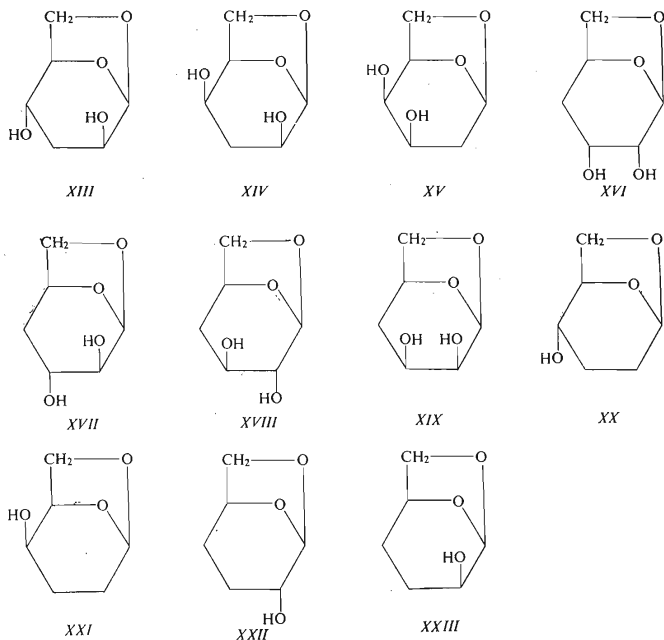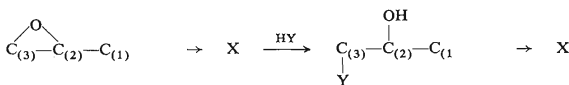
XIII   XIV   XV   XVI

XVII   XVIII   XIX   XX

XXI   XXII   XXIII
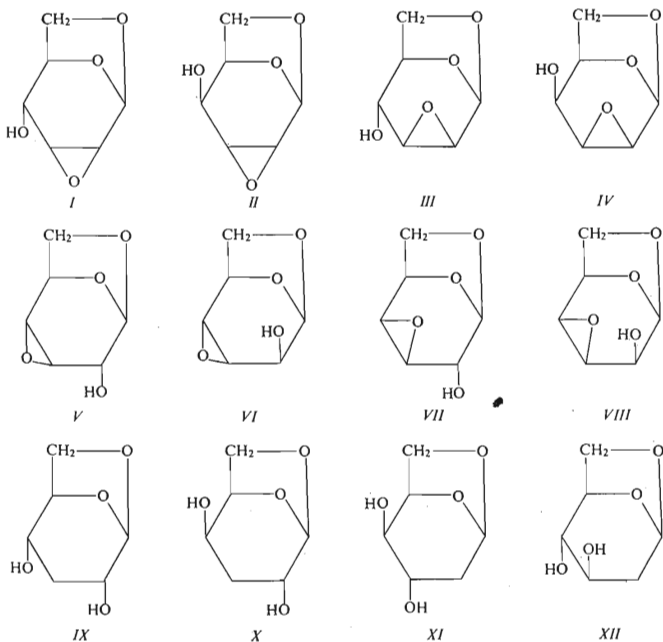
TABLE I

Yields (%) of 1,6-Anhydro-β-D-hexopyranoses at the Catalytic Reduction of 1,6 : 2,3- and 1,6 : 3,4-Dianhydro-β-D-hexopyranoses

Epoxy derivative	Monodeoxy derivatives		Dideoxy derivatives
2,3-*allo* I	3-*ribo* IX (80)	—	2,3-*erythro* XX (19)
2,3-*gulo* II	3-*xylo* X (78)	2-*xylo* XI (1)	2,3-*threo* XXI (20)
2,3-*manno* III	2-*arabino* XII (49)	3-*arabino* XIII (30)	2,3-*erythro* XX (18)
2,3-*talo* IV	2-*lyxo* XV (39)	3-*lyxo* XIV (39)	2,3-*threo* XXI (16)
3,4-*allo* V	3-*ribo* IX (78)	4-*ribo* XVI (2)	3,4-*erythro* XXII (20)
3,4-*altro* VI	3-*arabino* XIII (82)	4-*arabino* XVII (7)	3,4-*threo* XXIII (6)
3,4-*galacto* VII	4-*xylo* XVIII (83)	—	3,4-*erythro* XXII (15)
3,4-*talo* VIII	4-*lyxo* XIX (78)	3-*lyxo* XIV (3)	3,4-*threo* XXIII (17)

As follows from Table I, reduction of the 1,6 : 3,4-dianhydro-β-D-hexopyranoses takes place without exception diaxially with high selectivity. In the case of the 1,6 : 2,3-dianhydro-β-D-hexopyranoses is the situation more complicated. While reduction of the derivatives with D-*allo*- (*I*) and D-*gulo*-configuration (*II*) takes place also diaxially, are in the case of 1,6 : 2,3-dianhydro-β-D-mannopyranose (*III*) and 1,6 : 2,3-dianhydro-β-D-talopyranose (*IV*) the products of the corresponding diequatorial cleavage formed in considerable amounts. The comparison of the reduction results of the dianhydro derivatives *I* to *VIII* with the course of their cleavage with an aqueous solution of potassium hydroxide[9] shows that both reactions proceed similar in stereochemical respect. (In the case of the catalytic hydrogenation may take place polar interactions of the basic surface of the Raney nickel). During the reduction the dianhydro derivatives do not isomerise. The reduction of the 2,3-*manno*-epoxide *III* and of the 2,3-*talo*-epoxide *IV* could not be compared with the alkaline hydrolysis, since the former compound isomerised in alkaline medium rapidly into the dianhydro derivative *VI* and the latter compound decomposed[9].

In attempting to explain the different reduction course of the dianhydro derivatives *I* to *VIII* one has to take into consideration the polar effects of the oxygen atoms in the molecule. The influence of groups with an $-I$ effect upon the nucleophilic substitution has been thoroughly investigated by Parker[11] and can thus be summarized: The oxiran ring substituted on the neighbouring carbon atom $C_{(1)}$ by electron-attracting groups is preferentially cleaved at the carbon atom $C_{(3)}$:

$$C_{(3)}\overset{\displaystyle O}{-}C_{(2)}-C_{(1)} \quad \rightarrow \quad X \quad \xrightarrow{HY} \quad C_{(3)}-\underset{\displaystyle Y}{\overset{\displaystyle OH}{\underset{|}{\overset{|}{C}}}}_{(2)}-C_{(1} \quad \rightarrow \quad X$$

In the molecule of the 1,6 : 3,4-dianhydro derivatives is the influence of the oxygen atoms to the oxiran ring eliminated,

$$O \leftarrow C_{(5)}\overset{\displaystyle O}{-}C_{(4)}-C_{(3)}-C_{(2)} \rightarrow O$$
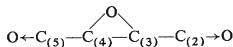
whereas in the 1,6 : 2,3-dianhydro derivatives not:

$$O-C_{(4)}\overset{\displaystyle O}{-}C_{(3)}-C_{(2)}-C_{(1)}\overset{\displaystyle \nearrow O}{\underset{\displaystyle \searrow O}{}}$$
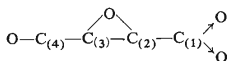
In considering only polar effects we should therefore expect a substantial higher reactivity on the carbon atom $C_{(3)}$ in comparison with $C_{(2)}$. However, in a steric controlled reaction, the oxiran ring, according to its configuration, supports the attack

of either the carbon atom $C_{(2)}$ or $C_{(3)}$. In the dianhydro derivatives with *allo-* (*I*) and *gulo*-configuration (*II*) the steric and polar effects strengthen each other, in the *manno-* (*III*) and *talo*-derivatives (*IV*) they act against each other and are thus responsible for the unselective reaction course. This question has already been discussed previously in connection with the cleavage of the 1,6 : 2,3-dianhydro-4-deoxy-β-D-hexopyranoses with potassium hydroxide[6]. The dideoxy derivatives *XX—XXIII* are not formed from the monodeoxy derivatives by a secondary reaction, since these compounds are stable in the reaction medium. The amount of the dideoxy derivatives formed is almost independent of the pressure and the temperature, but depends to a small extent on the activity of the Raney nickel used. From the monodeoxy derivatives can the dideoxy derivative be easily separated by chromatography or by extraction with light petroleum.

The described reduction is well suited for the preparation of the 3- and 4-deoxy derivatives of the 1,6-anhydro-β-D-hexopyranoses which on hydrolysis afford the corresponding hexoses, *i.e.* the 3-deoxy derivatives of D-glucose, D-galactose, and D-mannose, and the 4-deoxy derivatives of D-glucose and D-mannose.

EXPERIMENTAL

Melting points were determined on a Boetius micro-melting point apparatus. Optical rotations were measured at 25°C on an automatic polarimeter Bendix-Ericsson, Ltd., type 143 A. Samples for analysis were dried over phosphorus pentoxide at 0·01 Torr. Gas chromatography was carried out in a Chrom 3 apparatus (Laboratorní přístroje, Prague) fitted with a flame-ionisation detector. The acetylated monodeoxy and dideoxy derivatives of the 1,6-anhydro-β-D-hexopyranoses were separated at about 160°C (flow rate of 35 ml N_2/min) on a 280 cm long stainless steel column, 5 mm in diameter, packed with Chromosorb W-AW-HMDS coated with 5% of phase SE-30 and on a 192 cm long glass column, 4 mm in diameter, packed with Chromosorb G-AW-TMCS coated with 3% of phase OV-101. The nonacetylated dideoxy derivatives of the 1,6-anhydro-β-D-hexopyranoses were separated on a 192 cm long column packed with Chromosorb W which was coated with 12% of phase Carbowax 20 M. The area under the peaks was measured with an electronic integrator. The response of the detector was for all diacetyl monodeoxy derivatives almost the same; the response of the acetyldideoxy derivatives was approx. 1,3-times higher, which was taken into account in evaluation the percentage composition of the reaction mixtures (Table I). All acetates were chromatographed on thin layers of silica gel (9 : 1 ratio with gypsum) in benzene–acetone 9 : 1, and the deacetylated compounds in chloroform containing 5% of methanol. The vicinal diols were detected with the Bonner reagent[12] or unspecifically with 50% sulfuric acid and heating. Deacetylation was carried out with sodium methoxide in methanol by the usual method of Zemplén.

Reduction of the Epoxides

To a solution of 250 mg of the appropriate dianhydro derivative *I— VIII* in 7 ml of ethanol were added 4 ml of Raney nickel T-1[10]. The mixture was hydrogenated under atmospheric pressure at 40°C for 10—15 h (by heating with an infrared lamp). After the theoretical uptake of hydrogen (39 ml) was the catalyst filtered off with suction and the ethanol distilled off under reduced pres-

sure. The residue was then acetylated for 5 min by boiling in a mixture of acetic anhydride and sodium acetate. The reaction mixture was poured into water and extracted with chloroform. After drying the chloroform solution over calcium chloride was a sample feeded into the column of the gas chromatograph. Then was the chloroform distilled off and the mixture of the acetates separated on a column of silica gel.

1,6 : 2,3-Dianhydro-β-D-allopyranose (I): In the reaction mixture were present two acetates. After their separation on a column of silica gel was the acetate with the shorter retention time deacetylated under formation of 1,6-anhydro-2,3-dideoxy-β-D-*erythro*-hexopyranose (XX), m.p. 45—48°C, $[\alpha]_D$ —116·5° (c 0·75; water). This substance is identical with an authentic sample prepared by catalytic reduction of 2-deoxy-1,6 : 3,4-dianhydro-β-D-*ribo*-hexopyranose[13]. The acetate with the longer retention time was identified as 2,4-di-O-acetyl-1,6-anhydro-3-deoxy-β-D-*ribo*-hexopyranose, m.p. 114—116°C, $[\alpha]_D$ —74° (c 0·7; chloroform); literature[14] gives m.p. 114—116°C, $[\alpha]_D^{20}$ —74·0° (c 0·7; chloroform). Deacetylation of this substance gave the syrup IX with $[\alpha]_D$ —79° (c 0·8; water), in agreement with the literature[14].

1,6 : 2,3-Dianhydro-β-D-gulopyranose (II): In the reaction mixture were proved to be present three substances. The substance with the shortest retention time we failed to obtain in crystalline form; we assume it to be 1,6-anhydro-2,3-dideoxy-β-D-*threo*-hexopyranose (XXI) on account of the identical chromatographic properties with an authentic sample, prepared by catalytic reduction of 2-deoxy-1,6 : 3,4-dianhydro-β-D-*lyxo*-hexapyranose[13]. An identical product was formed by catalytic reduction of the dianhydro derivative IV. The substance with the longest retention time, which formed the main part of the mixture, was not detected with Bonner reagent, and was isolated in form of the acetate, m.p. 74—75°C, $[\alpha]_D$ +13·5° (c 0·7; chloroform), identical with authentic 2,4-di-O-acetyl-1,6-anhydro-3-deoxy-β-D-*xylo*-hexopyranose[9]. Deacetylation affords a substance, m.p. 131—137°C (subliming at 90°C), $[\alpha]_D$ +9·5° (c 0·8; water), which we assign the structure of 1,6-anhydro-3-deoxy-β-D-*xylo*-hexopyranose (X). For $C_6H_{10}O_4$ (146·1) calculated: 49·31% C, 6·90% H; found: 49·51% C, 6·91% H. A further substance, present only in traces, is probably 1,6-anhydro-2-deoxy-β-D-*xylo*-hexopyranose (XI).

1,6 : 2,3-Dianhydro-β-D-mannopyranose (III): In the reaction mixture were present three substances. The substance with the shortest retention time was after deacetylation identical with the product obtained by reduction of the dianhydro derivative I, i.e. the dideoxy alcohol XX; m.p. 46—48°C, $[\alpha]_D$ —116·5° (c 0·88; water). The acetate with the longest retention time was shown to be 2,4-di-O-acetyl-1,6-anhydro-3-deoxy-β-D-*arabino*-hexopyranose, m.p. 99—101°C, $[\alpha]_D$ —140° (c 0·85; chloroform); literature[14] gives m.p. 99·5—101°C and $[\alpha]_D^{20}$ —139,2° (c 0·37; chloroform). On deacetylation was obtained the syrupy deoxy alcohol XIII, $[\alpha]_D$ —156° (c 0·73; water) in agreement with the literature[14]. A further acetylated substance obtained as a syrup had after deacetylation m.p. 155—160°C and $[\alpha]_D$ —115·5° (c 0·85; water). The deacetylated substance we assume to be 1,6-anhydro-2-deoxy-β-D-*arabino*-hexopyranose (XII); the literature[15] records m.p. 159 to 160°C and $[\alpha]_D^{25}$ —118° (c 1·3; water).

1,6 : 2,3-Dianhydro-β-D-talopyranose (IV): In the reaction mixture were present three substances. The substance with the shortest retention time is the dideoxy alcohol XXI, according to the identical properties with the product prepared by reduction of the dianhydro derivative II. The remaining acetates were separated on a column of silica gel, and the substance with the longest retention time had after deacetylation an unsharp m.p. of around 176°C, $[\alpha]_D$ —77·5° (c 0·95; water), and this is evidently 1,6-anhydro-2-deoxy-β-D-*lyxo*-hexopyranose (XV), for which the literature[14] gives m.p. 181—182°C and $[\alpha]_D^{22}$ — 70° (c 1·0; water). The substance with the shorter retention time, m.p. 66—68°C, $[\alpha]_D$ —86·5° (c 0·75; water), we assume to be 1,6-anhydro-3-deoxy--β-D-*lyxo*-hexopyranose (XIV), as it is not detected with Bonner reagent. For $C_6H_{10}O_4$ (146·1) calculated: 49·31% C, 6·90% H; found: 49·50% C, 6·90% H.

1,6 : 3,4-*Dianhydro*-β-D-*allopyranose* (V): The mixture of three substances from the reaction mixture was separated as a column. The substance with the shortest retention time was after deacetylation identified as 1,6-anhydro-3,4-dideoxy-β-D-*erythro*-hexopyranose (XXII), m.p. 84 to 86°C, $[\alpha]_D$ −57·5° (c 0·96; water), by comparing with an authentic sample[13] with m.p. 85—86°C, $[\alpha]_D$ −58° (c 0·7; water). The substance with the longest retention time, 1,6-anhydro-3-deoxy-β-D-*ribo*-hexopyranose (IX), was identical with the product from the dianhydro derivative I. A further substance, which we did not succeed to isolate, was detected with the Bonner reagent. This substance is 1,6-anhydro-4-deoxy-β-D-*ribo*-hexopyranose (XVI) according to the agreement of its chromatographic behaviour with that of an authentic sample[16].

1,6 : 3,4-*Dianhydro*-β-D-*altropyranose* (VI): In the reaction mixture were shown to be present three substances. The substance with the shortest retention time was after deacetylation and comparing with an authentic sample identified as 1,6-anhydro-3,4-dideoxy-β-D-*threo*-hexopyranose (XXIII), a liquid with $[\alpha]_D$ −130° (c 0·69; water); the literature[13] records $[\alpha]_D$ −133° (c 0·5; water). The p-toluenesulfonate of substance XXIII had m.p. 83—85°C, $[\alpha]_D$ −78·5° (c 0·68; chloroform), literature[13] gives m.p. 83—85°C, $[\alpha]_D^{24}$ −82° (c 0·66; chloroform). The substance with the longest retention time was the acetate which after deacetylation gave 1,6-anhydro-3-deoxy-β-D-*arabino*-hexopyranose (XIII), identical with the product obtained by reduction of the dianhydro derivative III. The third substance was identified after deacetylation as 1,6-anhydro-4-deoxy-β-D-*arabino*-hexopyranose (XVII), m.p. 106—107°C, $[\alpha]_D$ −162° (c 0·68; water) in agreement with an authentic sample[6] with m.p. 105—107°C, $[\alpha]_D^{20}$ −164° (c 1·4; water).

1,6 : 3,4-*Dianhydro*-β-D-*galactopyranose* (VII): In the reaction mixture were present two substances. The substance with the shorter retention time gave after deacetylation substance XXII, identical with the product prepared from the dianhydro derivative V. From the second substance with the longer retention time was by deacetylation prepared 1,6-anhydro-4-deoxy-β-D-*xylo*-hexopyranose (XVIII), m.p. 156°C (sublimation at 85°C), $[\alpha]_D$ −37° (c 0·7; water), identical with an authentic sample[6] with m.p. 157—160°C, $[\alpha]_D^{20}$ −39° (c 2·4; water).

1,6 : 3,4-*Dianhydro*-β-D-*talopyranose* (VIII): In the reaction mixture were present three substances. Deacetylation of the substance with the shortest retention time gave the same substance XXIII as reduction of the dianhydro derivative VI. The further substance with the longest retention time gave on deacetylation 1,6-anhydro-4-deoxy-β-D-*lyxo*-hexopyranose (XIX), m.p. 85 to 100°C under simultaneous sublimation, thereafter m.p. 156°C (crystalline modification), $[\alpha]_D$ −89° (c 0·66; water). This substance is identical with an authentic sample[16] with m.p. 90—110°C (sublimation), $[\alpha]_D^{22}$ −87° (c 0·66; water); the properties of the dibenzoyl derivative of substance XIX coincided with that of an authentic sample[16]. The third compound present only in a small amount was not isolated in an entirely clean state, it is, however, chromatographically identical with substance XIV, prepared by reduction of the dianhydro derivative IV.

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