LACTONES. XV.*

SYNTHESIS OF 4,6-DIDEOXY-L-*lyxo*-HEXOPYRANOSE AND THE 4,6-DIDEOXY-L-*lyxo*-HEXONOLACTONE

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A number of our previous papers was aimed at the use of parasorbic acid (*I*) in the synthesis of derivatives of 4,6-dideoxyhexoses. Of the four possible stereoisomeric 4,6-dideoxyhexonolactones of the L-configuration, we obtained directly, *i.e.* using *cis*- and *trans*-hydroxylation, the L-*ribo* (*II*) and L-*xylo* (*III*)-isomers, respectively[1-3]. The L-*arabo*-isomer (*IV*) was prepared from the lactone *II* by epimerisation with an organic base[4]. The attempt to use an analogous procedure which would convert the lactone *III* into the remaining L-*lyxo*-isomer (*V*) was unsuccessful. In this study we describe a multistage synthesis of this lactone *via* the corresponding hexose.

As starting compound we chose the relatively well accessible[5] methyl 3,4-anhydro-6-deoxy-α-L-*talo*pyranoside (*VI*). Pressure hydrogenation of this compound on Raney-nickel afforded a mixture which after chromatography on silica gel yielded 12% of the starting anhydro-derivative *VI*, 13·5% of methyl 3,6-dideoxy-α-L-*lyxo*-hexopyranoside (*VII*) and 51·5% of methyl 4,6-dideoxy-α-L-*lyxo*-hexopyranoside (*IX*). The sirupy 3,6-dideoxyglycoside *VII* was characterised as the crystalline 2,3-di-O-methanesulphonyl ester *VIII*. After acidic hydrolysis and reduction with sodium borohydride the compound *VII* was identified as crystalline 3,6-dideoxy-L-*lyxo*-hexitol (*X*) the physical constants of which agreed with those given in the literature[6]. The crystalline 4,6-dideoxyglycoside *IX* was identical with the compound obtained by acid-catalysed methanolysis of methyl 2,3-O-isopropylidene-4,6-dideoxy-α-L-*lyxo*-hexopyranoside (*XI*), the preparation of which, together with a proof of its constitution, we had described previously[7,8]. Acid-catalysed hydrolysis of 4,6-dideoxyglycoside afforded in high yield crystalline 4,6-dideoxy-L-*lyxo*-hexopyranose (*XII*) which, after oxidation with bromine in water, gave the crystalline 4,6-dideoxy-L-*lyxo*-hexonolactone (*V*) in good yield. The corresponding amides *XIII* and *XIV* were prepared by treatment of a methanolic solution of the lactone *V* with liquid ammonia and dimethylamine, respectively. The positive difference between molecular rotation values of the amide *XIII* ($[M]_D$ + +101°) and that of the free 4,6-dideoxy-L-*lyxo*-hexonic acid (*XV*, $[M]_D$ +53°) (ref.[9]), proves, according the Hudson amide rule, the anticipated D-configuration at the $C_{(2)}$ carbon in the amide *XIII*.**

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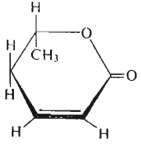
** In agreement with our findings[10] about the exceptional position of N,N-dialkylamides of aldonic acids concerning the Hudson amide rule, the difference between molecular rotation of the dimethylamide *XIV* and the acid *XV* is negative.

EXPERIMENTAL

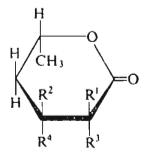
Melting points were determined on a Kofler block and, unless otherwise stated, they are corrected. Analytical samples were dried 10 hours *in vacuo* at 20—35°C. The thin-layer chromatography was carried out on 2·6 × 7·6 cm plates coated with NM-silica gel G (Macherey & Nagel, Germany). Plates were developed in benzene–ethanol 10 : 1 (system S_1), and chloroform–ethanol 5 : 1 (system S_2). Spots were detected by spraying with concentrated sulphuric acid followed by short heating with flame. Column chromatography was carried out on silica gel CH (Lachema, Brno).

Hydrogenation of the Pyranoside *VI*

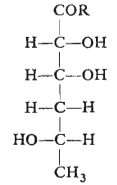
A solution of methyl 3,4-anhydro-6-deoxy-α-L-*talo*-pyranoside (*VI*) (ref.[5]), (1 g, 62·5 mmol) in methanol (100 ml) was hydrogenated 22 hours on Raney nickel (about 5 g) (105°C, 90 atm). After filtering and washing of the catalyst the solution was taken down leaving a sirupy residue (920 mg). According to thin-layer chromatography (system S_1), this residue consisted, in addition to the starting epoxide, of two compounds. The mixture was subjected to chromatography on a silica gel column (100 g). Gradient elution (benzene, then 1 – 5% ethanol–benzene) afforded



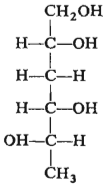
I



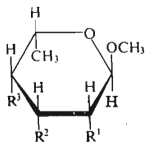
II, $R^1 = R^2 = OH$; $R^3 = R^4 = H$
III, $R^1 = R^4 = OH$; $R^2 = R^3 = H$
IV, $R^2 = R^3 = OH$; $R^1 = R^4 = H$
V, $R^3 = R^4 = OH$; $R^1 = R^2 = H$



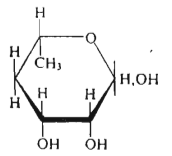
XIII, R = NH_2
XIV, R = $N(CH_3)_2$
XV, R = OH



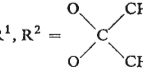
X



VI, $R^1 = OH$; $R^2, R^3 = -O-$
VII, $R^1 = R^3 = OH$; $R^2 = H$
VIII, $R^1 = R^3 = OSO_2CH_3$; $R^2 = H$
IX, $R^1 = R^2 = OH$; $R^3 = H$



XII



XI, $R^1, R^2 =$; $R^3 = H$

the *talo*-epoxide *VI* (122·6 mg, 12%), the sirupy pyranoside *VII* (134·5 mg, 13·4%) and the pyranoside *IX* (520 mg, 51·5%) which after three crystallisations from ethyl acetate–light petroleum melted at 102–102·5°C; $[\alpha]_D^{20}$ −90·0 ± 1·1° (*c* 0·7, chloroform). The literature[11] states m.p. 102°C; $[\alpha]_D^{20}$ −63·5° (*c* 0·66, chloroform). For $C_7H_{14}O_4$ (162·2) calculated: 51·84% C, 8·70% H; found: 51·79% C, 8·75% H.

Methyl 3,6-*dideoxy*-α-L-lyxo-*hexopyranoside* (VII) was purified by distillation in vacuum of an oil pump $[\alpha]_D^{20}$ −103·3 ± 1° (*c* 0·88, chloroform). For $C_7H_{14}O_4$ (162·2) calculated: 51·84% C 8·70% H; found: 51·50% C, 8·44% H.

Methyl 3,6-*dideoxy*-2,4-*di*-O-*methanesulphonyl*-α-L-lyxo-*hexopyranoside* (VIII) Treatment of the glycoside *VII* (244 mg, 1·5 mmol) with an equivalent amount of methanesulphonyl chloride in pyridine afforded, after the usual work-up procedure, the dimethanesulphonyl derivative *VIII* (464 mg, 98%) which after two crystallisations from chloroform–light petroleum melted at 153–154°C; $[\alpha]_D^{20}$ −48·5 ± 0·6° (*c* 0·89, chloroform). For $C_9H_{18}S_2O_8$ (318·4) calculated: 33·95% C, 5·69% H, 20·14% S; found: 33·97% C, 5·87% H, 20·07% S.

Methyl 4,6-dideoxy-α-L-*lyxo*-hexopyranoside (*IX*)

The isopropylidene-derivative *XI* (ref.[7,8]; 105 mg, 0·52 mmol) in 1% methanolic hydrogen chloride solution was heated to 60°C 60 minutes. After this time the starting material has completely disappeared as shown by thin-layer chromatography (system S_1). After neutralisation by shaking with silver oxide (0·5 g), the reaction mixture was taken down and the residue crystallised from ethyl acetate–light petroleum, giving 59 mg (70%) of the glycoside *IX*, m.p. 102–103°C; $[\alpha]_D^{22}$ −89·8 ± 0·1° (*c* 0·5, chloroform), identical with the compound from reduction of the *talo*-epoxide *VI*, as evidenced by mixed melting point and infrared spectra.

4,6-Dideoxy-L-*lyxo*-hexose (*XII*)

A solution of the glycoside *IX* (574 mg, 3·5 mmol) in 0·5M-H_2SO_4 (5 ml) was heated to 90°C. After 120 minutes the starting compound was no longer present as shown by thin-layer chromatography (system S_2, R_F glycoside: 0·64, R_F aldose: 0·32). The cooled reaction mixture was neutralised by filtration through an Amberlite IR - 4B column (in OH^- cycle). The column was washed with 100 ml water, the combined filtrates were taken to dryness and crystallisation of the residue (515 mg) from 2-propanol–light petroleum (4 : 3) afforded 417 mg (81%) of the dideoxyhexose *XII*, m.p. 137·5–138·5°C; $[\alpha]_D^{20}$ −10·6° (5 min) → −2·8° (const., *c* 0·5, water). For $C_6H_{12}O_4$ (148·2) calculated: 48·64% C, 8·16% H; found: 49·12% C, 8·24% H.

4,6-Dideoxy-L-*lyxo*-hexonolactone (*V*)

A solution of the hexose *XII* (417 mg, 2·8 mmol) in water (10 ml) was stirred with barium carbonate (3 g) and bromine (200 µl) for 24 hours at room temperature. The barium carbonate was filtered off and the excess bromine was removed by stream of nitrogen. The reaction mixture was shaken with silver carbonate (2 g) for 30 minutes, filtered, the inorganic salts washed and the solution passed through a Dowex 50 W (H^+ cycle) column (10 ml) which was afterwards washed with water. The combined filtrates were taken to dryness and the crystalline residue (394 mg) was crystallised from chloroform (1·5 ml)–carbon tetrachloride (0·5 ml) giving 281 mg (68·5%) of the lactone *V*, m.p. 113–113·5°C, $[\alpha]_D^{20}$ −77·3° (*c* 1, water), $[\alpha]_D^{23}$ −74·3 ± 0·8° (*c* 0·9, ethanol). For $C_6H_{10}O_4$ (146·1) calculated: 49·31% C, 6·90% H; found: 49·30% C, 6·77% H.

4,6-Dideoxy-L-*lyxo*-hexonic Acid Amide (*XIII*)

A solution of the lactone *V* (148 mg, 1 mmol) in methanol (2 ml) was allowed to stand with an excess of anhydrous ammonia for 24 hours at room temperature. Evaporation of the solvent, followed by two crystallisations of the residue (170 mg) from acetone–light petroleum, gave the amide *XIII*, m.p. 92–93·5°C, $[\alpha]_D^{22}$ +61·9 ± 1·1° (*c* 0·6, water). For $C_6H_{13}NO_4$ (163·2) calculated: 44·16% C, 8·03% H, 8·58% N; found: 44·38% C, 8·09% H, 8·85% N.

4,6-Dideoxy-L-*lyxo*-hexonic Acid Dimethylamide (*XIV*)

The lactone *V* (153 mg, 1·05 mmol) was treated with anhydrous dimethylamine (2 ml) in methanol (3 ml) for 48 hours at room temperature. After evaporation of the solvent the residue was repeatedly crystallised from dichloromethane–carbon tetrachloride, yielding thus 45 mg (22%) of hygroscopic crystals, m.p. 76–77°C, $[\alpha]_D^{22}$ +7·5 ± 1·3° (*c* 0·6, water). For $C_8H_{17}NO_4$ (191·2) calculated: 50·25% C, 8·96% H, 7·33% N; found: 50·33% C, 9·02% H, 7·30% N.

3,6-Dideoxy-L-*lyxo*-hexitol (*X*)

A solution of the glycoside *VII* (1·4 g, 8·6 mmol) in 0·5M-H_2SO_4 (20 ml) was heated to 100°C and the hydrolysis was followed by thin layer chromatography (system S_2; R_F glycoside 0·63, R_F aldose 0·34). After 3 hours the chromatography showed presence of the formed aldose and of some non-hydrolysed glycoside *VII* together with weak spots of compounds of higher R_F. The reaction mixture was filtered through 25 ml an Amberlite IR-4B column (25 ml, OH^-). After extraction of the partly concentrated aqueous solution with ether (6 × 20 ml) the sirupy 3,6-dideoxy-L-*lyxo*-hexose contained only negligible amount of impurities of higher R_F. Without further purification, the hexose (460 mg, 3·1 mmol) was reduced with sodium borohydride (100 mg) in water. After 24 hours' standing at 0°C the thin-layer chromatography showed absence of any aldose (system S_2, R_F hexitol 0·19). The reaction mixture was shaken with Dowex 50 (H^+) (5 ml) and repeatedly evaporated with methanol, giving thus 460 mg of a residue which after crystallisation from ethanol–ether–light petroleum afforded the product (319 mg, 69%), melting at 73–75°C, $[\alpha]_D^{22}$ −11·0 ± 1·2° (*c* 0·67, methanol). The literature[6] gives m.p. 75–77°C, $[\alpha]_D$ −11° (*c* 0·68, methanol). For $C_6H_{14}O_4$ (150·2) calculated: 47·99% C, 9·40% H; found: 48·03% C, 9·58% H.

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