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Synthesis of 3-hexuloses

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A general procedure for the syntheses of derivatives of 3-hexuloses from L-*threo*-hexeno-furano lactone is described[1].

Une méthode générale de synthèse de 3-hexuloses avec du L-*threo*-hexeno-furano lactone est décrite.

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The recent isolation from an antibiotic, and identification of coriose (1), as D-*altro*-3-heptulose, previously isolated by Begbie and Richtmyer (2) prompts us to give details of a general synthesis of 3-hexuloses. In an earlier publication (3) the synthesis of 2-*O*-methyl-3-hexuloses and 2-*O*-methyl-3-heptuloses was described and a modification of this synthesis was later (4) suggested which might lead to the 3-hexuloses. It is now shown that this suggested procedure does in fact lead to the synthesis of sugars named in the title of this paper.

L-Ascorbic acid (**1**, $R^2 = R^3 = H$) is readily acetonated to yield 5,6-*O*-isopropylidene-L-ascorbic acid (**2**, $R^2 = R^3 = H$) (5). Treatment of this substance with one equivalent of diazomethane produces mainly the 3-*O*-methyl ether (**2**, $R^2 = H$; $R^3 = CH_3$) (4). The sodium salt of this compound reacts with benzyl chloride to give crystalline **2** ($R^2 = CH_2Ph$; $R^3 = CH_3$). Elimination of acetone by acid hydrolysis yields 2-*O*-benzyl-3-*O*-methyl-L-ascorbic acid (**1**, $R^2 = CH_2Ph$; $R^3 = CH_3$). 2,3-Di-*O*-substituted derivatives of L-ascorbic acid rearrange in the presence of base (6), to yield furanoside derivatives by addition at the vinylic carbon, in this case to yield **3** ($R^2 = CH_2Ph$; $R^3 = CH_3$) which reduces 0.97 equivalent of periodate. Reduction of the lactone by lithium aluminium hydride then results in the formation of a methyl glycoside of a 3-hexulose derivative. If now the benzyl residue is removed by hydrogenation and the resultant glycoside **4** ($R^2 = H$; $R^3 = CH_3$) treated with acid a 3-hexulose **4** ($R^2 = R^3 = H$) results, which consumes 1.7 equivalent of periodate and yields 0.81 equivalent of formaldehyde. However in the rearrangement described above two new asymmetric centers are produced at C-2 and C-3, but only two products are detected. Models indicate that the addition at C-3 yields the less strained component which contains two *cis*-fused five-membered rings. The two isomers produced are separable by thin-layer and gas–liquid chromatography (t.l.c. and g.l.c.). The absolute configuration of the

[1]Abstracted from the Ph.D. Thesis of K.G.A. Jackson (1966).

L-*xylo*-isomer was determined by reducing the 3-hexulose to a mixture of glucitol and galactitol, the acetates of which were identified by g.l.c. (7). A syrupy dinitrophenylhydrazone **5** of **4** ($R^2 = R^3 = H$) was prepared. Its oxidation produced formaldehyde (1.5 moles) and formic acid (0.78) with a consumption of 2.8 moles of periodate per mole. These figures obtained from a product isolated by chromatography, are in reasonable agreement with the theoretical values which are 2.0, 1.0, and 3.0 respectively (see below). The subsequent isolation of 2,4-dinitrophenylazomalondialdehyde is in agreement with the structure postulated, **5** (8).

Experimental

For details of separations of sugar derivatives by paper chromatography and t.l.c. see Jackson and Jones (4).

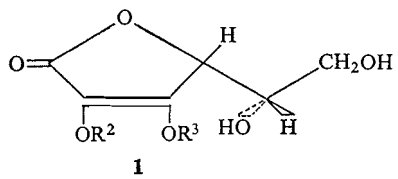
5,6-O-Isopropylidene-L-ascorbic acid (2, $R^2 = R^3 = H$)

A mixture of L-ascorbic acid (10 g) in acetone (40 ml) containing acetyl chloride (1.0 ml) was shaken mechanically. Crystalline 5,6-*O*-isopropylidene-L-ascorbic acid separated from the solution soon after the L-ascorbic acid had dissolved. After storage at 0° there was obtained on filtration, 10.1 g of needle-shaped crystals of m.p. 217–223° (5). This material was used in the next step without further purification.

2-O-Benzyl-5,6-O-isopropylidene-3-O-methyl-L-ascorbic acid (2, $R^2 = CH_2Ph$; $R^3 = CH_3$)

A methanolic solution of 5,6-*O*-isopropylidene-L-ascorbic acid (35 g) was treated at 0° with an ethereal solution of diazomethane to a yellow end point which persisted for about 1 min. Evaporation of the solvent yielded a mobile syrup which was dissolved in methanol and converted to the sodium salt by the addition of methanolic sodium methoxide (6.0 *N*, 21.0 ml).

After evaporation of the methanol the residual brown gum was dispersed in benzyl chloride (70 ml) and the mixture was heated at 80° (2.5 h) and then poured into water. After evaporation of excess benzyl chloride, the product crystallized and was recrystallized from methanol to yield the product (16.0 g) of m.p. 85–87°, identical with that described earlier (4) but in higher yield.



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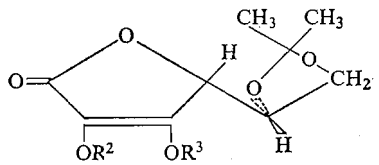

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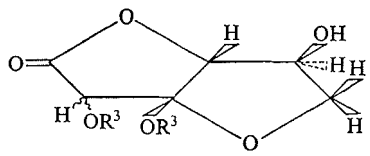

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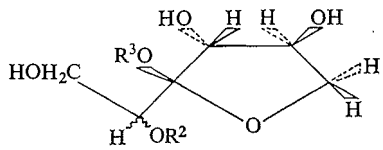

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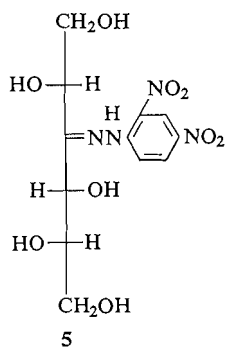

5

*2-O-Benzyl-3-O-methyl-*L*-ascorbic acid (**1**, $R^2 = CH_2Ph$; $R^3 = CH_3$)*

A solution of the above isopropylidene derivative (3.0 g) above in acetic acid (50%, 50 ml) was heated at 90–100° for 4 h. Water (200 ml) was then added and the solution was extracted with chloroform (2 × 200 ml). The chloroform extracts were dried ($MgSO_4$), filtered, and the filtrate was evaporated. The crystalline residue (1.3 g) was recrystallized from chloroform. The product had m.p. 124° and $[\alpha]_D = +48° \pm 1°$ (*c*, 1.0 in methanol).

Anal. Calcd. for $C_{14}H_{15}O_6$: C, 60.0; H, 5.7. Found: C, 59.6; H, 5.5.

The infrared (i.r.) spectrum (KBr disk) revealed strong absorptions at 1660, 1745, and 3300 cm^{-1}. The nuclear magnetic resonance (n.m.r.) spectrum (DMSO-d_6) revealed peaks at τ 2.61 (singlet, 5 aromatic protons), and 6.09 (singlet, 3 methyl protons) as well as other peaks.

*Methyl 2-O-Benzyl-*L*-(lyxo + xylo)-3-hexulofuranosidonolactones (**3**, $R^2 = CH_2Ph$; $R^3 = CH_3$)*

An aqueous solution of **1** ($R^2 = CH_2Ph$; $R^3 = CH_3$) (8.3 g) was saponified at 60° with sodium hydroxide (1.96 *N*, 11.2 ml). The solution was then passed down a column of ion exchange resin (H^+) and the acidic effluent collected. The column was washed with warm water until the effluent gave a negative Molisch test and the aqueous solutions were concentrated and extracted with chloroform (2 × 10 ml). The extracts were dried ($MgSO_4$), filtered, and the filtrate was evaporated to a syrup (6.6 g) which had $[\alpha]_D = -10° \pm 1°$ (*c*, 1.0 in methanol). Two components were detected by paper chromatograms (solvent *a*) and were visualized in iodine vapor. The i.r. absorption ($CHCl_3$) revealed absorptions at 1800 cm^{-1} (strong) and 3450 cm^{-1} (medium).

*Methyl 2-O-Benzyl-*L*-(lyxo + xylo)-3-hexulosides (**4**, $R^2 = CH_2Ph$; $R^3 = CH_3$)*

The syrupy product above (14.3 g from two preparations) was dissolved in ether (100 ml) and the solution added dropwise to a solution of $LiAlH_4$ (14.0 g) in ether (200 ml). An immediate precipitate resulted. Ten minutes after completion of the addition, excess of $LiAlH_4$ was destroyed with ethyl acetate (300 ml) followed by the cautious addition of water (200 ml). The ethyl acetate layer was separated and the residue was extracted with a further quantity of ethyl acetate (100 ml). The combined extracts were washed with water (100 ml), dried ($MgSO_4$), filtered, and the filtrate was evaporated to a pale yellow syrup (10.5 g) of $[\alpha]_D = -6° \pm 1°$ (*c*, 1.0 in methanol). Analysis by t.l.c. indicated the presence of two components of R_f 0.6 and 0.7 in the approximate ratio 2:3. The i.r. absorption of the mixture in chloroform indicated a peak at 3500 cm^{-1} (medium) but none at 1605–2000 cm^{-1}.

Periodate Oxidation of the Syrupy Mixture of Glycosides

Periodate uptake and formic acid yield on 116 mg of the mixture, dissolved in water (100 ml) were carried out in the usual way (4) using screened (methylene-blue)-methyl red indicator.

Found: Moles periodate consumed per mole of compound at the times indicated: 0.31, (0.5 h); 0.38 (1 h); 0.51 (2 h); 0.72 (4.5 h); 0.91 (20 h); 0.97 (94 h). The yield of formic acid rose from 0.02 to 0.08 in the same period.

Methyl L*-(lyxo + xylo)-3-hexulosides (**4**, $R^2 = H$; $R^3 = CH_3$)*

The syrupy mixture of glycosides (9.0 g) (above) was dissolved in ethanol (100 ml) and reduced with Raney nickel catalyst and hydrogen at 2 atmospheres pressure during 4 days. At the end of this time reaction was complete as judged by t.l.c. The solution was filtered and the filtrate evaporated to a syrup which was dissolved in water and extracted with chloroform (100 ml) to remove the last traces of toluene. Evaporation of the aqueous layer afforded a syrup (5.6 g) of $[\alpha]_D = +35° \pm 1°$ (*c*, 1.0 in methanol). Paper chromatography (solvent *a*) revealed one component with $R_f = 0.48$ and $R_{rhamnose} = 1.45$.

Periodate Oxidation of Methyl L*-(lyxo + xylo)-3-hexulosides*

Periodate uptake, formic acid production, and formaldehyde release were determined in the usual manner on 110 mg syrup in water (100 ml).

Found: Uptake of periodate at the times indicated: 0.91 (0.25 h); 1.05 (1 h); 1.26 (3.5 h); 1.45 (10 h); 1.64 (23 h); 1.70 (30 h). Formaldehyde yield: 0.02 (0.4 h); 0.81 (21 h). The formic acid yield changed from 0.01 (0.25 h) to 0.04 (23 h). All results are given in mole/mole of glycoside.

*Methyl 1,2,4,5-Tetra-O-acetyl-*L*-(lyxo + xylo)-3-hexulosides*

The mixed glycosides (1.0 g) were acetylated with pyridine (30 ml) and acetic anhydride (5 ml) at 0° for 12 h. The acetylated products were isolated in the usual manner as a clear colorless syrup. Thin-layer chromatography revealed components at $R_f = 0.60$ (medium) and 0.75 (major). Analysis by gas–liquid chromatography (g.l.c.) using 5% LAC-4-R-886 (Chromatographic Specialities, Brockville, Ontario) at 200° and at a flow rate of 100 cc/min (Pye Argon g.l.c.) showed two components, the L-*xylo* and L-*lyxo* derivatives respectively, 3.5 min and 5.8 min, in the ratio 55:45.

Separation of the Glycosides

A portion of the mixture was separated by preparative t.l.c. on plates 8 in. × 8 in. coated with silica gel G using chloroform, methanol (9:1 v/v) as eluant. The bands of material could be located visually or better with the aid of an ultraviolet lamp. The faster moving component (540 mg) isolated after extraction of the appropriate region of the silica gel G with acetone had a retention time of 3.5 min (see above) and had $[\alpha]_D = +14° \pm 1°$ (*c*, 1.0 in methanol) and was identified as methyl 1,2,4,5-tetra-*O*-acetyl-L-*xylo*-3-hexuloside (see below).

Anal. Calcd. for $C_{15}H_{22}O_{10}$: C, 49.7; H, 6.1. Found: C, 50.0; H, 6.4.

The slower moving component (200 mg) was therefore methyl 1,2,4,5-tetra-*O*-acetyl-L-*lyxo*-3-hexuloside with $[\alpha]_D = +5° \pm 1°$ (*c*, 1.0 in methanol). It was not further examined. The i.r. spectra of these two substances ($CHCl_3$) were indistinguishable and revealed absorption bands at 1730 cm^{-1} (strong) and at 1375 cm^{-1} (medium).

Purification of Methyl L*-xylo-3-hexuloside*

Methyl 1,2,4,5-tetra-*O*-acetyl-L-*xylo*-3-hexuloside (540 mg) was deacetylated by the method of Zemplén. After

12 h the product was isolated as a clear colorless syrup (250 mg) with $[\alpha]_D = -29° \pm 1°$ (*c*, 1.0 in methanol). On periodate oxidation of a sample (5.5 mg) formaldehyde (0.31 mole/mole, 21 h) was produced.

L-xylo-3-Hexulose (4, $R^2 = R^3 = H$)

The glycoside (100 mg) was dissolved in water (20 ml) and hydrolyzed at 80° with acid ion exchange resin (Amberlite IR-120) during 0.33 h. At the end of this time hydrolysis was complete as indicated by paper chromatography. The product in solvent *a* had $R_{rhamnose} = 0.69$; $R_{tagatose} = 1.25$ and $R_{sorbose} = 1.45$ and gave a bright-yellow color with the *p*-anisidine hydrochloride spray. The reducing sugar was isolated as a syrup after removal of the ion exchange resin and evaporation of the solution. It had $[\alpha]_D = +10° \pm 1°$ (*c*, 0.5 in water).

Sodium Borohydride Reduction of L-xylo-3-Hexulose (4, $R^3 = R^4 = H$) and Identification of the Resultant Hexitols

The ketose **4** ($R^3 = R^4 = H$) (20 mg) was reduced in water (50 ml) by addition of sodium borohydride (30 mg). When reduction was complete, as indicated by paper chromatography, the solution was passed through a column of ion exchange resin (Amberlite i.r. 120 H) and the effluent evaporated to dryness. Boric acid was removed as methyl borate by co-distillation with methanol and the residue acetylated (pyridine and acetic anhydride) in the usual way. The mixture of acetates was then examined by g.l.c. and was resolvable into two components which were indistinguishable, on an F and M model 500 g.l.c. machine, from sorbitol and dulcitol hexa-acetates under standardized conditions.

L-xylo-3-Hexulose 2,4-Dinitrophenylhydrazone (5)

The L-*xylo*-methyl glycoside (**4**, $R^2 = H$; $R^3 = CH_3$) (0.175 g) was dissolved in dimethyl sulfoxide (2 ml) containing 1 drop of conc. hydrochloric acid and 2,4-dinitrophenylhydrazine (0.165 g). After 2 h, paper chromatography (solvent *a*) indicated the presence of a yellow major component with $R_f = 0.66$, $R_{rhamnose} = 1.78$. This substance was isolated as a yellow gum after preparative chromatography on six 8 in. × 8 in. glass plates coated with silica gel G. The product (93 mg) had $[\alpha]_D = 20° \pm 4°$ (*c*, 0.9 in methanol) and was homogeneous by paper chromatography.

Periodate Oxidation of L-xylo-3-Hexulose 2,4-Dinitrophenylhydrazone

The hydrazone derivative (37.5 mg) was oxidized in duplicate in the usual manner.

Found: Mole of formic acid produced by moles of periodate consumed per mole of compound at the times indicated: 0.78, 2.8 (0.17 h); 0.7, 2.8 (0.67 h). Formaldehyde produced mole/mole 1.50 (0.5 h).

During the oxidation a yellow precipitate separated from solution. It had m.p. 160° and its i.r. spectrum (KBr disk) showed strong peaks at 1590, 1655, and 1685 cm^{-1} with no absorption in the region 1700–2300 cm^{-1}. The ultraviolet absorption was strong at $\varepsilon_{max} = 395$ mμ with $\varepsilon = 2.5 \times 10^4$. 2,4-Dinitrophenylazomalondialdehyde has m.p. 160–161°, $\varepsilon_{max} = 395$ mμ with $\varepsilon = 2.45 \times 10^4$ (8).

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Total synthesis of (±)ochotensine

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A total synthesis of (±)ochotensine is described.

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A very recently published total synthesis of (±)ochotensine (**1**) (1) by Irie *et al.* (2) has just come to our attention, prompting us to report an independent, but similar, synthesis of this alkaloid. An account (3) of our total synthesis of analogues **5** and **6** of ochotensine and ochotensimine respectively, appeared some months ago. We anticipated (3) that the synthesis of