183. 3-*Deoxy*-l-*xylose.*

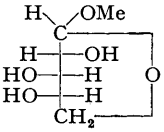
By S. Mukherjee and A. R. Todd.

In the course of experiments initiated in search of new synthetic routes to 2-deoxyribose derivatives, 2 : 3-*anhydro*-β-*methyl*-l-*ribopyranoside*, prepared from β-methyl-*l*-arabopyranoside, has been treated with sodium thiomethoxide and the product refluxed in alcohol with Raney nickel. The product was 3-*deoxy*-β-*methyl*-l-*xylopyranoside* containing at most only traces of a 2-deoxypentoside. Acid hydrolysis gave 3-*deoxy*-l-*xylose* as a syrup, characterised as its p-*nitrophenylosazone*, and yielding on oxidation *l-erythro*-1 : 3 : 4-trihydroxyvaleric acid isolated as its phenylhydrazide. Hydrogenolysis of the same anhydro-glycoside gave mainly 3-deoxy-β-methyl-*l*-xylopyranoside, apparently accompanied by a small amount of a 2-deoxypentoside, since the product showed a small uptake of oxidant on titration with periodate. 2 : 3-*Anhydro*-α-*methyl*-l-*ribopyranoside* treated in similar fashion with sodium thiomethoxide, followed by refluxing in alcohol with Raney nickel, also gave a product whose major constituent was 3-deoxy-α-methyl-*l*-xylopyranoside, since the syrupy sugar obtained from it by hydrolysis yielded 3-deoxy-*l*-xylose *p*-nitrophenylosazone on warming with *p*-nitrophenylhydrazine.

The work described in this paper was undertaken in connection with studies on the synthesis of purine and pyrimidine nucleosides in progress in this laboratory, and which required for extension to the deoxyribonucleosides considerable quantities of 2-deoxy-*d*-ribose. 2-Deoxy-*l*-ribose has been prepared from *l*-arabinose (Levene and Mori, *J. Biol. Chem.*, 1929, **83**, 803; Levene, Mikeska, and Mori, *ibid.*, 1930, **85**, 785) using the standard glycal route first developed by Fischer (*Ber.*, 1914, **47**, 196), but the exploration of other routes which might give better yields of 2-deoxyribose derivatives seemed desirable. The use of 2 : 3-anhydro-sugar derivatives as intermediates in the synthesis of deoxy-hexoses has recently been described by Prins, Reichstein, and their co-workers who have prepared in this way various derivatives of 3-deoxy-*d*-glucose (Prins, *Helv. Chim. Acta*, 1946, **29**, 1), 2-deoxy-*d*-allose (Jeanloz, Prins, and Reichstein, *ibid.*, p. 371), cymarose (Prins, *ibid.*, p. 378) and 3-deoxy-*l*-mannose (Bollinger and Prins, *ibid.*, p. 1061). Following a discussion with the Swiss workers it was agreed that we should seek to apply similar methods in the pentose series in the hope that they would lead to a preparative method for 2-deoxyribose derivatives. For convenience we first carried out the proposed sequence of reactions starting with *l*-arabinose, which was expected to yield finally either 2-deoxy-*l*-ribose or 3-deoxy-*l*-xylose or possibly a mixture of both. In fact, it was found that 3-deoxy-*l*-xylose was formed as the main product; no 2-deoxy-*l*-ribose derivative could be isolated, although there was some evidence that traces of 2-deoxy-derivatives were formed.

β-Methyl-*l*-arabopyranoside (I) condensed with acetone to give an acetone derivative whose formulation as 3 : 4-iso*propylidene* β-*methyl*-l-*arabopyranoside* (II) follows from the transformations described below. Treatment of (II) with *p*-toluenesulphonyl chloride in pyridine yielded 2-p-*tosyl* 3 : 4-iso*propylidene* β-*methyl*-l-*arabopyranoside* (III) hydrolysed to 2-p-*tosyl* β-*methyl*-l-*arabopyranoside* (IV). The location of the tosyl group in (IV), and hence the structures

allotted to (II) and (III), are confirmed by the fact that on titration of (IV) with periodate 1 mol. of oxidant is consumed. Cold methanolic sodium methoxide converted (IV) into a crystalline anhydro-compound formulated from its mode of preparation as 2 : 3-*anhydro*-β-*methyl*-l-*ribopyranoside* (V) which, warmed with methanolic sodium thiomethoxide, yielded a syrupy sulphur-containing glycoside. Assuming a *trans*-opening of the ethylene oxide ring of (V) with inversion at the carbon atom to which the sulphur attaches itself this product might have been 3-*methylthio* β-*methyl*-l-*xylopyranoside* (VI), 2-methylthio β-methyl-*l*-arabopyranoside, or a mixture of both. Although from the experience of Jeanloz, Prins, and Reichstein (*loc. cit.*) in the *d*-allose series production of the 2-methylthio-product in reasonable amount might have been expected, subsequent reactions show that our product consisted almost entirely of (VI), the 2-methylthio-compound being present at most in traces. The syrupy methylthio-compound was refluxed in alcoholic solution with Raney nickel, prepared according to Mozingo *et al.* (*J. Amer. Chem. Soc.*, **1943**, **65**, **1013**); it then yielded a sulphur-free glycoside which was stable to periodate, the uptake of oxidant on titration being within the limits of experimental error. This product we regard as 3-*deoxy*-β-*methyl*-l-*xylopyranoside* (VII). The possibility that it was contaminated by a trace of 2-deoxy-β-methyl-*l*-riboside cannot be excluded since it could not be crystallised and it gave a feeble green colouration in the Keller–Kiliani test commonly regarded as specific for 2-deoxy-sugars. Acid hydrolysis of (VII) yielded the free 3-*deoxy*-l-*xylose* (VIII) as a syrup yielding a crystalline p-*nitrophenylosazone*. The structure allotted to (VIII) was confirmed by oxidation with bromine water, lactonisation of the acid produced, and conversion into a crystalline phenylhydrazide, which agreed in m. p., analysis, and, within the limits of error, optical rotation with *l*(+)-*erythro*-1 : 3 : 4-trihydroxyvaleric acid phenylhydrazide (IX) prepared by Nef (*Annalen*, **1910**, **376**, 48), who on the basis of its dextrorotation described it as the *d-erythro*-compound.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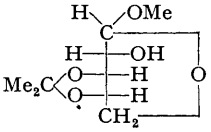
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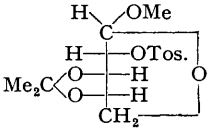
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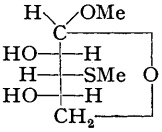
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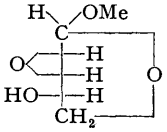
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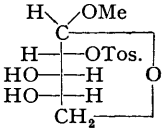
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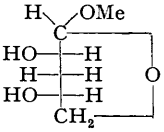
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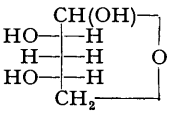
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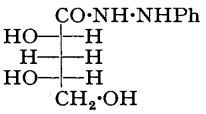
(IX.)

As an alternative route the ethylene oxide ring in (V) was opened by hydrogenolysis under pressure using a nickel catalyst. The syrupy product produced was again mainly (VII) but there was more evidence of the presence of an appreciable amount of a 2-deoxy-pentose derivative, since the green colour produced in the Keller–Kiliani test, although weak, was stronger than in the case of the product obtained *via* the methylthio-glycoside, and on periodate titration 0·17 mol. of oxidant was consumed. On acid hydrolysis followed by treatment of the syrupy free sugar with *p*-nitrophenylhydrazine, however, only the *p*-nitrophenylosazone of 3-deoxy-*l*-xylose could be isolated. No further attempts were made to isolate any 2-deoxy-pentose present, since it was evident that even if they were successful the method would hardly be of preparative value.

In the preparation of β-methyl-*l*-arabopyranoside a considerable amount of a syrupy mixture of the α- and the β-isomer was left after removal of the crystalline β-compound. This syrup was condensed with acetone and the product tosylated. After separation of a quantity of the crystalline 2-*p*-tosyl 3 : 4-*iso*propylidene β-methyl-*l*-arabopyranoside the residual syrup was subjected to mild hydrolysis; from the resulting syrup 2-p-*tosyl* α-*methyl*-l-*arabopyranoside* was isolated. By methods exactly analogous to those used above in the β-series this compound

was converted into 2 : 3-*anhydro*-α-*methyl*-l-*ribopyranoside*, the latter reacted with sodium thiomethoxide, and the product treated with Raney nickel. The resulting syrup gave analytical values corresponding to a deoxy-methylpentoside, and from the fact that it consumed *ca.* 0·3 mol./mol. of periodate on titration it appeared to be a mixture of (VII) with a smaller amount of a 2-deoxy-compound; on hydrolysis and treatment of the product with *p*-nitrophenylhydrazine only 3-deoxy-*l*-xylose *p*-nitrophenylosazone was isolated. This was rather surprising in view of the periodate titration value mentioned above, but it is possible that this value may give an exaggerated estimate of the content of 2-deoxy-pentoside in the mixture.

The results obtained indicate that the projected route to 2-deoxyribose from arabinose *via* the 2 : 3-anhydroarabinosides is unlikely to be of any practical interest if, indeed, it can be realised. The route, however, does form a fairly convenient method for the preparation of 3-deoxy-*l*-xylose and its derivatives, since the overall yield from methyl-*l*-arabopyranoside is very satisfactory. Other possible routes to 2-deoxyribose derivatives are under investigation and will be reported upon in due course.

Experimental.

β-Methyl-l-*arabopyranoside*.—Following the procedure of Hudson (*J. Amer. Chem. Soc.*, 1925, **47**, 267) we obtained from *l*-arabinose (100 g.) pure β-methyl-*l*-arabopyranoside (32 g.), together with a syrupy mixture of the α- and the β-isomer (*ca.* 75 g.).

3 : 4-iso*Propylidene* β-*Methyl*-l-*arabopyranoside*.—To an ice-cold suspension of finely powdered β-methyl-*l*-arabopyranoside (32 g.) in dry acetone (750 c.c.), phosphoric oxide (26 g.) was gradually added with stirring. The temperature was kept below 5° and stirring continued until the starting material dissolved (*ca.* 3 hours), then set aside overnight in the refrigerator. The supernatant liquid was decanted from the mixture of phosphoric acid, etc., which had settled to the bottom of the flask, and neutralised by gradually adding concentrated aqueous potassium hydroxide. The mixture was filtered and the filtrate concentrated under reduced pressure (bath temp. 35°). The syrupy product was distilled at 80—90° (bath temp.)/5×10^{-4} mm. giving the iso*propylidene* derivative as a colourless syrup (29 g.; 72·5%). $[\alpha]_D^{20°}$ +175·7°±0·5° (*c*, 5·2 in chloroform) (Found: C, 53·3; H, 7·7. $C_9H_{16}O_5$ requires C, 52·9; H, 7·8%). The same product was obtained although in much lower yield by carrying out the condensation of β-methyl-*l*-arabopyranoside with acetone in presence of anhydrous copper sulphate and sulphuric acid.

2-p-*Tosyl* 3 : 4-iso*Propylidene* β-*Methyl*-l-*arabopyranoside*.—*p*-Tosyl chloride (28·5 g.) was added to a solution of 3 : 4-*iso*propylidene β-methyl-*l*-arabopyranoside (27·3 g.) in dry pyridine (136 c.c.) and the mixture warmed at 40° for 24 hrs. A small amount of water (1 c.c.) was added, and the solution set aside at 0° for 30 minutes. More water (*ca.* 100 c.c.) and chloroform (*ca.* 250 c.c.) were added and the mixture was shaken. The chloroform layer was separated, and the aqueous layer extracted several times with small quantities of chloroform. The combined chloroform extracts were washed successively with ice-cold dilute sulphuric acid, sodium hydroxide, and water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue recrystallised from alcohol gave colourless rod-shaped prisms (37·5 g.), m. p. 133°, $[\alpha]_D^{18°}$ +187·3°±2° (*c*, 1·55 in chloroform) (Found: C, 53·8; H, 6·1; S, 8·6. $C_{16}H_{22}O_7S$ requires C, 53·6; H, 6·2; S, 8·9%).

2-p-*Tosyl* β-*Methyl*-l-*arabopyranoside*.—A solution of 2-p-*tosyl* 3 : 4-iso*propylidene* β-*methyl*-l-*arabopyranoside* (34 g.) in a mixture of methanol (1400 c.c.) and dilute sulphuric acid (280 c.c. of N) was heated at 40° for 4 hours; a further quantity of sulphuric acid (280 c.c. of N) was then added and the solution maintained at 40° for a further 4 hours, then cooled and neutralised by shaking with precipitated barium carbonate. Filtration followed by removal of solvents under reduced pressure (bath temp. 40°) gave a syrup which was taken up in ether; the solution was dried (Na_2SO_4) and evaporated. The residue solidified on removal of the last traces of solvent in a vacuum. The product (30 g.) could be purified by precipitation from ethereal solution with pentane; it then had m. p. *ca.* 43°, but was very hygroscopic. $[\alpha]_D^{20°}$ +115°±1° (*c*, 3·47 in chloroform) (Found: C, 49·1; H, 5·9. $C_{13}H_{18}O_7S$ requires C, 49·0; H, 5·7%).

2 : 3-*Anhydro*-β-*methyl*-l-*ribopyranoside*.—Ice-cold methanolic sodium methoxide (75 c.c. of a solution prepared by dissolving 6 g. sodium in 100 c.c. methanol) was added to a solution of 2-p-*tosyl* β-*methyl*-l-*arabopyranoside* (28·2 g.) in chloroform (350 c.c.) at 0°, and the mixture set aside in the refrigerator for 3 days with occasional shaking, then left at room temperature for a further 24 hours and neutralised with N-sulphuric acid. The chloroform layer was separated and the aqueous layer extracted with chloroform, and the combined chloroform extracts were dried (Na_2SO_4) and evaporated under slightly reduced pressure (bath temp. 40°). The *anhydro-glycoside* was obtained as a colourless syrup (11·4 g.), which on being kept in a desiccator over phosphoric oxide slowly set to a mass of needles which were so hygroscopic that a satisfactory m. p. determination could not be made. $[\alpha]_D^{18°}$ +35·7°±1° (*c*, 2·7 in chloroform) (Found: C, 49·3; H, 6·9. $C_6H_{10}O_4$ requires C, 49·3; H, 6·9%).

3-*Methylthio* β-*Methyl*-l-*xylopyranoside*.—2 : 3-Anhydro-β-methyl-*l*-ribopyranoside (5 g.) was dissolved in methanolic sodium thiomethoxide (37·5 c.c. containing 1·87 g. of sodium and 5 g. of methylthiol) and the solution refluxed for 2 hours, then cooled, exactly neutralised with N-sulphuric acid, and evaporated to dryness under reduced pressure (bath temp. 40°). The residue was extracted with chloroform, and the extract dried (Na_2SO_4) and evaporated. The brownish syrup (6·9 g.) could be purified by chromatography on active alumina in benzene solution; a small amount of material passed through the column, and elution of the adsorbed material with methanol gave the *product* (0·8 g. from 1 g.) as a faintly yellow syrup (Found: C, 43·2; H, 7·2. $C_7H_{14}O_4S$ requires C, 43·3; H, 7·3%).

3-*Deoxy*-β-*methyl*-l-*xylopyranoside*.—(1) *From* 3-*methylthio* β-*methyl*-l-*ribopyranoside*. The crude methylthio-compound (6 g.) was dissolved in a mixture of alcohol (300 c.c.) and water (70 c.c.), and

Raney nickel (150 g. prepared according to Mozingo *et al.*, *loc. cit.*) added. The mixture was heated under reflux for 2 hours and filtered, the nickel being thoroughly washed with alcohol, and the combined filtrate and washings were evaporated under reduced pressure. The residue was dissolved in water (35 c.c.), the solution thrice extracted with chloroform, and the aqueous phase evaporated under reduced pressure (bath temp. 40°) to a syrup, which was dissolved in acetone (30 c.c.) and filtered from inorganic material, and the acetone again evaporated under reduced pressure. The residue so obtained distilled at 110° (bath temp.)/4×10^{-3} mm. as a colourless hygroscopic syrup (3·6 g.). $[\alpha]_D^{18°}$ +142·2°±5° (*c*, 2·25 in chloroform) (Found: C, 48·0; H, 8·5. $C_6H_{12}O_4$ requires C, 48·6; H, 8·2%). The *product* was virtually unaffected by sodium metaperiodate (0·2163 g. consumed 0·02 c.c. of M-periodate in 24 hours; 0·07 c.c. in 48 hours) but it gave a feeble green coloration in the Keller–Kiliani test.

(2) *From* 2 : 3-*anhydro*-β-*methyl*-l-*ribopyranoside*. Raney nickel (4 g.) was added to the anhydro-compound (3·3 g.) dissolved in alcohol (60 c.c.) and the mixture hydrogenated at 110°/100 atm. during 24 hours. Catalyst was removed by filtration and the filtrate evaporated under reduced pressure, yielding a colourless syrup which distilled at 100—105° (bath temp.)/10^{-3} mm. The product (2·2 g.) had $[\alpha]_D^{19°}$ +143°±4° (*c*, 2·868 in chloroform) (Found: C, 48·7; H, 8·3; OMe, 19·9. $C_6H_{12}O_4$ requires C, 48·6; H, 8·2; OMe, 20·9). It gave a weak colour in the Keller–Kiliani test, and on titration with periodate it took up 0·17 mol. of reagent in 48 hours, suggesting that it may have been contaminated with some of the corresponding 2-deoxy-riboside.

3-*Deoxy*-l-*xylose*.—The syrupy glucoside obtained by method (1) above (0·3868 g.) was heated to 100° with dilute sulphuric acid (25 c.c. of 0·5N) until a constant rotation was attained (75 minutes). Specific rotations: after 60 minutes, +8·4°; after 75 minutes, +7·9°±1·5° (constant). The solution was neutralised with freshly precipitated barium carbonate, filtered, and evaporated under reduced pressure. The residual syrup was evaporated once under reduced pressure with methanol and dissolved in absolute alcohol. Inorganic matter was precipitated by addition of ether and the solution evaporated under reduced pressure yielding the *sugar* as a colourless syrup which immediately reduced Fehling's solution but could not be crystallised (Found: C, 44·4; H, 7·7. $C_5H_{10}O_4$ requires C, 44·8; H, 7·5%). Calculated from the final rotation of the hydrolysis solution the sugar had $[\alpha]_D^{18°}$ +8·7°±1·5°.

A similar product was obtained by hydrolysing a sample of 3-deoxy-β-methyl-*l*-xylopyranoside prepared by method (2) above; the specific rotation became constant after 90 minutes at +9°.

3-*Deoxy*-l-*xylose* p-*Nitrophenylosazone*.—This was prepared by heating 3-deoxy-*l*-xylose (230 mg. prepared *via* the methylthio-compound) in water (6 c.c.) with *p*-nitrophenylhydrazine (600 mg.) in glacial acetic acid (1 c.c.) for 1 hour on the steam-bath, and recrystallised from alcohol; dark red microcrystalline powder, m. p. 254—256° (Found: C, 51·2; H, 4·8; N, 20·9. $C_{17}H_{18}O_6N_6$ requires C, 50·7; H, 4·5; N, 20·9%). Similar treatment of a sample of the sugar prepared by the procedure involving hydrogenolysis of the anhydro-compound gave the same product; no other product could be isolated, although the m. p. of the crude *osazone* was somewhat lower.

l-erythro-1 : 3 : 4-*Trihydroxyvaleric Acid Phenylhydrazide*.—Bromine (0·25 c.c.) was added to a solution of 3-deoxy-*l*-xylose (470 mg.) in water (6 c.c.) and the mixture shaken in a closed vessel for 48 hours in the dark. Unchanged bromine was then removed under reduced pressure in a stream of air, the solution neutralised with freshly precipitated silver carbonate, and excess of silver removed with hydrogen sulphide. The solution obtained by filtering through charcoal was evaporated under reduced pressure and the residue evaporated once with methanol. The syrup (370 mg.) so obtained was lactonised by distillation at 120° (bath temp.)/3×10^{-4} mm. and the syrupy lactone (114 mg.) heated for 30 minutes at 100° with phenylhydrazine (100 c.mm.). After 3 hours a semi-crystalline mass had separated; ether was added and the colourless crystalline precipitate filtered off. Recrystallised from alcohol the hydrazide formed colourless needles, m. p. 149°, $[\alpha]_D^{18°}$ +4·5°±5° (*c*, 0·4 in alcohol) (Found: N, 11·7. Calc. for $C_{11}H_{16}O_4N_2$: N, 11·7%). Nef (*loc. cit.*) records for *d-erythro*-1 : 3 : 4-trihydroxyvaleric acid phenylhydrazide, m. p. 150° and $[\alpha]_D^{20°}$ +9·4°.

2-p-*Tosyl* α-*Methyl*-l-*arabopyranoside*.—The syrupy residue remaining after removing the crystalline β-methyl-*l*-arabopyranoside from the glycosidisation mixture from 100 g. of *l*-arabinose was condensed with acetone (1700 c.c.) in presence of phosphoric oxide (60 g.) as described above for the pure β-compound. The product (40 g.), a mixture of the α- and the β-isomer of 3 : 4-*iso*propylidene methyl-*l*-arabopyranoside, distilled at 100—110° (bath temp.)/10^{-3} mm. (Found: C, 52·8; H, 8·0. Calc. for $C_9H_{16}O_5$: C, 52·9; H, 7·8%).

The above α–β-mixture (40 g.) was dissolved in pyridine (200 c.c.) and tosylated as described under the β-compound. The product, a colourless syrup, was dissolved in a minimum amount of alcohol and set aside overnight in the refrigerator. Pure 2-*p*-tosyl 3 : 4-*iso*propylidene β-methyl-*l*-arabopyranoside (17·5 g.) separated, m. p. and mixed m. p. 133°. The alcoholic mother liquor gave on evaporation a syrup (42 g.) which was hydrolysed for 8 hours with methanol (1600 c.c.) and dilute sulphuric acid (650 c.c. of N). The hydrolysis solution was neutralised with precipitated barium carbonate, filtered, and evaporated under reduced pressure giving a syrup containing some crystalline material. This product was dissolved in ether, dried (Na_2SO_4), concentrated to *ca.* 250 c.c., and set aside overnight in the refrigerator. 2-p-*Tosyl* α-*methyl*-l-*arabopyranoside* separated as colourless needles (5·3 g.), m. p. 129—130°, $[\alpha]_D^{20°}$ −15·4°±0·4° (*c*, 4·88 in chloroform) (Found: C, 48·8; H, 5·7; S, 10·2. $C_{13}H_{18}O_7S$ requires C, 49·0; H, 5·7; S, 10·1%). On titration with sodium metaperiodate 1·1 mols. of oxidant were taken up.

2 : 3-*Anhydro*-α-*methyl*-l-*ribopyranoside*.—Prepared from 2-*p*-tosyl α-methyl-*l*-arabinoside (3·8 g.) in a manner similar to that described above for the β-isomer, the *anhydro-compound* (1·7 g.) was obtained as a syrup which crystallised on being kept for a few days in a desiccator and then had m. p. *ca.* 73° (sealed tube); $[\alpha]_D^{18}$ −145·1°±3° (*c*, 1·9 in chloroform) (Found: C, 49·2; H, 6·9. $C_6H_{10}O_4$ requires C, 49·3; H, 6·9%).

When the anhydro-compound (1·7 g.) was treated with methanolic sodium thiomethoxide and the product refluxed in alcohol with Raney nickel as described for the β-isomer, a hygroscopic syrup (1 g.) was obtained which distilled at 100—105° (bath temp.)/10^{-3} mm. and had $[\alpha]_D^{18°}$ −141·8°±1° (*c*, 2·48 in chloroform)(Found: C, 48·0; H, 8·0. Calc. for $C_6H_{12}O_4$: C, 48·6; H, 8·2%). It gave a weak green

Keller–Kiliani reaction and on titration with periodate took up *ca.* 0·3 mol./mol. That it contained 3-deoxy-α-methyl-*l*-xylopyranoside as its major constituent was proved by hydrolysis with 0·5N-sulphuric acid (specific rotations: after 20 minutes in the cold, −116°; after 30 minutes' heating, −3·4°; after 45 minutes' heating, +4·5° constant) when a syrupy sugar was obtained (Found: C, 44·4; H, 7·7. Calc. for $C_5H_{10}O_4$: C, 44·8; H, 7·5%). Warmed with *p*-nitrophenylhydrazine the sugar yielded 3-deoxy-*l*-xylose *p*-nitrophenylosazone, m. p. 254° undepressed in admixture with an authentic specimen (m. p. 254—256°) prepared above from the β-methylglycoside; no other crystalline material was isolated.

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