393. *Use of the Allyl Ether as a Protecting Group in a New Synthesis of* L-*Lyxose*

By Roy Gigg and C. D. Warren

Crystalline 2,3,4-tri-*O*-benzyl-D-galactose was prepared from allyl 6-*O*-allyl-2,3,4-tri-*O*-benzyl-α-D-galactopyranoside by isomerisation of the allyl groups to prop-1-enyl groups and removal by dilute-acid hydrolysis. Reduction by sodium borohydride gave crystalline 2,3,4-tri-*O*-benzyl-D-galactitol which was converted into 2,3,4-tri-*O*-benzyl-L-lyxose by oxidation with sodium periodate. Catalytic hydrogenation gave L-lyxose.

We recently showed [1] that the hydroxyl groups of carbohydrates can be protected during synthetic operations by conversion into allyl ethers. The hydroxyl groups are regenerated by conversion of the allyl ethers into prop-1-enyl ethers (by the action of potassium t-butoxide in dimethyl sulphoxide), and these are readily hydrolysed by dilute acids. In the present work this protecting group is used in a new synthesis of L-lyxose, derivatives of which are required as intermediates for synthetic studies in connection with the sphingolipids.

[1] J. Cunningham, R. Gigg, and C. D. Warren, *Tetrahedron Letters*, 1964, 1191.

L-Lyxose had been prepared [2] from calcium L-galactonate by a method employing the Ruff degradation and is also reported [3] to occur in the hydrolysis products of curamycin, an antibiotic isolated from *Streptomyces curacoi*.

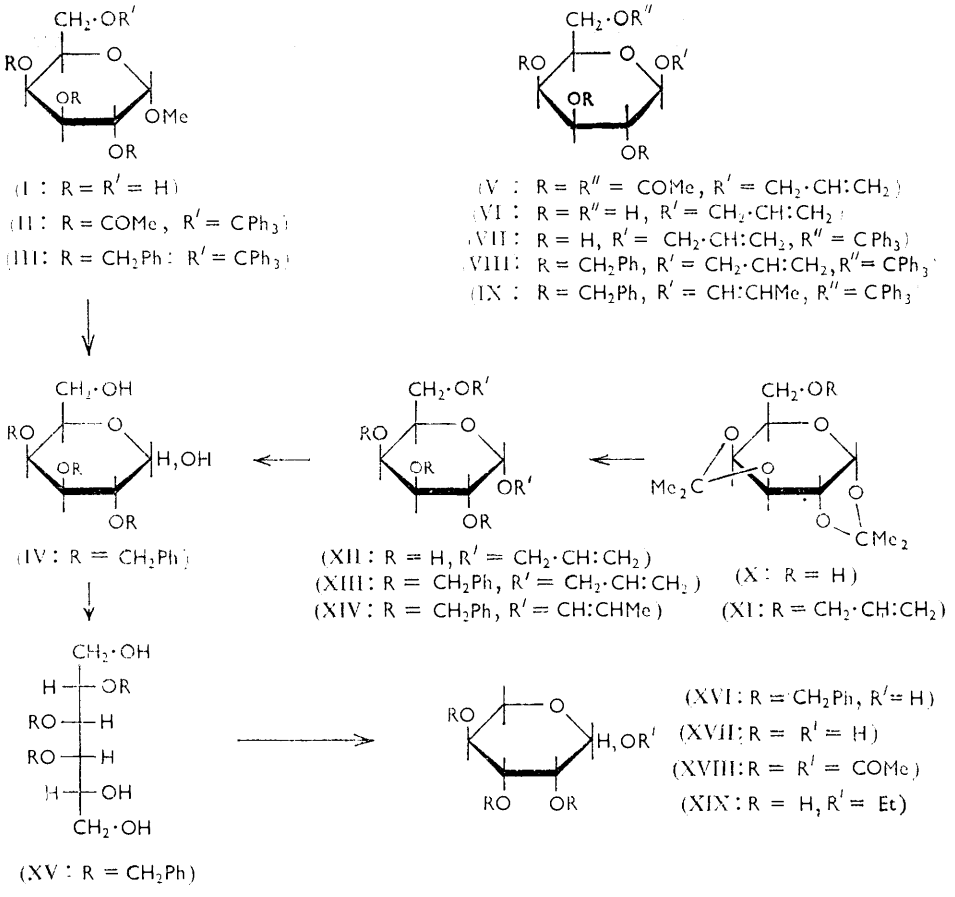
The new synthesis of L-lyxose required 2,3,4-tri-*O*-benzyl-D-galactopyranose (IV) as an intermediate. In the first approach to this compound, methyl α-D-galactopyranoside (I) was converted into crystalline methyl 2,3,4-tri-*O*-acetyl-6-*O*-trityl-α-D-galactopyranoside [4] (II) which was then treated with benzyl chloride and sodium hydroxide [5] to give methyl 2,3,4-tri-*O*-benzyl-6-*O*-trityl-α-D-galactopyranoside (III). The prolonged acid treatment required to hydrolyse the methyl glycoside linkage in compound (III) caused some decomposition which resulted in a poor yield of 2,3,4-tri-*O*-benzyl-D-galactopyranose (IV). Debenzylation during the acid hydrolysis of methyl glycosides of benzylated sugars had been observed previously.[5]

In order to overcome this difficulty, the corresponding β-allyl glycoside (VIII) was synthesised. Deacylation of the product obtained from the reaction between 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide [6] and allyl alcohol under the Koenigs–Knorr conditions [7] gave a crystalline allyl galactoside (VI). The β-configuration was assigned on the basis of the negative rotation and on the inversion expected in the Koenigs–Knorr reaction.[7] Compound (VI) was converted into the crystalline 6-*O*-trityl derivative (VII) from which allyl 2,3,4-tri-*O*-benzyl-6-*O*-trityl-β-D-galactopyranoside (VIII) was obtained by the action of benzyl chloride and sodium hydroxide.[5] The allyl group was rearranged [1] and the resulting prop-1-enyl glycoside (IX) was hydrolysed readily with dilute acid. After separation of the triphenylmethanol by chromatography on silicic acid, 2,3,4-tri-*O*-benzyl-D-galactopyranose (IV) was obtained in good yield.

In the third, and most convenient, preparation of 2,3,4-tri-*O*-benzyl-D-galactopyranose, the allyl group was used to protect both the 1- and 6-positions of galactose, thus avoiding contamination of the final product with triphenylmethanol. 1,2:3,4-Di-*O*-isopropylidene-D-galactose [8] (X) was converted into the 6-*O*-allyl ether (XI) which on treatment with a solution of hydrogen chloride in allyl alcohol gave the beautifully crystalline allyl 6-*O*-allyl-α-D-galactopyranoside (XII), the α-configuration being assigned on the basis of the high positive rotation. With benzyl chloride and sodium hydroxide,[5] compound (XII) gave allyl 6-*O*-allyl-2,3,4-tri-*O*-benzyl-α-D-galactopyranoside (XIII) as a syrup, and this was isomerised [1] to the corresponding prop-1-enyl derivative (XIV). Compound (XIV) was readily hydrolysed with dilute acid to give 2,3,4-tri-*O*-benzyl-D-galactopyranose (IV). After standing at room temperature for 12 hr. the product partially solidified, and pure 2,3,4-tri-*O*-benzyl-α-D-galactopyranose (the α-configuration was based on the high positive rotation) was obtained by recrystallisation from ether–petroleum.

Compound (IV) was reduced with sodium borohydride to give crystalline 2,3,4-tri-*O*-benzyl-D-galactitol (XV), which yielded galactitol on catalytic hydrogenation. 2,3,4-Tri-*O*-benzyl-D-galactitol was oxidised with sodium periodate in aqueous acetone to 2,3,4-tri-*O*-benzyl-L-lyxose (XVI). This was hydrogenated to give L-lyxose (XVII) as a syrup which could be crystallised by treatment with anhydrous ethanol. Since the crystals were hygroscopic the syrup was converted into a crystalline tetra-acetate, (XVIII), m. p. 96°, $[\alpha]_D$ −24°, by the action of sodium acetate and acetic anhydride. Tetra-*O*-acetyl-α-D-lyxopyranose, m. p.s 96 and 124°, $[\alpha]_D$ +25°, had been described,[9] and thus the tetra-acetate from L-lyxose was formulated as tetra-*O*-acetyl-α-L-lyxopyranose. The syrupy L-lyxose

[2] W. A. van Ekenstein and J. J. Blanksma, *Chem. Weekblad*, 1914, **11**, 189; R. L. Whistler and J. N. BeMiller, "Methods in Carbohydrate Chemistry," Academic Press, New York, 1962, Vol. 1, p. 79.
[3] O. L. Galmarini and V. Deulofeu, *Tetrahedron*, 1961, **15**, 76.
[4] F. Valentin, *Coll. Czech. Chem. Comm.*, 1932, **4**, 364.
[5] C. M. McCloskey, *Adv. Carbohydrate Chem.*, 1957, **12**, 137.
[6] W. T. Haskins, R. M. Hann, and C. S. Hudson, *J. Amer. Chem. Soc.*, 1942, **64**, 1852.
[7] W. L. Evans, D. D. Reynolds, and E. A. Talley, *Adv. Carbohydrate Chem.*, 1951, **6**, 27.
[8] R. S. Tipson, "Methods in Carbohydrate Chemistry," Academic Press, New York, 1963, Vol. II, p. 246.
[9] H. Zinner and H. Brandner, *Chem. Ber.*, 1956, **89**, 1507.



was also reduced by sodium borohydride to L-lyxitol (L-arabitol) identical with the product obtained by a similar reduction of L-arabinose.

A crystalline ethyl L-lyxopyranoside (XIX) was prepared by catalytic reduction of the mixed ethyl 2,3,4-tri-*O*-benzyl-L-lyxopyranosides obtained from 2,3,4-tri-*O*-benzyl-L-lyxopyranose (XVI) by the action of toluene-*p*-sulphonic acid in dry ethanol.

Experimental

Specific rotations were measured at 22—23° unless otherwise stated. The light petroleum had b. p. 60—80°. The alumina used was kept under ethyl acetate for 24 hr., washed with water and methanol, dried, and activated at 150° for 4 hr. Thin-layer chromatography was carried out on microscope slides coated with Silica Gel G (Merck), and compounds were detected by spraying with aqueous sulphuric acid (50% v/v) and heating at 200°.

Methyl 2,3,4-*Tri*-O-*benzyl*-6-O-*trityl*-α-D-*galactopyranoside* (III).—Methyl 2,3,4-tri-*O*-acetyl-6-*O*-trityl-α-D-galactopyranoside [4] (20 g.), benzyl chloride (200 ml.), and powdered sodium hydroxide (30 g.) were heated at 100° with stirring for 1 hr. Powdered sodium hydroxide (30 g.) was added, and the stirring and heating were continued for 6 hr. The cooled mixture was diluted with water (200 ml.) and extracted with ether. The ether extract was dried, and the ether, benzyl chloride, benzyl alcohol, and dibenzyl ether were removed by distillation under reduced pressure. The syrupy residue was dissolved in light petroleum–ethanol (2 : 1) and the *product* (10 g.) separated as needles, m. p. 126—127°, $[\alpha]_D$ +26° (*c* 1 in chloroform) (Found: C, 79·8; H, 6·3. $C_{47}H_{46}O_6$ requires C, 79·9; H, 6·5%).

2,3,4-*Tri*-O-*benzyl*-D-*galactopyranose* (IV).—A solution of methyl 2,3,4-tri-*O*-benzyl-6-*O*-trityl-α-D-galactopyranoside (430 mg.) in dioxan (15 ml.) and 6N-sulphuric acid (5 ml.) was heated

under reflux. After 7 hr., thin-layer chromatography (ether as the mobile phase) showed the presence of the required material (R_F 0·4; detected with aniline phthalate) together with partially hydrolysed material (R_F 0·7) and debenzylated material (R_F 0·15). After neutralisation with barium carbonate the solution was concentrated to a syrup which was chromatographed on alumina. Elution with ether removed the triphenylmethanol, and acetone–methanol (3 : 1) removed the partially hydrolysed material. The *product* (0·1 g., 33%) was eluted with methanol and recrystallised from ether–light petroleum (1 : 1), to give the α-isomer as needles, m. p. 70—71°, $[\alpha]_D$ +72·5° (*c* 0·8 in ether) (Found: C, 72·0; H, 7·1. $C_{27}H_{30}O_6$ requires C, 72·3; H, 7·0%).

Allyl β-D-*Galactopyranoside* (VI).—2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl bromide [7] (25 g.) in dry allyl alcohol (70 ml.) and anhydrous ether (200 ml.) was stirred with silver carbonate (20 g.) in the dark at room temperature for 14 hr. The mixture was filtered through layers of activated charcoal and Celite and the filtrate was evaporated to give a syrup. Thin-layer chromatography (ether–petroleum 1 : 1 as mobile phase) showed two components (R_F 0·3 and 0·15), and the syrup was chromatographed on a column of alumina (24 × 1·5 in.). Allyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (V) (12 g.) was eluted with ether (thin-layer chromatography as above, R_F 0·3) and was deacetylated by dissolving in a solution of sodium methoxide in dry methanol (100 ml.; 0·04N). After 30 min. at room temperature, thin-layer chromatography indicated that the deacylation was complete, and the solution was passed through a column of Amberlite I.R. 120 (H^+) resin and evaporated to give a syrup which was crystallised from ethyl acetate. The *product* (4·5 g.) was obtained as needles, m. p. 103—104°, $[\alpha]_D$ −20° (*c* 1 in methanol) (Found: C, 48·9; H, 7·0. $C_9H_{16}O_6$ requires C, 49·1; H, 7·3%) {lit.,[10] $[\alpha]_D$ −12·5° (*c* 2·7 in water)}.

Allyl 6-O-*Trityl*-β-D-*galactopyranoside* (VII).—A solution of allyl β-D-galactopyranoside (5·3 g.) and triphenylmethyl chloride (7·5 g.) in dry pyridine (20 ml.) was kept at room temperature until thin-layer chromatography (ethyl acetate–methanol 5 : 1 as the mobile phase) showed complete conversion of the starting material (R_F 0·35) into the trityl derivative (R_F 0·8) (16 hr.). The solution was poured into ice–water with stirring, and the solid product (9·5 g.) was collected, dried, and chromatographed on alumina (15 × 1·5 in.). Elution with benzene removed impurities, and elution with methanol–acetone (1 : 1) gave the *product* (7 g.) which crystallised from aqueous methanol as needles, softening to a glass between 95 and 120° and forming a meniscus at 148°; $[\alpha]_D$ −33° (*c* 1 in chloroform) [Found: C, 71·3; H, 6·3. $(C_{28}H_{30}O_6)_2H_2O$ requires C, 71·3; H, 6·6%]. Acetylation with acetic anhydride and pyridine and recrystallisation of the product from aqueous ethanol gave *allyl* 2,3,4-*tri*-O-*acetyl*-6-O-*trityl*-β-D-*galactopyranoside* as needles, m. p. 149—151°, $[\alpha]_D$ −44° (*c* 1 in chloroform) (Found: C, 69·1; H, 6·5. $C_{34}H_{36}O_9$ requires C, 69·3; H, 6·2%). The acetate was hydrolysed with sodium methoxide in methanol, and the product recrystallised from aqueous methanol, to give allyl 6-*O*-trityl-β-D-galactopyranoside with the same melting behaviour as that described above.

2,3,4-*Tri*-O-*benzyl*-D-*galactopyranose* (IV).—Allyl 6-*O*-trityl-β-D-galactopyranoside (6 g.) was converted into the benzyl derivative as described above for methyl 2,3,4-tri-*O*-acetyl-6-*O*-trityl-α-D-galactopyranoside. The crude product was chromatographed on basic alumina (15 × 1·5 in.), and elution with benzene gave allyl 2,3,4-tri-*O*-benzyl-6-*O*-trityl-β-D-galactopyranoside (VIII) (9 g.) as a syrup, $[\alpha]_D$ −2·5° (*c* 0·8 in chloroform); thin-layer chromatography (petroleum–ether 1 : 2 as mobile phase), R_F 0·7. The benzyl ether (3·5 g.) and dry potassium t-butoxide (3 g.) were dissolved in dry dimethyl sulphoxide (25 ml.), and the solution was kept at 100° for 20 min. Thin-layer chromatography (petroleum–ether 3 : 1 as mobile phase) showed that the isomerisation was complete, and the mixture was poured into water (50 ml.) and the product extracted with ether. After evaporation of the ether the crude prop-1-enyl galactoside (IX) was dissolved in a mixture of acetone (30 ml.) and N-sulphuric acid (3 ml.), and the solution was refluxed for 30 min., neutralised with barium carbonate, and concentrated, to give a syrup which was chromatographed on silicic acid (12 × 1 in.). Triphenylmethanol was eluted with petroleum–benzene (1 : 1), and the 2,3,4-tri-*O*-benzyl-D-galactopyranose (1 g., 54%) was eluted with ethyl acetate. Crystallisation from ether–petroleum gave needles, m. p. 70—71°.

6-O-*Allyl*-1,2:3,4-*di*-O-*isopropylidene*-D-*galactopyranose* (XI).—A solution of 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose [8] (50 g.) in dry benzene (100 ml.) was added slowly with stirring to a mixture of sodium hydride (6 g.), allyl bromide (25 ml.), and dry benzene (250 ml.) at 60°. After the addition was complete, the solution was refluxed for 4 hr. Methanol was added to decompose the excess sodium hydride, and the benzene solution was washed with water and

[10] E. Bourquelot and M. Bridel, *Compt. rend.*, 1913, **156**, 1104.

dried over anhydrous potassium carbonate. Removal of the benzene and distillation gave the *product* (50 g., 87%), b. p. 110°/0·06 mm. (Found: C, 59·7; H, 8·2. $C_{15}H_{24}O_6$ requires C, 60·0; H, 8·1%).

Allyl 6-O-*Allyl*-α-D-*galactopyranoside* (XII).—6-*O*-Allyl-1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (50 g.) in dry allyl alcohol (150 ml.) containing hydrogen chloride (3 g.) was heated at 70° for 2 hr. Concentrated aqueous ammonia solution (7 ml., 35%) was added to destroy the excess hydrogen chloride, and the allyl alcohol and other volatile materials were removed by distillation under reduced pressure. The semi-solid residue was treated with ether, and the crystalline material was separated and recrystallised from ethyl acetate to give the *product* (14 g.) as plates, m. p. 138—140°, $[\alpha]_D$ +162° (*c* 1 in water) (Found: C, 55·7; H, 7·8. $C_{12}H_{20}O_6$ requires C, 55·4; H, 7·8%). The ether soluble materials were re-treated with allyl alcohol and hydrogen chloride as above, and crystalline allyl galactopyranoside (XII) (8 g.) was obtained. A further treatment of the ether soluble materials from this reaction gave more of the allyl galactopyranoside (XII) (4 g.), making a total yield of 26 g. (60%).

2,3,4-*Tri*-O-*benzyl*-D-*galactopyranose* (IV).—Allyl 6-*O*-allyl-α-D-galactopyranoside (20 g.) was converted into the benzyl derivative as described above for methyl 2,3,4-tri-*O*-acetyl-6-*O*-trityl-α-D-galactopyranoside. Allyl 6-*O*-allyl-2,3,4-tri-*O*-benzyl-α-D-galactopyranoside (30 g.) was obtained as a syrup; thin-layer chromatography (ether–petroleum 1 : 2 as mobile phase), R_F 0·7, $[\alpha]_D$ +46° (*c* 1 in chloroform). The benzyl ether (30 g.) and dry potassium t-butoxide (10 g.) in dry dimethyl sulphoxide (150 ml.) were heated at 100° for 30 min. After this time thin-layer chromatography (petroleum–ether 2 : 1 as mobile phase) showed complete conversion of the starting material (R_F 0·6) into prop-1-enyl 2,3,4-tri-*O*-benzyl-6-*O*-(prop-1-enyl)-α-D-galactopyranoside (XIV) (R_F 0·8). The solution was cooled, diluted with water (300 ml.), and extracted with ether, and the extract washed with water and dried over magnesium sulphate. Removal of the ether gave a syrup which was dissolved in a mixture of acetone (300 ml.) and N-sulphuric acid (30 ml.), and the solution was refluxed for 15 min. After cooling and neutralisation with barium carbonate, the solution was filtered and evaporated to a syrup, which was chromatographed on a column of neutral alumina (30 × 1·5 in.). Elution with acetone removed some impurity, and further elution with methanol gave 2,3,4-tri-*O*-benzyl-D-galactopyranose (16 g., 61%) as a syrup. After standing for 12 hr. the product solidified, and recrystallisation from ether–petroleum gave the α-isomer, m. p. 70—71°.

2,3,4-*Tri*-O-*benzyl*-D-*galactitol* (XV).—Sodium borohydride (6 g.) was added to a solution of 2,3,4-tri-*O*-benzyl-D-galactopyranose (11 g.) in methanol (500 ml.), and, after standing for 2 hr. at room temperature, glacial acetic acid (50 ml.) was added to destroy the excess sodium borohydride. The solution was evaporated to dryness and the boric acid removed from the product by repeated evaporations of methanol–toluene. The residue was recrystallised from aqueous ethanol to give the *product* (8 g.), as needles, m. p. 111°, $[\alpha]_D$ −9° (*c* 1 in chloroform) (Found: C, 71·6; H, 7·1. $C_{27}H_{32}O_6$ requires C, 71·7; H, 7·1%).

2,3,4-Tri-*O*-benzyl-D-galactitol (1 g.) in glacial acetic acid (50 ml.) was hydrogenated at atmospheric pressure in the presence of 10% palladium–charcoal. When hydrogen uptake had ceased (150 ml. consumed) the catalyst was removed by filtration, the solution was evaporated to dryness, and the residue twice crystallised from aqueous ethanol, to give galactitol (0·28 g., 70%), m. p. 186—188°, mixed m. p. with material prepared from D-galactose 186—188° (lit.,[11] 185—186°).

L-*Lyxose* (XVII).—An aqueous solution of sodium metaperiodate (90 ml.; 0·25M) was added to a solution of 2,3,4-tri-*O*-benzyl-D-galactitol (10 g.) in acetone (250 ml.) and water (50 ml.). After 30 min., water (50 ml.) was added, and, after a further 2 hr., thin-layer chromatography (ether as mobile phase) indicated complete oxidation of the starting material (R_F 0·25) to a product of R_F 0·85. The acetone was removed by evaporation under reduced pressure, and the mixture was extracted with chloroform. The extract was dried over magnesium sulphate and evaporated, to give 2,3,4-tri-*O*-benzyl-L-lyxose (9 g.) as a syrup, $[\alpha]_D$ +5° (*c* 1 in chloroform). The syrup was dissolved in acetic acid (300 ml.) and hydrogenated at atmospheric pressure in the presence of 10% palladium–charcoal. When hydrogen uptake had ceased (1440 ml. consumed), the catalyst was removed by filtration and the solution evaporated to dryness under reduced pressure. Addition of anhydrous ethanol to the residue (3·5 g.) gave L-lyxose as a white hygroscopic solid, $[\alpha]_D$ +13° (*c* 0·92 in water) (lit.,[2] $[\alpha]_D$ −6° ⟶ +13·5°).

Tetra-O-*acetyl*-α-L-*lyxopyranose* (XVIII).—A mixture of L-lyxose (1 g.), anhydrous sodium

[11] J. V. Karabinos and A. T. Ballun, *J. Amer. Chem. Soc.*, 1953, **75**, 4501.

acetate (1 g.), and acetic anhydride (10 ml.) was stirred at 130° for 3 hr., cooled, and poured into ice–water. The product was extracted with chloroform and the extract washed with water and aqueous sodium hydrogen carbonate solution, and dried over magnesium sulphate. Evaporation of the chloroform gave a syrup which was crystallised from ethanol, and the *product* (0·65 g.) was obtained as needles, m. p. 95—96°, $[\alpha]_D$ −24° (*c* 1 in chloroform) (Found: C, 49·1; H, 5·7. $C_{13}H_{18}O_9$ requires C, 49·1; H, 5·7%).

L-*Lyxitol* (L-*Arabitol*).—Sodium borohydride (150 mg.) was added to a solution of L-lyxose (200 mg.) in methanol (20 ml.), and after 15 hr. at room temperature acetic acid (10 ml.) was added. The solution was passed through a column of Amberlite I.R. 120 (H^+) resin and evaporated to dryness. Boric acid was removed by repeated evaporations of methanol–toluene, and the residue was recrystallised from ethanol to give L-lyxitol (100 mg.), m. p. 99—100°, mixed m. p. with material prepared similarly from L-arabinose, 99—101° (lit.,[12] m. p. 102°).

Ethyl L-*Lyxopyranoside* (XIX).—A solution of 2,3,4-tri-*O*-benzyl-L-lyxopyranose (3 g.) and toluene-*p*-sulphonic acid (1·5 g.) in dry ethanol (300 ml.) was refluxed for 3 hr. Thin-layer chromatography (ether–petroleum 1 : 1 as mobile phase) showed complete conversion of the starting material (R_F 0·45) into two products (R_F 0·75 and 0·85). The solution was neutralised with barium carbonate and evaporated to dryness, to give a syrup which was hydrogenated in acetic acid at atmospheric pressure in the presence of 10% palladium–charcoal. Filtration and removal of the solvent gave a syrup which was crystallised from ethyl acetate, to give prisms (0·4 g.), m. p. 116—118°, $[\alpha]_D^{30}$ −54° (*c* 0·5 in ethanol) (Found: C, 47·4; H, 7·9. Calc. for $C_7H_{14}O_5$: C, 47·2; H, 7·9%).

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[12] H. Kiliani, *Ber.*, 1887, **20**, 1234, 1571.