979. *The Synthesis of Disaccharides.*

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Syntheses of 5-*O*-β-D-xylopyranosyl-L-arabinose and of 6-*O*-β-D-xylopyranosyl-D-galactose are described.

In recent years several new disaccharides and oligosaccharides have been isolated from the hydrolysis products of polysaccharides.[1] The proof of the structure of these oligosaccharides depends in the main on degradative evidence. The purpose of this paper is to describe the synthesis of two disaccharides, one of which has been isolated by hydrolysis of cholla gum.[2] The second disaccharide has not yet been isolated from natural products, but the corresponding residue may be present as part of polysaccharides such as cherry and damson gum.[3] Both disaccharides were prepared by the Koenigs–Knorr [4] procedure. This method has been discussed in detail by Evans, Reynolds, and Talley [5] who also list many disaccharides which have been prepared by this or other methods. The principal product is the β-D-xyloside when acetobromo-D-xylose reacts with another sugar derivative. This acetobromo-derivative condenses with the more reactive primary

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[1] Cf. Whistler and McGilvray, *J. Amer. Chem. Soc.*, 1955, **77**, 1884; Andrews and Jones, *J.*, **1954**, 4134.

[2] Andrews, Ball, and Jones, *J.*, 1953, 4090.

[3] Hirst and Jones, *J.*, 1938, 1174.

[4] Koenigs and Knorr, *Ber.*, 1901, **34**, 957.

[5] Evans, Reynolds, and Talley, *Adv. Carbohydrate Chem.*, 1951, **6**, 27.

alcohol group of methyl-L-arabofuranoside,[6] to yield the glycoside of the 1→5-linked disaccharide. The glycosidic methyl group, which was attached to the arabofuranose ring was removed under relatively mild conditions, to yield the non-crystalline reducing sugar, 5-*O*-β-D-xylopyranosyl-L-arabinose. This was chromatographically indistinguishable from a disaccharide isolated from cholla gum.[2] The derived phenylosazones were also indistinguishable. On reduction with sodium borohydride [7] the disaccharide gave an L-arabitol derivative which yielded a crystalline hepta-acetate. A derivative with identical physical properties was prepared from the disaccharide which had been isolated from cholla gum.[2] The synthesis of 2-*O*-β-D-xylopyranosyl-L-arabinose has been recently described.[8]

Acetobromo-D-xylose was condensed with 1 : 2-3 : 4-di-*O*-*iso*propylidene-D-galactose, yielding a disaccharide derivative. In order to destroy the excess of acetobromo-D-xylose the reaction mixture was boiled with sodium hydroxide solution, cooled, and de-ionised. Hydrolysis of the *iso*propylidene residues was carried out by hot dilute acetic acid. The resulting mixture of mono- and di-saccharides was fractionated on a cellulose column, from which 6-*O*-β-D-xylopyranosyl-D-galactose was obtained crystalline. Its optical rotation (—3·6°) indicates that according to Hudson's rule [9] the two sugars are linked by a β-glycosidic linkage. The mode of synthesis of the disaccharide proves that the glycosidic linkage is linked through position 6 of the galactose residue.

EXPERIMENTAL

Paper chromatography was carried out by the descending method [10] on Whatman No. 1 filter paper, the following solvents being used: (*a*) butan-1-ol–ethanol–water (3 : 1 : 1), (*b*) butan-1-ol–pyridine–water (10 : 3 : 3), (*c*) ethyl acetate–acetic acid–water (9 : 2 : 2), and (*d*) ethyl acetate–acetic acid–formic acid–water (18 : 3 : 1 : 4) (all v/v). The positions of sugars on chromatograms were determined by spraying them with silver nitrate in acetone, followed by sodium hydroxide in ethanol,[11] or with *p*-anisidine hydrochloride in butan-1-ol.[12] The rates of movement of the sugars are quoted relative to that of galactose (R_{gal}) on the same chromatogram. Optical rotations were determined at 23° ± 3° and, unless otherwise stated, aqueous solutions were used, and the figures quoted are equilibrium values. Solvents were removed under reduced pressure.

*Condensation of Acetobromo-*D*-xylose with Methyl* αβ-L-*Arabofuranoside.*—To a solution of methyl L-arabofuranosides (3·28 g., 0·02 mole) in dry chloroform (50 ml.) there were added Drierite (20 g.), silver oxide (10 g.), iodine (1 g.), and glass beads. The mixture was shaken in a brown glass bottle for 30 min. to dry the reagents. A solution of acetobromo-D-xylose (6·78 g., 0·02 mole) in dry chloroform was then added and shaking was continued. After 24 hr., a test for ionisable bromine was negative. The mixture was then filtered and the filtrate concentrated to a clear yellow syrup. On paper chromatography the major component was noted to yield a predominant, elongated spot, which moved at twice the speed of rhamnose in solvent (*a*) and strongly reduced the silver nitrate spray but gave only a faint reddish-brown colour with the *p*-anisidine hydrochloride reagent. It was distinct from methyl α- or β-L-arabofuranoside. The syrup was dissolved in methanol, cooled, treated with 0·2M-sodium methoxide in methanol (2 ml.), stored at 0° overnight, and neutralised with cold dilute sulphuric acid. Solids were removed at the centrifuge and the clear solution was concentrated to a syrup. The glycosidic methyl group was removed by 10% formic acid at 90° in 1 hr. Formic acid was then removed by repeated evaporation with the intermediate addition of water. (In a second preparation the condensation was carried out in dioxan in place of chloroform.) The syrupy product, obtained after removal of insoluble salts and solvent, was boiled with an excess of sodium hydroxide in methanol for 7 hr. to deacetylate the product and destroy the excess of reducing xylose derivatives. After filtration the product was de-ionised (Amberlite resins

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[6] Baker and Haworth, *J.*, 1925, **127**, 365.
[7] Wolfrom and Wood, *J. Amer. Chem. Soc.*, 1951, **73**, 2733; Abdel-Akher and Smith, *ibid.*, 4691.
[8] Aspinall and Ferrier, *Chem. and Ind.*, 1957, 819.
[9] Hudson, *J. Amer. Chem. Soc.*, 1916, **38**, 1566.
[10] Partridge, *Biochem. J.*, 1948, **42**, 238.
[11] Trevelyan, Procter, and Harrison, *Nature*, 1950, **166**, 444.
[12] Hough, Jones, and Wadman, *J.*, 1950, 1702.

IR-120 and IR-4B) and concentrated to a syrup. This material contained glycosides which were converted into the reducing sugars by 0·01N-sulphuric acid at 90° in 12 hr. After cooling, the solution was neutralised and then concentrated.

The syrupy products from the above two preparations were combined and a portion of the mixture was fractionated on a charcoal column.[13] Elution first with water and then with increasing concentrations of ethanol gave fractions which contained monosaccharides (1·15 g.) and disaccharides: mixtures A (1·63 g.), B (0·48 g.), and C (1·19 g.).

Fraction A contained components with R_{gal} 0·85 and 1·05 (in solvent *a*), 0·9 and 1·3 (in solvent *b*).

The component of R_{gal} 1·05 (solvent *a*) was indistinguishable from 5-*O*-β-D-xylopyranosyl-L-arabinose on paper chromatograms. Fraction A was refractionated on four sheets of filter paper (Whatman No. 3 MM) (solvent *a*). The components were located by means of guide strips and the fractions isolated in the usual way.[14] Fraction A1 (0·05 g.) was a mixture and was not investigated. Fraction A2 (0·25 g.) contained a major component which had R_{gal} 0·85 (solvent *a*) and $[\alpha]_D$ +35° (*c* 4·98). Fraction A3 (0·36 g.) was composed of a sugar which moved faster than galactose (R_{gal} 1·05) and had $[\alpha]_D$ −41° (*c* 2·88). Fraction A4 (0·10 g.) was a mixture.

A sample of Fraction A3 was chromatographically indistinguishable from the required disaccharide, and its optical rotation (−41°) was in fair agreement with that recorded (−34°). In order to verify the identification the synthesised disaccharide was converted into the crystalline hepta-acetate of 5-*O*-β-D-xylopyranosyl-L-arabitol: A portion of the syrup (65 mg.) was dissolved in water and to the solution was added sodium borohydride (15 mg.) in water. After 2 days, reduction was complete. The solution was acidified with acetic acid and de-ionised on exchange resins. The filtrate was concentrated to a syrup which was acetylated with pyridine (3 ml.) and acetic anhydride (2 mg.) in the usual way. The product recrystallised from ethanol and then had m. p. 96—96·5°. This material showed no depression of m. p. on admixture with an authentic sample which was prepared from the cholla gum disaccharide and had $[\alpha]_D$ −62° (*c* 1·9 in $CHCl_3$). The synthetic *acetate* had $[\alpha]_D$ −61° (*c* 2·3 in $CHCl_3$) (Found: C, 50·0; H, 6·0; OAc, 52·0. $C_{24}H_{34}O_{16}$ requires C, 49·8; H, 5·9; OAc, 52·1%).

*Condensation of Acetobromo-*D*-xylose and* 1 : 2-3 : 4-*Di*-O-iso*propylidene*-D-*galactose*.—1 : 2-3 : 4-Di-*O*-*iso*propylidene-D-galactose (2·6 g., 0·01 mole), which had been purified through its crystalline 6-toluene-*p*-sulphonate, was dissolved in purified dioxan (25 ml.) in a dark brown glass bottle and Drierite (10 g.), silver oxide (5 g.), and glass beads were added. The mixture was shaken for 1 hr. and acetobromo-D-xylose (6·78 g., 0·2 mole), in dioxan (20 ml.), and iodine (0·5 g.) were then added and shaking was continued. After 13 hr. a test for ionisable bromine was negative. The mixture was filtered and the filtrate concentrated to a colourless syrup. This was boiled with a solution of potassium hydroxide (25% w/v) in methanol (15 ml.) for 3 hr. The dark brown solution was diluted with water, then filtered, and the filtrate de-cationised on Amberlite IR-120 resin. The acidic effluent (300 ml.) was heated at 80° for 4 hr. in order to hydrolyse *iso*propylidene groups and then de-ionised by passage through a column of Amberlite resin IR-4B. Concentration of the neutral effluent gave a syrup (2·27 g.) which consisted of galactose, a trace of xylose, and two substances with (i) R_{gal} 0·48 (solvents *a* and *b*) and 0·42 in solvent (*c*) and (ii) R_{gal} 0·56 (solvents *a* and *b*) and 0·50 in solvent (*d*). A portion of the above syrup was fractionated at 41° on a cellulose column which was irrigated with butan-1-ol saturated with water at 41°[15] and yielded four fractions. Fraction 1 (0·08 g.) contained the faster-moving compound. It was not identified. Fractions 2 (0·35 g.), 3 (0·90 g.), and 4 (0·06 g.) contained mainly the slower-moving *disaccharide*. Fraction 2 crystallised and fractions 3 and 4 also crystallised on nucleation. The crystalline product was recrystallised from moist methanol. The yield was 0·20 g., the m. p. 194—196°, and $[\alpha]_D$ $-23·6° \text{ (5 min.)} \longrightarrow -3·6°$ (2 hr., const.) (*c* 2·5) (Found: C, 42·1; H, 6·6. $C_{11}H_{20}O_{10}$ requires C, 42·2; H, 6·4%). The product on hydrolysis with hot dilute acid gave equal amounts of galactose and xylose.

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[13] Whistler and Durso, *J. Amer. Chem. Soc.*, 1950, **72**, 677.

[14] Flood, Hirst, and Jones, *J.*, 1948, 1679.

[15] Counsell, Hough, and Wadman, *Research*, 1951, **4**, 143.