622. *Branched-chain Sugars. Part IV.*[1] *The Synthesis of* D-*Hamamelose and* D-*Epihamamelose*

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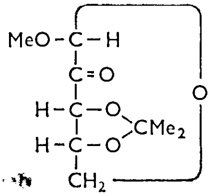
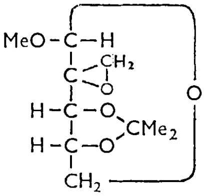
Syntheses of 2-*C*-hydroxymethyl-D-ribose and -D-arabinose are described.

We have described[1] syntheses of L-hamamelose (2-*C*-hydroxymethyl-L-ribose) and its epimer (2-*C*-hydroxymethyl-L-arabinose) based on the treatment of methyl 3,4-*O*-isopropylidene-β-L-*erythro*-pentopyranosidulose with a Grignard reagent. We report now a more direct synthesis of the D-isomers.

When methyl 3,4-*O*-isopropylidene-β-D-*erythro*-pentopyranosidulose (I)[1] is treated with a slight excess of diazomethane in diethyl ether–methanol it affords a mixture of the two possible isomeric methyl 2,2′-anhydro-2-*C*-hydroxymethyl-3,4-*O*-isopropylidene-β-D-pentosides (II). This mixture when hydrolysed successively with sodium hydroxide and sulphuric acid gives a crystalline mixture of the two branched-chain sugars (named in the title) as their methyl glycosides. This mixture can be separated by fractional crystallisation from ethanol and ethanol–ethyl acetate. The less soluble isomer in these solvents, methyl 2-*C*-hydroxymethyl-β-D-ribopyranoside (methyl β-D-hamamelopyranoside) (III), is the main product. Since the action of Grignard reagents on compound (I) leads predominantly to branched-chain sugars with the *arabino*-configuration the two routes can be regarded as complementary. Both glycosides (III and IV) can be hydrolysed in high yield to the corresponding free sugar with an acidic resin, a method which also serves to obtain crystalline L-hamamelose from methyl 2-*C*-hydroxymethyl-β-L-ribopyranoside. 2-*C*-Hydroxymethyl-D-ribose (D-hamamelose) (V) was so obtained as a viscous syrup which slowly crystallised. This sugar has not previously been reported crystalline. A solution in water of the solid rapidly underwent mutarotation, equilibrium being reached in 30 min. The sugar was characterised by formation of the crystalline *p*-nitrophenylhydrazone and toluene-*p*-sulphonylhydrazone. [The m. p. of the latter differed from that reported[2] for the substance derived from natural D-hamamelose and from the synthetic L-isomer.[1] The use of different purification procedures with samples obtained from a series of preparations failed to afford a product with a m. p. akin to that previously reported[2] and the anomaly remains unexplained.]


(I)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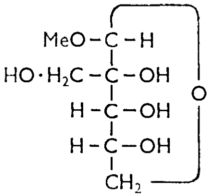
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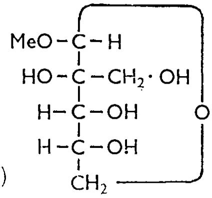
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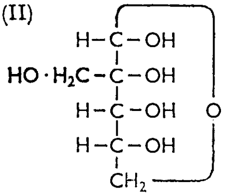
(V)

The 2-*C*-hydroxymethyl-D-arabinose (D-epihamamelose) was obtained as a syrup from the hydrolysate of methyl 2-*C*-hydroxymethyl-D-arabinopyranoside (IV) but this afforded a crystalline toluene-*p*-sulphonylhydrazone.

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[1] Part III, J. S. Burton, W. G. Overend, and N. R. Williams, preceding Paper.
[2] K. Freudenberg and F. Blümmel, *Annalen*, 1924, **440**, 45.

EXPERIMENTAL

Methyl 2,2′-*Anhydro*-2-C-*hydroxymethyl*-3,4-O-*isopropylidene*-β-D-*pentoside*. Diazomethane (1·5 g.) in ether (90 ml.) was added portionwise at 0° to a solution of methyl 3,4-*O*-isopropylidene-β-D-*erythro*-pentopyranosidulose (5·5 g.) (prepared according to Burton *et al.*,[1] m. p. 98—99°) in methanol (90 ml.). Between additions the initial vigorous effervescence was permitted to subside. The solution was stored overnight at room temperature and then the solvent was evaporated. [This procedure was preferred to that of Weygand and Schmiechen [3] who used a similar reaction in their synthesis of apiose; they passed a stream of diazomethane into a chloroform–methanol (2 : 1) solution of the oxo-compound.] The residue was distilled as a colourless syrupy *glycoside* (5·79 g., 98%), b. p. 76—77°/0·1 mm., $[\alpha]_D^{20}$ $-194°$ (*c* 1·5 in MeOH) (Found: C, 55·6; H, 7·95; O, 36·6. $C_{10}H_{16}O_5$ requires C, 55·5; H, 7·4; O, 37·0%) which gave a positive Ross test [4] for epoxides.

Methyl β-D-*Hamamelopyranoside and Epihamamelopyranoside*.—The above anhydroglycoside (5·7 g.) was dissolved in N-sodium hydroxide (70 ml.) and heated on a water-bath for 0·5 hr. The cooled solution was cautiously acidified with concentrated sulphuric acid (4 ml.), kept at 35° for 1·5 hr., recooled, and neutralised with sodium hydroxide. Evaporation of the solution and extraction of the residue with ethanol (2 × 50 ml.) gave after filtration a solution which afforded a mixture of crystalline glycosides (5·18 g.) on removal of the solvent. Fractional crystallisation, first from ethanol and then from ethanol–ethyl acetate (1 : 10, v/v) afforded pure forms of the components. *Methyl* 2-C-*hydroxymethyl*-β-D-*ribopyranoside* (methyl β-D-hamamelopyranoside) was recrystallised from ethanol as white prisms (2·86 g., 55%), m. p. 132—133°, $[\alpha]_D$ $-148°$ (*c* 1·0 in H_2O) (Found: C, 43·04; H, 7·08; O, 49·85. $C_7H_{14}O_6$ requires C, 43·3; H, 7·2; O, 49·5%) and methyl 2-*C*-hydroxymethyl-β-D-arabinopyranoside was recrystallised from ethanol–ethyl acetate (1 : 10, v/v) as white flakes (0·42 g., 7%), m. p. 123, $[\alpha]_D$ $-129°$ (*c* 2·1 in H_2O). Burton *et al.*[1] give m. p. 122—123°, $[\alpha]_D$ $+128·5°$ in MeOH for the L-isomer.

2-C-*Hydroxymethyl*-D-*ribose* (D-*Hamamelose*).—A stirred solution of methyl 2-*C*-hydroxymethyl-β-D-ribopyranoside (2·0 g.) in water (75 ml.) was heated under reflux for 24 hr. with Amberlite IR-120 resin (H^+ form) (10 g.). The cooled, yellow solution was filtered, decolourised with charcoal, and neutralised with barium carbonate. Filtration and evaporation of the filtrate yielded a clear syrup (1·61 g.) which slowly crystallised on storage. Crystallisation from methanol yielded fibrous white crystals of D-hamamelose (1·22 g., 66%), m. p. 110—111°, $[\alpha]_D^{21}$ $+7·7°$ (2·3 min.) $\longrightarrow$ $-7·0°$ (30 min., equilibrium value) (Found: C, 39·8; H, 6·6; O, 53·5. $C_6H_{12}O_6$ requires C, 40·0; H, 6·7; O, 53·3%). The sugar (0·238 g.) in ethanol (1·0 ml.) when heated under reflux for 1 hr. with *p*-nitrophenylhydrazine (0·16 g.) gave on cooling yellow needles of the *p*-nitrophenylhydrazone which after recrystallisation from ethanol had m. p. 161—163°. Freudenberg and Blümmel [2] give m. p. 165—166°; Burton *et al.*[1] report m. p. 163—164° for the L-isomer.

D-*Hamamelose Toluene*-p-*sulphonylhydrazone*.—D-Hamamelose (0·251 g.) in ethanol (0·8 ml.) was heated under reflux with toluene-*p*-sulphonylhydrazine (0·22 g., 0·8 mol. equiv.) for 0·75 hr. On cooling, white crystals slowly separated which, recrystallised from ethanol or methanol, had m. p. 146—147°, $[\alpha]_D^{21}$ $+90°$ (10 min.) $\longrightarrow$ $+52°$ (24 hr.) (*c* 0·7 in C_5H_5N) (Found: C, 45·0; H, 5·8; N, 7·0; S, 9·8. $C_{13}H_{20}N_2O_7S$ requires C, 44·8; H, 5·8; N, 8·0; S, 9·2%). The m. p.s in the literature for both the D- and L-forms are 155—156°,[1,2] but repeated preparations of this compound, varying the conditions and purification procedures, failed to raise the m. p.

2-C-*Hydroxymethyl*-D-*arabinose* (D-*Epihamamelose*).—Methyl 2-*C*-hydroxymethyl-β-D-arabinopyranoside (0·537 g.) was hydrolysed with resin as for hamamelose. A viscous syrup (0·507 g.) was obtained, $[\alpha]_D^{20}$ $-0·4°$ (*c* 5·0 in MeOH). This syrup (0·126 g.) in methanol (0·5 ml.) was heated under reflux with toluene-*p*-sulphonylhydrazine (0·133 g.) for 0·75 hr. On cooling, the solution deposited white fibrous crystals which were recrystallised twice from ethanol–water (4 : 1, v/v). The *toluene*-p-*sulphonylhydrazone* had m. p. 154—155° (cf. 158—159° for L-isomer [1]), $[\alpha]_D^{21}$ $-69·6°$ (10 min.) $\longrightarrow$ $-53·6°$ (24 hr.) (*c* 0·5 in C_5H_5N) (Found: C, 45·1; H, 6·0; N, 7·7; S, 8·6. $C_{13}H_{20}N_2O_7S$ requires C, 44·8; H, 5·8; N, 8·0; S, 9·2%).

2-C-*Hydroxymethyl*-L-*ribose* (L-*Hamamelose*) (This experiment was carried out by Dr. J. S. BURTON).—A solution of methyl 2-*C*-hydroxymethyl-β-L-ribopyranoside (2·2 g.) in water

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[3] F. Weygand and R. Schmiechen, *Chem. Ber.*, 1959, **92**, 535.

[4] W. C. J. Ross, *J.*, 1950, 2257.

(100 ml.) was stirred and heated under reflux with Amberlite resin (IR-120 H^+) (12·0 g.) for 24 hr. The supernatant liquid was decanted and the resin was washed with water (3 × 15 ml.). The combined aqueous solution was evaporated under diminished pressure to a syrup [1·9 g., 96%, $[\alpha]_D$ +7·1° (*c* 2·0 in H_2O)] which crystallised on storage. 2-*C*-Hydroxymethyl-L-ribose (0·80 g., 39%) was obtained as colourless rhombs, m. p. 110—111°, $[\alpha]_D^{22}$ +1·3° (3 min.) $\longrightarrow$ +7·3° (equil., 17 min.) (*c* 2·2 in H_2O) (Found: C, 39·8; H, 6·5; O, 53·6. Calc. for $C_6H_{12}O_6$: C, 40·0; H, 6·7; O, 53·3%). Burton *et al.*[1] give m. p. 108—109°, $[\alpha]_D^{22}$ +7·1° (equil.) (in H_2O).

When the hydrolysis was carried out with 0·5N-sulphuric acid at reflux temperature for 11 hr. a higher yield (67%) of L-hamamelose was obtained, but the material was less pure and could not be crystallised.

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