184. *Configurational Correlation of "α"-D-Glucosaccharinolactone and Hamamelose.*

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That the same absolute configuration is possessed by "α"-D-glucosaccharinolactone (2-*C*-methyl-D-ribono-1→4-lactone) and hamamelose (2-*C*-hydroxymethyl-D-ribose), the structures of which have been assigned by independent arguments, has been confirmed by the conversion of each into 5-deoxy-2-*C*-methyl-D-ribitol by the use of conventional reactions.

The D-*ribo*-configuration has been assigned[1] to "α"-D-glucosaccharinolactone, a 2-*C*-methylpentono-1→4-lactone which can be isolated in poor yield after the treatment of D-fructose with lime water,[2] and to hamamelose, a 2-*C*-hydroxymethylpentose[3] present in the bark of the witch hazel *Hamamelis virginiana* L. We now report a configurational correlation between these compounds by the conversion of each into 5-deoxy-2-*C*-methyl-D-ribitol.

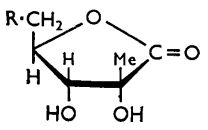
The first approach envisaged for the conversion of "α"-D-glucosaccharinolactone (I) into the 5-deoxy-derivative involved treatment of the 2,3-*O*-isopropylidene-5-*O*-toluene-*p*-sulphonyl derivative[1] with sodium thiobenzoate in dimethylformamide,[4] followed by reductive desulphuration. Although the exchange product, 5-benzoylthio-5-deoxy-2,3-*O*-isopropylidene-2-*C*-methyl-D-ribono-1→4-lactone was obtained in good yield it could not easily be purified and, moreover, on mild acidic hydrolysis it gave only a poor yield of the crystalline de-acetonated product. This route was not followed further.

With sodium iodide in acetone, 2,3-*O*-isopropylidene-2-*C*-methyl-5-*O*-toluene-*p*-sulphonyl-D-ribono-1→4-lactone gave a good yield of the 5-deoxy-5-iodo-derivative, from which the iodine was removed with Raney nickel to give the 5-deoxy-derivative. Subsequent cleavage of the isopropylidene residue from the last compound with dilute acid gave the known[1] 5-deoxy-2-*C*-methyl-D-ribono-1→4-lactone (II). Reduction[5] of the lactone (II) with sodium borohydride at pH 4—5 gave a crystalline form of 5-deoxy-2-*C*-methyl-D-ribose, which, from the direction of mutarotation (−11° to a more positive value), appeared to be the β-furanose form (III) since pyranose forms are precluded. Reduction of the free sugar (III) with sodium borohydride under alkaline conditions gave 5-deoxy-2-*C*-methyl-D-ribitol (IV).

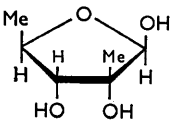
5-Deoxy-2-*C*-methyl-D-ribose (III) may be regarded as a pentose analogue of mycarose,[3] a 2,6-dideoxy-3-*C*-methylhexose present in the macrolide antibiotic magnamycin. No significant *in vitro* antibacterial activity was shown by 5-deoxy-2-*C*-methyl-D-ribose against *Staph. pyogenes*, *Strep. pyogenes*, *Klebsiella aerogenes*, and *E. coli*.

[1] Sowden and Strobach, *J. Amer. Chem. Soc.*, 1960, **82**, 3707.
[2] Sowden, *Adv. Carbohydrate Chem.*, 1957, **12**, 43.
[3] Shafizadeh, *Adv. Carbohydrate Chem.*, 1956, **11**, 263.
[4] Bukhari, Foster, Lehmann, Webber, and Westwood, *J.*, 1963, 2291.
[5] Wolfrom and Wood, *J. Amer. Chem. Soc.*, 1951, **73**, 2933.

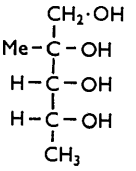
During this work, a simplified procedure was evolved for the isolation of hamamelitannin from witch hazel bark. Glycosidation of the tannin with 1% methanolic hydrogen chloride, either boiling for 5 hr. or heating at 30—40° for 1 week, reaction of the product with acetone and sulphuric acid, and saponification of the galloyl residues gave a poor



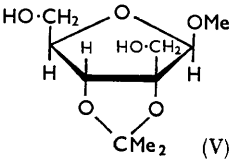
(I : R = OH)
(II : R = H)



(III)



(IV)



(V)

yield of a crystalline isopropylidene derivative. The structure methyl 2-*C*-hydroxymethyl-2,3-*O*-isopropylidene-β-D-ribofuranoside (V) has been assigned to the compound for the following reasons. That the glycoside (V) contained two primary hydroxyl groups was proved when reduction of its di-*O*-methanesulphonate with lithium aluminium hydride gave a sulphur-free product which contained no hydroxyl groups and which, on acidic hydrolysis, gave a reducing sugar with chromatographic properties indistinguishable from those of 5-deoxy-2-*C*-methyl-D-ribose (III). Further, reduction of the reducing sugar with sodium borohydride gave an alcohol which was identical with 5-deoxy-2-*C*-methyl-D-ribitol (IV) described above. Thus, if the glycoside (V) has two primary hydroxyl groups it must be in the furanose form with a 2,3-isopropylidene group. Since the hamamelose in hamameli-tannin has its two primary hydroxyl groups substituted with galloyl residues,[3] the formation of a furanoside on glycosidation and a 2,3-ketal on subsequent acetonation would be expected if the galloyl groups were not hydrolysed during these reactions. The outcome of the above series of reactions also establishes the configurational correlation between " α "-D-glucosaccharinolactone and hamamelose; the D-*ribo*-configuration of hamamelose has now been rigorously established,[6] and hence confirmation of the same configuration of " α "-D-glucosaccharinolactone is provided.

The assignment of the β-configuration to the glycoside (V) on the basis of its optical rotation (−61° in chloroform) is supported by the infrared spectral data, in the hydroxyl stretching region, for a 0·005M-solution of the compound in carbon tetrachloride. The spectrum showed bands at 3642 (ε 19), 3604 (Δν 38, ε 52), 3574 (Δν 68, ε 26), and 3485 cm.$^{-1}$ (Δν 157, ε 55), which may be assigned [7] as follows: 3642 cm.$^{-1}$, free hydroxyl groups; 3604 cm.$^{-1}$, intramolecular hydrogen bond involving a 5-membered ring (cf. 2-methoxyethanol,[7] Δν 31), *i.e.*, the hydroxyl group of the 2-CH_2·OH group bonded to the 2-oxygen and/or the 5-OH bonded to the ring oxygen atom; 3574 cm.$^{-1}$, intramolecular hydrogen bond involving a 6-membered ring (cf. 3-methoxypropanol,[7] Δν 87), which can only be associated with the hydroxyl group of the 2-CH_2·OH group bonded to the 1-oxygen; 3485 cm.$^{-1}$, intramolecular hydrogen bond involving a 7-membered or larger ring. This last bond could be either between the hydroxyl groups at C-5 and in the 2-CH_2OH group (9-membered ring), or between the 5-OH group and the 1-oxygen (7-membered ring). In acylic systems there is little tendency [7] to form rings greater than 7-membered by the intramolecular hydrogen bonding of hydroxyl groups to oxygen atoms, but restriction of rotation about the bonds in a chain of carbon atoms may permit the formation of larger rings.[8] The ring system (*cis*-fusion of two 5-membered rings) of the glycoside (V) is relatively rigid and intramolecular hydrogen bonding between the two hydroxyl groups, which would form a 9-membered ring, is a possibility which cannot be discounted in the

[6] Burton, Overend, and Williams, *Chem. and Ind.*, 1961, 175; *Proc. Chem. Soc.*, 1962, 181; Ferrier, Overend, Rafferty, Wall, and Williams, *ibid.*, 1963, 133.
[7] Haines, Foster, and Stacey, *Tetrahedron*, 1961, **16**, 177.
[8] Biggins, Cairns, Eglinton, Haslam, and Haworth, *J.*, 1963, 1750.

absence of data for suitable model compounds. It can be seen from molecular models that the two hydroxyl groups in the glycoside (V) can make a close aproach. In the α-anomer of the glycoside (V) intramolecular hydrogen bonding involving 5-membered (2-CH_2·OH→2-O and 5-OH→ring O) and 9-membered rings (2-CH_2·OH→5-OH) can occur but not for 6- and 7-membered rings, and hence the spectrum for this anomer would be expected to contain only three absorptions in the hydroxyl stretching region under the conditions noted above.

Experimental

5-Benzoylthio-5-deoxy-2-C-methyl-D-ribono-1→4-lactone.—A solution of 2,3-*O*-isopropylidene-2-*C*-methyl-5-*O*-toluene-*p*-sulphonyl-D-ribono-1→4-lactone [1] (1·75 g.) and sodium thiobenzoate (4 g.) in dimethylformamide (50 ml.) was boiled under reflux for 50 min. The cooled solution was poured into water (400 ml.) and the mixture was extracted twice with chloroform (total 200 ml.). Concentration of the chloroform solution, and distillation of the residue, gave the impure 5-benzoylthio-5-deoxy-compound (1·3 g.) with b. p. 160—180°/0·1 mm. owing to slight decomposition during distillation. The product (3 g.) was directly treated with a boiling mixture of methanol (75 ml.), concentrated hydrochloric acid (4·5 ml.), and water (6 ml.) for 2 hr. Evaporation of the hydrolysate under diminished temperature and pressure, and removal of the last traces of acid in the presence of sodium hydroxide, gave the *product* (0·8 g.), m. p. 139—140° (from ether), $[\alpha]_D$ +45° (*c* 0·5 in $CHCl_3$) (Found: C, 55·5; H, 4·8. $C_{13}H_{14}O_5S$ requires C, 55·3; H, 5·0%).

5-Deoxy-2,3-O-isopropylidene-2-C-methyl-D-ribono-1→4-lactone.—A solution of 2,3-*O*-isopropylidene-2-*C*-methyl-5-*O*-toluene-*p*-sulphonyl-D-ribono-1→4-lactone [1] (1·8 g.) and sodium iodide (1·7 g.) in dry acetone (15 ml.) was boiled under reflux for 4 hr.; separation of sodium toluene-*p*-sulphonate began after 5—10 min. The cooled solution was filtered, concentrated to *ca.* 5 ml., diluted with chloroform (60 ml.), washed with water and aqueous sodium thiosulphate, dried ($MgSO_4$), and concentrated, and the residue was distilled to yield *5-deoxy-5-iodo-2,3-O-isopropylidene-2-C-methyl-D-ribono-1→4-lactone* (1·33 g., 83%), b. p. 110°/0·1 mm., $[\alpha]_D$ −55° (*c* 1·5 in $CHCl_3$) (Found: C, 34·95; H, 4·3; I, 39·7. $C_9H_{13}IO_4$ requires C, 34·6; H, 4·2; I, 40·7%). The iodo-compound rapidly decomposed.

A solution of the iodo-compound (5 g.) in methanol (300 ml.) was boiled under reflux in the presence of Raney nickel [9] (100 ml.) for 3 hr. The nickel was separated from the cooled solution by decantation and well washed with hot methanol. The combined solution and washings were concentrated and the residue crystallised from light petroleum (b. p. 80—100°), to give 5-deoxy-2,3-*O*-isopropylidene-2-*C*-methyl-D-ribono-1→4-lactone (2·1 g., 70%), m. p. 90°, $[\alpha]_D$ −74° (*c* 0·3 in $CHCl_3$); Sowden and Strobach [1] record m. p. 91—92° and $[\alpha]_D$ −74° for this compound prepared by a different procedure.

5-Deoxy-2-C-methyl-D-ribose (III).—A solution of 5-deoxy-2-*C*-methyl-D-ribono-1→4-lactone (II) (0·7 g. prepared from the foregoing isopropylidene derivative by Sowden and Strobach's method [1]) in water (15 ml.) at 0° was treated with a solution of sodium borohydride (0·4 g.) in water (20 ml.) dropwise with the concurrent addition of 0·5N-sulphuric acid to maintain a pH of 4—5; the temperature was kept below 10°. Cations were removed from the mixture with Amberlite resin IR-120 (H^+ form), but on attempting to remove anions with Amberlite IR-45 (OH^- form) the reducing sugar was also adsorbed, presumably as the borate complex. Elution of the resin with 30% acetic acid removed the sugar and borate but not sulphate ions. Concentration of the eluate and distillation of methanol thrice from the residue gave a product from which the last traces of acetic acid were removed by storage *in vacuo* over potassium hydroxide. Distillation of the residue gave *5-deoxy-2-C-methyl-D-ribose* (84%), b. p. 130—150°/0·1 mm., $[\alpha]_D$ +37° (*c* 0·8 in H_2O) (Found: C, 50·0; H, 8·0. $C_6H_{12}O_4$ requires C, 48·6; H, 8·2%). The sugar appeared homogeneous on paper chromatography [R_F 0·63 using the organic phase butanol–ethanol–water (4 : 1 : 5) and detection with aniline hydrogen phthalate [10]] and on ionophoresis [11] (M_G 0·77 with a borate buffer of pH 10). On storage the sugar partly crystallised and the crystals were separated using a porous plate. Recrystallisation from light

[9] Pavlic and Adkins, *J. Amer. Chem. Soc.*, 1947, **69**, 3039.
[10] Partridge, *Nature*, 1949, **164**, 443.
[11] Foster, *Chem. and Ind.*, 1952, 1050; *J.*, 1953, 982.

petroleum (b. p. 40—60°) gave a product with m. p. 72—75°, $[\alpha]_D$ −11° (*c* 1·2 in H_2O; 5 min.) (Found: C, 48·7; H, 8·0%).

5-*Deoxy*-2-C-*methyl*-D-*ribitol* (IV).—(*a*) A solution of the foregoing sugar (50 mg.) in water (5 ml.) was treated with sodium borohydride (50 mg.) at room temperature overnight. Excess of reductant was destroyed with acetic acid and cations were removed from the mixture with Amberlite IR-120 (H^+ form). Concentration of the solution and repeated distillation of methanol from the residue gave the crystalline *product* m. p. 123—124° (from ethanol–ether), $[\alpha]_{5461}$ +7° (*c* 0·9 in H_2O); the m. p. was not changed after sublimation (Found: C, 48·2; H, 9·8. $C_6H_{14}O_4$ requires C, 48·0; H, 9·4%).

(*b*) A mixture of 2,3-*O*-isopropylidene-2-*C*-methyl-5-*O*-toluene-*p*-sulphonyl-D-ribono-1→4-lactone [1] (3·5 g.), lithium aluminium hydride (2 g.), and ether (50 ml.) was boiled under reflux for 24 hr. Excess of reductant was destroyed with ethyl acetate, and alkoxides with water. Sufficient chloroform was added to keep the mixture liquid which was then heated under reflux until the insoluble material granulated. The filtered solution was concentrated and the residue crystallised from ether–light petroleum (b. p. 40—60°) to yield 5-*deoxy*-2,3-O-*isopropylidene*-2-C-*methyl*-D-*ribitol* (1 g.), m. p. 103—104°, $[\alpha]_D$ −36° (*c* 1·0 in $CHCl_3$) (Found: C, 57·0; H, 9·4. $C_9H_{15}O_4$ requires C, 56·8; H, 9·5%).

A solution of the foregoing isopropylidene compound (0·2 g.) in 0·1N-hydrochloric acid (20 ml.) was boiled under reflux for 2 hr. and then evaporated *in vacuo* over sodium hydroxide. Crystallisation of the residue gave the same product as (*a*).

Isolation of Hamameli-tannin.—Bark (*ca.* 5 kg.) of the witch hazel *Hamamelis virginiana* L. was thrice extracted with acetone (5 l. portions) by rolling in a 10-l. jar at room temperature for 72 hr. The combined extracts were concentrated to *ca.* 1·5 l. at room temperature/~12 mm., and the resultant black syrup was extracted with benzene (5 × 500 ml.). The residual oil was extracted continuously with ethyl acetate for 72 hr. with frequent changes of solvent in order to avoid decomposition of the tannin. The combined extracts were concentrated at 40°/~12 mm., and a solution of the residue in water was decolourised with charcoal at 60° and then concentrated under diminished temperature and pressure to *ca.* 20 ml. Hamameli-tannin (10 g.) crystallised during 2 days. Recrystallisation from water gave a product with $[\alpha]_D$ +17° (*c* 5·6 in MeOH; 5 min.) changing to +12·5° (equil. 24 hr.) and an infrared spectrum (Nujol) indistinguishable from that of an authentic sample.[12]

Methyl 2,3-O-*Isopropylidene*-β-D-*hamamelofuranoside.*—Hamameli-tannin (8 g.) was treated with boiling 1% methanolic hydrogen chloride (200 ml.) for 5 hr. The cooled solution was neutralised with silver carbonate, filtered, and concentrated at room temperature/~12 mm. The resultant syrup was treated with acetone (200 ml.) containing concentrated sulphuric acid (0·2 ml.) at room temperature for 18 hr. The mixture was neutralised with anhydrous potassium carbonate, concentrated, and the residue treated with a boiling mixture of methanol (96 ml.) and water (54 ml.) containing sodium hydroxide (20 g.) for 4 hr. Methanol was then removed from the mixture by distillation and the residual aqueous solution (*A*) was extracted with chloroform (4 × 50 ml.). The combined extracts were washed with water, dried ($MgSO_4$), and concentrated, yielding the *product* (0·5 g.), m. p. 117—120° (from benzene), $[\alpha]_D$ −61° (*c* 0·6 in $CHCl_3$) (Found: C, 51·5; H, 7·85. $C_{10}H_{18}O_6$ requires C, 51·3; H, 7·75%). The glycoside appeared homogeneous by thin layer chromatography on silica gel with methanol–benzene 1 : 9 and detection with iodine vapour or vanillin–sulphuric acid.[13]

The initial glycosidation could also be performed by dissolving hamameli-tannin (7 g.) in 1% methanolic hydrogen chloride and storing the solution at 30—40° for a week. The mixture was then processed as above to yield the glycoside (0·35 g.).

Continuous extraction of the aqueous solution *A* with chloroform for 24 hr., and concentration of the extract, gave a product (0·5 g.) with b. p. 180—200° (bath)/0·1 mm. which was, presumably, a mixture of the methyl glycosides of hamamelose. Hydrolysis of this product with 0·5N-hydrochloric acid at 90° for 3 hr., followed by neutralisation with silver carbonate, gave a solution which appeared to contain hamamelose as the sole sugar component [paper chromatography with the organic phase of butanol–ethanol–water (4 : 1 : 5) and detection with silver nitrate [14]]. Concentration of the solution and crystallisation of the

[12] Schmidt, *Annalen*, 1929, **476**, 250.
[13] E. Merck AG, Darmstadt, "Chromatography," 2nd edn., p. 30.
[14] Trevelyan, Proctor, and Harrison, *Nature*, 1950, **166**, 444.

residue from ethanol–ether gave a product with m. p. 110—112° alone or in admixture with D-hamamelose.

Conversion of the Foregoing Isopropylidene Compound into 5-*Deoxy*-2-C-*methyl*-D-*ribitol* (IV). —Methanesulphonyl chloride (0·5 g.) was added to a solution of methyl 2,3-*O*-isopropylidene-β-D-hamamelofuranoside (0·52 g.) in pyridine (3 ml.), and the mixture was stored at room temperature for 2 hr. Water (100 ml.) was then added and the mixture was extracted with chloroform (4 × 25 ml.). The combined extracts were washed successively with ice-cold 0·1N-hydrochloric acid (2 × 25 ml.), aqueous sodium carbonate, and water, dried ($MgSO_4$), and concentrated, to yield a di-methanesulphonate which failed to crystallise but which had no infrared absorption for hydroxyl (toluene-*p*-sulphonylation at room temperature failed to give a hydroxyl-free product).

A solution of the methanesulphonate in ether (100 ml.) was treated with lithium aluminium hydride (0·5 g.), and the mixture was boiled under reflux for 48 hr. Excess of reductant was destroyed with ethyl acetate, and alkoxides with water. The filtered solution was washed with water, dried ($MgSO_4$), concentrated, and a solution of the residue in benzene was passed through a column (5 × 1 cm.) of alumina. Concentration of the eluate gave a sulphur-free product which had no infrared absorption for hydroxyl. This product was hydrolysed with boiling 0·5N-hydrochloric acid for 2 hr. After neutralisation of the hydrolysate with silver carbonate, and concentration, a residue (70 mg.) was obtained which appeared homogeneous on paper chromatography containing a component with R_F value and detection characteristics indistinguishable from those of 5-deoxy-2-*C*-methyl-D-ribose described above. Since the product only partially crystallised (cf. the results with the authentic compound) it was dissolved in water (1 ml.) and treated with sodium borohydride (50 mg.) at room temperature for 5 hr. Excess of reductant was destroyed with acetic acid and the solution was freed from cations with Amberlite resin IR-120 (H^+ form); it was then concentrated and methanol was repeatedly distilled from the residue. Crystallisation of the product from ethanol–ether gave 5-deoxy-2-*C*-methyl-D-ribitol, m. p. 118—121 and 121—123° in admixture with the authentic compound described above, $[\alpha]_{5461}$ +5° (*c* 0·7 in H_2O). Final identification was by comparison of infrared spectra.

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