L-GALACTOSACCHARINIC ACIDS: NEW SACCHARINIC ACIDS FORMED BY CALCIUM HYDROXIDE TREATMENT OF L-SORBOSE

ATSUSHI ISHIZU*, KOICHI YOSHIDA, AND NOBORU YAMAZAKI
Faculty of Agriculture, Tokyo Noko University, Tokyo (Japan)

(Received August 26th, 1971; accepted for publication, September 21st, 1971)

ABSTRACT

The new saccharinic acids, α- and β-L-galactosaccharinic acids (2-*C*-methyl-L-xylonic and 2-*C*-methyl-L-lyxonic acids), have been synthesized. The same acids were isolated, as their lactones, from the syrup obtained by treatment of L-sorbose with calcium hydroxide. The acids were produced in comparable amounts, and the factors that might regulate the stereoselectivity of the benzylic acid type of rearrangement are discussed.

INTRODUCTION

Three new saccharinic acids, 3-deoxy-2-*C*-hydroxymethyl-D-*threo*-pentonic acid[1], 2-*C*-methyl-D-threonic acid, and 2-*C*-methyl-D-erythronic acid[2], were recently isolated from the syrups produced by treatment of sugars with calcium hydroxide. Although α-D-glucosaccharinic acid (2-*C*-methyl-D-ribonic acid) was formed by the action of calcium hydroxide on 1-*O*-substituted D-fructoses, no β-D-glucosaccharinic acid (2-*C*-methyl-D-arabinonic acid) was detected[1]. Of all the C-5 and C-6 saccharinic acids possible according to the Nef–Isbell theory, only the α- and β-galactosaccharinic acids (2-*C*-methylxylonic and 2-*C*-methyllyxonic acids) (D and L isomers) are unknown[3].

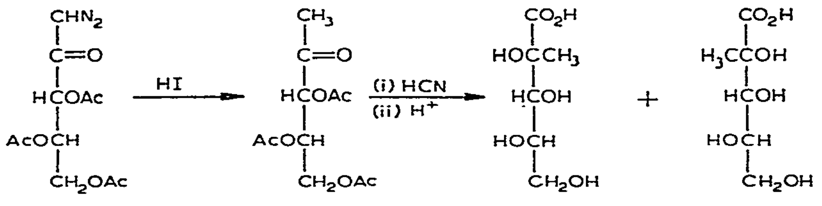
Although Sowden and Mao[4] treated 1-*O*-methyl-L-sorbose with calcium hydroxide in order to produce these two acids, only α-L-glucosaccharinic acid was isolated. In the present communication, the isolation of these acids from the syrup obtained by treatment of L-sorbose with calcium hydroxide is reported.

RESULTS AND DISCUSSION

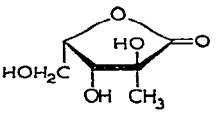
Treatment of 3,4,5-tri-*O*-acetyl-1-deoxy-1-diazo-L-*threo*-pentulose[5] (**1**) with hydroiodic acid gave 3,4,5-tri-*O*-acetyl-1-deoxy-L-*threo*-pentulose (**2**), from which α- and β-L-galactosaccharinic acids (**3** and **4**) were synthesized by treatment with hydrogen cyanide and subsequent acid hydrolysis of the respective products. The acids produced were converted into their lactones (**5** and **6**), which were separated by chromatography on a cellulose column.

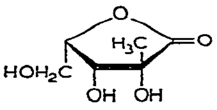
---

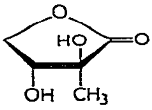
*Present address: Faculty of Agriculture, Tokyo University, Bunkyo-Ku, Tokyo (Japan)

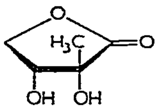

1 2 3 4

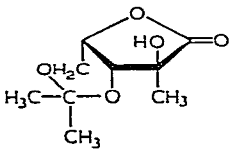
The isomer having the higher R_F value (lactone *A*) responded much more rapidly than did lactone *B* to silver nitrate–sodium hydroxide. On the other hand, lactone *A* gave a negative reaction with sodium periodate–benzidine, whereas lactone *B* gave a positive reaction. Previously, 2-*C*-methyl-D-threono-1,4-lactone (7), which contains a *trans* α-glycol grouping, was found to give a negative reaction with the periodate–benzidine reagent, while 2-*C*-methyl-D-erythrono-1,4-lactone (8), having a *cis* α-glycol grouping, gave a positive reaction[2]. The lactones *A* and *B* are therefore presumed to be the α-isomer (5, 2-*C*-methyl-L-xylono-1,4-lactone) and the β-isomer (6, 2-*C*-methyl-L-lyxono-1,4-lactone), respectively.

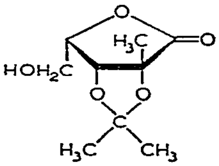

5


6


7


8


9


10

In order to confirm this assumption, isopropylidene derivatives were prepared from the lactones, and their n.m.r. spectra were determined in methyl sulphoxide. The isopropylidene derivative (9) of the α-isomer should contain a tertiary hydroxyl group, and that (10) of the β-isomer a primary hydroxyl group. The n.m.r. spectrum of the isopropylidene derivative of lactone *A* showed a singlet at τ 3.88, which disappeared on addition of deuterium oxide, proving[6] that the hydroxyl group is tertiary and that lactone *A* is the α-isomer (5) as expected. The isopropylidene derivative of lactone *B* showed a triplet at τ 4.94, proving[6] that the hydroxyl group is primary and that lactone *B* is the β-isomer (6).

The acids formed by treatment of L-sorbose with calcium hydroxide were separated as their lactones into five fractions by cellulose-column chromatography. These fractions were trimethylsilylated and analyzed by g.l.c. The lactones were identified by comparison of their chromatographic mobilities with those of authentic samples. The relative proportions of the different components were determined by g.l.c. (Table I).

TABLE I

LACTONES FORMED FROM THE REACTION OF L-SORBOSE AND CALCIUM HYDROXIDE

Fraction	*Lactone No.*[a]	R_F[b]	T[c]	*Structure, 1,4-lactone*
1	1	0.79	0.51	2-*C*-Methyl-threono-
	2	0.79	0.66	3-Deoxytetrono-
2	3	0.71	0.66	not determined
	4	0.71	0.75	2-*C*-Methyl-erythrono-
	5	0.68	1.30	2-*C*-Methyl-xylono-
	6	0.66	0.55	3-Deoxy-2-*C*-hydroxymethyl-tetrono-
3	7	0.60	1.00	2-*C*-Methyl-ribono-
	8	0.60	1.23	3-Deoxy-*erythro*-pentono-
4	9	0.51	1.57	3-Deoxy-*threo*-pentono-
	10	0.50	1.72	2-*C*-Methyl-lyxono-
5	11	0.41	1.23	3-Deoxy-2-*C*-hydroxymethyl-*erythro*-pentono-
	12	0.39	1.37	3-Deoxy-2-*C*-hydroxymethyl-*threo*-pentono-
	13	0.34	3.14	3-Deoxy-*lyxo*-hexono-
	14	0.24	2.68	3-Deoxy-*xylo*-hexono-

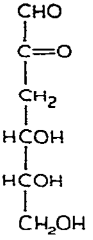
[a] Percentages (calculated as the ratio of the corresponding peak areas to the total peak area in g.l.c.) of lactones were 1, 7; 2+3, 12; 4, 5; 5, 13; 6, 3; 7, 6; 8+11, 14; 9, 4; 10, 17; 12, 5; 13, 6; 14, 8. [b] Butanone, saturated with water. [c] Relative retention times on g.l.c.; $T = 1$ for lactone 7.

The main component in fraction 2 was obtained crystalline and was indistinguishable from authentic 2-*C*-methyl-L-xylono-1,4-lactone (**5**). The main component in fraction 4 was chromatographically indistinguishable from 2-*C*-methyl-L-lyxono-1,4-lactone (**6**). After benzoylation of the fraction, the crystalline tribenzoate of **6** was isolated.

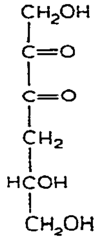
2-*C*-Methyl-L-ribono-1,4-lactone was detected in the reaction product of L-sorbose and calcium hydroxide (Table I). The yield (determined by g.l.c.) was approximately one fifth of the combined yield of α- and β-L-galactosaccharino-1,4-lactones. Thus, considerable isomerization occurs during treatment with calcium hydroxide, as has been observed previously[2].

According to the Nef–Isbell theory[3], saccharinic acids are formed by a benzilic acid type of rearrangement of the dicarbonyl intermediates produced during the alkaline treatment of sugars. 3-Deoxy-D-*erythro*-hexosulose[7,8] (**11**), 4-deoxy-D-*glycero*-2,3-hexodiulose[9,10] (**12**), and 1-deoxy-D-*erythro*-2,3-hexodiulose[11] (**13**), the postulated intermediates in the formation of D-glucometasaccharinic, D-glucoisosaccharinic, and D-glucosaccharinic acids, were synthesized or isolated after alkaline treatment of suitably substituted sugars and their facile conversions into the corresponding saccharinic acids on calcium hydroxide treatment have been demonstrated.

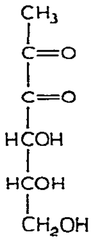
From the first two intermediates, the two possible isomeric saccharinic acids ("α" and "β") are formed in comparable amounts. From the last intermediate (**13**), however, the α-isomer was the main product. As only the intermediate **13** has an asymmetric carbon atom adjacent to the dicarbonyl grouping, Feast *et al.*[1] suggested that the stereoselectivity was due to the presence of this asymmetry. In agreement with this, alkaline treatment of D-glucosone (D-*arabino*-hexosulose) produced predominantly D-mannonic and only traces of D-gluconic acid[12]. It was observed, however, that treatment of D-xylose with calcium hydroxide gives 2-*C*-methyl-D-erythronic and 2-*C*-methyl-D-threonic acids in comparable amounts[2]. It has now been demonstrated that the galactosaccharinic acids formed by treatment of L-sorbose with calcium hydroxide, presumably *via* 1-deoxy-L-*threo*-2,3-hexodiulose (**14**), are formed in comparable amounts. Consequently, several factors may influence the stereoselectivity of the benzilic acid type of rearrangement, the detailed mechanism of which is not well understood.



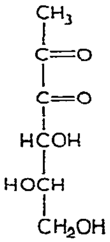
11



12



13



14

EXPERIMENTAL

General methods. — Concentrations were carried out under diminished pressure below 45°. Melting point are uncorrected. The solvent system used for paper chromatography (on Toyo Roshi No. 50) was butanone saturated with water. The solvent systems used for t.l.c. of isopropylidene derivatives on Wakogel B-5 (silica gel) and of benzoates of lactones on Kieselgel HF_{254} were ethyl acetate–benzene 1:1 and 1:9, respectively. Conventional spraying reagents for acids and lactones were used. Periodate–benzidine reagent[13] was used for detection of glycols.

I.r. spectra for solids (KBr disc) and for liquids were recorded with a Shimazu IR-27G spectrophotometer. N.m.r. spectra were recorded at 60 MHz on a Nippon Denshi C-60HL spectrometer. The spectra of benzoates were determined in deuteriochloroform, and those of isopropylidene derivatives in methyl sulphoxide and deuterioacetone.

G.l.c. of trimethylsilyl ethers, prepared according to Sweeley and co-workers[14], was carried out on a poly(butane-1,4-diol succinate) column at 160°, using a Shimazu GC-4APF instrument. Pyridine used for trimethylsilylation was removed by distillation and trimethylsilyl ethers were injected as solutions in hexane[2].

*3,4,5-Tri-O-acetyl-1-deoxy-*L-threo-*pentulose* (**2**). — This compound was synthesized from 3,4,5-tri-*O*-acetyl-1-deoxy-1-diazo-L-*threo*-pentulose, following the procedure for the synthesis of the corresponding benzoate[5]. T.l.c. (ethyl acetate–benzene, 1:1 v/v) of the resulting syrup showed one major (R_F 0.65) and one minor spot (R_F 0.3). The syrup was purified by chromatography on a column (5 × 45 cm) of silica gel, using ethyl acetate–benzene (1:1). The main product, a colourless syrup (6.8 g from 9.5 g of starting material), crystallized on storage and, when recrystallized from ethyl ether–light petroleum (b.p. 30–60°), it gave **2**, m.p. 30–32°, $[\alpha]_D^{21}$ $-53°$ (*c* 4.6, chloroform); ν_{max} 1742 (OAc) and 1215 cm^{-1} (OAc) (Found: C, 50.54; H, 6.13. $C_{11}H_{16}O_7$ calc.: C, 50.76; H, 6.20%).

*2-C-Methyl-*L*-xylonic acid* (**3**) *and 2-C-methyl-*L*-lyxonic acid* (**4**). — These compounds were synthesized from **2** (4.2 g), following the procedure for the synthesis of 2,4-dihydroxy-2-hydroxymethylbutanoic acid from 1,4-diacetoxybutan-2-one[15]. A paper chromatogram of the resulting syrup showed the presence of two lactones (R_F 0.70 and 0.50). The syrup was fractionated on a cellulose column, using butanone saturated with water. Comparable yields (1.0 g) of the two lactones were obtained.

2-*C*-Methyl-L-xylono-1,4-lactone (**5**), after recrystallization from ethyl acetate, had m.p. 159–162°, $[\alpha]_D^{19}$ $-97°$ (*c* 4.0, water); ν_{max} 1776 (γ-lactone), 1120, and 1015 cm^{-1} (Found: C, 44.33; H, 6.06. $C_6H_{10}O_5$ calc.: C, 44.44; H, 6.22%).

2-*C*-Methyl-L-lyxono-1,4-lactone (**6**), after recrystallization from ethyl acetate, had m.p. 105–108°, $[\alpha]_D^{19}$ $-79°$ (*c* 3.9, water); ν_{max} 1776 (γ-lactone), 1110, and 1020 cm^{-1} (Found: C, 44.29; H, 6.10. $C_6H_{10}O_5$ calc.: C, 44.44; H, 6.22%).

*3,5-O-Isopropylidene-2-C-methyl-*L*-xylono-1,4-lactone* (**9**). — 2-*C*-Methyl-L-xylono-1,4-lactone (180 mg) was dissolved in acetone (9 ml), and conc. sulphuric acid (0.07 ml) and anhydrous cupric sulphate (300 mg) were added to the solution. After standing for 2 days at room temperature with occasional shaking, the cupric sulphate was filtered off, and the filtrate was passed through a column of Amberlite IR-45 (free base) resin. Evaporation of the solvent under reduced pressure gave a solid residue, which was purified by chromatography on a column (3 × 10 cm) of silica gel, using ethyl acetate–benzene (1:1). The product (110 mg) was recrystallized from acetone–light petroleum to give **9** as fine needles, m.p. 155–157°, $[\alpha]_D^{29}$ $-73°$ (*c* 1.95, chloroform), R_F 0.7 (t.l.c.); ν_{max} 3420 (OH) and 1760 cm^{-1} (γ-lactone) (Found: C, 53.39; H, 6.95. $C_9H_{14}O_5$ calc.: C, 53.47; H, 6.93%). N.m.r. data (methyl sulphoxide): τ 3.88 (1-proton singlet, OH); (deuterioacetone): τ 4.84 (1-proton singlet, OH), 5.25 (1-proton multiplet, H-4), ~5.9 (3 protons, H-3 and CH_2), 8.50, 8.65, and 8.70 (3-proton singlets, CH_3 and CMe_2).

*2,3-O-Isopropylidene-2-C-methyl-*L*-lyxono-1,4-lactone* (**10**). — 2-*C*-Methyl-L-lyxono-1,4-lactone (160 mg) was converted into the isopropylidene derivative and purified as described above for **9**. The product **10** was a syrup (124 mg), $[\alpha]_D^{18}$ $-75°$ (*c* 2.6, chloroform), R_F 0.5 (t.l.c.); ν_{max} 3450 (OH), 1784 (γ-lactone), 1378 (CH_3), 1220, and 1105 cm^{-1}. N.m.r. data (methyl sulphoxide): τ 4.95 (1-proton triplet, *J* 11.2 Hz, OH); (deuterioacetone): τ 8.43 (3-proton singlet, CH_3) and 8.65 (6-proton singlet, CMe_2).

*2,3,5-Tri-O-benzoyl-2-C-methyl-*L*-xylono-1,4-lactone.* — To 160 mg of 2-*C*-methyl-L-xylono-1,4-lactone (5), dissolved in anhydrous pyridine (1 ml, 0°), benzoyl chloride (0.42 ml) was added. After standing at 0° for 1 h and then at room temperature for 24 h, 75% ethanol was added to the reaction mixture. Evaporation of the solvent under reduced pressure at 45° gave a syrup, which was repeatedly dissolved in toluene and the solution concentrated under reduced pressure. The resulting syrup was purified by chromatography on a silica gel column (3.5 × 14 cm), using ethyl acetate–benzene (1:9). The benzoate (400 mg) was a colourless syrup, $[\alpha]_D^{21}$ −131° (*c* 3.0, chloroform), R_F 0.8 (t.l.c.); ν_{max} 1795 (γ-lactone) and 1720 cm^{-1} (OBz). N.m.r. data ($CDCl_3$): τ 8.25 (3-proton singlet, CH_3), 5.35 (2-proton doublet, CH_2), 4.56 (1-proton sextet, H-4), 3.78 (1-proton doublet, H-3), and 1.8–2.9 (two multiplets, 15 protons, aromatic).

*2,3,5-Tri-O-benzoyl-2-C-methyl-*L*-lyxono-1,4-lactone.* — 2-*C*-Methyl-L-lyxono-1,4-lactone (6) (170 mg) was benzoylated, and the benzoate was purified as described above. The benzoate was recrystallized from 75% ethanol to yield colourless needles, m.p. 109–110.5°, $[\alpha]_D^{17}$ −76° (*c* 2.1, chloroform), R_F 0.7 (t.l.c.); ν_{max} 1786 (γ-lactone) and 1720 cm^{-1} (OBz) (Found: C, 68.08; H, 4.66. $C_{27}H_{22}O_8$ calc.: C, 68.35; H, 4.67%). N.m.r. data: τ 8.07 (3-proton singlet, CH_3), 5.32 (A_2 part of A_2B system, CH_2), 4.87 (1-proton multiplet, H-4), 3.94 (1-proton doublet, H-3), and 1.9–3.0 (two multiplets, 15 protons, aromatic).

Calcium hydroxide treatment of L*-sorbose.* — L-Sorbose (100 g) was treated with calcium hydroxide (50 g) in water (1 litre) with occasional shaking for 40 days at 30°. The product was worked up as described by Whistler and BeMiller[16]. The decationized, concentrated solution was given a brief treatment with Amberlite IR-45 (free base) resin, in order to remove acids, and concentrated. The syrupy residue (20 g) was fractionated on a cellulose column (6 × 65 cm) using butanone saturated with water. Fractions were investigated by g.l.c. after trimethylsilylation (Table I).

Fraction 2 partly crystallized on standing in a desiccator for several days. The crystals were separated from the syrup by filtration using ethyl acetate and recrystallized from ethyl acetate to give 2-*C*-methyl-L-xylono-1,4-lactone (5) which was indistinguishable from an authentic sample (mixed m.p. and i.r.).

Fraction 4 was benzoylated and the benzoate was purified as described above. Recrystallization of the benzoate from 75% ethanol gave 2,3,5-tri-*O*-benzoyl-2-*C*-methyl-L-lyxono-1,4-lactone as white needles, indistinguishable from an authentic sample (mixed m.p., i.r., and n.m.r.).

ACKNOWLEDGMENTS

The authors are very grateful to Professor B. Lindberg for criticism of this manuscript. They are indebted to Professor Tohjun Takashima for his interest and encouragement, and to Mrs. Michiko Tsuchimoto for determining the n.m.r. spectra. This work was supported by a grant from the Ministry of Education.

REFERENCES

1 A. A. J. Feast, B. Lindberg, and O. Theander, *Acta Chem. Scand.*, 19 (1965) 1127.
2 A. Ishizu, B. Lindberg, and O. Theander, *Acta Chem. Scand.*, 21 (1967) 424.
3 J. C. Sowden, *Advan. Carbohyd. Chem.*, 12 (1957) 35.
4 J. C. Sowden and I. I. Mao, *J. Org. Chem.*, 25 (1960) 1461.
5 M. L. Wolfrom and R. B. Bennett, *J. Org. Chem.*, 30 (1965) 458.
6 O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, 86 (1964) 1256.
7 E. F. L. J. Anet, *J. Amer. Chem. Soc.*, 82 (1960) 1502.
8 G. Machell and G. N. Richards, *J. Chem. Soc.*, (1960) 1932.
9 R. L. Whistler and J. N. BeMiller, *J. Amer. Chem. Soc.*, 82 (1960) 3705.
10 G. Machell and G. N. Richards, *J. Chem. Soc.*, (1960) 1932.
11 A. Ishizu, B. Lindberg, and O. Theander, *Carbohyd. Res.*, 5 (1967) 329.
12 B. Lindberg and O. Theander, *Acta Chem. Scand.*, 22 (1968) 1782.
13 J. A. Cifonelli and F. Smith, *Anal. Chem.*, 26 (1954) 1132.
14 C. C. Sweeley, R. Bentley, M. Makita, and W. W. Wells, *J. Amer. Chem. Soc.*, 85 (1963) 2497.
15 G. O. Aspinall, M. E. Carter, and M. Los, *J. Chem. Soc.*, (1956) 4807.
16 R. L. Whistler and J. N. BeMiller, *Methods Carbohyd. Chem.*, 2 (1963) 484.