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296. *The Ring Structure of Methylgalactofuranoside.*

By W. N. Haworth, E. L. Hirst, D. I. Jones, and H. Woodward.

An improved preparation of methylgalactofuranoside (contaminated with a little of the pyranoside) is described. Methods are given for obtaining pure 2 : 3 : 5 : 6-tetramethyl galactofuranose and 2 : 3 : 5 : 6-tetramethyl γ-galactonolactone from the mixture of methyl derivatives obtained by methylating the crude methylgalactoside. It is shown that tetramethyl galactofuranose is transformed on heating into an *octamethyl digalactofuranose* of the trehalose type. Oxidation of 2 : 3 : 5 : 6-tetramethyl γ-galactonolactone by nitric acid gives *d*-dimethoxysuccinic acid, unaccompanied by trimethoxyglutaric acid. This observation, taken in conjunction with the evidence for the pyranose structure of ordinary methylgalactoside, proves the structure of tetramethyl γ-galactonolactone.

The ring structure of normal galactose was established by oxidative methods (Haworth, Hirst, and Jones, J., 1927, 2428) and at the same time a study of the constitution of methylgalactofuranoside by similar methods was completed but has not yet been published. Methylgalactofuranoside was prepared by a modification of the method of Haworth, Ruell, and Westgarth (J., 1924, **125**, 2468) which shortened the procedure and allowed of the preparation being made on a larger scale. Sulphuric acid was employed instead of hydrogen chloride as the catalyst, and the reaction between galactose and the acid alcohol was conducted, not in the cold (which requires 24—96 hrs.), but at 80° and for 2 hrs. only. The product so obtained ($[\alpha]_D$ — 48·5°) contained a slightly higher proportion of methylgalactopyranoside than that prepared by the earlier method ($[\alpha]_D$ — 52·7°), but the practical advantages were obvious and methods were found for removing the pyranose derivative.

The crude methylgalactofuranoside was methylated successively with methyl sulphate and methyl iodide, and the syrupy product ($[\alpha]_D^{23°}$ — 33·6° in water) was submitted to simultaneous hydrolysis and oxidation by treatment with hydrobromic acid and bromine. It was estimated that the lactone formed in this way contained about 85% of tetramethyl γ-galactonolactone together with some 15% of the corresponding δ-lactone. Purification of the γ-lactone was effected through the crystalline p-*bromophenylhydrazide* of 2 : 3 : 5 : 6-*tetramethyl galactonic acid* (m. p. 134—136°), which was readily obtained pure. Hydrolysis of this substance under carefully controlled conditions gave 2 : 3 : 5 : 6-tetramethyl γ-galactonolactone, $[\alpha]_D$ — 32·6° in water (for precautions necessary, see p. 1576). The lactone is obtainable also by methylation of γ-galactonolactone, followed by purification of the resulting crude tetramethyl lactone by the method just outlined.

The pure tetramethyl γ-galactonolactone may be prepared in another way depending on an interesting and unexpected property of tetramethyl galactofuranose, which is transformed when heated by itself into *octamethyl digalactofuranose*, a fully methylated sugar of the trehalose type, in which both reducing groups are involved in the disaccharide link. No such reaction occurs with tetramethyl galactopyranose. This behaviour of 2 : 3 : 5 : 6-tetramethyl galactofuranose recalls that of 2 : 3 : 5-trimethyl lyxofuranose which, on heating, gives rise to a crystalline hexamethyl dilyxofuranose (Bott, Hirst, and Smith, J., 1930, 665). The methylated disaccharide has a high b. p., and it is possible therefore to obtain a pure furanose derivative from the mixture of furanose and pyranose sugars obtained on methylation of the crude methylgalactoside described above. On hydrolysis, octamethyl digalactofuranose gives rise to two molecules of 2 : 3 : 5 : 6-tetramethyl galactose, $[\alpha]_D$ − 30° in water, and the latter substance on oxidation with bromine water gives pure 2 : 3 : 5 : 6-tetramethyl γ-galactonolactone.

The lactone ring in tetramethyl γ-galactonolactone is remarkably stable, and oxidation with nitric acid at 90° proceeds with difficulty. Under more drastic conditions of oxidation the chief product was *d*-dimethoxysuccinic acid (characterised as the amide, m. p. 278—280°, decomp., and the methylamide, m. p. 204—205°). No trimethoxyglutaric acid was formed. Since normal α-methylgalactoside and its derivatives are known to possess a six-membered ring structure, these observations suffice to establish the five-membered ring structure of tetramethyl γ-galactonolactone and therefore of methylgalactofuranoside.

EXPERIMENTAL.

Modified Preparation of Methyl-d-*galactofuranoside*.—Galactose (50 g.) was gently boiled with dry methyl alcohol (400 c.c.) containing 1% of sulphuric acid until complete solution was achieved (2 hrs.), and the reaction was then terminated by cooling ($[\alpha]_D$ − 27·2°, calculated on the weight of galactose used). After neutralisation with lead carbonate and filtration, the solution was taken to dryness, and the residue repeatedly extracted with cold ethyl acetate. After 9 extractions, the weight of extract was 34·5 g., $[\alpha]_D$ − 48·5° (*c*, 1·89) in water. (The rotation value indicates that the extracted syrup contained a higher proportion of methylfuranosides than did the original reaction mixture.)

Tetramethyl δ-*Galactonolactone*.—Crude methylgalactofuranoside (46 g.), prepared as above, was methylated twice by methyl sulphate and sodium hydroxide, methylation being completed by two treatments with methyl iodide and silver oxide. The tetramethyl methylgalactoside so obtained ($[\alpha]_D^{23°}$ − 33·6° in water) was hydrolysed by heating at 85° for 2 hrs. with 3% hydrobromic acid. Bromine was then added, and the temperature maintained at 50° until the solution was non-reducing (3 hrs.). The lactone was isolated in the usual way and distilled, but little sign of separation into fractions was observed (bath temp. 120—130°/0·04 mm., $n_D^{18°}$ 1·4475—1·4500; weight of distillate, 34 g.).

When heated on the water-bath with *p*-bromophenylhydrazine (1 mol.), the distillate gave the p-*bromophenylhydrazide* of 2 : 3 : 5 : 6-*tetramethyl galactonic acid* (34 g.), which separated from benzene–light petroleum in long needles, m. p. 134—136°, $[\alpha]_D^{17°}$ + 19·5° in methyl alcohol (*c*, 2·3) (Found: C, 45·7; H, 6·0; N, 6·9. $C_{16}H_{25}O_6N_2Br$ requires C, 45·6; H, 6·0; N, 6·7%).

The *p*-bromophenylhydrazide (10 g.) was heated for 3 hrs. at 90° with the amount of N/10-hydrochloric acid requisite to neutralise the liberated *p*-bromophenylhydrazine. The solution was boiled with charcoal, filtered, and evaporated to dryness at 50°/15 mm. The residue was extracted with ether, and on removal of the ether, tetramethyl γ-galactonolactone (4·5 g.) was obtained, b. p. 120—125° (bath temp.)/0·10 mm., $n_D^{15°}$ 1·4505, $[\alpha]_D^{20°}$ − 32·6° (initial value in water, *c*, 3·9); 31·4° (72 hrs.); − 27·8° (144 hrs.); − 27·8° (192 hrs.). The rotation of 2 : 3 : 5 : 6-tetramethyl galactonic acid was determined in the usual way by dissolving the lactone (0·3014 g.) in warm N/2-sodium hydroxide (5 c.c.). After cooling and acidification with N/2-sulphuric acid (5 c.c.), the observed rotation for the acid (*c*, 2·01, calc. as lactone) was $[\alpha]_D^{24°}$ − 5·5° (initial value); − 7·0° (2·5 hrs.); − 13° (18 hrs.); − 20° (42 hrs.); − 22° (66 hrs.); − 25° (144 hrs., constant value). The lactone on treatment with methyl-alcoholic ammonia gave the corresponding amide, m. p. 151—153° (compare Humphreys, Pryde, and Waters, J., 1931, 1298), and on treatment with phenylhydrazine it gave the phenylhydrazide, long needles, m. p. 123—125°.

It is necessary to proceed with caution in the regeneration of the lactone from the *p*-bromophenylhydrazide, since extensive degradation may take place if excess of acid is used or if the product is heated too long in the presence of *p*-bromophenylhydrazine hydrochloride.

Octamethyl Digalactofuranose.—Tetramethyl methylgalactofuranoside (21 g.), containing some of the corresponding pyranose derivative, was prepared by the method described above and was hydrolysed by N/10-hydrochloric acid at 100° until the rapid reaction (hydrolysis of the furanoside) was complete. The course of the hydrolysis was followed polarimetrically, and the product was isolated in the usual way and distilled, the following fractions being obtained: (*a*) 7 G. bath temp. 110—125°/0·02 mm., $n_{\mathrm{D}}^{15^\circ}$ 1·4480—1·4530 (mixture of tetramethyl methylgalactopyranoside and tetramethyl galactose). (*b*) 6 G., bath temp. 135°/0·02 mm., $n_{\mathrm{D}}^{15^\circ}$ 1·4550, $[\alpha]_{\mathrm{D}}^{20^\circ}$ — 21° in water: this was mainly tetramethyl galactofuranose, as was shown by its transformation into a lactone, $[\alpha]_{\mathrm{D}}$ — 21°, which gave in good yield 2 : 3 : 5 : 6-tetra methyl galactonamide, m. p. 153°, alone or when mixed with an authentic sample. The rotations of sugar and lactone indicate contamination with some pyranose derivative. (*c*) *Octamethyl digalactofuranose,* 10 g., bath temp. 193°/0·02 mm., $n_{\mathrm{D}}^{15^\circ}$ 1·4580, $[\alpha]_{\mathrm{D}}^{19^\circ}$ — 67° in water (*c*, 2·19) [Found: C, 52·5; H, 8·3; OMe, 54·5. $C_{12}H_{14}O_3(OCH_3)_8$ requires C, 52·8; H, 8·35; OMe, 54·5%]. This substance was non-reducing to boiling Fehling's solution, but became strongly reducing after hydrolysis with mineral acid. The rotation fell from $[\alpha]_{\mathrm{D}}$ — 67° to — 31° in the course of 10 hrs. when the hydrolysis was carried out by N/20-acid on the boiling water-bath. The product was isolated in the usual way. On distillation, the first fraction (2 : 3 : 5 : 6-tetramethyl galactofuranose) was a colourless oil, bath temp. 129°/0·02 mm., $n_{\mathrm{D}}^{18^\circ}$ 1·4532, $[\alpha]_{\mathrm{D}}^{21^\circ}$ — 31° in water (*c*, 1·46) (Found: OMe, 51·2. Calc. for $C_{10}H_{20}O_6$: OMe, 52·6%). Later fractions contained octamethyl digalactofuranose.

On oxidation with bromine water 2 : 3 : 5 : 6-tetramethyl galactofuranose (the product described above, before distillation, can be used) gave in good yield 2 : 3 : 5 : 6-tetramethyl γ-galactonolactone, distilling at bath temp. 125°/0·1 mm., $n_{\mathrm{D}}^{15^\circ}$ 1·4505, $[\alpha]_{\mathrm{D}}^{20^\circ}$ — 32° in water (*c*, 2·7) (initial value: mutarotation curve exactly similar to the one given above). The lactone gave the characteristic amide of 2 : 3 : 5 : 6-tetramethyl galactonic acid, m. p. 153°, and was identical with the purified sample of tetramethyl γ-galactonolactone already described. Both samples appear to be free from contamination with the corresponding δ-lactone. These observations incidentally provide complete proof of the structure of the octamethyl digalactofuranose.

Methylation of γ-Galactonolactone.—Galactonolactone was methylated five times in succession with methyl iodide and silver oxide. It was necessary to add methyl alcohol as a solvent in the first two methylations. The methylated lactone was purified by formation of the barium salt (by warming for 2 hrs. at 90° with N-barium hydroxide solution) and regeneration by the addition of an exact equivalent of dilute sulphuric acid. The main fraction of the purified lactone distilled at bath temp. 150°/0·11 mm. It had $n_{\mathrm{D}}^{15^\circ}$ 1·4535, $[\alpha]_{\mathrm{D}}^{18^\circ}$ — 21·0° in water (*c*, 2·48). The *p*-bromophenylhydrazide was obtained in the usual way in 55% yield. After recrystallisation from alcohol–ether it had m. p. 133—135°, alone or in admixture with the specimen prepared previously. Pure tetramethyl γ-galactonolactone is obtained, as above, by regeneration from the *p*-bromophenylhydrazide.

Oxidation of Tetramethyl γ-Galactonolactone with Nitric Acid.—Oxidation of the γ-lactone with nitric acid under the usual conditions (*d*, 1·42; temp. 95°) proceeded slowly and more drastic conditions were required. The lactone (2 g.) was dissolved in nitric acid (*d* 1·42), placed in a water-bath at 70°, and the temperature quickly raised to and kept at 100° for 6 hrs. The flask was then transferred to an oil-bath and heated for 2 hrs. at 115—120°. The product was extracted and esterified by the usual methods, and the ester distilled at 0·2 mm.:

Fraction.	Bath temp.	Weight (g.).	$n_{\mathrm{D}}^{13^\circ}$.
1	113—115°	0·10	1·4388
2	115—120	0·35	1·4420
3	125—130	0·60	1·4558

Fraction 1 was methyl *d*-dimethoxysuccinate, and fraction 2 contained 60% of this ester, which was characterised as the amide (m. p. 278—280°, decomp.) and the methylamide (m. p. 204—205°). Fraction 3 was submitted to further oxidation with nitric acid. On the assumption that it is the γ-lactone ring which occasions the extreme stability to oxidising agents, the sodium salt of fraction 3 was first formed by treatment with 30% sodium hydroxide solution (3 c.c.) for ½ hr. at 100°. Nitric acid (*d* 1·42, 25 c.c.) was then added, and the solution heated for 1 hr. at 100° and for 6 hrs. (under reflux) at 115°. The product was isolated and esterified as before. The ester distilled at bath temp. 120—125°/0·11 mm. and had $n_{\mathrm{D}}^{17^\circ}$ 1·4360. It was pure methyl *d*-dimethoxysuccinate and gave the amide in 80% yield.

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THE A. E. HILLS LABORATORIES,
THE UNIVERSITY, EDGBASTON, BIRMINGHAM.

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