367. *Methylation of Monocarboxylic Acids derived from Aldoses. Structure of Pentamethyl α-Gluco-heptono-γ-lactone.*

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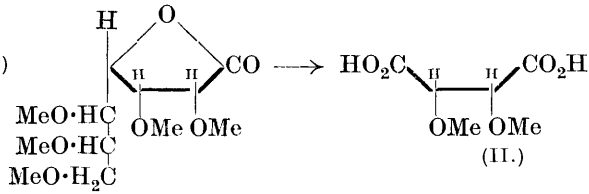
It has been known for some time that the hydroxyl group in position 4 in galactonic acid resists methylation by silver oxide and methyl iodide (Pryde, J., 1923, **123**, 1808). We have now found that this resistance to etherification is encountered also when alkali salts of galactonic acid are methylated by methyl sulphate and alkali. Inasmuch as both 2 : 3 : 5 : 6-tetramethyl γ-galactonolactone and 2 : 3 : 4 : 6-tetramethyl galactonic acid were obtained in this way

from galactonic acid, it follows that the difficulty of methylation applies both to position 4 and to position 5. The rate of etherification of the various hydroxyl groups in the aldonic acids is dependent on the stereochemical arrangement of the molecule. In certain cases methylation of the hydroxyl group in position 4 proceeds so slowly that treatment of the sugar acid with methyl sulphate and alkali affords an advantageous and efficient method for the preparation of the fully methylated γ-lactone. Two examples of this are mannonic acid and α-glucoheptonic acid, from which 2 : 3 : 5 : 6-tetramethyl γ-mannonolactone and 2 : 3 : 5 : 6 : 7-*pentamethyl α-glucoheptono-γ-lactone* (I) may be obtained in excellent yield. The method is all the more satisfactory in that the usual method of treating the γ-lactone of the sugar acid with methyl iodide and silver oxide gives inferior yields and the methylation is accompanied by degradative oxidation processes.

The methylation of γ-galactonolactone with methyl iodide and silver oxide provides a further example of resistance of positions 4 and 5 to etherification. After four methylations in the presence of methyl alcohol, followed by esterification and distillation, a crystalline trimethyl γ-galactonolactone was obtained which on further methylation gave tetramethyl γ-galactonolactone and on oxidation with dilute nitric acid yielded *d*-2 : 3-dimethoxysuccinic acid. No methylated mucic acid was detected and we therefore identify the lactone provisionally as 2 : 3 : 6-trimethyl γ-galactonolactone.

2 : 3 : 5 : 6 : 7-Pentamethyl α-glucoheptono-γ-lactone, m. p. 104°, has not hitherto been described. Accordingly an examination was made of its optical rotatory power in various solvents and of its mutarotation in water. Like other γ-lactones which possess *cis*-methoxyl groups in positions 2 and 3, it hydrolyses with extreme slowness in aqueous solution, and its rotatory power is markedly dependent on the solvent. In view of the fact that 2 : 3 : 4 : 6 : 7-pentamethyl α-glucoheptono-δ-lactone (Haworth, Hirst, and Stacey, J., 1931, 2864) is known and its structure has been proved, the structure of the present lactone as a γ-lactone follows from its oxidation by nitric acid to *i*-dimethoxysuccinic acid (II) unaccompanied by trimethoxyglutaric acid or higher acids.

(I.)



(II.)

Methylation of arabonic acid and gluconic acid by methyl sulphate and alkali could not be utilised in the preparation of the corresponding methylated γ-lactones. The fourth group reacted easily and the completely methylated acids were obtained.

EXPERIMENTAL.

2 : 3 : 5 : 6 : 7-Pentamethyl α-Glucoheptono-γ-lactone.—Sodium α-glucoheptonate (10 g.), dissolved in H_2O (15 c.c.), was methylated in the presence of acetone (30 c.c.) at 55° by Me_2SO_4 (100 c.c.) and 30% NaOH aq. (200 c.c.). After acidification with H_2SO_4 the clear solution (A) was extracted with $CHCl_3$. Removal of the $CHCl_3$ under diminished press. left a colourless viscid syrup (7 g.), which, after being heated at 100°/12 mm. for 1 hr., was methylated once by Purdie's reagents. The product extracted by Et_2O was a colourless cryst. mass (7 g.). An additional 3 g. of cryst. material were obtained from the aq. portion (A) after conc. and further extraction. Recrystn. from dry Et_2O or from Et_2O-light petroleum (b. p. 40—60°) gave *2 : 3 : 5 : 6 : 7-pentamethyl α-glucoheptono-γ-lactone* in long rods with pyramidal ends, m. p. 104°. $[\alpha]_D^{20°}$ — 13° in H_2O (initial value; *c*, 0·8); + 41° in $CHCl_3$ (*c*, 2·2); + 69° in Et_2O (*c*, 1·6); + 43° in C_6H_6 (*c*, 1·3); + 41° in acetone (*c*, 0·9) (Found : C, 51·7; H, 8·3; OMe, 55·3. $C_{12}H_{22}O_7$ requires C, 51·8; H, 8·0; OMe, 55·7%).

In aq. solution hydrolysis of the lactone proceeded slowly. $[\alpha]_D^{20°}$ — 13·2° (initial value; *c*, 0·8); —13·1° (1 day); — 13° (2 days); — 12·5° (6 days); — 11·9° (8 days); — 11·5° (13 days); — 10·7° (20 days); — 10·1° (23 days); — 9·6° (30 days : const. value). The rotation of the acid (calc. as lactone) was $[\alpha]_D^{20°}$ + 26·3° (initial value in H_2O; *c*, 1·14). This decreased slowly and reached the const. value $[\alpha]_D^{20°}$ — 9·5° after 17 days. The proportion of acid and lactone at equilibrium was 9% and 91% respectively.

Six successive treatments of α-glucoheptonolactone with Purdie's reagents (MeOH being added during the first five methylations) gave the above cryst. pentamethyl α-glucoheptonolactone, m. p. 104°, in inferior yield accompanied by oxidation products. Amongst the latter were methyl oxalate and methyl *i*-dimethoxysuccinate, m. p. 68°.

Oxidation of 2 : 3 : 5 : 6 : 7-Pentamethyl α-Glucoheptonolactone.—The lactone (1·8 g.) was oxidised at 90° for 6 hrs. by HNO_3 (10 c.c.; *d* 1·42). The acid was removed in the usual way and the product was esterified by boiling with 4% methyl-alc. HCl (100 c.c.). After neutralisation and removal of the solvent a syrup (1·3 g.) was obtained which rapidly crystallised. Recrystn. from Et_2O gave methyl *i*-dimethoxysuccinate (1·1 g.), m. p. 68° alone or when mixed with an authentic sample. The crystals gave quantitatively on treatment with methyl-alc. methylamine the characteristic *i*-dimethoxysuccinomethylamide, m. p. 210°. The mother-liquors from the crystn. of the methylamide were examined for the presence of trimethoxyglutaromethylamides, but none could be detected.

Methylation of γ-Mannonolactone.—The lactone (5 g.), m. p. 151°, dissolved in H_2O (20 c.c.), was methylated as described above by Me_2SO_4 (71 g.) and KOH (68 g. in 50 c.c. H_2O) in the presence of acetone (35 c.c.). The product (3·5 g.) was extracted by $CHCl_3$ and after being heated at 100°/12 mm. for 2 hrs. was methylated once by Ag_2O and MeI. It then crystallised and on recrystn. from dry Et_2O 2 : 3 : 5 : 6-tetramethyl γ-mannonolactone was obtained in

long needles with pointed ends, m. p. 108°, alone or when mixed with an authentic sample. $[\alpha]_D^{20°}$ + 62° in H_2O (initial value; *c*, 1·0).

Methylation of γ-Galactonolactone.—(i) γ-Galactonolactone monohydrate (5 g.), m. p. 68°, was methylated with Me_2SO_4 and KOH in the manner described for mannonolactone. The product (3 g.) was methylated once by Ag_2O and MeI and distilled, giving (a) 2·2 g., b. p. about 115°/0·09 mm., $n_D^{16°}$ 1·4478, and (b) 0·7 g., b. p. 125°/0·09 mm., $n_D^{16°}$ 1·4495. Fraction (b) was mainly 2 : 3 : 5 : 6-tetramethyl γ-galactonolactone. It had $[\alpha]_D^{20°}$ − 31° in H_2O (*c*, 1·1) ⟶ − 26° after 8 days (const. value) (Found : OMe, 51·8. Calc. for $C_{10}H_{18}O_6$: OMe, 53·0%. 0·131 G. required 5·7 c.c. of *N*/10-NaOH. Calc., 5·6 c.c.).

Fraction (a) was dissolved in H_2O and heated at 40° for 15 mins. with a slight excess of NaOH. After acidification the solution was extracted with $CHCl_3$. Removal of the $CHCl_3$ left a pale yellow, mobile syrup (2·2 g.), which crystallised rapidly when rubbed. Recrystn. from Et_2O–light petroleum (b. p. 40—60°) gave 2 : 3 : 4 : 6-tetramethyl galactonic acid (2·0 g.) as short rods, m. p. 85°, $[\alpha]_D^{21°}$ + 18° (initial value in H_2O; *c*, 1·03) ⟶ + 26° after 3 days (const. value) (Found : C, 47·5; H, 8·3; OMe, 50·1. Calc. for $C_{10}H_{20}O_7$: C, 47·6; H, 8·0; OMe, 49·2%).

(ii) γ-Galactonolactone monohydrate was heated at 100°/12 mm. until the H_2O of crystn. was removed. The lactone was then methylated four times by Ag_2O and MeI in the presence of MeOH. After esterification by heating with 4% methyl-alc. HCl the product was distilled, giving in equal amount two fractions : (a) b. p. about 100°/0·06 mm., $n_D^{13°}$ 1·4392, (b) b. p. about 130°/0·06 mm., $n_D^{13°}$ 1·4584. The first fraction gave oxamide on treatment with methyl-alc. NH_3 and was mainly methyl oxalate. The second fraction crystallised slowly at − 5°. Recrystn. from Et_2O–light petroleum (b. p. 40—60°) gave a *trimethyl galactonolactone* in clusters of thick rods, m. p. 99° (yield, 20% of wt. of lactone methylated). $[\alpha]_D^{17°}$ − 40° in H_2O (initial value; *c*, 1·55) ⟶ − 28° in 14 days (const. value). The rotation of the acid (calc. as lactone) in H_2O was $[\alpha]_D^{21°}$ + 6° ⟶ − 28° (const. value) (*c*, 0·92). In $CHCl_3$ the lactone had $[\alpha]_D^{20°}$ − 29° (*c*, 1·84) (Found : C, 49·3; H, 7·2; OMe, 42·3. 0·0569 G. required 2·60 c.c. *N*/10-NaOH. $C_9H_{16}O_6$ requires C, 49·1; H, 7·3; OMe, 42·3%; *N*/10-NaOH, 2·60 c.c.).

On methylation with MeI and Ag_2O the lactone gave quantitatively 2 : 3 : 5 : 6-tetramethyl galactonolactone, b. p. 115°/0·05 mm., $n_D^{17°}$ 1·4500, $[\alpha]_D^{18°}$ − 32° in H_2O ⟶ − 26° after 8 days. The latter substance was further characterised by its quantitative conversion into 2 : 3 : 5 : 6-tetramethyl galactonamide, m. p. 153°, $[\alpha]_D^{21°}$ + 6° in acetone (compare Humphreys, Pryde, and Waters, J., 1931, 1298).

The lactone (1·0 g.) was oxidised by heating at 65° for 6 hrs. with HNO_3 (6 c.c., *d* 1·2). The product was isolated as the methyl ester in the usual manner. The mobile syrup (0·8 g.) so obtained gave on distillation (a) 0·3 g., b. p. 105°/0·03 mm., $n_D^{20°}$ 1·4335 (Found : OMe, 57%), (b) 0·45 g., b. p. about 135°/0·03 mm., $n_D^{20°}$ 1·4550. The second fraction crystallised and consisted mainly of unchanged lactone, m. p. 99°. Fraction (a) had $[\alpha]_D^{20°}$ + 56° in MeOH (*c*, 1·0) and on treatment with methyl-alc. NH_3 gave in 70% yield *d*-dimethoxysuccinamide, m. p. and mixed m. p. with an authentic sample 280—285° (decomp.), $[\alpha]_D^{20°}$ + 95° in H_2O (*c*, 1·1). The presence of a methylated mucic acid could not be detected.

Methylation of γ-arabonolactone and γ-gluconolactone under the conditions

described for *d*-α-glucoheptono-γ-lactone gave almost entirely the completely methylated derivatives, methylation of the OH group at the fourth carbon atom being readily effected in these instances.

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[*Received, August 3rd,* 1932.]