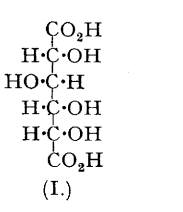
154. *Lactones of Glucosaccharic Acid. Part II.* 2 : 3 : 5- *and* 2 : 4 : 5-*Trimethyl Glucosaccharolactone.*

By F. Smith.

The saccharolactone obtained by Sohst and Tollens from glucose by oxidation with nitric acid is shown to be a mixture of glucosaccharo-3 : 6- (X) and -1 : 4-lactone (II). This follows from the methylation of the mixture which affords 2 : 4 : 5-*trimethyl glucosaccharo*-3 : 6-*lactone* 1-*methyl ester* (XI) and 2 : 3 : 5-*trimethyl glucosaccharo*-1 : 4-*lactone* 6-*methyl ester* (III). Both these substances have been identified, and the latter has been synthesised from glucose.

Oxidation of glucose or starch with nitric acid affords glucosaccharic acid (I), which can be readily isolated in the form of its acid potassium salt. This salt can be converted into a calcium salt, which upon treatment with oxalic acid yields (in solution) saccharic acid. Evaporation of the solvent from such a solution of saccharic

acid gives a syrup which slowly crystallises. Recrystallisation of this product from ether gives the so-called " saccharolactone " (Sohst and Tollens, *Annalen*, 1888, **245**, 1, 19). Potassium hydrogen saccharate can, however, be converted directly into " saccharolactone " by addition of sulphuric acid, followed by elimination of potassium sulphate. This " saccharolactone " was thought to be glucosaccharo-**3** : **6**-lactone (X) (Rehorst and Scholz, *Ber.*, 1936, **69**, 524), but the work herein described proves that it is a mixture of (X) and glucosaccharo-**1** : **4**-lactone (II). This conclusion has been reached as a result of the observation that among the products of the methylation of Sohst and Tollens's saccharolactone (m. p. 133°) with silver oxide and methyl iodide there have been found **2** : **3** : **5**-*trimethyl glucosaccharo*-**1** : **4**-*lactone* **6**-*methyl ester* (III) and **2** : **4** : **5**-*trimethyl glucosaccharo*-**3** : **6**-*lactone* **1**-*methyl ester* (XI).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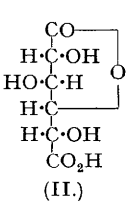
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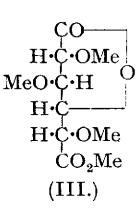
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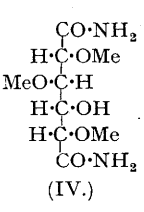
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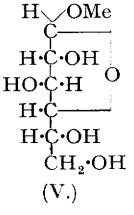
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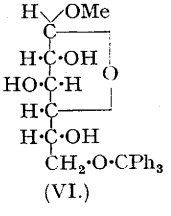
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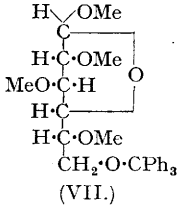
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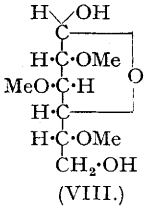
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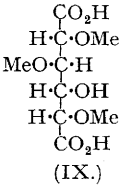
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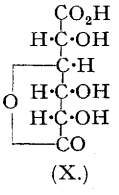
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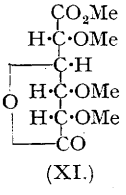
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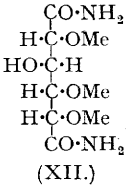
(XII.)

The crystalline ester (III) was identified by the following experimental facts. Analysis showed that it had the formula $C_{10}H_{16}O_7$ and contained four methoxyl groups. The presence of a carbomethoxy-group in (III) was proved by the fact that upon treatment with sodium hydroxide one methoxyl group was eliminated. Moreover, during this saponification 2 equivs. of alkali were consumed, and hence the existence of a lactone ring was indicated. The presence of an ester methoxyl group and a lactone ring in the ester (III) was confirmed by the observation that treatment of the latter with methyl-alcoholic ammonia effected removal of one methoxyl group and formation of the crystalline *diamide* (IV) of a trimethyl saccharic acid. This diamide showed a negative Weerman test for α-hydroxy-amides (*Rec. Trav. chim.*, 1917, **36**, 16). Hence both hydroxyl groups at C_2 and C_5 must be blocked by methyl residues. The location of two of the methyl groups at C_2 and C_5 was supported by the observation that vigorous treatment of (III) with nitric acid caused no breakdown of the chain of six carbon atoms. It was thus evident that the third methyl group must be in either position **3** or **4**, in which case (III) is either the **2** : **3** : **5**- or the **2** : **4** : **5**-trimethyl derivative of saccharic acid. The former view was proved to be correct by the synthesis of **2** : **3** : **5**-trimethyl glucosaccharo-**1** : **4**-lactone **6**-methyl ester as follows: Treatment of glucose with 1% methyl-alcoholic hydrogen chloride gave methylglucofuranoside (V), and when this was allowed to react with trityl chloride, **6**-*trityl methylglucofuranoside* (VI) was produced. Methylation of (VI) first with methyl sulphate and sodium hydroxide and then with silver oxide and methyl iodide yielded **6**-*trityl* **2** : **3** : **5**-*trimethyl methylglucofuranoside* (VII). The trityl group in this substance was easily removed by means of ethereal hydrogen chloride, giving **2** : **3** : **5**-*trimethyl methylglucofuranoside*, from which **2** : **3** : **5**-*trimethyl glucose* (VIII) was readily obtained by hydrolysis with dilute sulphuric acid. Oxidation of either (VIII) or its methylglucoside with nitric acid transformed both the reducing group at C_1 and the primary alcoholic group at C_6 into carboxyl groups, and there resulted **2** : **3** : **5**-trimethyl saccharic acid (IX). Esterification of the latter followed by distillation gave rise to crystalline **2** : **3** : **5**-trimethyl glucosaccharo-**1** : **4**-lactone **6**-methyl ester. This and its diamide proved to be identical respectively with the ester (III) and the diamide (IV) derived from the so-called saccharolactone.

The structure (XI) assigned to the second trimethyl glucosaccharolactone methyl ester is based upon the fact that the crystalline *diamide* (XII) obtained from (XI) by means of methyl-alcoholic ammonia gave a negative Weerman test, thus proving that both the hydroxyl groups at C_2 and C_5 are substituted with methyl residues. The ester lactone (XI) must therefore be either a **2** : **3** : **5**- or a **2** : **4** : **5**-trimethyl derivative. The diamide now under discussion, however, was different from the foregoing diamide (IV), and hence this second trimethyl glucosaccharolactone methyl ester must be the **2** : **4** : **5**-trimethyl derivative (XI).

The identification of the two trimethylglucosaccharolactone methyl esters (III) and (XI) demonstrates that Sohst and Tollens's saccharolactone is a mixture of the **3** : **6**- (X) and the **1** : **4**-lactone (II).

In addition to the formation of the two trimethyl saccharolactone methyl esters (III) and (XI), the methylation of the so-called saccharolactone also afforded **2** : **5**-dimethyl Δ^4-glucosaccharo-**3** : **6**-lactone **1**-methyl ester (Smith, J., this vol., p. 513), methyl oxalate, and methyl dimethoxyerythrosuccinate. The formation of the last two susbstances probably results by oxidative cleavage of the six-carbon chain between C_2 and C_3 by the agency of the silver oxide, but which substance undergoes this breakdown is not clear.

Experimental.

Fractional Distillation of Syrup obtained by Methylation of Saccharolactone with Silver Oxide and Methyl Iodide.—Saccharolactone (m. p. 133°) was subjected to methylation with silver oxide and methyl iodide in the presence of acetone according to the conditions previously given (Smith, this vol., p. 514). After each methylation the excess of solvent was distilled off by heating the reaction mixture on the water-bath. Towards the end of the operation a crystalline sublimate was detected in the condenser. This was removed mechanically, and shown to be methyl oxalate by m. p. and mixed m. p. 53°, and by the fact that a solution of it gave a white precipitate (insoluble in acetic acid) when treated with calcium chloride solution. The crystalline 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester was separated and had m. p. and mixed m. p. 89°. Removal of solvent from the mother-liquors accumulated from several preparations gave a pale yellow liquid which was subjected to fractional distillation from a Widmer flask: the following fractions were obtained.

Fraction.	OMe, %.	Ester OMe,* %.	Wt., g.	B. p./0·02 mm. (bath temp.).	$n_D^{17°}$.	$[\alpha]_D$ in H_2O.	Equiv.†
I	58·5	30·3	1·1	115—125°	1·4340—1·4390	+21°	105
II	54·6	23·4	1·8	135—140	1·4610—1·4630	+10	115
III	53·0	19·6	3·73	135—140	1·4630	+ 6	120
IV	50·0	17·3	3·33	140—150	1·4630—1·4640	+25	114
V	45·9	14·8	1·7	150—165	1·4660—1·4675	+47	119
VI	45·6	18·4	1·2	>165	1·4720	+45	108

* The ester methoxyl content was determined by heating 10—20 mg. of the fraction with 0·3N-barium hydroxide (3 c.c.) for 1 hour at 60°. Excess barium hydroxide was neutralised by passing carbon dioxide over the surface of the liquid, which was shaken. The excess of solvent was removed by heating the mixture in a current of dry air, and any final traces were eliminated by heating in a vacuum for 30 minutes at 70—80°. These operations were performed in a semimicro-Zeisel apparatus and a methoxyl determination was carried out upon the residue consisting of the barium salt of the organic acid and barium carbonate. The ester methoxyl value was obtained by subtracting the methoxyl value obtained by this operation from that of the original fraction.

† The equivalent weight was determined by heating 10—20 mg. of the fraction with 0·02N-sodium hydroxide (10 c.c.) for 1½ hours at 55°, care being taken to prevent ingress of carbon dioxide from the air. The solution was then cooled, and the amount of sodium hydroxide required for hydrolysis determined by titration of the excess with 0·02N-sulphuric acid. A blank experiment was carried out simultaneously.

Identification of Methyl Dimethoxyerythrosuccinate (*Methyl Dimethyl* meso*Tartrate*).—Fraction (I) crystallised spontaneously, and the crystals were separated by tiling a portion; they then had m. p. 63—67°. The main bulk of the fraction was triturated with light petroleum–ether, and the crystals were washed by decantation with the same mixed solvent. Two crystallisations from ether gave methyl dimethoxyerythrosuccinate, m.p. 68°; this ester was optically inactive in methyl alcohol (*c*, 1·5) (Found: OMe, 60·1. Calc. for $C_8H_{14}O_6$: OMe, 60·1%). Treatment of the methyl ester with methyl-alcoholic ammonia for 2 days at −5° gave crystals of dimethyl *meso*tartramide, which were separated by decantation, washed with methyl alcohol, and crystallised from water; m. p. and mixed m. p. 257° (Found: OMe, 35·7. Calc. for $C_6H_{12}O_4N_2$: OMe, 35·2%).

Identification of 2 : 3 : 5-*Trimethyl Glucosaccharo*-1 : 4-*lactone* 6-*Methyl Ester* (III).—Fraction (III) crystallised after several days. Trituration of the crystals with ether–light petroleum, followed by recrystallisation from ether, gave the ester (III) (0·4 g.), m. p. and mixed m. p. with a synthetic specimen, 78°; $[\alpha]_D^{18°}$ −10° in water (*c*, 0·7) (Found: C, 48·3; H, 6·5; OMe, 50·1; equiv., by heating with 0·02N-sodium hydroxide, 123. $C_{10}H_{16}O_7$ requires C, 48·4; H, 6·45; OMe, 50·0%; equiv. 124). After hydrolysis with barium hydroxide, the "residual OMe" (see above) was 37·0%, corresponding to ester OMe, 13% (Calc. for loss of 1OMe: residual OMe, 37·5%).

Direct treatment of fraction (III) with methyl-alcoholic ammonia gave a crystalline amide. This was triturated with ethyl alcohol–ether, collected, and recrystallised twice from ethyl alcohol and once from ethyl alcohol–ether. The *amide* (IV) of 2 : 3 : 5-trimethylsaccharic acid had m. p. 213° (decomp.); $[\alpha]_D^{17°}$ +18° in water (*c*, 2·0) (Found: C, 43·4; H, 7·4; N, 11·3; OMe, 37·4. $C_9H_{18}O_6N_2$ requires C, 43·2; H, 7·2; N, 11·2; OMe, 37·2%). The same amide was obtained from the pure crystalline 2 : 3 : 5-trimethyl saccharolactone methyl ester. A Weerman test for α-hydroxy-amides carried out upon the diamide (20 mg.) was negative (for conditions, see Smith, J., 1939, 753).

Identification of 2 : 4 : 5-*Trimethyl Glucosaccharo*-3 : 6-*lactone* 1-*Methyl Ester* (XI).—The syrup fraction (II) was allowed to react with methyl-alcoholic ammonia for 2 days at −5°. Removal of the solvent under reduced pressure gave a crystalline residue which was purified by several crystallisations from ethyl alcohol. The *amide* (XII) of 2 : 4 : 5-trimethyl saccharic acid had m. p. 194°; $[\alpha]_D^{18°}$ +21° in water (*c*, 1·0) (Found: C, 43·2; H, 7·5; N, 11·1; OMe, 38·1. $C_9H_{18}O_6N_2$ requires C, 43·2; H, 7·2; N, 11·2; OMe, 37·2%).

This amide gave a depression of the m. p. when mixed with the amide (m. p. 193°) of 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone prepared from 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester with methyl-alcoholic ammonia. The amide (XII) gave a negative Weerman test for α-hydroxy-amides (tested on 20 mg.). Fraction (IV) failed to give a crystalline amide, but fraction (V) afforded in small yield an unidentified crystalline amide, m. p. 203° (after recrystallisation from ethyl alcohol–ether). Fraction (VI) when treated with methyl-alcoholic ammonia yielded the monoamide of 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone, m. p. and mixed m. p. 193° (after recrystallisation from ethyl alcohol).

Synthesis of 2 : 3 : 5-*Trimethyl Saccharo*-1 : 4-*lactone* 6-*Methyl Ester*.—A solution of methylglucofuranoside (18·7 g.) [prepared by the interaction of glucose with 1% methyl-alcoholic hydrogen chloride (Fischer, *Ber.*, 1914, **47**, 1982)] in pyridine (30 c.c.) which had been dried by three distillations over phosphoric oxide, was cooled in ice, and treated with trityl chloride (29 g.). The mixture was kept at room temperature for 3 days in a desiccator and shaken from time to time, and then warmed to 40° and poured with stirring into water. The syrupy product was triturated with water to remove as much pyridine as possible, and then dissolved in chloroform (200 c.c.). The chloroform solution was washed several times with dilute sulphuric acid to remove pyridine, with sodium hydrogen carbonate solution (twice), and water (once). After being dried (anhydrous magnesium sulphate), the solution was filtered and evaporated under reduced pressure to dryness. The 6-*trityl methylglucofuranoside* (VI) was a hard glass (Found: OMe, 6·3. $C_{26}H_{28}O_6$ requires OMe, 7·1%).

This compound (VI) was dissolved in acetone (150—200 c.c.) and treated slowly (2½—3 hours) with methyl sulphate (50 c.c.) and sodium hydroxide solution (200 c.c., 30%) at 35°, the mixture being stirred vigorously during the addition; the methylation was completed by heating to 60° to expel the acetone. The partly methylated product readily separated on the surface of the hot liquid; it was separated by decantation, washed once with hot water, and remethylated. After three methylations in this manner the methylated trityl compound was purified by dissolving it in chloroform (150 c.c.) and washing the solution with water. The chloroform solution was dried over anhydrous magnesium sulphate,

filtered, and evaporated to dryness under diminished pressure. The glassy product thus obtained was subjected to six methylations with silver oxide (20 g.) and methyl iodide (30 c.c.) at 45° for 8 hours. After each methylation the excess of the methyl iodide was distilled off, and the methylated trityl compound was isolated by means of acetone. The *6-trityl 2 : 3 : 5-trimethyl methylglucofuranoside* (VII) thus obtained was a pale yellow glassy solid (Found: OMe, 24·8. $C_{29}H_{34}O_6$ requires OMe, 25·95%).

2 : 3 : 5-Trimethyl methylglucofuranoside. A solution of the 6-trityl 2 : 3 : 5-trimethyl methylglucofuranoside in ether (250 c.c.) was cooled in ice and saturated with hydrogen chloride. After standing for 30 minutes at 0°, the solution was removed from the ice-bath, kept at room temperature for 4 hours, and then extracted five times with water (50 c.c.). The combined aqueous extracts were neutralised with lead carbonate, filtered, and evaporated to dryness under diminished pressure. Extraction of the residue with acetone gave *2 : 3 : 5-trimethyl methylglucofuranoside* as a colourless mobile liquid. This evidently contained some 2 : 3 : 5-trimethyl glucose because it reduced boiling Fehling's solution slightly. Hence, the liquid was dissolved in dry methyl alcohol (210 c.c.) containing hydrogen chloride (2 g.). After 18 hours, when the rotation of the solution had been constant for several hours, the solution was neutralised with silver carbonate, filtered, and evaporated to dryness. Extraction of the residue with ether gave 2 : 3 : 5-trimethyl methylglucofuranoside (9 g.), b. p. (bath temp.) 120°/0·01 mm., $n_D^{22°}$ 1·4540; $[\alpha]_D^{19°}$ −11° in water (*c*, 1·8) (Found: OMe, 52·0. $C_{10}H_{20}O_6$ requires OMe, 52·6%).

2 : 3 : 5-Trimethyl glucose. When a solution of 2 : 3 : 5-trimethyl methylglucofuranoside (1·9 g.) in 0·5N-sulphuric acid was heated on the boiling water-bath for 5 hours, the specific rotation changed from $[\alpha]_D$ −12° to + 14·5° (constant value). The solution was neutralised with barium carbonate, filtered, and evaporated to dryness under diminished pressure. The syrupy residue was purified by extraction with ether and then distilled, giving *2 : 3 : 5-trimethyl glucose* (VIII) as a colourless liquid (1·4 g.), b. p. (bath temp.) 140°/0·02 mm.; $n_D^{16°}$ 1·4690; $[\alpha]_D^{15°}$ +17° in water (*c*, 1·8) (Found: OMe, 41·0. $C_9H_{18}O_6$ requires OMe, 41·9%).

2 : 3 : 5-Trimethyl γ-gluconolactone. A solution of 2 : 3 : 5-trimethyl glucose (1·1 g.) in water (10 c.c.) was treated with bromine (0·7 c.c.) in the presence of lead carbonate (2 g.). After 2 days the excess of the bromine was removed from the solution by aeration. The solution was filtered, and hydrogen sulphide admitted until all the lead had been precipitated as sulphide, and thereafter treated with charcoal, filtered, and concentrated under diminished pressure to half volume. This solution, containing some hydrobromic acid produced by the action of hydrogen sulphide upon dissolved lead bromide, was then neutralised with silver oxide, and filtered before and after treatment with hydrogen sulphide. Evaporation of the solvent yielded a syrup which was extracted with ether. Two disillations of the product gave *2 : 3 : 5-trimethyl γ-gluconolactone* as a colourless, fairly mobile liquid (0·7 g.), b. p. (bath temp.) 140°/0·05 mm.; $n_D^{17°}$ 1·4650; $[\alpha]_D^{18°}$ +62° initial value in water (*c*, 1·7); +59° (after 9 days); +54° (after 47 days) (mutarotation still incomplete) (Found: OMe, 43·0. $C_9H_{16}O_6$ requires OMe, 42·3%).

When this gluconolactone (0·1 g.) was heated with phenylhydrazine (0·06 g.) for 1 hour on the boiling water-bath, a crystalline phenylhydrazide was obtained in good yield. Trituration with ether to remove excess of phenylhydrazine, followed by recrystallisation from ethyl alcohol, gave the *phenylhydrazide* of 2 : 3 : 5-trimethyl gluconic acid, m. p. 156°; $[\alpha]_D^{16°}$ +32° in methyl alcohol (*c*, 0·4) (Found: C, 54·9; H, 7·35; N, 8·7; OMe, 28·1. $C_{15}H_{24}O_6N_2$ requires C, 54·9; H, 7·3; N, 8·5; OMe, 28·4%).

2 : 3 : 5-Trimethyl glucosaccharo-1 : 4-lactone 6-methyl ester. A solution of 2 : 3 : 5-trimethyl glucose (0·5 g.) was oxidised with nitric acid (3 c.c., *d* 1·42) by heating on the water-bath for ½ hour at 50° and for 2 hours at 95° (boiling water-bath). The mixture was diluted with water, and freed from nitric acid by distillation under reduced pressure. In the initial stages water was added from time to time to facilitate this operation and in the final stages methyl alcohol was added to eliminate any remaining nitric acid and water. The dry, acid residue was esterified by boiling for 8 hours with 1% methyl-alcoholic hydrogen chloride. Neutralisation of the mineral acid with silver carbonate, followed by removal of solvent under reduced pressure, yielded a syrupy product. This was purified by extraction with ether, followed by distillation, giving the methyl ester lactone as a colourless liquid (0·3 g.), b. p. (bath temp.) 135—140°/0·01 mm. The distillate crystallised spontaneously, and after recrystallisation from ethyl alcohol–ether–light petroleum, the 2 : 3 : 5-trimethyl glucosaccharo-1 : 4-lactone methyl ester (III) had m. p. 78°, alone or in admixture with a specimen prepared from glucosaccharo-1 : 4-lactone. This synthetic trimethyl ester lactone had $[\alpha]_D^{20°}$ −9·5° initial value in water (*c*, 0·9); −8° (after 3 days); + 6° (102 days) (Found: C, 48·6; H, 6·5; OMe, 49·5%). This compound may also be prepared by direct oxidation of 2 : 3 : 5-trimethyl methylglucofuranoside with nitric acid. There was no evidence of the presence of the characteristic 2 : 3 : 4-trimethyl glucosaccharolactone methyl ester in the material obtained by oxidation of the trimethyl glucose followed by esterification, showing that, throughout the series of experiments commencing with methyl-glucofuranoside, no ambiguity had arisen as a result of the latter being contaminated with methylglucopyranoside. Treatment of the synthetic 2 : 3 : 5-trimethyl glucosaccharo-1 : 4-lactone methyl ester (20 mg.) with methyl-alcoholic ammonia at room temperature for 2 days, followed by removal of the excess of the solvent gave the diamide of 2 : 3 : 5-trimethyl saccharic acid; $[\alpha]_D^{18°}$ +18° in water (*c*, 1·5); m. p. 213° (decomp.), undepressed on admixture with that prepared from saccharolactone (above).

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