144. *The Synthesis of Some Galactaric (Mucic) Acid Derivatives.*

By K. Butler, D. R. Lawrance, and M. Stacey.

The synthesis of some acetal, ketal, and acyl derivatives of galactaric acid is described.

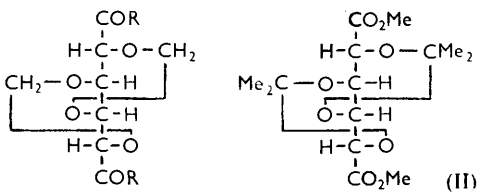
In the course of a survey of polyamide intermediates derived from carbohydrates, several novel derivatives of galactaric acid have been prepared. The acid was of interest because it is potentially available from natural sources such as lactose and fruit pectin and its hydroxyl groups are symmetrically disposed. Earlier work by Haworth, Heath, and Wiggins [1] on other hexaric acids established that inactivation of the hydroxyl groups during polymerisation was essential if linear polymers were to be made. Acylation, ketal, and acetal formation afford possible methods of protection and these have been studied in our experiments.

A dimethylene derivative of mucic acid has been described by Lobry de Bruyn and van Ekenstein.[2] Its melting point, the only characteristic reported, does not agree with our value and this derivative may have a different arrangement of acetal rings. In this respect it should be noted that the orientation of the methylene and *iso*propylidene groups assigned to the compounds described here has not been established. However, if the rules

[1] Haworth, Heath, and Wiggins, *J.*, 1944, 155.
[2] Lobry de Bruyn and van Ekenstein, *Rec. Trav. chim.*, 1902, **21**, 316.

postulated by Barker, Bourne, and Whiffen [3] for acetal rings in polyhydric alcohols are applicable to acetal and ketal derivatives of hexaric acids, the groups should bridge positions 2 : 4 and 3 : 5. It is known that reduction of our dimethyl di-*O*-methylenegalactarate gives a di-*O*-methylenedulcitol identical with one derived from 1 : 6-di-*O*-benzoyldulcitol.[4] We have therefore provisionally assigned the 2 : 4-3 : 5-structure to dimethyl di-*O*-methylenegalactarate on the assumption that the alcohol itself is not an exception to the rules and that the acetal rings do not assume a different configuration during the reduction.

(I): R = OMe.
(Ia): R = OH.
(Ib): R = Cl.
(Ic): R = OPh.
(Id): R = OEt.
(Ie): R = O·CH_2·CH:CH_2.
(If): R = NH_2.



(II)

Attempts to remove the cyclic acetal groups in dimethyl 2 : 4-3 : 5-di-*O*-methylenegalactarate by acid hydrolysis showed them to be extremely stable and to require boiling 12N-sulphuric acid for complete hydrolysis. The ketal groups in dimethyl di-*O*-*iso*propylidenegalactarate, however, proved to be more labile and were completely removed in either dilute mineral acid or 80% acetic acid.

Polymerisation of some of these galactaric acid derivatives with straight-chain diamines has given fibre-forming polyamides.[5]

Experimental

Dimethyl Galactarate.—A suspension of galactaric acid (210 g.) in B.S.S.-grade methanol (1 l.) containing concentrated sulphuric acid (15 ml.) was heated under reflux for 3—4 days. The mixture was left overnight at 0° and the crystalline product (218 g., 96%), m. p. 186—188° (decomp.), was filtered off, washed with water, and dried. The crude ester was usually contaminated with a small quantity of galactaric acid but was sufficiently pure for the preparation of dimethyl 2 : 4-3 : 5-di-*O*-methylenegalactarate. Pure dimethyl galactarate, m. p. 196—198° (decomp.) [lit.,[6] 205° (decomp.)], could be obtained by recrystallisation of the above product from boiling methanol (Found: C, 40·4; H, 5·9. Calc. for $C_8H_{14}O_8$: C, 40·3; H, 5·9%).

Dimethyl 2 : 4-3 : 5-*Di*-O-*methylenegalactarate* (I).—The method used for the preparation of dimethyl di-*O*-methylene-D-glucosaccharate [7] was applied with modifications. A stirred mixture of dimethyl galactarate (205 g.), paraformaldehyde (103 g.), and concentrated sulphuric acid (80 ml.) was heated at 75—80° for 20—30 min. The melt was allowed to cool, methanol (900 ml.) added, and the mixture heated under reflux for 6 hr. After hot filtration to remove unchanged paraformaldehyde the filtrate was cooled and dimethyl 2 : 4-3 : 5-di-*O*-methylenegalactarate, together with some dimethyl galactarate, was precipitated. The product was filtered off and dried. The methylene derivative was purified by extraction with dry chloroform at room temperature, the insoluble dimethyl galactarate being removed by filtration. After removal of solvent under reduced pressure the residue was crystallised from methanol, to give *dimethyl* 2 : 4-3 : 5-*di*-O-*methylenegalactarate* (113 g., 50%), m. p. 106—107° (Found: C, 45·8; H, 5·3. $C_{10}H_{14}O_8$ requires C, 45·8; H, 5·3%). Note: The insoluble dimethyl galactarate could be recycled to give an overall yield of 64% of the methylene derivative.

2 : 4-3 : 5-*Di*-O-*methylenegalactaric Acid* (Ia).—Aqueous barium hydroxide was used to hydrolyse the ester groups as in the preparation of di-*O*-methylene-D-glucosaccharic acid.[7] Barium hydroxide octahydrate (124 g.) was added to a hot aqueous solution (1750 ml.) of

[3] Barker, Bourne, and Whiffen, *J.*, 1952, 3865.
[4] Butler and Cummings, *J.*, 1956, 636.
[5] B.P. 750,822.
[6] Holleman, *Rec. Trav. chim.*, 1898, **17**, 326.
[7] Haworth, Jones, Stacey, and Wiggins, *J.*, 1944, 61.

dimethyl 2 : 4-3 : 5-di-*O*-methylenegalactarate (60·5 g.), and the mixture maintained at 80° for 90 min. The barium salt of the acid was decomposed with aqueous sulphuric acid (27·9 ml.; 1 : 1 v/v), the mixture was boiled for 15 min., then filtered hot, and the aqueous filtrate taken down to dryness under reduced pressure. The residue recrystallised from boiling water, giving 2 : 4-3 : 5-*di*-O-*methylenegalactaric acid* as a highly crystalline monohydrate (52·4 g., 96%), m. p. (anhydrous) 180—182° (decomp.) (Found: C, 40·8; H, 4·4. $C_8H_{10}O_8$ requires C, 40·9; H, 4·3%).

2 : 4-3 : 5-*Di*-O-*methylenegalactaroyl Chloride* (Ib).—Anhydrous, finely powdered 2 : 4-3 : 5-di-*O*-methylenegalactaric acid (40 g.) was suspended in thionyl chloride (220 ml.; freshly distilled from linseed oil). The mixture was heated under gentle reflux for 6 hr. and excess of thionyl chloride removed under reduced pressure, leaving a thick syrup which crystallised. The crude *acid chloride* was dissolved in benzene and reprecipitated by the addition of an equal volume of light petroleum (b. p. 60—80°) as fine crystals (42 g., 83%), m. p. 70—72° (Found: C, 35·4; H, 3·4. $C_8H_8O_6Cl_2$ requires C, 35·4; H, 3·0%).

Diphenyl 2 : 4-3 : 5-*Di*-O-*methylenegalactarate* (Ic).—A solution of 2 : 4-3 : 5-di-*O*-methylenegalactaroyl chloride (60 g.) and phenol (120 g.) in freshly distilled, dry pyridine (300 ml.) was heated under reflux for 2 hr. The solution was cooled and kept at 0° for 12 hr., then poured into iced water (2—3 l.), the *diphenyl ester* being precipitated. The crude ester was thoroughly washed with ether and dried (40·5 g.). Decolorising with charcoal and two recrystallisations from benzene–light petroleum (b. p. 60—80°) afforded fine needles (36·5 g., 43%), m. p. 143—145° (Found: C, 62·1; H, 4·6. $C_{20}H_{18}O_8$ requires C, 62·2; H, 4·7%).

Diethyl Galactarate.—This compound, m. p. 168—169°, was prepared from galactaric acid as described by Tipson and Clapp,[8] in 77% yield.

Diethyl 2 : 4-3 : 5-*Di*-O-*methylenegalactarate* (Id).—A stirred mixture of diethyl galactarate (21·5 g.), paraformaldehyde (10 g.), and concentrated sulphuric acid (7 ml.) was heated on a water-bath at 75° for 20 min. The solution was allowed to cool, absolute ethanol (75 ml.) added, and the mixture heated under reflux for 4 hr. The solution was concentrated to half volume and filtered hot. A crystalline product (11·1 g.) was deposited on cooling. The alcoholic mother-liquor was concentrated to about 25 ml., an equal volume of ether added, and the mixture kept at 0° for 12 hr.: a further crop (1·2 g.) was deposited. The combined crops were purified by extraction with dry chloroform (50 ml.) at room temperature and the insoluble diethyl galactarate (1·4 g.) was filtered off. The chloroform solution was taken down to dryness and the residue after recrystallisation from absolute ethanol afforded *diethyl* 2 : 4-3 : 5-*di*-O-*methylenegalactarate* (6·1 g., 24%), m. p. 68—69° (Found: C, 50·1; H, 6·2. $C_{12}H_{18}O_8$ requires C, 49·8; H, 6·2%).

Diallyl 2 : 4-3 : 5-*Di*-O-*methylenegalactarate* (Ie).—Finely powdered 2 : 4-3 : 5-di-*O*-methylenegalactaric acid (5 g.) was suspended in 1% allyl-alcoholic hydrogen chloride (30 ml.) and boiled gently under reflux for 10 hr., the acid slowly dissolving. The solution was neutralised with lead carbonate (*ca.* 10 g.) and filtered. The filtrate was evaporated to dryness, leaving a syrup which rapidly crystallised. Recrystallisation from methanol afforded fine needles of the *diallyl ester* (4·4 g., 66%), m. p. 63·5° (Found: C, 53·5; H, 5·8. $C_{14}H_{18}O_8$ requires C, 53·5; H, 5·8%).

Dimethyl 2 : 4-3 : 5-*Di*-O-iso*propylidenegalactarate* (II).—Dry, finely powdered dimethyl galactarate (30 g.) was suspended in dry acetone (2 l.) containing hydrogen chloride (20 g.). The mixture was heated under gentle reflux until dissolution was complete (*ca.* 2 hr.). The solution was cooled, made alkaline (pH 8—9) with 3% sodium carbonate solution (*ca.* 600 ml.), and extracted with chloroform (3 × 500 ml.). The combined extracts were dried ($MgSO_4$) and the solvent was removed. The residual syrup crystallised at 0°. The iso*propylidene derivative* (11·3 g., 31%), m. p. 97—98°, recrystallised from methanol (Found: C, 52·9; H, 6·8. $C_{14}H_{22}O_8$ requires C, 52·8; H, 6·9%).

2 : 4-3 : 5-*Di*-O-*methylenegalactaramide* (If).—A stirred, ice-cold suspension of finely powdered dimethyl 2 : 4-3 : 5-di-*O*-methylenegalactarate (50 g.) in dry methanol (1 l.) was saturated with ammonia and set aside at 0° for 12 hr. The crystalline product was filtered off and washed with methanol. Recrystallisation from water gave 2 : 4-3 : 5-*di*-O-*methylenegalactaramide* (43 g., 97%), m. p. 215° (decomp.) (Found: C, 41·3; H, 5·4; N, 12·2. $C_8H_{12}O_6N_2$ requires C, 41·3; H, 5·2; N, 12·1%).

Hydrolysis of the Acetal Groups in Dimethyl 2 : 4-3 : 5-*Di*-O-*methylenegalactarate*.—Three

[8] Tipson and Clapp, *J. Org. Chem.*, 1953, **18**, 952.

samples of ester (0·5 g.) were dissolved in three aliquot parts (100 ml.) of 3N-, 6N-, and 12N-sulphuric acid. The solutions were heated under steam-distillation conditions (so that the concentration of the acid remained constant during the hydrolysis) for 45 min. The liberated formaldehyde was collected in a water-trap and estimated by the sodium sulphite method.[9] The results are summarised in the Table.

Strength of acid used	3N	6N	12N
Formaldehyde evolved (%)	1·3	10·2	22·9
Theor. available formaldehyde		22·96%	

Attempted hydrolysis by glacial acetic acid, 80% acetic acid, or 5% phosphoric acid was unsuccessful.

Hydrolysis of the Ketal Groups in Dimethyl 2 : 4-3 : 5-*Di*-O-iso*propylidenegalactarate*.—The ester (0·5 g.) in N-sulphuric acid (12·5 ml.) was heated under reflux for 1 hr. The solution was kept at 0° overnight and the precipitated galactaric acid filtered off and dried [0·28 g., 85%; m. p. 209—211° (decomp.); lit.,[10] 206° (decomp.)] (Found: C, 34·3; H, 5·1. Calc. for $C_6H_{10}O_8$: C, 34·2; H, 4·8%). A similar result was obtained on using 80% acetic acid as hydrolytic reagent.

Dimethyl 2 : 3 : 4 : 5-*Tetra*-O-*benzoylgalactarate*.*—Finely powdered dimethyl galactarate (1·0 g.), suspended in dry pyridine (10 ml.), was left with freshly distilled benzoyl chloride (2 ml.) at room temperature for 60 hr. The solid product was filtered off, washed with water, and dried. Crystallisation from methanol gave *dimethyl* 2 : 3 : 4 : 5-*tetra*-O-*benzoylgalactarate* (1·3 g., 49·1%), m. p. 167—169° (Found: C, 65·8; H, 4·8. $C_{36}H_{30}O_{12}$ requires C, 66·1; H, 4·6%).

2 : 3 : 4 : 5-*Tetra*-O-*acetylgalactaroyl Chloride*.—This compound, m. p. 181°, was prepared as described by Müller,[12] in 73% yield.

Diphenyl 2 : 3 : 4 : 5-*Tetra*-O-*acetylgalactarate*.—A mixture of 2 : 3 : 4 : 5-tetra-*O*-acetylgalactaroyl chloride (10·4 g.) in dry benzene (100 ml.) and phenol (4·9 g.) was heated under reflux for 48 hr. The solution was cooled and the precipitated ester filtered off. Recrystallisation from benzene afforded fine needles of the *diphenyl ester* (8·7 g., 73%), m. p. 168° (Found: C, 58·7; H, 5·0. $C_{26}H_{26}O_{12}$ requires C, 58·8; H, 4·9%).

The authors thank Mr. N. J. Miles for assistance with the experimental work, and British Nylon Spinners, Limited, for permission to publish these results.

Research Department, British Nylon Spinners, Limited,
Pontypool, Monmouthshire.
The Chemistry Department, The University,
Edgbaston, Birmingham, 15.

[*Received, June 14th*, 1957.]

* Since this paper was written this compound has been reported by Baelor and Gorin.[11]

[9] Lemme, *Chem.-Ztg.*, 1903, **27**, 896.
[10] Tollens and Kent, *Annalen*, 1885, **227**, 221.
[11] Baelor and Gorin, *J. Org. Chem.*, 1957, **22**, 65.
[12] Müller, *Ber.*, 1914, **47**, 2654.