THE PREPARATION OF 5-KETOMANNONIC ACID*

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The preparation of 5-keto-D-mannonic acid (D-lyxo-5-hexulosonic acid) by oxidation of L-gulose or L-gulonolactone with bromine has been described by Hart and Everett.[1] This method offers a simple means of synthesis, but requires a long reaction time, gives a poor yield with a number of by-products, and involves a tedious separation of lead and silver salts.

Siddiqui and Purves[2] have discussed the Lobry de Bruyn–van Ekenstein rearrangement of D-glucuronic acid with sodium hydroxide. These authors obtained mannuronic acid together with an unidentified keto acid which they believed to be 5-ketomannonic acid.

The formation of 5-keto-L-galactonic acid from galacturonic acid using calcium hydroxide solution was described by Ehrlich and Guttmann.[3] These authors also applied this reaction to glucuronic acid in an attempt to prepare 5-ketogluconic acid, but they obtained a mixture from which they were unable to isolate any 5-ketogluconic acid. Presumably this reaction is also a type of Lobry de Bruyn–van Ekenstein rearrangement and when applied to glucuronic acid should yield 5-ketomannonic and not 5-ketogluconic acid.

In the present investigation D-glucuronolactone acid was treated with saturated calcium hydroxide solution at room temperature under a variety of conditions and the products studied by ion-exchange and paper chromatography. Under these conditions a precipitate of calcium salt separated from the reaction solution. After filtration and removal of cations with Dowex 50, this salt yielded 5-ketomannonic acid, identified by comparison with an authentic sample prepared from L-gulonolactone by the method of Hart and Everett[1] (Table 1). The yield of 5-ketomannonic acid depended on the reaction conditions, an excess of calcium hydroxide favouring the formation of mannuronic acid and other by-products. The best yield (60–70%) was obtained when glucuronolactone was treated with calcium hydroxide solution at pH 9 to split the lactone, after which the pH was raised to 11 and held at this figure for 2 days by periodic additions of calcium hydroxide. Room temperature was used throughout. Under these conditions only a trace of mannuronic acid was formed and about

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[1] Hart, J. P., and Everett, H. R., *J. Am. chem. Soc.*, 1939, **61**, 1822.

[2] Siddiqui, I. R., and Purves, C. B., *Can. J. Chem.*, 1963, **41**, 382.

[3] Ehrlich, F., and Guttmann, R., *Ber. dt. chem. Ges.*, 1934, **67**, 573.

half of the 5-ketomannonic acid precipitated as the calcium salt in almost pure form. The rest of the ketomannonic acid remained in solution together with unchanged glucuronic acid and a trace of mannuronic acid, from both of which it could be separated by anion-exchange chromatography in acetic acid. Alternatively, the whole reaction mixture including precipitate can be treated with cation-exchange resin and the resulting mixture of acids separated by anion-exchange chromatography. Either way, the method provides a simple and convenient preparation of 5-ketomannonic acid.

TABLE 1

CHROMATOGRAPHIC DATA

For D_v value see ref.[4]. R_{GL} is migration on paper chromatograms relative to that of glucuronolactone (1·00) in ethyl acetate–pyridine–water–acetic acid (5 : 5 : 1 : 3)[5]

Compound	D_v 0·08M NaOAc	D_v 1·0M HOAc	R_{GL}
5-Ketomannonic acid from glucuronic acid	14·0	15·1	0·60
Glucuronic acid	12·2	22·0	1·00, 0·48
Mannuronic acid	13·5	18·3	0·95, 0·54
5-Ketomannonic acid from gulonolactone	14·0	15·1	0·60
Gulonic acid	8·4	6·4	0·91, 0·41

Hart and Everett's method was modified to replace the precipitations of lead and silver salts by a separation on an anion-exchange column as described in the experimental part.

The isolation of 5-ketomannonic acid as the chief product of the action of calcium hydroxide on glucuronic acid suggests that the keto acid described by Siddiqui and Purves[2] was 5-ketomannonic acid as these authors supposed.

Experimental

Preparation of 5-Ketomannonic Acid from D-*Glucuronolactone*

Saturated calcium hydroxide solution was added dropwise at room temperature to glucuronolactone (178 mg) to bring the pH to 9, at which value it was maintained for 4 hr. At the end of this period the pH was raised to 11 by further addition of calcium hydroxide, and was kept at this value for two days by periodic additions of the same reagent (55 ml total). At the end of the reaction period, the precipitate which had formed was filtered, treated with Dowex 50(H^+) to remove cations, and the resulting solution evaporated to dryness under reduced pressure below 35°. The yield of dry product was 60 mg. Examination by ion-exchange and paper chromatography showed that the material consisted of 5-ketomannonic acid containing traces of mannuronic and glucuronic acids. The filtrate from the calcium salt was also treated with Dowex 50 and evaporated. The recovered material consisted of a mixture of glucuronic acid and 5-ketomannonic acid in roughly equal amounts, accompanied by a small quantity of mannuronic acid. The 5-ketomannonic acid could be readily separated from the other acids by ion-exchange chromatography on Dowex 1(Ac^-) using acetic acid as eluent. The total yield of 5-ketomannonic acid was 60–70%. The compound gave a brucine salt, m.p. 193°, $[\alpha]_D^{25}$ −16°, as described by Hart and Everett.[1]

[4] Samuelson, O., "Ion Exchange Separations in Analytical Chemistry." (John Wiley: New York 1963.)

[5] Fisher, F. G., and Dörfel, H., *Hoppe-Seyler's Z. physiol. Chem.*, 1955, **301**, 224.

Preparation of 5-Ketomannonic Acid from L-*Gulonolactone*

The method was essentially that due to Hart and Everett[1] except that, after the removal of bromine at the end of the reaction period (34 days, cf. 42 days used by the original authors), the reaction mixture was applied to a column of Dowex 1-X8(Ac^-). Washing with 30% acetic acid resulted in elution of monoprotic hydroxy acids, while any dibasic acids and hydrogen bromide formed in the reaction were retained on the resin. Evaporation of the eluate gave a mixture of acids which was treated with 0·05M sodium hydroxide at pH 8 for 4 hr at room temperature to split

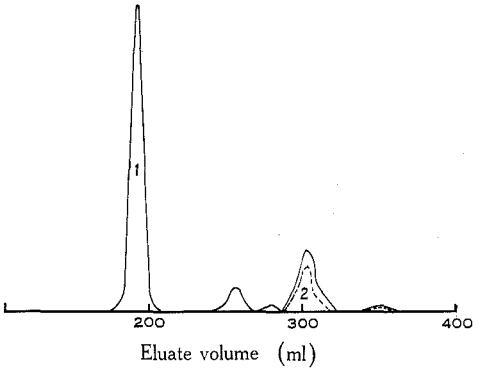

Fig. 1.—Separation in 0·08M NaOAc of products of oxidation of gulonolactone with bromine. Band 1: unchanged gulonolactone; band 2: 5-ketomannonic acid. Full line shows response to analysis by dichromate, broken line to analysis by carbazole.

lactones and then separated on a column of Dowex 1-X8(Ac^-) using 1·0M acetic acid or 0·08M sodium acetate as eluent. As is seen from Figure 1, a number of products were produced, along with much unchanged gulonolactone (band 1). The principal product was 5-ketomannonic acid (band 2). The yield was not measured accurately but was about 15%. Hart and Everett did not state their yield of pure acid, but the amount of brucine salt which they obtained corresponded to a yield of *c.* 10% of keto acid.

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