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A New Synthesis of L-Ascorbic Acid (Vitamin C)

By JAN BAKKE[a] and OLOF THEANDER[b]*

[[a] *Bofors AB. Bofors, Sweden (present address: Chemistry Institute, University of Trondheim, Trondheim, Norway);* [b] *Chemistry Department, Swedish Forest Products Research Laboratory, Box* 5604, *S*-114 86 *Stockholm, Sweden*]

Summary A new synthesis of L-ascorbic acid is described, involving a one-step oxidation of 1,2-*O*-isopropylidene-α-D-glucofuranose to 1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranurono-6,3-lactone-5-ulose and acid treatment of the latter, followed by reduction.

L-ASCORBIC ACID (IV) is conventionally synthesised (Reichstein and Grüssner method[1] and modifications) by hydrogenation of D-glucose to D-glucitol and oxidation of the latter to L-sorbose. L-Sorbose is converted into the 2,3 : 4,6-di-*O*-isopropylidene-sorbofuranose and the unprotected terminal hydroxy-group oxidised to a di-*O*-isopropylidene derivative of 2-keto-L-gulonic acid (after separation of the mono-*O*-isopropylidene product from the di-*O*-isopropylidene-sorbose). Removal of the isopropylidene groups by acid hydrolysis gives the unprotected acid, which undergoes lactonisation and enolisation to L-ascorbic acid. A recent modification of the above method[2] uses an alkyl α-L-sorbopyranoside as an intermediate for the introduction of the carboxyl group, but the yield reported is very low.

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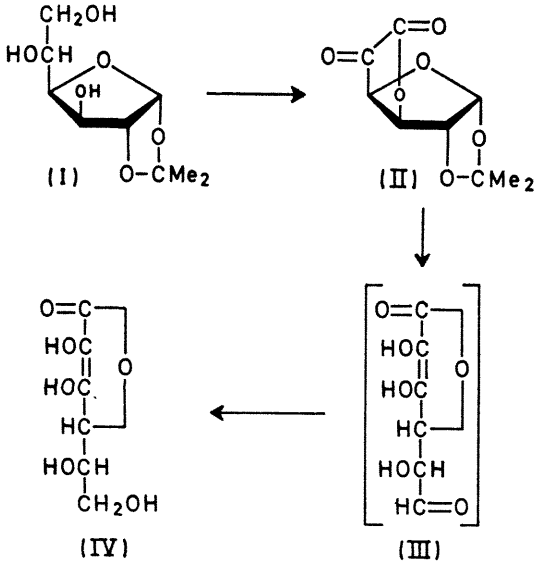
We report a shorter route to L-ascorbic acid (IV) from D-glucose. Chromium trioxide oxidation of 1,2-*O*-isopropylidene-α-D-glucofuranose (I) gave a compound identified as 1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranurono-6,3-lactone-5-ulose (II) in a low yield together with other oxidation products.[3] It seemed possible to transform (II) into (IV) if the aldehyde group could be selectively reduced after removal of the isopropylidene group. In this connection it was of interest also to improve the yield of (II).



Compound (I) was oxidised in one step to compound (II) (*ca.* 70% yield) using platinum/oxygen under slightly acidic conditions (pH 3—4·5).[4] The reaction product crystallised readily during work-up. The m.p. (128—130°) and $[\alpha]_D^{22}$ (+73°; *c* 1, water) of the hydrate obtained after recrystallisation from water were in agreement with literature values[5,6] as were also the i.r. and n.m.r. data.[5] Examinations by t.l.c. of samples taken during the oxidation indicated that the carboxyl group at C-6 is initially formed *via* the aldehyde, then lactonised and the lactone oxidised at the C-5.

The preparation of D-glucuronic acid is usually carried out by catalytic oxidation of (I) at pH 8—9 and in this procedure, the 1,2-*O*-isopropylidene-α-D-glucufuronic acid is isolated as the calcium salt.[7] The corresponding 6,3-lactone has recently been oxidised to compound (II) with chromium trioxide[5] (yield 20%) and active manganese dioxide[6] (no yield is quoted).

Compound (II) was treated with 1N-aqueous sulphuric acid (96°; 45 min) and the product obtained reduced with borohydride at pH *ca.* 7 to give a product containing L-ascorbic acid (IV).[8] Cation-exchange resin was added, the filtered solution evaporated and the boric acid removed by distillation (three times) with methanol in the usual way. The presence of L-ascorbic acid was shown by paper chromatography in many solvents and paper electrophoresis (pH 4·5) using an authentic reference sample and the conventional spray reagents for carbohydrates and acids as well as 0·05N-iodine–potassium iodide solution. The amount of L-ascorbic acid in the product was determined iodometrically in the usual way [40–50% yield based on (II)]. This analysis is reliable since no other compound than (IV) was detected on the chromatograms sprayed with iodine solution. When authentic (IV) was subjected to similar reduction and work-up procedure, the recovery of (IV) as determined iodometrically was 89%. If the distillation with methanol was avoided, the recovery was 96%. The 5,6-*O*-isopropylidene derivative of (IV) was prepared directly from the mixture,[9] and was shown to be indistinguishable from an authentic sample by paper chromatography, i.r., and n.m.r. The m.p. (and mixed m.p.) 220—222° and $[\alpha]_D^{22}$ + 14° (*c* 0·5, ethanol) were also identical with literature values.[9] This derivative was converted into L-ascorbic acid (m.p. 190°) by treatment with 50% acetic acid at 45° for 2 h.

These results correlate with previous findings[1,2] about acid treatment of derivatives of 2-keto-L-gulonic acid and make it likely that the aldehydo-compound (III) is formed when (II) is treated with acid.

The present synthesis of (IV) offers the advantage that the readily available mixture of mono-(I) and di-*O*-isopropylidene-D-glucose can be used as starting material. The 5,6-*O*-isopropylidene group in the latter can be readily removed at the start of the oxidation step without any significant cleavage of 1,2-*O*-isopropylidene groups.

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