A New Route to L-Ascorbic Acid (Vitamin C)

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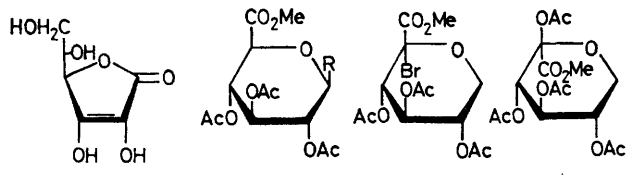
Summary Photochemical bromination of methyl tri-*O*-acetyl-2,6-anhydro-L-gulonate (**2**) with *N*-bromosuccinimide gives methyl tri-*O*-acetyl-α-L-*xylo*-hexulopyranosylonate bromide (**5**) which, on acetoxylation and hydrolysis, provides a further synthetic route to L-ascorbic acid.

THE synthesis of vitamin C (**1**) effectively requires the preparation of L-*xylo*-hexulosonic acid, and has been achieved: (i) most importantly, by oxidation of derivatives of L-sorbose,[1] (ii) by the extension of such compounds as L-*threo*-pentos-2-ulose[2] and L-threose,[3] (iii) by inversion at C-5 of D-*arabino*-hexulosonic acid,[4] and (iv) from D-glucuronic acid by processes[5] which involve oxidation at C-5

and reduction at C-1. We now report a further approach which is related to the last of these but utilises a C-1 reduced D-glucopyranuronic acid derivative and effects oxidation at C-5 by a specific bromination process.



(1) (2), R = H (3), R = OAc (4), R = SPh (5) (6)

Compound (**2**) {m.p. 116—117 °C, $[\alpha]_D$ + 39° ($CHCl_3$)} was prepared efficiently from commercial D-glucuronic acid by way of the tetra-acetate (**3**) and the thioglycoside (**4**)[6] which was reduced by heating in refluxing ethanol with Raney nickel. In keeping with other methyl D-glucopyranuronate derivatives investigated,[7] the deoxy compound (**2**) underwent bromination with retention of configuration at C-5 when treated with *N*-bromosuccinimide in refluxing carbon tetrachloride under a 250 W i.r. lamp, and it afforded the crystalline bromo-compound (**5**) {m.p. 103—107 °C, $[\alpha]_D$ − 132° ($CHCl_3$)} in 47% yield. This derivative has previously been synthesised by treatment of methyl L-*xylo*-hexulopyranosonate with phosphorus tribromide in acetic anhydride containing acid[8] which provides good evidence for the configuration at the tertiary centre, since under these conditions, the thermodynamically preferred product would be obtained and this would have the electronegative bromine axial and the other ring substituents equatorial. Since the reactions of methyl D-glucopyranuronate derivatives with *N*-bromosuccinimide did not proceed in refluxing carbon tetrachloride in the dark, but could be induced with added benzoyl peroxide, they are concluded to be homolytic processes.

Treatment of the bromide (**5**) with mercury(II) acetate in hot acetic acid gave the syrupy acetate (**6**) {$[\alpha]_D$ + 51° ($CHCl_3$)}, *i.e.* seemingly the anomer of the known[8] methyl tetra-*O*-acetyl-α-L-*xylo*-hexulopyranosonate ($[\alpha]_D$ − 77°) which indicates that the introduction of the acetoxy group proceeded with inversion of configuration. Deacetylation with sodium methoxide (0·2M) in methanol[4] followed by neutralisation with methanolic hydrogen chloride and removal of solvent gave a quantitative yield of a solid believed to be the methyl ester of the desired acid. I.r. analysis indicated that it was not ascorbic acid (see ref. 4). Removal first of the salt by extraction of the product into aqueous acetic acid (80%), and then of the extracting solvent, gave a syrup which, taken up in methanol containing concentrated hydrochloric acid (10%) and again taken to dryness, gave a buff coloured powder in 90% yield. A sample recovered from aqueous acetic acid (80%) and purified by washing with ethanol had m.p. 175—182 °C (lit.,[4] 189—191 °C) and gave i.r., c.d., and *X*-ray powder diffraction spectra consistent with those obtained from L-ascorbic acid. Further evidence was provided by titration with acidic iodine solution, and by the identical properties of the synthetic and authentic acids on paper chromatograms.

Compounds (**2**)—(**5**) all gave ^1H n.m.r. and analytical data consistent with the assigned structures. The syrupy tetra-acetate (**6**) gave an appropriate ^1H n.m.r. spectrum.

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