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CATALYTIC HYDROGENATION OF L-ASCORBIC ACID (VITAMIN C): A STEREOSELECTIVE PROCESS FOR THE PRODUCTION OF L-GULONO-1, 4 - LACTONE

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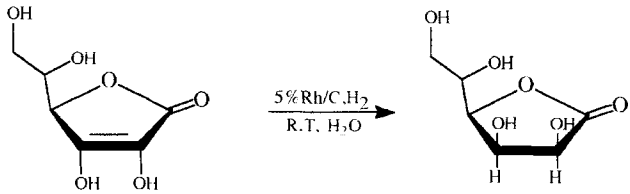
Introduction:

Reduction of functional groups with hydrogen gas is one of the most important reactions in organic chemistry, dating to the first hydrogenation of ethene to ethane reported by Von Wilde in 1874[1]. Indeed, alkenes are generally rapidly hydrogenated, in the presence of a catalyst, usually, platinum, Raney nickel, palladium, or rhodium on carbon, to the corresponding alkane via heterogeneous reaction. Most undergraduate, introductory texts introduce this reaction as occurring via a stereospecific syn addition, although this is an oversimplification, due to possible rearrangements on the catalyst surface[2]. While the chemistry of Vitamin C (L-ascorbic acid), in regards to oxidative degradation, is well studied, its behavior under reductive conditions has been relatively overlooked. The catalytic reduction of ascorbic acid has been reported earlier (24 hours, palladium catalyst, water, 50°) by workers at Pfizer[3].

During our investigations into different conditions for the facilr hydrogenation of 1, we have found Rhodium on Carbon (Caution: please refer to reference 3, in regards to the danger of activated Raney Nickel catalyst!) to be most effective catalyst and have found the process suitable facile for batch-quality production of the title compound. We have found, in agreement with prior work, that the hydrogenation proceeds with delivery of hydrogen from the least hindered side of the enono-lactone moiety opposite the side-chain of 1 to yield a

single stereoisomer L-gulono-1, 4-lactone 2. This process is, indeed, the exact reversal of the biochemical process found in organisms that bio-synthesize ascorbic acid where 2 is enzymatically dehydrogenated to 1 via the enzyme L-gulonolactone oxidase[4].

There is currently a great deal of interest in 2 as a source of enantiomerically pure compounds for treatment of epilepsy, glaucoma, and hypertension[5]. As Ascorbic Acid is an item of commerce, this process represents an economic avenue for the production of relatively inexpensive drug candidates in the pharmaceutical industry and should serve as an interesting introduction to catalysis for the undergraduate chemistry major.



L-Ascorbic Acid

1

L-Gulono-1,4-lactone

2

Experimental:

Commercially available L-ascorbic acid and 5% rhodium on carbon (Aldrich Chemical) were used as supplied. Reaction time and isolated yields (75-90%) are average and based on several trials. A Parr hydrogenator (catalog #3911, Parr Equipment Company, Moline IL.) was used for the hydrogenation studies. Optical activity measurements were conducted with an I^2R polarimeter (I^2R, Cheltenham, PA.).

A 500 ml Parr flask (tested to 1200 p.s.i.) was charged with 10.0 g L-ascorbic acid (176 g mol^{-1}, .057 mol) and 200 mL distilled water. To the homogeneous solution is added 1.0 g of 5% rhodium on carbon, followed by evacuation of the flask. The flask is then charged with sufficient hydrogen from the reserve tank to generate 55 p.s.i. pressure. The solution is shaken and the steady uptake of hydrogen noted. After about 90 minutes, uptake of hydrogen ceases, (corresponding to the uptake of one mol-equivalent of hydrogen) and the flask and reserve tank are carefully drained with water aspiration. The

contents of the flask is filtered, to remove the catalyst, and the filtrate added to a 250 ml round-bottomed flask, was concentrated by rotary-evaporation under vacuum. The water bath should be maintained at a temperature no higher than 45°C. The clear, residual syrup is added to a small beaker and the material allowed to crystallize overnight in the refrigerator. The white crystals are collected on a Buchner funnel and allowed to air-dry to constant weight. A typical trial yields 8.0 g of L-gulonolactone, m.p.: 187-190, lit.[6]: 187-190°C, F.T. i.r. (KBr) : 1780 cm, 300 MHZ. n.m.r. (D_2O) : 3.35-3.8 (m,3H), 4.15-4.45 (m,3H). $[\alpha]_{21}^{D}$ 52.8 (c= 0.17, H_2O)

Acknowledgments:

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Literature Cited:

[1] Smith, M.B.; Organic Synthesis: McGraw-Hill, NY. 1994, page 423.

[2] Mackie, R.K.; Smith, D.M.; Guidebook to Organic Synthesis; Longman Group Limited, Essex, England, 1983, page 174.

[3] Andrews, G.C.; Crawford, T.C.; Bacon, B.E., J. Org. Chem. 1981, 46, pp. 2976- 2977. We have found that complete reduction, with 10% palladium on carbon, proceeds in about 18 hours at ambient temperature. We evaluated the usual catalysts (Pt., Ru, Ni, etc.) and found minimal activity. CAUTION: in the case of activated Raney nickel (J. Org. Chem., Volume 26, 1961, page 1625) rapid decomposition of the ascorbic acid occurred, resulting in rapid pressure build-up leading to explosion of the Parr flask!

[4] Dixon, M.; Webb, E.C., Enzymes; 3rd. Ed.; Academic Press, NY. 1979.

[5] Hubschwerlen, C., Synthesis, 1986, pp 962-964.

[6] Material has m.p. range identical to the L-gulono-1, 4-lactone of commerce. See: Aldrich Chemical catalog, 1994-1995, page 744.(cat. #31,030-1).

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