previously reported,[5] made unnecessary the prior use of a cation column.[13]

The eluate from the anion column was evaporated at 30° *in vacuo* under nitrogen. The pale yellow sirup was dissolved in 30 ml. of absolute alcohol and 400 ml. of peroxide-free absolute ether was added. A small amount of flocculent precipitate was removed by filtration. The clear filtrate was evaporated under nitrogen. The resulting crystals of ascorbic acid were washed with 1:1 absolute ethanol–redistilled ligroin until the supernatant was no longer colored, followed by an additional wash with absolute ether.

The colorless crystals of ascorbic acid (667 mg.) had an absolute activity of 2.6 μc./mg. when counted as barium carbonate, which represented a yield of 58% based on the radioactive sodium cyanide. Additional amounts of less active material were recovered from the ether precipitate and supernatants by adding carrier ascorbic acid. The over-all yield of ascorbic acid based on radioactive sodium cyanide was 70%. The ascorbic acid was pure, as measured by indophenol dye titration, and melted at 187–189°. The specific activity remained constant during recrystallization and preparation of the isopropylidene derivative. Analysis of the product from a trial synthesis with non-radioactive cyanide, after one crystallization from glacial acetic acid, gave the following results.

Anal. Calcd. for $C_6H_8O_6$: C, 40.9; H, 4.58. Found: C, 40.8, 40.8; H, 4.69, 4.56.

NEW YORK, N. Y.

(13) Subsequent work has resulted in a further improvement in the isolation procedure, to be published later.

[CONTRIBUTION FROM THE DIVISION OF AGRICULTURAL BIOCHEMISTRY, UNIVERSITY OF MINNESOTA]

Synthesis of Ascorbic Acids by the Osone–Cyanide Method[1]

BY J. KELVIN HAMILTON AND F. SMITH

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Conversion of sugars into the corresponding osones is readily brought about by the action of alcoholic cupric acetate. Without further purification, these osones may be converted into ascorbic acids by condensation with potassium cyanide followed by hydrolysis with dilute mineral acid. If carried out at 95° rather than 45–50° as formerly prescribed the hydrolysis can be completed in 3 hours instead of 1–2 days.

Vitamin C (L-xyloascorbic acid) is essential for the prevention of scurvy[2] but little is known of its actual role in biochemical systems: In attempts to throw light on this problem, experiments devised by Dr. C. D. May and his associates required D-(levo)-ascorbic acid (the enantiomorph of vitamin C).[3] By investigating the effect of this compound which has no antiscorbutic activity[4] it seemed likely that information would be forthcoming which would indicate whether D-ascorbic acid, with the same oxidation–reduction potential as vitamin C, could be utilized by an animal in certain specific biological oxidation–reduction systems.

The work reported herein deals with a simple synthesis of D-xyloascorbic acid, a substance that is virtually unobtainable at the present time. The method finally adopted for this purpose, which involves the reaction of a sugar osone with alkali cyanide, can also be used for the preparation of vitamin C or any of its analogs, with radioactive carbon at C_1. When osones are available this reaction, first used by Haworth and his associates,[5] provides an excellent route to the corresponding ascorbic acids. Hitherto, the methods normally used for preparing osones, such as the action of fuming hydrochloric acid on hexose phenylosazones[6] or benzaldehyde on pentose phenylosazones[5,7,8] provide at best poor yields and consequently the availability of certain ascorbic acids is thereby greatly restricted. This is true in spite of alternative methods for synthesizing ascorbic acid and its analogs.[9–12]

Osones are said to be obtainable in yields of 40–60% by heating an aldose or ketose with cupric acetate in methanol.[13] This is by far the best method for making osones but it does not seem to have received the recognition that it deserves.

When D-xylose is oxidized with cupric acetate a 50–55% yield of D-xylosone is readily produced and this upon condensation with potassium cyanide in aqueous solution immediately gives the corresponding imino-D-xyloascorbic acid. Formerly, the latter was converted into the corresponding D-ascorbic acid by hydrolysis with dilute mineral acid for 40–48 hr. at 40–50°.[5] It is shown herein that when carried out at 95–100° the reaction is complete in 3 hours and good yields of D-ascorbic acid (m.p. 192° dec., $[\alpha]_D$ −23° in water) can readily be isolated. By using the cupric acetate method for preparing osones and allowing the latter to react with $NaC^{14}N$, ascorbic acid and its analogs labeled at C_1 with radioactive carbon become readily accessible.[14]

Experimental

D-Xylosone.—To a solution of D-xylose (12 g.) in water (30 ml.), methanol (750 ml.) and cupric acetate (60 g.) were added. The mixture was quickly brought to the boil, refluxed for 10 minutes, cooled and filtered to remove cuprous oxide. The copper acetate in the filtrate was precipitated by hydrogen sulfide and after adding charcoal the solution was filtered and concentrated *in vacuo* at 35–40°. The D-xylosone was obtained as a colorless sirupy substance.[13] It

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readily reduced Fehling solution and gave D-xylose phenylosazone when allowed to react with phenylhydrazine in acetic acid at room temperature.

1-Imino-D-xyloascorbic Acid.—The sirupy osone from 12 g. of D-xylose was dissolved in water (250 ml.) and the solution neutralized by adding ammonium hydroxide. A solution of potassium cyanide (5 g.) in water was added whereupon the rotation changed from α_D (2 dm.) −0.23° to −21.0° in ten minutes. Titration of a sample (1 ml.) of the reaction mixture with 0.01 *N* iodine after acidification with dilute hydrochloric acid showed that a total yield of 6.1 g. of imino-D-xyloascorbic acid had been produced. The solution containing the imino-ascorbic acid was made acid to congo red by adding dilute hydrochloric acid and then evaporated *in vacuo* until inorganic salts commenced to crystallize. (Here and elsewhere, unless stated otherwise, the concentration of solutions was carried out *in vacuo* in an atmosphere of carbon dioxide at 30–40° (bath temp.) to minimize the oxidation of the enediol system.) The residue was extracted with methanol (50 ml.), filtered, the salts being well washed with methanol, and the solution concentrated to about 30 ml. This solution of imino-D-xyloascorbic acid was adjusted to 100 ml. by adding water and kept in the cold room (3°) (solution A).

Conversion of 1-Imino D-Xyloascorbic Acid to D-Xyloascorbic Acid. (A) Hydrolysis with Formic Acid.—A 10-ml. aliquot of solution A containing 0.6 g. of imino D-xyloascorbic acid was treated with 88% formic acid (10 ml.) and the mixture heated on the boiling water-bath. The following changes in rotation were noted: α_D (2 dm.) −4.05° (initial value); −2.88° (after 30 minutes); −2.15 (60 minutes); −1.75 (95 minutes); −1.58 (133 minutes); −1.43 (163 minutes); −1.33 (253 minutes); −1.30 (313 minutes); −1.25 (360 minutes) constant value. Titration of an aliquot with 0.01 *N* iodine showed that 0.17 g. of D-ascorbic acid was present in the solution after hydrolysis was complete.

(B) Hydrolysis with Hydrochloric Acid at 95°.—A 10-ml. aliquot of solution A was treated with water (25.5 ml.) to which had been added hydrochloric acid (1 ml., *d* 1.2) and the mixture heated on the boiling water-bath. The progress of the hydrolysis was followed polarimetrically, α_D (2 dm.) −2.88° (initial value), −1.70° (60 minutes), −1.60° (120 minutes), −1.54° (180 minutes), constant value. At the end of the hydrolysis the solution contained 0.47 g. of D-ascorbic acid as shown by iodine titration.

(C) Hydrolysis with Hydrochloric Acid at 48°.—A 10-ml. aliquot of solution A was treated with water (40 ml.) to which had been added hydrochloric acid (2 ml. *d* 1.2). The mixture was warmed on a water-bath at 48° and the progress of the hydrolysis followed polarimetrically thus: α_D (2 dm.) −1.06° (initial value); −0.70 (48 hours); −0.56 (55 hours) constant value. Titration of a portion of the final hydrolysis solution with 0.01 *N* iodine showed the presence of 0.43 g. of D-ascorbic acid.

Isolation of D-Xyloascorbic Acid.—A solution of imino-D-xyloascorbic acid, corresponding to solution A above and containing 3.8 g. of imino compound as shown by iodine titration, was adjusted to a *p*H of 1 by adding 6 *N* hydrochloric acid. The solution was heated on the boiling water-bath for 3 hours when the rotation was constant. The solution which then contained 2.2 g. of D-ascorbic acid (tested by iodine titration) was treated with lead acetate solution until no more precipitate of lead chloride was formed. Filtration, aided by the addition of charcoal, before and after treatment with hydrogen sulfide, followed by evaporation *in vacuo* gave a pale yellow sirup which was extracted with ethanol at room temperature. After again removing the solvent the residue was dissolved in ethanol (100 ml.) and treated with ether (250 ml.). After adding a little charcoal the flocculent inorganic precipitate was removed and the filtrate evaporated *in vacuo* to a sirup. The latter was dissolved in ethanol (250 ml.) and treated with a warm solution of lead acetate in 95% ethanol until no more lead D-ascorbate was precipitated (tested by centrifuging a portion of the solution and adding more lead acetate). The pale yellow precipitate was centrifuged, washed with ethanol, suspended in water (200 ml.) and treated with hydrogen sulfide to liberate the D-xyloascorbic acid. The solution was treated with a little charcoal, filtered to remove lead sulfide and concentrated *in vacuo* to a sirup. The latter was stirred with methanol (1 ml.), nucleated with a crystal of D- or L-xyloascorbic acid and when crystallization was complete, the crystals were triturated with dry acetone, filtered, washed with acetone and dried *in vacuo* (yield 720 mg.). A further amount (180 mg.) was obtained from the mother liquor (total yield 900 mg.). The crystals were colorless and appeared to be quite pure, m.p. and mixed m.p. 192° (with decomposition). After crystallization from the minimum of water the D-ascorbic acid showed m.p. 192° dec., $[\alpha]^{21}D$ −22° in water (*c* 2.0), 100 mg. reacted with 11.25 ml. 0.1 *N* iodine, corresponding to a purity of 99%.

Anal. Calcd. for $C_6H_8O_6$: C, 40.9; H, 4.6. Found: C, 41.0; H, 4.7.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

Free Radical Rearrangements. I. The Free β-Methyl-β-α-tolylpropyl (*p*-Methylneophyl) Radical[1]

BY W. H. URRY AND N. NICOLAIDES

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The free *p*-methylneophyl radical is postulated as the reactive intermediate in (1) the cobaltous chloride-catalyzed reaction of ethylmagnesium bromide with *p*-methylneophyl chloride, and (2) the peroxide-induced decarbonylation of β-*p*-tolylisovaleraldehyde. The rearranged and unrearranged products (*p*-tolyl derivatives) were obtained in approximately the same yields as the corresponding ones (phenyl derivatives) from the reactions of the free neophyl radical generated in the same ways (1 and 2). The free 2,2-dimethylbutyl radical prepared as in (1) gave 2,2-dimethylbutane and a dimer. In these free radical rearrangements it is concluded that: (1) no β-alkyl migration occurs, (2) the β-aryl group undergoes a 1,2-shift, and (3) the migratory aptitudes of the phenyl and *p*-tolyl groups are approximately equal.

Introduction

The rearrangement of the free neophyl (β,β-dimethylphenethyl) radical is postulated as the mechanism leading to rearranged products in two reactions: (1) the cobaltous chloride-catalyzed reaction of phenylmagnesium bromide with neophyl chloride to give isobutylbenzene, β,β-dimethylstyrene and 2-methyl-3-phenylpropene-1[2a]; and (2) the decarbonylation of β-phenylisovaleraldehyde with *t*-butyl peroxide (10 mole %) to give isobutylbenzene.[2b] It is characteristic of these free-radical reactions that unrearranged products are also formed: reaction 1, *t*-butylbenzene and bineo-

(1) The material of this paper (taken from the Ph.D. thesis of N. Nicolaides, University of Chicago, 1950) was presented in summary before the Organic Division of the American Chemical Society at Chicago, September, 1950; and at the Twelfth National Organic Symposium, Denver, Colorado, June, 1951.

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