[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

Improvements in the Preparation of *d*-Arabinose from Calcium Gluconate[1]

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Arabinose is unique among sugars in that both its stereochemical isomers are relatively easy to obtain. The *l*-form is a constituent of many plant gums, while the *d*-form may be prepared from *d*-glucose by degradation. In many researches involving the use of this sugar it is a matter of indifference which isomer is employed; thus the choice between them will be determined in such cases only by their relative availability in a pure condition. A method of preparation therefore is to be judged according to the cheapness and accessibility of the raw material and the ease and rapidity with which it can be converted into practical quantities of a highly pure product, rather than upon the basis of the yield of crude impure sugar.

The publication by Anderson and Sands[3] of explicit details for the preparation of *l*-arabinose from mesquite gum aroused the hope that a ready source of the pure sugar had been placed in the hands of investigators. However, studies in this Laboratory by F. H. Goldman have led to the conclusion that mesquite gum cannot be considered a good source of a product with a specific rotation even as great as $[\alpha]_D^{20}$ + 102° (+104–105° is correct for pure *l*-arabinose), since many recrystallizations are necessary to bring it to this rotation; the removal of remaining impurities presents many time-consuming difficulties and the final yield is small.[4] Attention is therefore naturally directed toward the question of the relative availability of highly pure *d*-arabinose. On account of the increasing accessibility of high quality calcium gluconate prepared from glucose either by the action of microörganisms[5] or by electrolytic oxidation,[6] we were encouraged to reinvestigate Ruff's[7] method of degrading this salt by oxidation with hydrogen peroxide in the presence of ferric acetate.

An improved method for the preparation of an active and reliable catalyst, by the double decomposition of ferric sulfate with barium acetate, has led to a very easy and rapid method of performing the reaction. Moreover, quantitative studies of the yields under various conditions have made possible the selection of those which give about 50% on the basis of theory, or about double the yields which have been reported previously. The cheapness of the raw material together with the high purity of the product ($[\alpha]_D^{20}$ at equil. −104.8° after two recrystallizations) lead us to endorse the *d*-isomer of arabinose as the one actually more available under present conditions, for all researches that do not positively require the *l*-modification.

Substantially the same method has been used very successfully for preparing *d*-lyxose from calcium galactonate pentahydrate. The yields obtained by direct crystallization, however, amount to only about 17% of the theoretical. After one recrystallization from four parts of warm absolute methyl alcohol, the $[\alpha]_D^{20}$ at equil. was +13.9°,[8] m. p. 101.5–102.5° (corr.). A little more lyxose may be obtained as the phenylhydrazone by adding phenylhydrazine to the alcoholic mother liquors.

Experimental Part

A solution of 20.86 g. of barium acetate monohydrate in 60 cc. of water and a solution of 10.2 g. of ferric sulfate[9] in 60 cc. of water (equimolecular quantities) are poured into 2 liters of distilled water in a 4-liter glass beaker. Two hundred grams of calcium gluconate dihydrate[10] is added and the solution heated to boiling with stirring. It is then removed from the flame, allowed to settle and filtered on a Buchner funnel precoated with filtercel. To the clear amber-colored filtrate, a liter of water is added and the solution cooled to 35°. Then 120 cc. of

(1) Publication authorized by the Surgeon General, U. S. Public Health Service.

(2) National Research Fellow, October, 1929 to April, 1931.

(3) "Organic Syntheses," Vol. VIII, 1928, p. 18.

(4) A commercial *l*-arabinose examined by us, which had been prepared from mesquite gum showed $[\alpha]_D^{20}$ at equilibrium +94° (*cf.* Ref. 17).

(5) Herrick and May, *Ind. Eng. Chem.*, **21**, 618 (1929); U. S. Patent 1,726,067.

(6) Isbell and Frush, *B. Standards J. Research*, **6**, 1145 (1931); **8**, 571 (1932).

(7) Ruff, *Ber.*, **32**, 553 (1899); **35**, 2360 (1902).

(8) Hudson and Yanovsky, THIS JOURNAL, **39**, 1013 (1917), give $[\alpha]_D^{20}$ at equilibrium +14°. *Cf.* Clark, *J. Biol. Chem.*, **31**, 605 (1917).

(9) We used a sample of $Fe_2(SO_4)_3$ + aqua which contained 21.0% of Fe by our analysis and which dissolved without residue to give a clear solution. A weight of 13.56 g. of this salt was equivalent to 10.2 g. of anhydrous ferric sulfate. Stock solutions of the salts were prepared in quantity so that the desired amounts could rapidly be pipetted out when needed. No deterioration of these stock solutions has been observed. *Cf.* National Formulary, 3rd edition, Baltimore, 1906, p. 219.

(10) We wish to acknowledge our indebtedness to H. T. Herrick and O. E. May of the U. S. Bureau of Chemistry and Soils for much of the material used.

30% hydrogen peroxide is added. Within a few minutes an evolution of gas begins and the temperature rises spontaneously to about 55°. The reaction is complete in about half an hour as indicated by the sudden appearance of a dark purple color. After cooling to 40° a second 120 cc. volume of peroxide is added, whereupon a new reaction takes place very similarly.[11] The dark turbid solution is then filtered through carbon[12] on a Buchner funnel and concentrated in a vacuum to 250 cc. To this, 1500 cc. of methanol[13] are added with shaking and the granular precipitate which forms is filtered on a Buchner funnel precoated with carbon. Three hundred cubic centimeters of methanol are used for rinsing. To the clear filtrate is added 900 cc. of ether with shaking.[14] After five minutes of settling, the new granular precipitate is filtered on a carbon-coated Buchner funnel. The filtrate is concentrated in a vacuum to a sirup. When it has become so stiff as barely to flow[15] it is taken up in about 100 cc. of warm methanol and poured out into an Erlenmeyer flask, 25 cc. more being used for rinsing. Crystallization takes place readily without seeding. After a few hours in the refrigerator, the sugar is filtered, washed with methyl alcohol and dried. The yield is 55 to 65 g. or about 50% of the theoretical amount. It is recrystallized by dissolving in two-thirds its weight of water,[16] filtering with carbon rapidly while hot, and adding five volumes of methanol. Sharp prisms of *d*-arabinose separate in a yield of 80% of the crude substance used. After washing and drying *in vacuo* at 60° for two hours, the $[\alpha]_D^{20}$ at equilibrium was $-103.3°$,[17] m. p. 155.5–156.5° (corr.). After a second recrystallization, the $[\alpha]_D^{20}$ at equilibrium was $-104.8°$, ash 0.0% (visible). The time required to the first crystallization is about one working day.

(11) Analyses for reducing sugar at various stages showed that a second oxidation with the same amount of hydrogen peroxide greatly increases the yield of pentose. Further quantities of oxidant cause a drop in yield.

(12) The activated carbons employed often contained copper, and were therefore soaked in 3.5% hydrochloric acid and then washed acid-free with distilled water and dried before use.

(13) A commercial synthetic methanol labeled "from 99 to 100% pure" was found satisfactory, and is much cheaper than "reagent quality."

(14) Acetone may be used with equally good results.

(15) Crystallization sometimes takes place in the distillation flask. In this case the crystals may be dissolved in a little water and the concentration then continued to the proper stage.

Summary

Improved directions are given for the preparation of *d*-arabinose by oxidation of calcium gluconate with hydrogen peroxide in the presence of ferric acetate (Ruff's method). The ease with which practical quantities of this sugar can be obtained in a state of high purity recommends the *d*-isomer for use in such investigations as do not specifically require the *l*-modification, which is very difficult to prepare in good purity.

(16) There should be very little calcium present at this point but if the amounts of lime salts are appreciable, they may be prevented from separating by adding 2 cc. of concentrated nitric acid to the solution.

(17) Hudson and Yanovsky, *loc. cit.*, found $[\alpha]_D^{20}$ at equilibrium $-105°$ for pure *d*-arabinose. The over-all yield of virtually pure *d*-arabinose may therefore be fairly stated as 40% of the theoretical without working up mother liquors.

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The Cleavage of Glycosides by Catalytic Hydrogenation[1]

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Recent investigations have shown that various benzyl and benzal compounds, including esters of benzyl and diphenylmethyl alcohols,[2] benzaldehyde acetals,[3] and benzyl ethers of phenols and alcohols[4] can be cleaved by hydrogen in the presence of palladium catalysts. For example, $C_6H_5OCH_2C_6H_5 + H_2 \longrightarrow C_6H_5OH + C_6H_5CH_3$. In 1928 this reaction was adapted to the synthesis of sugar derivatives by K. Freudenberg,[5] who found that the benzyl group could be eliminated from benzyl ethers of sugars, and from benzyl glycosides, by hydrogen and platinum in glacial acetic acid, but not in alcohol.

In the same year Kariyone and Kondo,[6] working on the glucoside aucubin, reported that catalytic hydrogenation with neutralized platinum chloride in aqueous solution resulted in cleavage to glucose and a reduced aglucone of unknown structure; with platinum oxide in alcohol, however, no cleavage took place. The Japanese investigators then studied two phenyl glucosides, arbutin and salicin. Arbutin with aqueous neutralized platinum chloride absorbed four moles of hydrogen to yield about one mole of glucose and, presumably, hexahydrophenol. Sali-

(1) Presented in part before the Division of Organic Chemistry, at the St. Petersburg meeting of the American Chemical Society, March 27, 1934.

(2) Rosenmund and Heise, *Ber.*, **54**, 2038 (1921).

(3) Kariyone and Kimura, *J. Pharm. Soc. Japan*, No. **500**, 746 (1923).

(4) Merck, German Patents 407,487 (1924); 417,926 (1925).

(5) Freudenberg, Dürr and von Hochstetter, *Ber.*, **61**, 1739 (1928); Freudenberg, Toepffer and Andersen, *ibid.*, **61**, 1754 (1928).

(6) Kariyone and Kondo, *J. Pharm. Soc. Japan*, **48**, 684 (1928).