

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Lead Tetraacetate Oxidations in the Sugar Group. X.¹ Crystalline 2,4,3,5-Diethylidene-*aldehydo*-L-xylose and Several of its Derivatives²

BY ROBERT C. HOCKETT AND FREDERIC C. SCHAEFER³

In 1935, Appel⁴ described an "improved method for the preparation of L-xylose" which he isolated, however, only in the form of two derivatives, the osazone and β -tetraacetate. The preparation was based upon sorbitol which was converted by the following series of reactions:

1. Sorbitol and paraldehyde were condensed to produce a sirupy product to which the author refers as "triethylidene sorbitol," though it was certainly a complex mixture.

2. The sirupy "triethylidene sorbitol" was subjected to partial hydrolysis after which crystalline diethylidene sorbitol⁵ was isolated in a yield of 26%.

3. The crystalline diethylidenesorbitol was oxidized by lead tetraacetate in an acetic acid-benzene solution.

4. Without isolation of the diethylidene-L-xylose presumably formed in this reaction, a hydrolysis was performed and an impure amorphous sample of L-xylose recovered, which was converted into L-xylosazone and tetraacetyl- β -L-xylose for identification.

We have restudied these reactions with some care and have introduced a number of modifications and additions:

1. By a systematic study of the condensation of sorbitol with paraldehyde in the presence of sulfuric acid we have found conditions under which thirty-four per cent. yields of crystalline 1,3,2,4-diethylidenesorbitol are obtained directly, without hydrolysis of the triethylidene derivative. The yield of diethylidenesorbitol is a function of time, as might be expected in the case of an intermediate product capable of further condensation. Moreover we believe from our experience that the product obtained by Appel in his condensation must have been a complex mixture, which undoubtedly contained triethylidenesorbitol but certainly did not consist entirely of this product. We regularly obtained some crystalline triethylidenesorbitol in our condensations.

(1) Number IX in this series, *THIS JOURNAL*, **68**, 922 (1946).

(2) The material in this paper is taken from a thesis submitted by Frederic C. Schaefer to the Graduate School of the Massachusetts Institute of Technology in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in October, 1943. It was read before the Division of Sugar Chemistry and Technology at the Chicago meeting of the American Chemical Society in September, 1946.

(3) Present addresses: Robert C. Hockett, Scientific Director, Sugar Research Foundation, 52 Wall St., New York. Frederic C. Schaefer, American Cyanamid Co., Stamford, Conn.

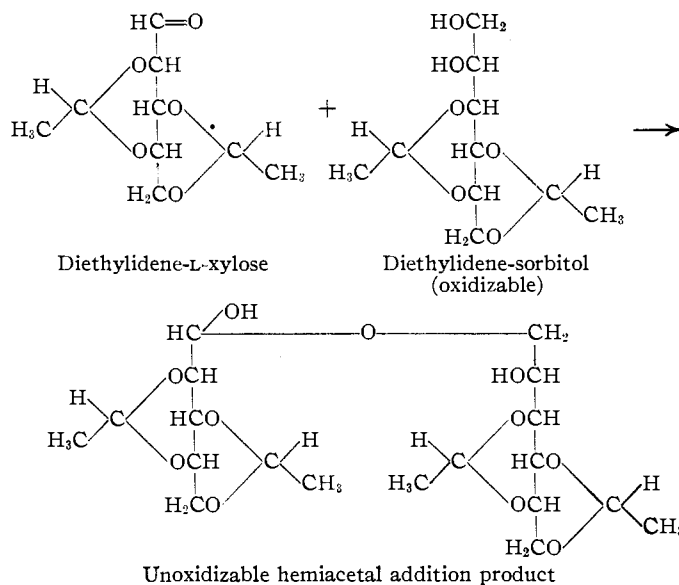
(4) Appel, *J. Chem. Soc.*, 425 (1935); German Patent 627,249.

(5) This derivative is described as "1,2,3,4-diethylidenesorbitol." Subsequently, Gätzi and Reichstein, *Helv. Chim. Acta*, **21**, 186 (1938), showed that the ethylidene groups occupy the 1,3 and 2,4 positions, respectively.

Equally good yields of diethylidenesorbitol were obtained when commercial sorbitol sirups were used in the condensation with adjustment of added water to allow for that contained in the sirups.

2. The oxidation of diethylidenesorbitol under the conditions described by Appel, followed by concentrating the solution, regularly produced a product not reported by that author. This by-product of the oxidation,⁶ whose nature has not yet been fully determined, reduces the yields of L-xylose that are obtained in the reaction. We have obtained the pentose both crystalline and in the form of derivatives as described by the German investigator, but in yields considerably short of the theoretical (Appel's yield was 48%).

3. The formation of the by-product was ascribed originally to interaction of diethylidene-L-xylose with unoxidized diethylidenesorbitol⁶ in such a way as to prevent further oxidation of the latter.



This hypothesis, though not wholly confirmed, nevertheless suggested conducting the oxidation in hydroxylated solvents which would themselves combine with the oxidation product and prevent inactivation of the sorbitol derivative. The first one used was alcohol.⁷ More recently

(6) This substance was discovered by the senior author and investigated by Hockett and Nickerson who made a preliminary report upon it before the Division of Sugar Chemistry and Technology at the Memphis meeting of the American Chemical Society in April, 1942. The structure proposed at that time is now considered doubtful although it expresses nearly all of the properties satisfactorily.

(7) Thesis submitted by Mortimer H. Nickerson to the Graduate School of the Massachusetts Institute of Technology in partial fulfil-

water has been used with great success.⁸

4. Oxidations of 1,3,2,4-diethylidenesorbitol in aqueous solutions by one molar equivalent of lead tetraacetate dissolved in glacial acetic acid, followed by removal of lead as sulfide and cautious evaporation, have permitted isolation of crystalline 2,4,3,5-*aldehydo*-L-xylose in yields of eighty-nine per cent. of the theoretical. This compound has been characterized further by means of a crystalline oxime and a crystalline dimethone.

5. Crystalline L-xylose has been obtained regularly in 85–89% yields by oxidation of diethylidenesorbitol in water followed by hydrolysis with sulfuric acid, removal of inorganic salts and evaporation.

The series of reactions described in this paper probably constitutes, in terms of combined simplicity and yield, the best published procedure for preparing L-xylose.⁹ However, because of the relatively low yield of diethylidenesorbitol which is obtainable from the hexitol, we have sought other derivatives suitable for oxidation to L-xylose, which might be prepared more simply and in higher yield. Subsequent communications will report such derivatives.

Experimental

1,3,2,4-Diethylidenesorbitol (Hockett and Nickerson).—Crystalline sorbitol (50.0 g., 0.26 mole) was dissolved in 10 cc. of water, and 50 cc. (equivalent to 1.14 moles of acetaldehyde) of paraldehyde was added. This mixture was cooled in ice and stirred while 10 cc. of concentrated sulfuric acid was added. The reaction mixture was then shaken at room temperature for exactly thirty hours. At the end of this time, the mixture was filtered quickly to remove small amounts of suspended material, and two volumes of water was added. The water solution was rapidly neutralized to congo red with barium hydroxide, and then the residual sulfuric acid was neutralized exactly, at leisure, with care to avoid having present an appreciable excess of barium hydroxide at any time. The precipitated barium sulfate was filtered out, and the solution was evaporated to a thick sirup which was taken up in 40 cc. of absolute alcohol and allowed to crystallize overnight. The solid which separated was filtered from the mixture and washed with a little absolute alcohol. The yield was 21 g. of diethylidenesorbitol, m. p. 191–200°, or 34%, based on the sorbitol used. After recrystallization to constant properties from reagent alcohol, the product melted at 211–213° and showed a specific rotation,¹⁰ of 12.15° (*c*, 1.7; H₂O).

Commercial sorbitol sirup may be substituted for an equivalent amount of crystalline sorbitol and water.

L-Xylose.—Diethylidenesorbitol (5.00 g., 0.0212 mole), prepared by the described modification of the method of Appel, was dissolved in 150 cc. of water. This solution was stirred vigorously while 9.5 g. (0.0213 mole) of lead tetraacetate, dissolved in 60 cc. of hot glacial acetic acid, was added continuously over a period of five minutes.

ment of the requirements for the degree of Doctor of Philosophy in May, 1940.

(8) The use of water as a solvent in which to carry out oxidations by lead tetraacetate has also been described by Baer, Grosheintz and H. O. L. Fischer, *THIS JOURNAL*, **61**, 2607 (1939).

(9) Cf. Fischer and Ruff, *Ber.*, **33**, 2145 (1900); von Vargha, *ibid.*, **68**, 23, 1337 (1935); Wolfe, Hann and Hudson, *THIS JOURNAL*, **64**, 1493 (1942).

(10) Specific rotations reported in this paper are specific rotations of the D line of sodium at 20°. Concentrations are stated in grams of substance in one hundred cubic centimeters of solution. Melting points are corrected.

(The reaction mixture usually remains nearly water-white but may develop a red color during the oxidation. In any event, the solution remains clear until all the lead tetraacetate has been added, after which a slight excess of the reagent causes a permanent dark brown precipitate of lead dioxide.) The mixture was stirred for fifteen minutes following the addition of the reagent. One hundred cc. of 1 *N* sulfuric acid was then added, and, after the mixture was allowed to stand at room temperature for one hour, the precipitated lead sulfate was filtered out of the solution. The filtrate, which was then approximately 0.2 *N* in sulfuric acid, was heated at 100° for five hours to complete the hydrolysis of the acetal linkages. After this hydrolysis, the sulfuric acid was neutralized exactly with barium hydroxide. After the additional precipitate was filtered out, the neutral solution was evaporated to a sirup. This was taken up in 70 cc. of absolute alcohol whereupon a small amount of inorganic material separated. The mixture was heated nearly to boiling, filtered hot and again evaporated to a sirup which partly crystallized. Addition of a small amount of absolute alcohol hastened more complete crystallization. The alcohol was then evaporated to approximately 2 cc., and the residual slurry was allowed to stand overnight in the ice box. The crystalline product was separated by filtration, washed with a little absolute alcohol followed by anhydrous ether, and dried in air. This procedure gave 2.66 g. of nearly white crystalline L-xylose, m. p. 135–137°, rotating¹⁰ –18.1° (equil.; *c*, 0.83; H₂O).

An additional 0.15 g. of L-xylose was recovered from the filtrate and alcoholic washings. This result brought the total yield of L-xylose to 88%. In several experiments the average yield was 85%.

aldehydo-2,4,3,5-Diethylidene-L-xylose.—Diethylidene-L-xylose, which is the direct product of the oxidation of diethylidenesorbitol by lead tetraacetate and must be an intermediate in the preparation of L-xylose, was isolated as described below.

Thirty grams of diethylidenesorbitol was oxidized with lead tetraacetate as described for the preparation of L-xylose. After the oxidation was completed the lead was removed quantitatively by precipitation with hydrogen sulfide. The lead-free solution was then evaporated to a solid residue. The evaporation temperature was kept below 30°. The residue was taken up in 300–400 cc. of water, and the solution was again evaporated dry. During the last stages of this evaporation, the temperature was allowed to rise to 80°, and the solid residue was heated at this temperature for one to three hours at 15–20 mm. pressure. This process was stopped when the walls of the flask became coated with the needle-like crystals which slowly formed. The material left in the flask at this point weighed 27 g. and was slightly gray owing to the presence of a trace of lead sulfide. The solid residue was dissolved in 250 cc. of boiling *n*-butyl ether which had previously been saturated in the cold with diethylidene-L-xylose. The solution was filtered hot, and the filtrate was allowed to cool. Granular crystals separated immediately. After the partly crystalline mixture had been allowed to stand in the ice box overnight, the crystals were filtered out, washed with a little *n*-butyl ether, and, after they had been pumped dry, washed with anhydrous ethyl ether. The product melted at 145–148° after being dried in the hot air oven. The yield of recrystallized product was 23.0 g. or 89%.

Two recrystallizations of the product from dioxane (3 cc. per g.) gave large, clear crystals melting at 162–163°, and rotation¹⁰ –12.4° (*c*, 2.9; H₂O).

Anal. Calcd. for C₈H₁₄O₅: C, 53.46; H, 6.98. Found: C, 53.40, 53.70; H, 6.97, 6.95.

aldehydo-2,4,3,5-Diethylidene-L-xylose Oxime.—One gram of crude diethylidene-L-xylose (m. p. 145–148°) was heated under reflux with 1.0 g. of hydroxylamine hydrochloride and 1.0 g. of anhydrous sodium acetate in a mixture of 5 cc. of water and 15 cc. of methanol for twenty minutes. The mixture was then filtered hot, and water was added dropwise until a slight permanent haziness was

produced. After the mixture had been allowed to stand overnight in the ice box, large clusters of needle-shaped crystals had separated. These melted at approximately 250° with decomposition. The yield of the oxime was 0.70 g. or 66%.

Recrystallization of the crude product from reagent alcohol (35 cc. per g.) gave lustrous plates, m. p. 256–257° (with dec.), and rotating¹⁰ –97.8° (*c*, 1.6; pyridine).

Anal. Calcd. for C₉H₁₃O₃N: N, 6.46. Found: N, 6.32, 6.53.

aldehydo-2,4,3,5-Diethylidene-L-xylose Dimethone.—Crude diethylidene-L-xylose (0.85 g.) was dissolved in a few cc. of water and added to a nearly boiling solution of 1.6 g. of dimethyldihydroresorcinol in 200 cc. of water. Within two minutes solid began to separate. After the mixture had been allowed to stand for ten minutes, 200 cc. of water was added, and the mixture was placed in the ice box overnight to complete the crystallization. The solid product was recrystallized from the smallest possible amount of a boiling mixture of reagent alcohol and water (5 parts to 3 by volume). This gave 0.76 g. of white needles, m. p. 196–200° (dec.). The yield was 39%.

Further recrystallization gave a product melting at 196–199° (dec.), and rotating¹⁰ +40.3° (*c*, 1.2; CHCl₃).

The product was soluble in dilute alkali and gave a coloration with ferric chloride in alcohol. It is, therefore, the dimethone rather than the dimethone "anhydride."

Anal. Calcd. for C₂₅H₃₆O₃: C, 64.7; H, 7.77. Found: C, 63.3, 63.6; H, 8.58, 8.14.

Summary

A method for preparing L-xylose from sorbitol by way of a diethylidenesorbitol which is oxidized by lead tetraacetate, has been restudied and the yields improved at every stage. Following oxidations in aqueous solution, the free sugar has been isolated directly in addition to the two derivatives which were obtained by the previous author. The *aldehydo-2,4,3,5-diethylidene-L-xylose* presumed previously to be an intermediate in the preparation has been isolated in a crystalline state and further characterized by preparation of two derivatives a crystalline oxime and dimethone which are described.

RECEIVED OCTOBER 9, 1946

[CONTRIBUTION FROM THE CENTRAL RESEARCH LABORATORIES, MONSANTO CHEMICAL COMPANY]

Vinyl Aromatic Compounds. IV. *i*-Propenylchlorobenzenes¹

BY DAVID T. MOWRY, W. FREDERICK HUBER² AND EUGENE L. RINGWALD

Recently Brooks³ has described the synthesis of a series of mono- and dichloro-styrenes. The present paper briefly describes the preparation and properties of a similar series of homologous compounds, the *o*-, *m*- and *p*-monochloro- and the 2,5- and 3,4-dichloroisopropenylbenzenes.

These materials were all prepared by the dehydration of the appropriate aryl dimethylcarbinols by the action of acetic anhydride in the presence of a trace of sulfuric acid. This is a convenient method for the dehydration of tertiary aryl carbinols of this type but does not always give high yields because of the tendency to form dimers and low molecular weight polymers.⁴ Thus, in the preparation of 3,4-dichloroisopropenylbenzene this method gave a 37% yield, while the vapor phase dehydration technique described earlier⁵ gave an 85% yield. The properties and analytical data for the unsaturated compounds are given in Table I.

The carbinols used were prepared by conventional methods by the action of methylmagnesium iodide on the appropriate acetophenone or benzoic ester. *m*-Chlorophenyldimethylcarbinol was prepared from *m*-chlorophenylmagnesium bromide and acetone. In some cases the carbinols were not isolated in a state of analytical purity because of a tendency to dehydrate upon distillation.

Experimental

Dimethylphenylcarbinols.—The preparation of 3,4-dichlorophenyldimethylcarbinol is typical. Methyl iodide (206 g., 1.46 moles) was converted to the Grignard reagent using 1 liter of dry ether and 35 g. of magnesium. Then 260 g. (1.0 mole) of 3,4-dichloroacetophenone,⁶ m. p. 74–75°, was slowly added with stirring at reflux temperature and the mixture was allowed to stand overnight. The ether solution was hydrolyzed with ice and ammonium chloride solution, washed with dilute sulfuric acid and dried over calcium chloride. Rapid distillation gave 238 g. (85%) of 3,4-dichlorophenyldimethylcarbinol, b. p. 128° (6.5 mm.), *n*_D²⁰ 1.5519.

By similar methods were prepared 2,5-dichlorophenyldimethylcarbinol⁷ which was dehydrated in the crude form. *o*-Chlorophenyldimethylcarbinol, b. p. 112–114° (3 mm.), *n*_D²⁰ 1.5396, was prepared by the action of the methyl Grignard reagent on methyl *o*-chlorobenzoate in 94% yield.⁸ The Grignard reagent from *m*-chlorobromobenzene reacted in the conventional manner with acetone at 5–10° to give a 78% yield of *m*-chlorophenyldimethylcarbinol,⁹ b. p. 119–120° (19 mm.), *n*_D²⁰ 1.5352.

***i*-Propenylbenzenes.**—The dehydration of 2,5-dichlorophenyldimethylcarbinol is typical of the method used. A mixture of the carbinol (337 g., 1.64 moles), 500 g. (4.9 moles) of acetic anhydride and 1 cc. of concentrated sulfuric acid was refluxed for fifteen hours. It was quenched in several volumes of water, and the layers separated. The water layer was neutralized with sodium hydroxide and extracted with benzene. Distillation of the combined organic portions gave 272 g. (89%) of 2,5-dichloro-*i*-propenylbenzene, b. p. 63–64° (3 mm.), *n*_D²⁵ 1.5492.

The results of similar dehydrations are given in Table I.

(1) Preceding paper of this series, *THIS JOURNAL*, **68**, 1159 (1946).

(2) Present address: Department of Chemistry, University of Michigan, Ann Arbor, Michigan.

(3) Brooks, *ibid.*, **66**, 1295 (1944).

(4) See Staudinger and Breusch, *Ber.*, **62**, 442 (1929).

(5) Mowry, Renoll and Huber, *THIS JOURNAL*, **68**, 1105 (1946).

(6) Glynn and Linnell, *Quart. J. Pharm. Pharmacol.*, **5**, 480 (1932).

(7) Similarly prepared but not isolated by Ellingboe and Fuson, *THIS JOURNAL*, **55**, 2960–2966 (1933).

(8) Bradsher and Wert, *ibid.*, **65**, 1643 (1943), report b. p. 94° (8 mm.), for a similar preparation in 82% yield.

(9) Bergmann and Weizmann, *Trans. Faraday Soc.*, **32**, 1327 (1936), report b. p. 124–126° (18 mm.), for a sample prepared from methyl *m*-chlorobenzoate and the methyl Grignard reagent.