TABLE I

DIALKYL ETHERS OF 2,2-BIS-(4-HYDROXYPHENYL)-PROPANE, $ROC_6H_4C(CH_3)_2C_6H_4OR$

R	CH_3	C_2H_5	C_3H_7	C_4H_9	C_5H_{11}
M. p., °C.	59–61.5	49–50	....	20	34.5–35.5
B. p., °C. (mm.)	190 (5)	....	200–202 (3)	212–213 (3)	225–230 (3)
n^{20}_D	1.5696[a]	1.5556[a]	1.5448	1.5368	1.5306[a]
d^{20}_4	....	....	1.0156	0.9961	....
Calcd. % C	79.63	80.23	80.72	81.11	81.46
Found % C	....	79.81	80.65	80.79	81.34
Calcd. % H	7.88	8.52	9.03	9.49	9.86
Found % H	....	8.57	9.14	9.37	9.89

[a] Value determined using the supercooled liquid.

and the heating continued for three hours. The alkali-insoluble portion of the reaction product was isolated by ether extraction, and the dibutyl derivative obtained by distillation of this solution. The yield was 35 g., or 51% of the theoretical, assuming the utilization of only one of the alkyl groups of the sulfate. It was necessary to further purify this material.

Diamyl Ether of 2,2-Bis-(4-hydroxyphenyl)-propane. The Alcohol-Sulfuryl Chloride Method.—One mole (88 g.) of pentanol-1 was cooled with an ice-bath, and 0.5 mole of sulfuryl chloride added slowly so that the reaction mixture remained cold. This was allowed to stand protected from moisture for one week. It was then neutralized with sodium hydroxide solution (approximately 0.75 mole in the form of a 10 *N* solution was needed), and a solution of 0.5 mole of 2,2-bis-(4-hydroxyphenyl)-propane in 150 cc. of potassium hydroxide (500 g. per liter) added. This was then treated and worked up as described above. The yield was 24 g., or 26% of the theoretical, assuming the formation of 0.5 mole of diamyl sulfate and the utilization of one of the alkyl groups of this sulfate in the alkylation. The product was further purified by recrystallization from methanol.

The writers wish to thank E. I. du Pont de Nemours and Co. and The Goodyear Tire and Rubber Co. for supplying certain of the materials used, and Mr. C. A. Sluhan for help with the experimental work.

Summary

This paper describes the preparation and properties of the di-*n*-alkyl ethers of 2,2-bis-(4-hydroxyphenyl)-propane from methyl to amyl.

DELAWARE, OHIO RECEIVED SEPTEMBER 3, 1935

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

The Chemistry of the Tetrose Sugars. I. A Crystalline Triacetate of *d*-Threose from the Degradation of Strontium Xylonate with Hydrogen Peroxide. Nomenclature in the Tetrose Group[1]

BY ROBERT C. HOCKETT

Within recent years so many sugars previously prepared by synthetic methods in the laboratory have been found playing an important role in natural processes that new attention is focused upon the necessity of filling those gaps which still remain in the sugar family. Particularly does this necessity apply to the sugars of low carbon atom content which are those most likely to be encountered as intermediates in the physiological degradation of glucose. The tetroses are still among the least known members of the sugar group despite the fact that the first efforts toward their preparation were made nearly fifty years ago.[2] The general methods of degrading sugars devised by Wohl and Ruff seemed at first to furnish a very promising means of attacking the problem, and centered an interest upon the tetroses particularly from 1899 to 1901,[3] but the results proved disappointing in that all the classic methods of preparing sugars are beset by special difficulties when applied to this group, so that very few crystalline compounds were prepared and few data recorded. Except for the later application of Weerman's[4] method of degradation

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[1] Publication authorized by the Surgeon General, U. S. Public Health Service. An abstract of this paper was presented before the Organic Division of the American Chemical Society in Chicago, September, 1933.

[2] Fischer and Tafel, *Ber.*, **20**, 1090 (1887).

[3] Wohl, *Ber.*, **26**, 743 (1893); *ibid.*, **32**, 3666 (1899); Ruff and Meusser, *ibid.*, **32**, 3672 (1899); Ruff, Meusser and Kohn, *ibid.*, **34**, 1362 (1901); Maquenne, *Compt. rend.*, **130**, 1402 (1900); Bertrand, *ibid.*, **130**, 1330 (1900); Fenton and Jackson, *J. Chem. Soc.*, **75**, 1 (1899); Morrell, *ibid.*, **81**, 674 (1902); Jackson, *ibid.*, **77**, 130 (1900).

[4] Weerman, *Rec. trav. chim.*, **37**, 16 (1918).

which resulted in little actual new success, the field was abandoned until recent years.

In January, 1931, we decided to undertake a complete resurvey of the known methods of degradation to determine whether advancing knowledge would now permit some of the difficulties to be surmounted. *d*-Threose was chosen as the object of search because it has received much less attention than the erythroses, and the Ruff degradation was selected as a method. In the undertaking, we had certain advantages over predecessors. (1) Xylose, our starting material, once very rare, is now available in quantity. (2) Our independent preparation of crystalline strontium xylonate[5] made possible the use of a pure anhydrous salt in the oxidation experiments. The results were far superior to those obtained by using amorphous calcium xylonate. (3) The announcement by Isbell and Frush[6] of their electrolytic oxidation of aldoses provided us with a method which proved very efficient when applied to the preparation of strontium xylonate. (4) A new method of making the ferric acetate catalyst proved to be very rapid and reliable.[7]

With these advantages, colorless strontium-free *d*-threose sirups were prepared in relatively good yield. One of these which was acetylated, after a year or more yielded crystals of the acetate which is fully described in the experimental part, and which thereafter was obtained readily. It represents a substance which can be highly purified, weighed and deacetylated almost quantitatively to give an aqueous solution of the tetrose whose concentration is pretty accurately known, thus making the sugar available in a form suitable for a variety of chemical investigations and for biological experiments, some of which are in progress.

This acetate was rigidly identified by the determination of carbon, hydrogen, acetyl and molecular weight, while the free sugar was converted into four known crystalline derivatives: erythrosazone, dibenzylidene-*d*-threitol, brucine *d*-threonate and potassium levo-bitartrate.

A standard aqueous solution of the free sugar prepared as described was used for determining its equilibrium specific rotation, which was found to be approximately[8] $-12.3°$. This result was surprising because W. Freudenberg[9] had meanwhile announced the preparation of a crystalline *d*-threose showing a positive specific rotation in water of $+19.59°$. Deulofeu[10] had also announced the preparation of *l*-threose diacetamide rotating $-7.68°$ in cold $N/3$ sulfuric acid, which changed to $-24.6°$ after heating for forty-five minutes to remove the acetamide groups. His conclusion was that the latter value represents the rotation of *l*-threose. These two reports, harmonious with one another and opposite to our result, suggested the possibility that an acetyl group had failed to be dislodged by our method of saponification with sodium methylate. Experiments involving two successive deacetylations or the use of other agents such as barium hydroxide, however, all gave us levorotatory solutions of the sugar. The discrepancy was therefore left to be explained when a totally different method of preparing *d*-threose could be carried out and the products compared. The second paper of this series will discuss this work.

It was observed that the deposition of the crystalline threose acetate always leaves a levorotatory mother liquor which suggests the presence of isomeric acetates as in the case of higher-carbon sugars. Stronger evidence is provided by the fact that a threose sirup prepared by saponification of pure acetate, when reacetylated, yields only one-third of the original acetate and two-thirds of a levorotatory sirup rotating roughly $-19.4°$ in chloroform. When the deacetylation and reacetylation is repeated upon this sirup, again one-third is recovered as the crystalline acetate and two-thirds as levorotatory sirup, strongly suggesting the existence of two (or more) closely related isomers of which at least one presumably is a ring form.

A dried *d*-threose sirup when treated with 2% dry hydrogen chloride in methanol, loses all reducing power and reaches a constant rotation in about twenty minutes at room temperature. Such behavior is to be expected of a sugar whose chain is too short for the formation of methyl pyranosides and which must form either methyl furanosides or a dimethyl acetal (Fig. 1).

Nomenclature in the Tetrose Group

Several errors and inconsistencies have arisen in the nomenclature of substances in the four-

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(5) Hockett, THIS JOURNAL, **56**, 994 (1934). *Cf.* Isbell, *Bur. Standards J. Research*, **14**, 359 (1935).

(6) Isbell and Frush, *ibid.*, **6**, 1145 (1931).

(7) Hockett and Hudson, THIS JOURNAL, **56**, 1632 (1934). *Cf.* National Formulary, 3rd edition, Baltimore, 1906, p. 219.

(8) Throughout this paper, rotations refer to specific rotations of the sodium line at 20° unless otherwise specified.

(9) W. Freudenberg, *Ber.*, **65**, 168 (1932).

(10) Deulofeu, *J. Chem. Soc.*, **225**, 2458 (1929). See also *ibid.*, 2602 (1930) and 2973 (1932).

carbon group owing in part to the small attention they have received during developments elsewhere.

In 1906, Rosanoff[11] proposed certain reforms in Fischer's nomenclature involving a change in the name of dextrorotatory xylose from *l*- to *d*-xylose. This change, promptly accepted by American[12] and British chemists in the interest of logical harmony within the system, came into general acceptance about 1923.[13] It has repercussions among names formerly assigned to certain derivatives of xylose which should be brought into conformity, as will be shown.

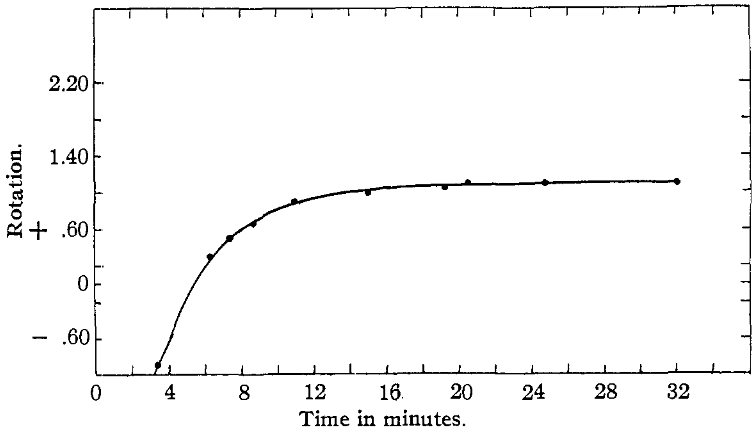

Fig. 1.—The action of 2% hydrogen chloride in methanol upon threose.

Maquenne,[3] by degrading what we now call *d*-xylose, prepared a sirup of *d*-threose (Fig. 2, I) which he erroneously called *l*-erythrose. By reducing this sugar, he obtained the alcohol which should be known as *d*-threitol (II), but which he called *l*-erythritol. Bertrand[3] meanwhile made a four-carbon ketose by the action of sorbose bacteria on the natural inactive erythritol (III). His product might *a priori* have been either *d*- or *l*-erythrulose depending upon which carbon was attacked (IV or V). That he actually obtained *l*-erythrulose (V) is indicated by the behavior of the ketose on reduction. We should expect two products, the original inactive erythritol (III) and an active alcohol either identical or enantiomorphous with Maquenne's *d*-threitol (II or VI). The products actually obtained were inactive erythritol and *l*-threitol (VI)[14] (which they called *d*-erythritol). In no text or reference work that we have examined has Bertrand's name "*d*-erythrulose" been corrected to "*l*-erythrulose" as required by consistency.

Consistency also strongly urges limiting the term "erythritol" to the natural inactive alcohol (m. p. 120–121.3°) which may also be obtained by reduction of either *d*- or *l*-erythrose, and using the terms "*d*-threitol" (rotating +4.33° in water) and "*l*-threitol" (rotating −4.4° in water) for the active tetritols derived, respectively, from the two threoses, since elsewhere in the sugar group, only enantiomorphous alcohols bear the same name, being distinguished by prefix, and forms of different configuration bear different names.

On oxidation with nitric acid, *d*-threose is converted into a dibasic acid which might consistently be called *d*-threodihydroxysuccinic acid were it not already well known as *l*-tartaric acid (VII). The latter, long ago named from its actual rotation, is not in harmony with the arbitrary standard set up by Fischer for assignment of prefixes in the sugar group, and appears destined to constitute a permanent anomaly in our nomenclature.

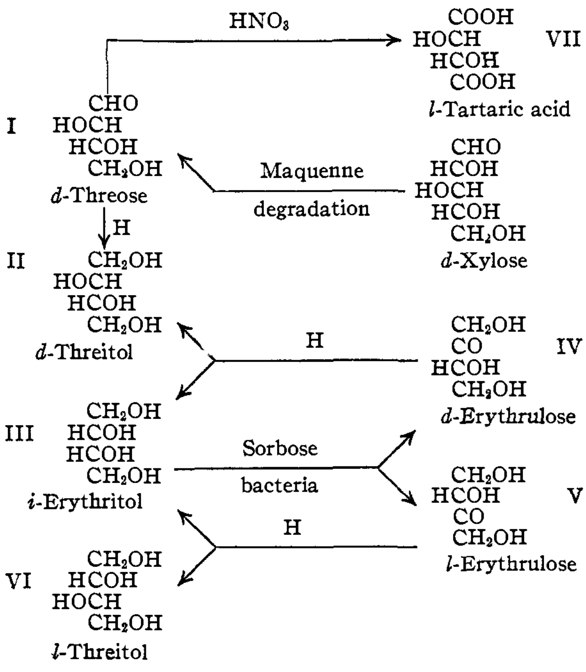

Fig. 2.

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[11] Rosanoff, THIS JOURNAL, **28**, 114 (1906); *cf*. Fischer, *Ber*., **40**, 102 (1907).

[12] Hudson and Brauns, THIS JOURNAL, **38**, 1217 (1916); *cf*. Armstrong, "The Simple Carbohydrates and the Glucosides," Longmans, Green & Co., London, 1919, pp. 78 and 80.

[13] Wohl and Momber, *Ber*., **50**, 455 (1917); Wohl and Freudenberg, *ibid*., **56**, 309 (1923).

[14] Maquenne and Bertrand, *Compt. rend*., **132**, 1419 (1901).

Experimental

Strontium *d*-xylonate.[6]—One hundred grams of xylose, 20 g. of sodium bromide, 130 g. of strontium carbonate and two liters of water are warmed to 60°, placed in a glass cell equipped with carbon electrodes providing about 200 sq. cm. of anode surface, and electrolyzed with the current from a tungar battery charger at about 10 volts and 2.6 amperes for twenty-four hours with good mechanical stirring. Another 100 g. of xylose is added each twenty-four hours until 400 g. has been used and electrolysis is continued until the reducing power toward Fehling's solution is virtually gone. After filtering, evaporating to one-half its volume, cooling and seeding, the solution crystallizes rapidly and must be stirred to prevent formation of a too solid cake. Filtered, washed with 50% alcohol and dried at 60°, the combined first and second crops represent 95% of the theoretical yield. The salt is readily recrystallized from water as the pentahydrate; drying as described yields the powdery anhydrous salt rotating +13.2° (0.4266 g. in 25 cc. of soln. in water; 2-dm. tube; 0.45° to the right).

Anal. Calcd. for $(C_5H_9O_6)_2Sr{\cdot}5H_2O$: H_2O, 17.74. Found: H_2O, 17.72. Calcd. for $(C_5H_9O_6)_2Sr$: Sr, 20.98; C, 28.72; H, 4.34. Found: Sr, 20.79, 20.77; C, 28.77; H, 4.49.

***d*-Threose Triacetate.**—Seventy-five cubic centimeters of molar barium acetate and 50.2 cc. of half-molar ferric sulfate are added to two liters of water. Then 200 g. of anhydrous strontium xylonate is added, the solution is heated to boiling, allowed to settle, filtered through filtercel, diluted with a liter of water and cooled to 35°. One hundred twenty cubic centimeters of 30% hydrogen peroxide is added and a vigorous evolution of gas ensues. When the reaction has ended (ten minutes) the solution is cooled to 35°, and another 120 cc. of hydrogen peroxide added.

After settling the solution is filtered on filtercel, concentrated *in vacuo* to 250 cc., taken up in 1500 cc. of dry methanol, warmed and shaken, and ultimately filtered. The salts are washed with 300 cc. of warm methanol. Nine hundred cubic centimeters of ether or acetone is added to the filtrate, which is stirred and allowed time to separate a flocculent precipitate. The colorless filtrate is concentrated *in vacuo* to blubbering, taken up in dry methanol and reconcentrated. Finally it is distilled down in the presence of a little ethyl acetate to remove alcohol. Ten grams of fused sodium acetate and 100 cc. of acetic anhydride are added and the mixture is warmed on a steam-bath for an hour with frequent shaking. After acetylation is complete, the mixture is poured into ice water and neutralized with sodium bicarbonate. The solution is extracted several times with chloroform, which is separated, dried with anhydrous sodium sulfate, filtered through carbon and concentrated *in vacuo*. The thick sirup is taken up in absolute alcohol, transferred to a beaker and seeded with threose acetate, which separates on cooling; yield, to 12 g. Since the crystalline isomer represents one-third of the total, the yield represents about 15% of the theoretical.

Recrystallized from absolute alcohol as very sharp, well-formed prisms, the substance after pulverizing and drying at 60° shows m. p. 117–118° (corr.) and rotates +35.55° (0.8910 g. in 26.18 cc. of chloroform soln.; 4.83° to the right; 4-dm. tube). The acetate is somewhat soluble in hot water, sparingly so in absolute alcohol, methanol and ether, and easily in chloroform, acetone and ethyl acetate.

Anal. Calcd. for $C_{10}H_{14}O_7$: C, 48.76; H, 5.73; CH_3CO, 52.44. Found: C, 48.51; H, 5.77; CH_3CO, 52.64.

Molecular Weight of Threose Acetate.—Cottrell's ebullioscopic apparatus was used with acetone as the solvent. The sample was weighed in a calibrated 25-cc. flask, made up to the mark with acetone and reweighed. An aliquot was introduced into the apparatus by pipet. A weight of 2.6272 g. of the acetate caused a dT of 0.203° in 117.6 cc. of acetone. Molecular weight found, 240; calculated for $C_{10}H_{14}O_7$, 246. The substance is clearly a monomer.

***d*-Threose.**—Five grams of crystalline *d*-threose triacetate was dissolved in 10 cc. of dried chloroform, cooled below zero and treated with 10 cc. of approximately 2% sodium methylate in dry methanol. After twenty minutes, below 0°, 10 cc. of water was added with shaking and then an exactly equivalent volume of approximately 0.5 *N* sulfuric acid (as determined by previous titration against the sodium methylate). The whole mixture was concentrated nearly to dryness *in vacuo* at a low temperature and the sugar was taken up in 90% alcohol, leaving behind most of the sodium sulfate. Successive extractions eliminated all but a trace of salt and yielded a colorless solution of the sugar.

An accurately weighed sample, so deacetylated, concentrated to dryness and then made up to volume with water in a 50-cc. calibrated flask showed an equilibrium rotation for the free sugar of −12.3° (1.1268 g. of sugar (calcd.) in 50 cc. soln. in water; 0.277° to the left; 1-dm. tube). After elimination of practically all the sodium sulfate, the rotation was virtually unchanged.

Another sample was deacetylated with a clear aqueous solution of barium hydroxide at 30°. After complete solution of the acetate and quantitative removal of barium, the solution was levorotatory.

Barium methylate did not remove the acetyls completely.

After two successive deacetylations with sodium methylate, the same specific rotation was obtained.

***d*-Threosazone (*d*-Erythrosazone).**—An aqueous solution of *d*-threose, acidified with acetic acid and warmed for three-quarters of an hour with 5 cc. of phenylhydrazine, deposited yellow needles on cooling. Recrystallized from benzene and dried at 55°, these showed m. p. 164–165° when heated at one degree per minute. Erythrosazone has been reported about a dozen times[3] with melting point from 163 to 174°. The most frequent value is 164°.

Dibenzylidene-*d*-threitol.—The sugar from five grams of the triacetate was diluted to 100 cc. with water and well stirred at room temperature while 2% sodium amalgam was added in 50-g. portions and 20% sulfuric acid added dropwise to maintain a slight acidity to Congo red. After addition of 450 g. of amalgam, the reducing power had disappeared. The mercury was separated, the solution neutralized to phenolphthalein, concentrated to a sirup and the threitol extracted from sodium sulfate with 50 cc. of hot absolute alcohol. The extract was concentrated to a thick sirup, taken up in absolute alcohol, filtered from traces of sodium sulfate, and then reconcentrated. Finally, the sodium-free substance in 30 cc. of alcohol solution was saturated with dry hydrogen chloride and 5 cc. of benzaldehyde added whereupon fine needles promptly separated. Refrigerated, filtered, washed free of acid with absolute alcohol and dried, they weighed 7 g. After recrystallization from fifteen parts of hot benzene as clusters of fine needles, filtration, washing with cold benzene and drying *in vacuo* at 75°, they rotated −78.2° (0.1860 g. in 25 cc. of chloroform soln.; 1.163° to the left; 2-dm. tube) and melted 214–216° (corr.).

After further recrystallization from a mixture of 50 cc. of chloroform with 15 cc. of absolute alcohol and drying at 90° in a high vacuum, the substance showed m. p. 218–222° (corr.) with heating at a half-degree per minute, and rotated −78.3° (0.2102 g. in 25 cc. of chloroform soln.; 1.315° to the left; 2-dm. tube).

The substance dissolves in cold chloroform to about one part in one hundred; much more on warming. About seven parts per hundred dissolve in boiling benzene and less in alcohol.

Ruff[3] gives a melting point of 204–205° for dibenzylidenethreitol. Ours is the first report of its rotation.

Brucine *d*-Threonate.—The sugar from 5 g. of the triacetate was dissolved in 150 cc. of water and treated with 1.2 cc. of bromine in the presence of 12 g. of barium benzoate for forty-eight hours. The reducing power having then disappeared, the solution was worked up in the usual way[15] and the concentrated aqueous solution of threonic acid was treated with a slight excess of purified brucine. On concentrating further, the salt crystallized in the flask; free brucine was extracted with absolute alcohol and the salt purified by two recrystallizations from 85% alcohol as fine clear needles. Dried for two hours in a vacuum at 60°, they melted 197–198° (corr.) with heating at 3° per minute. The rate of heating had a strong effect upon the melting point which was only 187–190° at 1° per minute. The crystals rotated −36.8° (0.4420 g. in 25 cc. of water soln.; 1.025° to the left; 2-dm. tube). Anderson[16] gives m. p. 213–214° and rotation −32.40°. On account of our limited amount of material, we did not attempt to set a new standard of value for these constants, but consider the agreement good evidence of identity. Wohl and Momber[13] give m. p. 204° and rotation −29.9° (at 17°).

Oxidation of *d*-Threose to *l*-Tartaric Acid.—A solution of 1.5 g. of threose in 6 cc. of nitric acid (sp. gr. 1.2) was allowed to stand at room temperature until a violent reaction had occurred. The next morning the acid was distilled off *in vacuo* to a thin sirup which was several times taken up in water and reconcentrated. The sirup nearly free of nitric acid was dissolved in water and neutralized with caustic potash. Then several cubic centimeters of 10% acetic acid were added, and alcohol to a concentration of 50%, which precipitated a gum. After several days, the mother liquor was decanted and fresh 50% alcohol added to the gum whereupon it became crystalline through the separation of needles of potassium *l*-bitartrate. They were recrystallized by dissolving in a little water, filtering through carbon, and adding alcohol, were washed with dilute, then pure alcohol, and dried at 50°.

Anal. Subs. 0.1845 g. Calcd. for titration of $KH(C_4H_4O_6)$, 4.91 cc. of 0.2000 *N* NaOH. Found: 4.89 cc.

The neutralized solution of sodium potassium *l*-tartrate rotated −29.40° (at 24°) (0.2061 g. in 50 cc. of water soln.; 0.242° to the left; 2-dm. tube). Landolt[17] gives +29.7° for sodium potassium *d*-tartrate.

We wish to express to Dr. C. S. Hudson, Chief of the Division of Chemistry, our gratitude for the patient and sympathetic interest which made this work possible. Our thanks are also due Dr. F. H. Goldman, Dr. E. L. Jackson and Mr. C. G. Remsburg for analyses reported in this paper.

Summary

1. Ruff's method of degrading sugars has been applied in an improved form to the preparation of *d*-threose from crystalline strontium *d*-xylonate.

2. The electrolytic oxidation of xylose and preparation of the strontium salt is described.

3. The oxidation of strontium *d*-xylonate with 30% hydrogen peroxide yielded 15% of *d*-threose in an impure sirup.

4. The sugar was separated as a crystalline triacetate which is described, and from which after purification, aqueous threose sirups of known concentration can be prepared for chemical and biological study.

5. The sugar was identified by conversion into four known crystalline derivatives.

6. Its equilibrium rotation in water was found to be approximately −12.3°, a result in conflict with two reports by other investigators of a dextrorotation.

7. Some errors in nomenclature in the tetrose group are corrected.

WASHINGTON, D. C. RECEIVED AUGUST 2, 1935

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(15) Hudson and Isbell, THIS JOURNAL, **51**, 2225 (1929).

(16) Anderson, *Am. Chem. J.*, **42**, 423 (1909).

(17) Landolt, *Ber.*, **6**, 1076 (1873).