THE SYNTHESIS OF D-ERYTHRO-PENTULOSE

DISSERTATION

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for the Degree Doctor of Philosophy in the
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By

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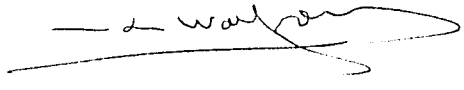
Approved by



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INTRODUCTION

When we consider the progress that has been made in the field of organic chemistry in the past century, it is not too difficult to both understand and appreciate the tremendous amount of research that has been directed toward the general area of carbohydrate chemistry. Although the subject is large and extensive and early attracted numerous investigators, the great tendency of carbohydrates to resist attempts at crystallization allowed little early progress in the field.

Prior to 1884 only three aldoses (D-glucose, D-galactose and L-arabinose) and two ketoses (D-fructose and L-sorbose) were known. In that year Emil Fischer (1), through the discovery

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(1) E. Fischer, Ber., 17, 579 (1884).

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that phenylhydrazine would yield crystalline derivatives with carbohydrates, began his brilliant classical investigations concerning the structures and stereochemical relationships (2)

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(2) E. Fischer, "Untersuchungen über Kohlenhydrate und Fermente," Springer, Berlin (1909).

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of the carbohydrates. Thus with this and other powerful tools that had become available, by 1890 (3), twenty-one aldoses,

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(3) E. Fischer, Ber., 23, 2114 (1890).

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including some methyloses, were recognized. Of the ketoses, "glycerose" (a mixture of glyceraldehyde and dihydroxyacetone), D-fructose, L-fructose, DL-fructose (α-acrose), DL-sorbose (β-acrose), and L-sorbose were known.

Since that time many investigators have added a tremendous amount of information to our general knowledge of carbohydrate chemistry, including such fundamental information as the question of the ring structures of the saccharides (4) and more recently,

(4) W. N. Haworth, "The Constitution of Sugars," Arnold, London (1929).

evidence concerning the true aldehydic nature (5) of the

(5) M. L. Wolfrom, Carbohydrates I, Gilman's "Organic Chemistry," Vol. II, 2nd Ed., John Wiley and Sons, New York (1943).

monosaccharides.

The ketoses, however, have not been so thoroughly investigated as the aldoses, because they are less readily available from natural sources and also because the past synthetic methods, other than not being generally applicable to all ketoses, usually produce complex and difficultly separable mixtures in low yields by rather tedious methods.

A general method for the synthesis of ketoses, devoid of most of these objections, has been developed in this laboratory

by M. L. Wolfrom and co-workers (6,7). This synthetic method

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(6) M. L. Wolfrom, S. W. Waisbrot and R. L. Brown, J. Am. Chem. Soc., 64, 2329 (1942).
(7) M. L. Wolfrom and J. B. Miller, J. Am. Chem. Soc., 80, 1678 (1958).

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consists of the conversion of an aldose to the next higher - carbon ketose and utilizes a carbohydrate diazomethyl ketone as a labile intermediate.

This dissertation therefore describes further developments of this technique and represents the first extension of this method to the synthesis of a five-carbon ketose, D-erythro-pentulose ("D-ribulose").

STATEMENT OF THE PROBLEM

The objectives of this work have been ——

1. To synthesize the ketopentose possessing the D-*erythro* configuration in the acyclic or free *keto*-form as a crystalline tetraester utilizing the diazomethyl ketone ketose synthesis.

2. To prove the free *keto*-structure of the crystalline ketopentose tetraester.

3. To transform the acyclic ketopentose tetraester into the free carbohydrate.

4. To demonstrate the identity of the free pentulose from the diazomethyl ketone ketose synthesis to that of the compound obtained from the pyridine interconversion of D-arabinose via a suitable crystalline derivative.

HISTORICAL

The Reaction of Diazomethane upon Acyclic Carbohydrate Derivatives

The Reaction of Diazomethane upon Carbohydrate Acid Chlorides

The first recorded preparation of a diazo compound was the isolation of a yellow crystalline substance as a result of the diazotization of 3-aminocamphor (8). This method

(8) R. Schiff, Ber., 14, 1375 (1881).

was extended by Curtius (9) in 1883 to α-amino esters with

(9) T. Curtius, Ber., 16, 2230 (1883).

the preparation of ethyl diazoacetate from ethyl glycinate. In 1894 von Pechmann (10) produced a diazoalkane, diazomethane,

(10) H. von Pechmann, Ber., 27, 1888 (1894).

by the action of alcoholic potassium hydroxide on N-methyl-N-nitrosobenzamide. It was not until twenty years later in 1914 that Geake and Nierenstein (11) first treated a carbohydrate

(11) A. Geake and M. Nierenstein, Hoppe-Seyler's Z. physiol. Chem., 92, 149 (1914).

substance, cellulose, with a diazo compound in an attempt to prepare the methyl ethers of the free hydroxyl groups.

The action of diazomethane upon an acid chloride was first studied by Clibbens and Nierenstein (12) who obtained α-chloro-

(12) D. A. Clibbens and M. Nierenstein, J. Chem. Soc., 1491 (1915).

acetophenone from benzoyl chloride and diazomethane. Arndt and co-workers (13) demonstrated that such a reaction may follow a

(13) F. Arndt, B. Eistert and W. Partale, Ber., 60, 1364 (1927); F. Arndt and J. Amende, Ber., 61, 1122 (1928).

different course and obtained diazomethyl ketones from a number of acid chlorides.

The initial products formed in the reaction of diazomethane with an acid halide are the diazomethyl ketone and hydrogen halide. This latter compound can thus further react with the diazomethyl ketone unless excess diazomethane or an added base, such as triethylamine (14), is present. From this reaction we can thus

(14) M. S. Newman and P. Beal, III, J. Am. Chem. Soc., 71, 1506 (1949).

obtain diazomethyl ketones (13,15,16) or halomethyl ketones

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(15) W. Bradley and R. Robinson, J. Chem. Soc., 1310 (1928).
(16) W. Bradley and G. Schwarzenbach, J. Chem. Soc., 2904 (1928).

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depending on the exact way in which the reaction is carried out.

$$RCOX + CH_2N_2 \rightarrow RCOCHN_2 + HX \rightarrow RCOCH_2X + N_2$$

$$\downarrow CH_2N_2$$

$$CH_3X + N_2$$

This subtlety of conditions had been overlooked and resulted in a published dispute in the American literature by British authors (17,18).

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(17) T. Malkin and M. Nierenstein, J. Am. Chem. Soc., 52, 1504 (1930).
(18) W. Bradley and R. Robinson, J. Am. Chem. Soc., 52, 1558 (1930).

The first carbohydrate diazo compound was produced in 1938 by Gätzi and Reichstein (19) who obtained a diazomethyl ketone

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(19) K. Gätzi and T. Reichstein, Helv. Chim. Acta, 21, 186 (1938).

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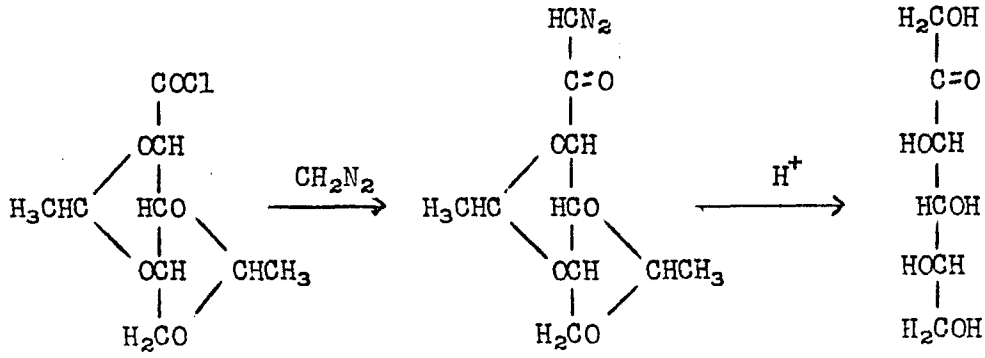
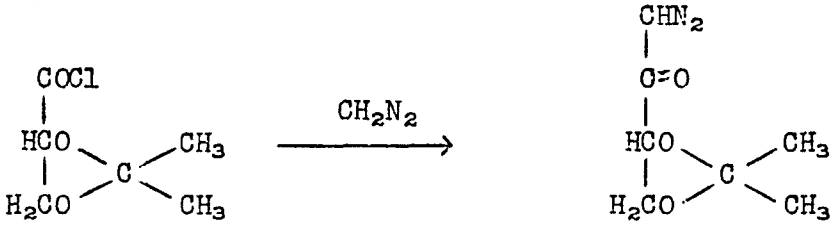
from the action of diazomethane upon di-O-ethylidene-L-xylonyl



chloride. Hydrolysis of the sirupy diazomethyl ketone with dilute sulfuric acid gave L-sorbose. Simarly, Iwadare (20)

(20) K. Iwadare, Bull. Chem. Soc. Japan, 14, 131 (1939); C. A., 33, 6250 (1939).

obtained a sirupy diazomethyl ketone by the reaction of isopropylidene-D-glyceryl chloride with diazomethane.

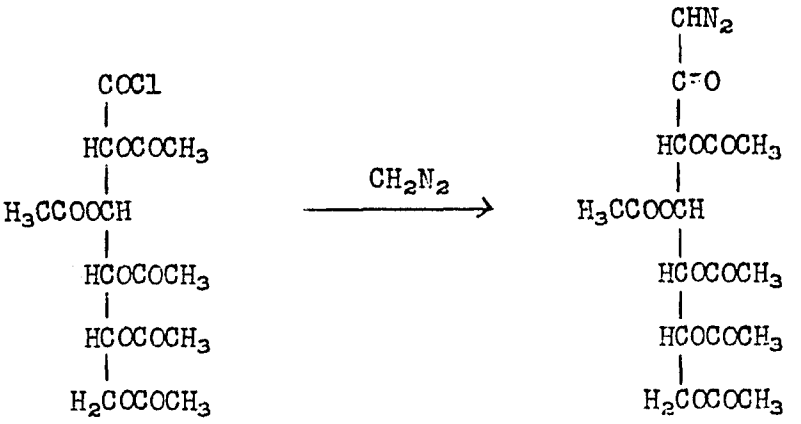


In 1941, Wolfrom and co-workers (21) reported the synthesis

(21) M. L. Wolfrom, D. I. Weisblat, W. H. Zophy and S. W. Waisbrot, J. Am. Chem. Soc., 63, 201 (1941).

of the first crystalline carbohydrate diazomethyl ketone, 1-deoxy-1-diazo-keto-D-gluco-heptulose pentaacetate from the

reaction of D-gluconyl chloride pentaacetate with diazomethane.



Since that time some nineteen carbohydrate diazomethyl keto-esters, including one free diazomethyl ketone, have been prepared and studied by Wolfrom and co-workers. Table I is a listing of these compounds and their constants prepared to date.

The Reaction of Carbohydrate Diazomethyl Ketones

In 1912, Wolff (34,35) reported a rearrangement of diazomethyl

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(34) L. Wolff, Ann., 394, 23 (1912).
(35) L. Wolff and R. Gruelich, Ann., 394, 36 (1912).

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ketones which today forms the most essential part of the Arndt-Eistert (36) method for carbon chain extension. Isotopic

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(36) F. Arndt and B. Eistert, Ber., 68, 200 (1935).

$$RCO_2H \rightarrow RCOX \rightarrow RCOCHN_2 \rightarrow [R\text{-}CH{=}C{=}O] \rightarrow RCH_2CO_2H$$

Table I

Carbohydrate Diazomethyl Ketones

1-Deoxy-1-diazo-keto-	M.p., °C.	[α] D	Reference
D-gluco-Heptulose pentaacetate	106-106.5	+65.8	21
D-Fructose tetraacetate	93-94	-11	22
1,8-Bis(diazo)-mucyldimethane tetraacetate (1,8-dideoxy-di-keto-gala-octadiulose 3,4,5,6-tetraacetate	179-180		6
D-gala-Heptulose pentaacetate	136-137	+64	23
D-gala-Heptulose	140 (dec.)	+82	23
D-Sorbose tetraacetate	124.5-125.5	+44.5	24
D-Psicose tetraacetate	73-75	+2.0	25
L-Fructose tetraacetate	93-94	+11	26
DL-Fructose tetraacetate	113-114.5		26
D-gluco-L-tagato-Octose hexaacetate	110-111	+84.6	27
L-gala-Heptulose pentaacetate	136.5-137.5	-59	28
D-gala-L-tagato-Octose hexaacetate	120-122	+22	29
D-gala-L-sorbo-Octose hexaacetate	133-135	-29.5	29
D-manno-L-fructo-Octose hexaacetate	128-130	+50	30
L-manno-Heptulose pentaacetate	75-76	-12	31

Table I (Contd.)

1-Deoxy-1-diazo-keto-	M.p., °C.	[α] D	Reference
D-altro-Heptulose pentaacetate	sirup		32
D-erythro-L-manno-Nonulose heptaacetate	156-157	+12.7	33
D-erythro-L-gluco-Nonulose heptaacetate	74-76	-26.5	33
D-erythro-Pentulose tribenzoate	95-96	-28	This work

(22) M. L. Wolfrom, S. W. Waisbrot and R. L. Brown, J. Am. Chem. Soc., 64, 1701 (1942).

(23) M. L. Wolfrom, R. L. Brown and E. F. Evans, J. Am. Chem. Soc., 65, 1021 (1943).

(24) M. L. Wolfrom, S. M. Olin and E. F. Evans, J. Am. Chem. Soc., 66, 204 (1944).

(25) M. L. Wolfrom, A. Thompson and E. F. Evans, J. Am. Chem. Soc., 67, 1793 (1945).

(26) M. L. Wolfrom and A. Thompson, J. Am. Chem. Soc,, 68, 791 (1946).

(27) M. L. Wolfrom and A. Thompson, J. Am. Chem. Soc., 68, 1453 (1946).

(28) M. L. Wolfrom, J. M. Berkebile and A. Thompson, J. Am. Chem. Soc., 71, 2360 (1949).

(29) M. L. Wolfrom and P. W. Cooper, J. Am. Chem. Soc., 71, 2668 (1949).

(30) M. L. Wolfrom and P. W. Cooper, J. Am. Chem. Soc., 72, 1345 (1950).

(31) M. L. Wolfrom and H. B. Wood, J. Am. Chem. Soc., 73, 730 (1951).

(32) M. L. Wolfrom, J. M. Berkebile and A. Thompson, J. Am. Chem. Soc., 74, 2197 (1952).

(33) M. L. Wolfrom, H. B. Wood, Jr., J. Am. Chem. Soc., 77, 3096 (1955).

labeling (37) as well as the isolation, in some cases (38,39),

(37) C. Huggett, R. T. Arnold, and T. S. Taylor, J. Am. Chem. Soc., 64, 3043 (1942).
(38) G. Schroeter, Ber., 42, 2336 (1909); 49, 2697 (1916).
(39) H. Staudinger and H. Hirzel, Ber., 49, 2522 (1916).

of the ketene intermediate has proved that a true rearrangement occurs.

In the carbohydrate field the Wolff rearrangement has been applied to 1-diazo-1-deoxy-keto-D-gluco-heptulose pentaacetate with the production of a 2-deoxy lactone, 2-deoxy-D-gluco-heptono-δ-lactone tetraacetate (22). This method might provide for an excellent synthetic route to the 2-deoxy sugars but requires a demonstration of configuration at C3 of the deoxy compound since epimerization could occur at this point during the rearrangement. According to Lane and Wallis (40), this rearrangement may take

(40) J. F. Lane and E. S. Wallis, J. Org. Chem., 6, 443 (1941).

place with racemization provided that the terminal carbon of the migrating group contains a hydrogen atom. The extent of the rearrangement depends largely on the conditions employed (41).

(41) K. B. Wiberg and F. W. Hutton, J. Am. Chem. Soc., 78, 1640 (1956).

This structural prerequisite was present in the carbohydrate diazomethyl ketone, 1-diazo-1-deoxy-keto-D-gluco-heptulose pentaacetate and accordingly a mixture (not necessarily equimolecular) of the gluco- and manno-heptonic acids (or lactones) would be predictable. Only one product was isolated in 70 per cent yield and was provisionally assigned the gluco- structure.

In 1885 Curtius (42) demonstrated that the diazomethyl

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(42) T. Curtius, Ber., 18, 1283 (1885).

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group would react readily with iodine to form a diiodomethyl group. This reaction was applied to the carbohydrate field by Wolfrom and Brown (43) with the synthesis of crystalline

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(43) M. L. Wolfrom and R. L. Brown, J. Am. Chem. Soc., 65, 1516 (1943).

1-deoxy-1,1-diiodo-keto-D-gala-heptulose pentaacetate (see Table II).

In 1910, Forster and Zimmerli (44) found that ammonium

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(44) M. O. Forster and A. Zimmerli, J. Chem. Soc., 97, 2156 (1910).

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sulfide may reduce a diazo group to a hydrazone and thus demonstrated the complete reversibility of the diazo-hydrazone

Table II

Carbohydrate Halo-keto-acetates

Halogen Compounds	M.p., °C.	[α] D	Reference
1-Chloro-1-deoxy-keto-D-fructose tetraacetate	77.5-78	+68	22
1-Bromo-1-deoxy-keto-D-fructose tetraacetate	67-68	+65	43,22
1-Deoxyl-1-iodo-keto-D-fructose tetraacetate	55-56	+63	43
1-Chloro-1-deoxy-keto-D-gluco-heptulose pentaacetate	100-101	- 2.8	43,22
1-Bromo-1-deoxy-keto-D-gluco-heptulose pentaacetate	87-88	- 5.5	43,22
1-Deoxy-1-iodo-keto-D-gluco-heptulose pentaacetate	79-81,89-90	- 9.9	43
1,8-Dichloro-mucyldimethane tetraacetate (1,8-dichloro-1,8-dideoxy-di-keto-gala-octadiulose 3,4,5,6-tetraacetate	174-175		6
1-Chloro-1-deoxy-keto-D-gala-heptulose pentaacetate	89-90,101-102	-32.5	43
1-Bromo-1-deoxy-keto-D-gala-heptulose pentaacetate	124-125	-36	43
1-Deoxy-1-iodo-keto-D-gala-heptulose pentaacetate	144-146	-44.8	43
1-Deoxy-1,1-diiodo-keto-D-gala-heptulose pentaacetate	160-163	+13	43

Table II (Contd.)

Halogen Compounds	M.p., °C.	$[\alpha]_D$	Reference
1-Chloro-1-deoxy-keto-D-psicose tetraacetate	89-91	-26	25
1-Bromo-1-deoxy-keto-D-psicose tetraacetate	77-79	-15.1	25
1-Deoxy-1-iodo-keto-D-psicose tetraacetate	64-65	+ 6.8	25

system. Staudinger (45) has also reported that reduction of a

(45) H. Staudinger, L. Hammet and J. Siegwart, Helv. Chim. Acta, 4, 228 (1921).

$$R_2CN_2 \underset{[O]}{\overset{(NH_4)_2S}{\rightleftharpoons}} R_2C\ NNH_2$$

diazo group with hydrogen sulfide is unsuccessful in the absence of ammonium hydroxide. Hydrazones are also reported to result by reduction with ferrous oxide (46) and ferrous sulfate (47).

(46) P. Karrer, "Organic Chemistry," Elsevier Publishing Company, Inc., New York (1950), p. 294.
(47) A. Darapsky and M. Prabhakar, Ber., 45, 1654 (1912).

Many products have been reported for the reduction of the diazo group with sodium amalgam (47), zinc and sodium hydroxide (48),

(48) R. Jay and T. Curtius, Ber., 27, 775 (1894).

aluminum amalgam (49), zinc and acetic acid (8,9,44,47,50) and

(49) H. Staudinger, Alice Gaule and J. Siegwart, Helv. Chim. Acta, 4, 212 (1921).
(50) T. Curtius, J. prakt. Chem., 146, 396 (1888).

catalytic reduction with palladium and hydrogen (51).

(51) L. Birkofer, Ber., 80, 83 (1947).

Reduction with hydrogen sulfide in the presence of ammonium hydroxide gave the 1-hydrazone of 3,4,5,6-tetra-O-acetyl-D-arabino-hexosone from 1-deoxy-1-diazo-keto-D-fructose tetraacetate and 3,4,5,6,7-penta-O-acetyl-D-gala-heptosone-1-hydrazone from 1-deoxy-1-diazo-keto-D-gala-heptulose pentaacetate (7). Attempts to cleave the hydrazone and obtain an acyclic osone acetate were not successful. Aluminum amalgam reduction of 1-deoxy-1-diazo-keto-D-gala-heptulose pentaacetate gave 1-deoxy-keto-D-gala-heptulose pentaacetate but in inferior yield to the hydriodic acid method of Wolfrom and Brown (43).

Halogen acids react with diazo compounds with the elimination of nitrogen (9,50,52). This reaction has been utilized in the

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(52) T. Curtius, Ber., 16, 753 (1883).

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carbohydrate field by Wolfrom and co-workers (43) to prepare a variety of 1-deoxy-1-halo-keto-acetates (see Table II). Hydrogen iodide can be used, depending on the concentration, to produce either the monoiodo compound or the methyl ketone. The latter compound can also be prepared from either the 1-deoxy-1-iodo- or the 1-deoxy-1,1-diiodo-compound with hydriodic acid.

$$RCOCHN_2 + HI \rightarrow RCOCH_2I + N_2$$

$$RCOCHN_2 + I_2 \rightarrow RCOCHI_2 + N_2$$

$$\left.\begin{matrix} RCOCHN_2 \\ RCOCH_2I \\ RCOCHI_2 \end{matrix}\right\} + HI \rightarrow RCOCH_3$$

Curtius reported in 1883 (9) that the reaction of a diazo compound with an organic acid would produce an ester. This

$$R'CO_2H + R_2CN_2 \rightarrow N_2 + R'CO_2CHR_2$$

reaction thus enables one to convert an aldehyde to a hydroxymethyl ketone.

$$RCHO \rightarrow RCO_2H \rightarrow RCOCl \rightarrow RCOCHN_2 \rightarrow RCOCH_2OCOR \rightarrow RCOCH_2OH$$

This reaction sequence was first employed in the carbohydrate field to produce the known fructose derivative (6). The diazomethyl ketone obtained from D-arabinonyl chloride tetraacetate and diazomethane was found to react smoothly with glacial acetic acid to produce the open chain or keto form of D-fructose pentaacetate, a derivative that had been synthesized by Hudson and Brauns (53) by a direct acetylation procedure and whose

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(53) C. S. Hudson and D. H. Brauns, J. Am. Chem. Soc., 37, 2736 (1915).

---

open-chain structure is established (54,55).

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(54) E. Pacsu and F. V. Rich, J. Am. Chem. Soc., 55, 3018 (1933).

(55) M. L. Wolfrom and A. Thompson, J. Am. Chem. Soc., 56, 880 (1934).

By replacing acetic acid by several acetylated aldonic acids some novel 1 → 1 ester linked disaccharides have been prepared (43).

Diazomethyl ketones have also been demonstrated to react with sulfuric acid (56).

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(56) M. S. Newman and P. F. Beal, III, J. Am. Chem. Soc., 72, 5161 (1950).

$$2\ RCOCHN_2 + H_2SO_4 \rightarrow (RCOCH_2)_2SO_4 + 2\ N_2$$

With the proper catalysts, diazomethyl ketones will react with alcohols (56).

$$C_6H_5COCHN_2 + ROH \xrightarrow[ET_2O]{BF_3} C_6H_5COCH_2OR + N_2$$

The Reaction of Diazomethane upon Carbohydrate aldehydo-Acetates

An extensive amount of work has been directed to the reaction of diazomethane with aldehydes (57) to give, as the usual products,

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(57) C. D. Gutsche, Organic Reactions, 8, 364 (1954).

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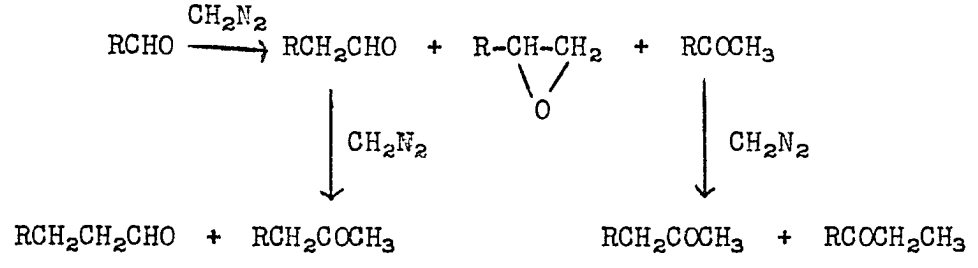
the homologous epoxides or carbonyl compounds.



In the carbohydrate field, Brigl and co-workers (58) first

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(58) P. Brigl, H. Mühlschlegel and R. Schinle, Ber., 64, 2921 (1931).

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reported the action of diazomethane upon an aldehydo-sugar and obtained from 3,4,5,6-tetra-O-benzoyl-D-glucose a product which was probably 1-deoxy-4,5,6,7-tetra-O-benzoyl-keto-D-gluco-heptulose. Wolfrom and co-workers (21) have contributed the only major effort in this field having treated aldehydo-D (and L)-arabinose tetraacetate, aldehydo-D-glucose pentaacetate and aldehydo-D-galactose pentaacetate with diazomethane.

From the arabinose derivative there was obtained 1-deoxy-keto-D (and L)-fructose tetraacetate (14), a dimethylene compound which has been shown to be 1,2-dideoxy-3-keto-D (and L)-arabino-heptulose tetraacetate (this work) and a compound which represents the addition of one methylene group to the starting material. The latter compound on reduction and acetylation failed to give 2-deoxy-D-arabino-hexitol pentaacetate ("2-deoxy-sorbitol pentaacetate"). This fact, along with the reported properties of 2-deoxy-aldehydo-D-arabino-hexose tetraacetate ("2-deoxy-aldehydo-D-glucose tetraacetate") seems to indicate that the monomethylene compound is either 2-deoxy-aldehydo-D-xylo-hexose tetraacetate ("2-deoxy-aldehydo-D-idose tetraacetate") or one of the possible epoxides.

Recently the action of diazomethane on the pentaacetates of aldehydo-D-glucose and aldehydo-D-galactose has been reported (59). In this manner 1,2-dideoxy-3-keto-D-gala-octulose

(59) M. L. Wolfrom, D. I. Weisblat, E. F. Evans, and J. B. Miller, J. Am. Chem. Soc., 79, 6454 (1957).

pentaacetate, 1,2-dideoxy-3-keto-D-gluco-octulose pentaacetate, and 1-deoxy-keto-D-gluco-heptulose pentaacetate were obtained in definitive crystalline form consistent with the established reaction scheme as illustrated previously.

The Diazomethyl Ketone Ketose Synthesis

The reaction of diazomethyl ketones with organic acids, introduced by Curtius in 1888 (50), was utilized by Bradley and Robinson (60) who described the reaction of a diazomethyl ketone

(60) W. Bradley and R. Robinson, J. Chem. Soc., 1310 (1928); ibid., 1545.

with acetic acid to produce an acetoxymethyl ketone. With the availability in the sugar series of crystalline diazomethyl ketones, the application of the reaction of Bradley and Robinson to these compounds by Wolfrom and co-workers (6,7) thus made feasible the general synthesis of ketoses in their acyclic or keto-acetate structure. This reaction therefore provides for the transformation of an aldose into the next higher ketose.

$$RCHO \rightarrow RCO_2H \rightarrow RCOCl \rightarrow RCOCHN_2 \rightarrow RCOCH_2OCOR \rightarrow RCOCH_2OH$$

In order to utilize this sequence of reactions it is necessary to convert the aldose into an aldonic acid. The tendency of aldonic acids to lactonize presents difficulties and, even for those cases where the free aldonic acid can be suitably prepared, the free hydroxyl groups must be blocked as any reagent to effect the transformation of an acid to an acid halide would also react with the hydroxyl groups. This problem has been solved by Wolfrom and co-workers with the synthesis of blocked aldonic acids from blocked aldonamides as is also illustrated by this work. This method undoubtedly owes its success to the fact that each component reaction leads in general to but a single molecular species thus favoring the isolation of the products in crystalline form. Recently, 4-deoxy-L-glycero-tetrulose diacetate ("1,3-di-O-acetyl-4-deoxy-L-erythrulose") (61), an important compound in

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(61) J. Fried, Doris E. Waley, and O. Wintersteiner, J. Am. Chem. Soc., 68, 2746 (1946).

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the proof of structure of streptomycin, has been synthesized by this method.

Thus this general preparative method, introduced by Wolfrom and co-workers (6), has provided for the synthesis of all the keto-acetates of the hexuloses (except tagatose) along with some of the heptuloses, octuloses and nonuloses. Deacetylation has afforded the free ketoses. Table III is a listing of the keto-esters and their constants prepared to date by this synthetic route.

Table III

Carbohydrate keto-Esters

Compounds	M.p., °C.	[α] D	Reference
keto-D-Fructose pentaacetate	69-70	+35	6
keto-D-gluco-Heptulose hexaacetate	104-105	+18.7	6
1,8-Dihydroxy-mucyldimethane hexaacetate (1,8-dihydroxy-1,8-dideoxy-di-keto-gala-octadiulose 1,3,4,5,6,8-hexaacetate)	193-195		6
keto-D-gala-Heptulose hexaacetate	101.5-102.5 (116-117)	- 1.6	23
keto-D-gala-Heptulose pentaacetate-1-(penta-O-acetyl-D-galactonate)	171.5-172.5	+13.0	43
keto-D-gala-Heptulose pentaacetate-1-(penta-O-acetyl-D-gluconate)	112-113	+22.0	43
keto-D-gala-Heptulose pentaacetate-1-(tetra-O-acetyl-D-arabonate	155.5-156.5	+22.5	43
keto-D-Sorbose pentaacetate	97.5-98.5	- 2.5	24
keto-DL-Sorbose pentaacetate	83-84	0	24
keto-D-Psicose pentaacetate	63-65	-21.5	25
keto-L-Fructose pentaacetate	69-70	-35	26

Table III (Contd.)

Compounds	M.p., °C	[α] D	Reference
keto-DL-Fructose pentaacetate	99-100	0	26
keto-D-gluco-L-tagato-Octose heptaacetate	77-79	+35	27
keto-L-gala-Heptulose hexaacetate	101.5-102.5	+21.5	28
keto-DL-gala-Heptulose hexaacetate	149.5-150.5	0	28
keto-D-gala-L-tagato-Octose heptaacetate	sirup	+31	29
keto-D-gala-L-sorbo-Octose heptaacetate	104-106	+11	29
keto-D-manno-L-fructo Octose heptaacetate	86-88	-14.9	30
keto-L-manno-Heptulose hexaacetate	97-98	- 3.6	31
keto-D-altro-Heptulose hexaacetate	sirup		32
keto-D-erythro-L-manno-Nonulose octaacetate	sirup	+16.8	33
keto-D-erythro-L-gluco-Nonulose octaacetate	amorphous	+ 7.5	33
keto-D-erythro-Pentulose tetrabenzoate	142-143	+31.5	This work

D-erythro-Pentulose

Previous Synthetic Work

Near the beginning of the present century, the first attempts at the synthesis of the ketopentoses were made. These experiments led to poorly defined mixtures about which little information could be gained. The first claim for the possible isolation of a ketopentose was in a sirupy product obtained from the action of calcium hydroxide upon formaldehyde (62,63). Most

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(62) E. Fischer, Ber., 21, 988 (1888).
(63) E. Fischer and F. Passmore, Ber., 22, 359 (1889).

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of the work at this time had as its basis, however, the direct oxidation of the available sugar alcohols. In this way, Fischer (64,65) obtained a sirupy reducing product from the

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(64) E. Fischer, Ber., 26, 633 (1893).
(65) E. Fischer, Ber., 27, 2486 (1894).

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oxidation of ribitol with bromine in the presence of sodium carbonate. Similarly, in 1902 Neuberg (66,67) produced reducing

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(66) C. Neuberg, Ber., 35, 959 (1902).
(67) C. Neuberg, Ber., 35, 2626 (1902).

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sirups from the action of lead oxide and hydrochloric acid upon ribitol and by the reaction of hydrogen peroxide with D-arabinitol.

The preparative problem of the erythro-pentuloses essentially laid dormant until Levene and Hill (68) reported in 1933 that

(68) P. A. Levene and D. W. Hill, J. Biol. Chem., 102, 563 (1933).

the method of Fischer and co-workers (69) of the pyridine

(69) H. O. L. Fischer, C. Taube and E. Baer, Ber., 60, 479 (1927).

interconversion of the aldoses to the ketoses had produced a ketopentose from ribose but none was detected from arabinose. The error in the ketopentose detection method of these later workers was made evident in 1934 when Schmidt and Heintz (70)

(70) O. T. Schmidt and K. Heintz, Ann., 515, 77 (1934).

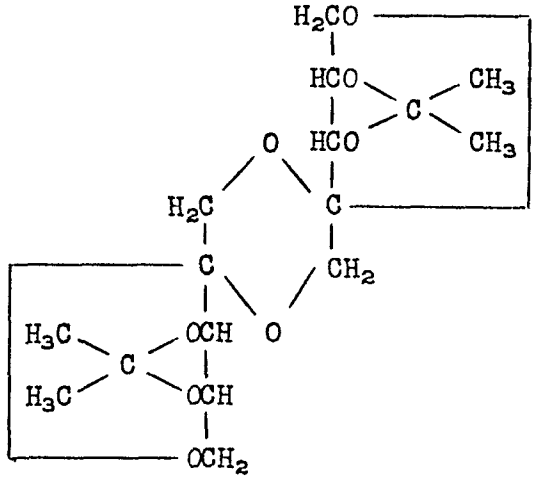
produced sirupy D- and L-erythro-pentulose by treatment of the corresponding aldopentoses with pyridine.

In 1934 Reichstein (71) produced the first pure sample of

(71) T. Reichstein, Helv. Chim. Acta, 17, 996 (1934).

an erythro-pentulose by treatment of ribitol with the bacteria Acetobacter suboxydans. The first two pure crystalline derivatives of the intact ketopentose structure were reported in this work as

the o- and p-nitrophenylhydrazones. Treatment of the L-erythro-pentulose o-nitrophenylhydrazone with benzaldehyde gave pure (sirupy) L-ketose, $[\alpha]^{19}D$ +15.8° (+16.3° after 3 days). Also reported were sirupy methyl 3,4-O-isopropylidene-L-erythro-pentuloside, crystalline 1,2:3,4-di-O-isopropylidene-L-erythro-pentulose and a crystalline product considered to be a cyclic dimeric 3,4-O-isopropylidene-L-erythro-pentulose.



In 1935 Glatthaar and Reichstein (72) produced sirupy

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(72) C. Glatthaar and T. Reichstein, Helv. Chim. Acta, 18, 80 (1935).

D-erythro-pentulose, and its crystalline o-nitrophenylhydrazone, from D-arabinose by treatment with pyridine. Levene and Tipson (73) obtained sirupy L-erythro-pentulose ([α] D +16.6°)

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(73) P. A. Levene and R. S. Tipson, J. Biol. Chem., 115, 731 (1936).

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from L-arabinose and separated the product as the crystalline (m.p. 5°) diisopropylidene derivative. By treatment of N-L-arabityl-3,5-dibromo-4-aminotoluene with bromine, Weygand and Schaefer (74) reported obtaining a mixture of L-erythro-

(74) F. Weygand and G. Schaefer, Ber., 84, 603 (1951).

pentulose and L-arabinose. Matsushima and Imanaga (75,76)

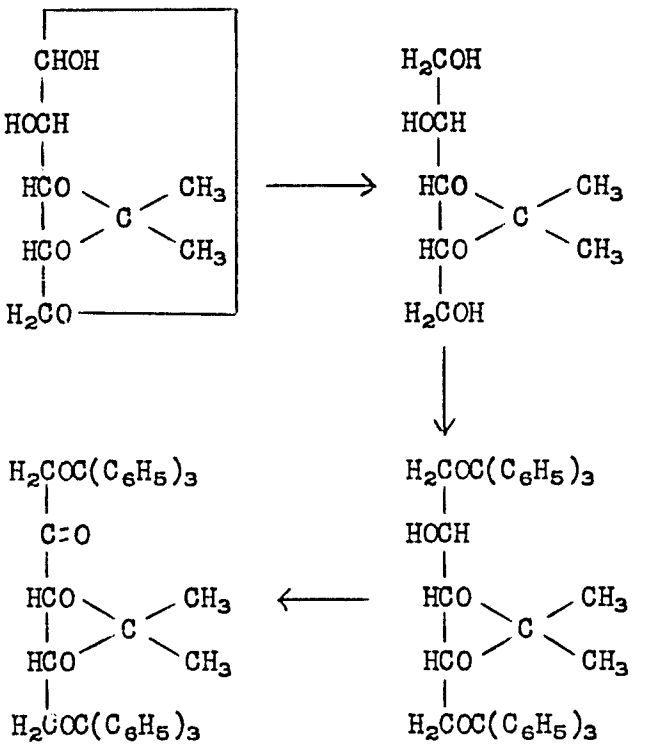
(75) Y. Matsushima and Y. Imanaga, Nature, 171, 475 (1953).
(76) Y. Matsushima and Y. Imanaga, Bull. Chem. Soc. Japan, 26, 506 (1953); C. A., 49, 11560 (1955).

further reported the synthesis of D-erythro-pentulose and D-erythro-pentulose o-nitrophenylhydrazone from D-arabinose for use as a precursor in their synthesis of 2-deoxy-D-erythro-pentose ("2-deoxy-D-ribose").

The last reported synthetic work concerned with D-erythro-pentulose was reported by Rammler, Dekker and MacDonald (77) for

(77) D. H. Rammler, C. A. Dekker and D. L. MacDonald, Abstracts Papers Am. Chem. Soc., 133, 8D (1958).

the synthesis of 1,5-di-O-trityl-3,4-O-isopropylidene-keto-D-erythro-pentulose.



Naturally Occurring Material

The question of the biosynthesis of a carbohydrate from carbon dioxide, and vice versa, has always been a fundamentally intriguing problem to every organic chemist. The question of carbon dioxide fixation in photosynthesis has been intimately studied since the turn of the century but it remained for the modern techniques of radioactive tracers and chromatography to allow great strides in this area.

It has been recently recognized that the prime intermediates in photosynthesis are largely phosphorylated hydroxy acids and

sugars. In 1951 Benson (78) reported the identification of

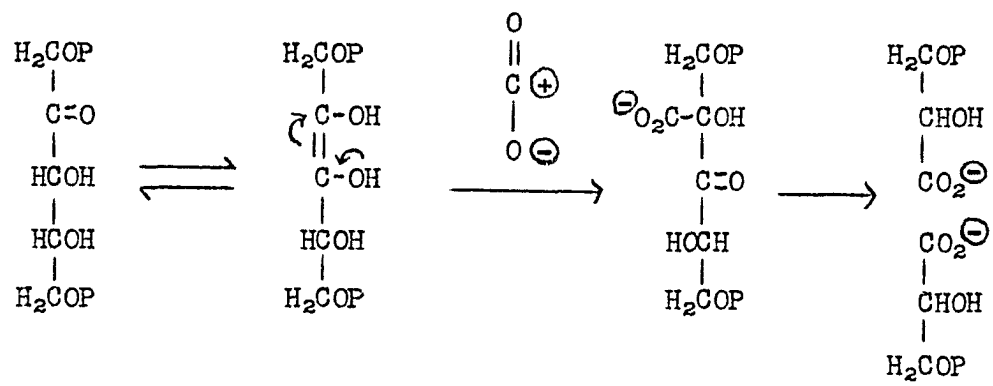
(78) A. A. Benson, J. Am. Chem. Soc., 73, 2971 (1951).

D-erythro-pentulose ("D-ribulose") 1,5-diphosphate and D-erythro-pentulose 5-phosphate during the first few seconds of $C^{14}O_2$ photosynthesis. The isolation of these ketopentoses, as well as the identification of sedoheptulose (79), allowed the earlier

(79) A. A. Benson, J. A. Bassham and M. Calvin, J. Am. Chem. Soc., 73, 2970 (1951).

isolated polyhydroxy members to be now placed in a consistent "path of carbon" cycle. D-erythro-Pentulose 1,5-diphosphate occupies the unique cyclic position of acting as the carbon dioxide acceptor (80,81) with the resultant production of two

(80) A. T. Wilson and M. Calvin, J. Am. Chem. Soc., 77, 5948 (1955).
(81) V. Moses and M. Calvin, Proc. Nat. Acad. Sci. U. S., 44, 260 (1958).



molecules of 3-phosphoglyceric acid. The exact relationship of D-erythro-pentulose 1,5-diphosphate to the cycle, its precursors, and its transformations are reviewed in an excellent summary of the available knowledge concerning the "path of carbon" in photosynthesis (82).

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(82) M. Calvin, J. Chem. Soc., 1895 (1956); see also J. A. Bassham and M. Calvin, "The Path of Carbon in Photosynthesis," Prentice-Hall, Inc., Englewood Cliffs, N. J. (1957).

In 1932, Warburg (83) and his collaborators discovered an

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(83) O. Warburg and W. Christian, Biochem. Z., 254, 438 (1932).

---

enzyme system in red blood cells which catalyzed the oxidation of D-glucose 6-phosphate with triphosphopyridine nucleotide as the coenzyme. The product of the reaction, identified as "6-phosphogluconate" (84) was later found to be further oxidized

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(84) O. Warburg, W. Christian and A. Griese, Biochem. Z., 282, 157 (1935).

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in the presence of the same coenzyme (85). This work, together

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(85) O. Warburg and W. Christian, Biochem. Z., 292, 287 (1937).

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with studies by Lipmann (86) and Dickens (87,88) indicated the

(86) F. Lipmann, Nature, 138, 588 (1936).
(87) F. Dickens, Nature, 138, 1057 (1936).
(88) F. Dickens, Biochem. J., 32, 1626, 1636 (1938).

existence of a pathway for the direct oxidation of D-glucose 6-phosphate which was distinct from the Embden-Meyerhof glycolytic mechanism. The formation of pentose phosphate in the oxidation of "6-phosphogluconate," first demonstrated by Dickens (88), was confirmed and extended by Scott and Cohen (89) and by Horecker,

(89) D. B. M. Scott and S. S. Cohen, J. Biol. Chem., 188, 509 (1951).

Smyrniotis and Seegmiller (90,91). D-erythro-Pentulose

(90) B. L. Horecker, P. Z. Smyrniotis and J. E. Seegmiller, J. Biol. Chem., 193, 383 (1951).
(91) J. E. Seegmiller and B. L. Horecker, J. Biol. Chem., 194, 261 (1952).

("D-ribulose") 5-phosphate was identified as the product of the oxidative decarboxylation of "6-phosphogluconate" in yeast, animal and plant tissues and this ester was shown to be in equilibrium with D-ribose 5-phosphate (90).

Many investigators, too numerous to be mentioned in this brief description, have added extensively to the knowledge of this oxidation pathway. The current knowledge concerning the cycle

can be briefly formulated as illustrated (92).

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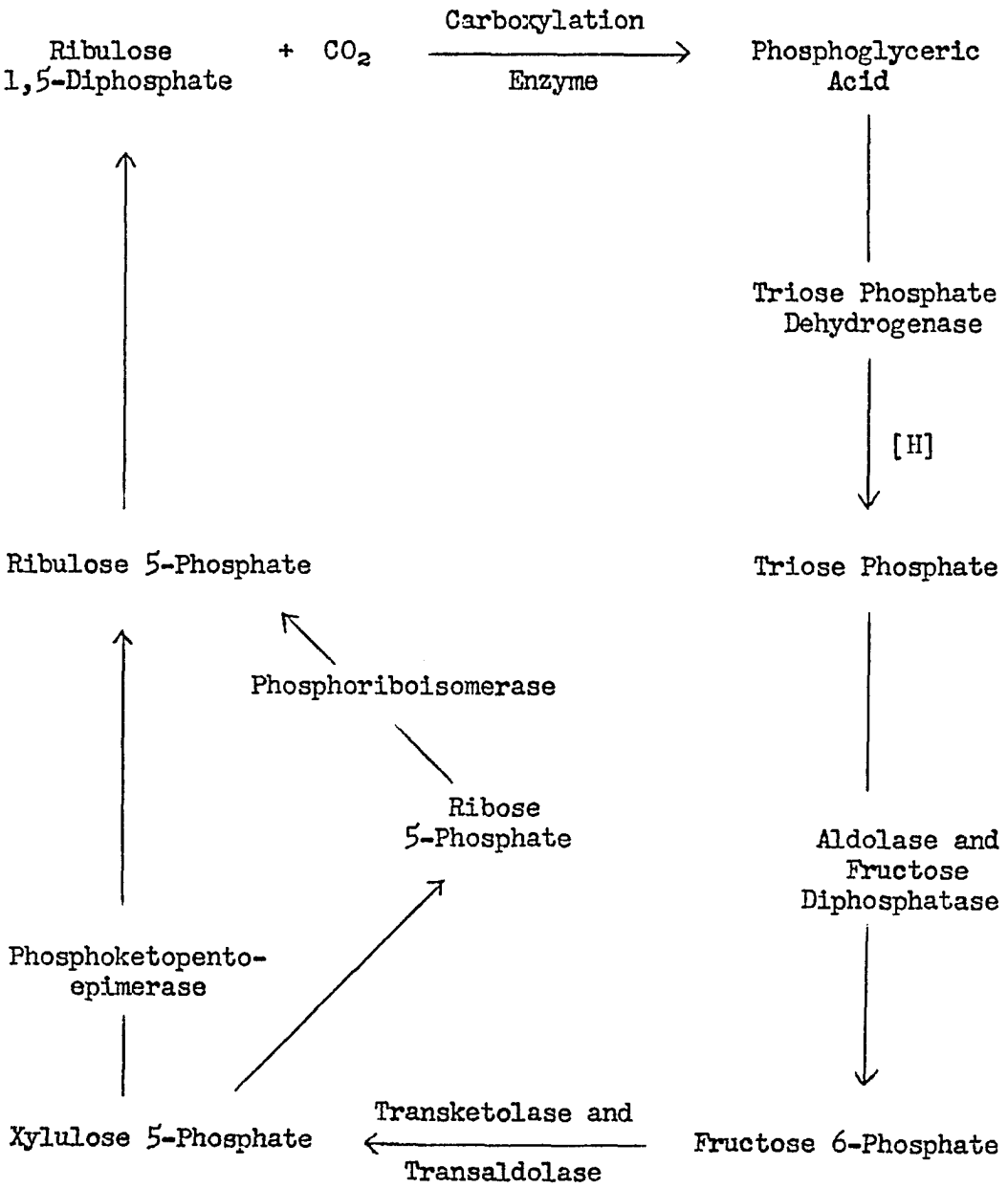
(92) J. Hurwitz, A. Weissbach and B. L. Horecker, Abstracts Papers Am. Chem. Soc., 129, 24C (1956).



DISCUSSION OF RESULTS

The Prepration of the Starting Materials

D-Erythrono-1,4-lactone

The structural requirements for the starting material involved in the synthesis of D-erythro-pentulose by the diazomethyl ketone ketose synthetic route demanded first, a tetronic acid with the cis or erythro configuration of both of the asymmetric secondary hydroxyl groups and secondly, that those hydroxyl groups be of the D-configuration. This required tetronic acid, D-erythronic acid, has never been isolated in crystalline form but is known as a crystalline product in the form of the 1,4-lactone. It was therefore recognized that this lactone, or at least its precursor material the aldotetrose, D-erythrose, would have to be made directly available in sufficient quantities for the synthesis of the ketopentose. It was also realized that it is this nonavailability of pure derivatives of the lower-chain carbohydrates that has been responsible for the limited research in this area.

After a consideration of the known preparative procedures for D-erythrono-1,4-lactone described in the literature, it was decided that the alkali-oxygen degradation procedure of Hardegger, Kreis and El Khadem (93) should be applied to D-arabinose as a

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(93) E. Hardegger, K. Kreis and H. El Khadem, Helv. Chim. Acta, 34, 2343 (1951).

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possible source of supply for the lactone. This method consists of the degradation of an alkaline solution of an aldose to the next lower aldonic acid by passing a stream of oxygen through the solution. Application of this method (93) to D-arabinose gave extremely poor yields of impure D-erythrono-1,4-lactone. The rate of degradation of the D-arabinose, as determined by observation of the reducing value of the solution, was difficult to control and the isolation of the product tedious. An attempt was made to improve the isolation of the product by utilizing the crystallizing properties of the phenylhydrazide of the acid but these experiments were not successful. It was therefore decided to abandon the attempt to prepare D-erythrono-1,4-lactone directly but instead to obtain the lactone by oxidation of its precursor aldotetrose, D-erythrose.

A survey of the available methods for the preparation of D-erythrose had been made in 1949 by Overend, Stacey and Wiggins (94). Of the four methods available in the literature

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(94) W. G. Overend, M. Stacey and L. F. Wiggins, J. Chem. Soc., 1358 (1949).

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at that time the authors evaluated each and recommended that Hockett and Hudson's (95) modification of the Ruff (Fenton)

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(95) R. C. Hockett and C. S. Hudson, J. Am. Chem. Soc., 56, 1632 (1934).

---

degradation as applied to calcium D-arabinonate would afford the best yield of D-erythrose. This method was repeated and involved first, the oxidative conversion of D-arabinose into calcium D-arabinonate. Degradation of the calcium D-arabinonate to D-erythrose with hydrogen peroxide and ferrous ion provided an overall yield of D-erythrose from D-arabinose of 32 per cent. The D-erythrose sirup prepared in this way was oxidized with bromine in the presence of calcium carbonate to give crystalline D-erythrono-1,4-lactone in an overall yield of 19 per cent.

The method of Perlin and Brice (96) for the selective

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(96) A. S. Perlin and C. Brice, Can. J. Chem., 33, 1216 (1955).

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degradation of D-glucose to D-erythrose, using lead tetraacetate as the oxidant, utilizes D-glucose as the readily available starting material and is both a rapid and efficient method for the preparation of D-erythrose. For the production of small quantities of the aldotetrose this method is the preparation of choice but because of the large quantities of acetic acid used as a solvent and the large amount of lead ions to be removed, the method is not too practical for large scale productions of D-erythrose.

When an article dealing with the structure proof of the ascorbic acid analogs (97) was noted in the literature, it became

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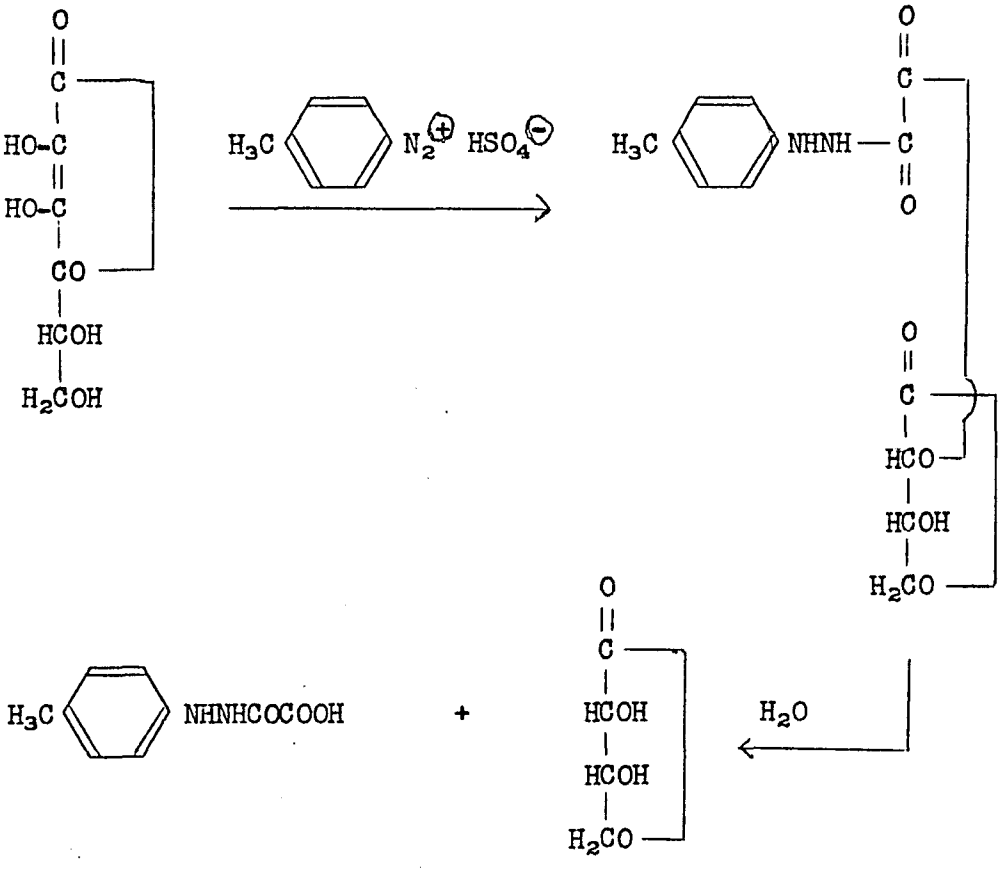
(97) R. Weidenhagen, H. Wegner, K. H. Lung, and L. Nordström, Ber., 72, 2010 (1939).

---

apparent that this same technique could be used for the direct preparation of D-erythrono-1,4-lactone without involving D-erythrose as an intermediate. The desired ascorbic acid analog, D-erythro-2-hexulosono-1,4-lactone 2,3-cis-enediol ("D-arboascorbic acid"), necessary for this preparation is industrially available and therefore sufficient material could be readily obtained for the preparation of D-erythrono-1,4-lactone by this degradative route. This procedure involves the use of an apparently quite stable diazonium salt, p-toluene diazonium sulfate, as a mild oxidant for the cleavage of the 2,3-enediol system present in the starting material. In this way, the water soluble starting material was reacted with the water soluble diazonium salt and, after a reaction time of one hour, the first intermediate precipitated from solution. This product was washed, filtered and boiled with water to effect cleavage of the oxalyl ester linkage. The hydrolysis solution was cooled and the by-product, the p-tolylhydrazide of oxalic acid, crystallized from solution leaving only an aqueous solution of the desired D-erythrono-1,4-lactone. In this way, D-erythrono-1,4-lactone

was made available as a pure product in approximately 70 per cent yield. The major portion of the lactone used in this work was therefore prepared in this manner.



Diazomethane

The diazomethane used in this work was prepared by two different methods. In the initial work it was generated from N-methyl-N-nitrosourea according to the method of Arndt (98)

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(98) F. Arndt, "Organic Synthesis," Vol. XV. pp. 3, 48, John Wiley and Sons, New York (1935).

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by the action of alcoholic potassium hydroxide on the substituted urea derivative. The ethereal diazomethane solution was dried over solid potassium hydroxide followed by drying over sodium wire and standardization with benzoic acid.

In the later stages of this work the diazomethane was generated by the more elegant method of De Boer (99) from N-methyl-

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(99) T. J. De Boer and H. J. Backer, Rec. trav. chim., 73, 229 (1954).

N-nitroso-p-toluenesulfonamide. The solvent for this reaction was 2-(2-ethoxyethoxy)-ethanol, a high boiling alcohol. This solvent therefore avoided contamination of the ethereal diazomethane solution with low boiling alcohols which would react with the sensitive acid halide reactant.

Nitrosyl Chloride

The nitrosyl chloride used in the early stages of this work was prepared by heating together, in the dry state, anhydrous aluminum chloride and sodium nitrite. This method of production

$$3\ NaNO_2 + 2\ AlCl_3 \rightarrow 3\ NaCl + Al_2O_3 + 3\ NOCl$$

is not detailed in the literature and is presented here as representing a quick, small-scale, method for the production of nitrosyl chloride. The nitrosyl chloride prepared in this way contains aluminum chloride as an impurity which sublimes over into

the product during the reaction. This contamination can be easily removed, however, by redistillation of the nitrosyl chloride.

For long range work with nitrosyl chloride its low boiling point makes storage a problem. Consequently, for the latter parts of this problem the nitrosyl chloride used was that as purchased from industrial sources and was contained in a nickel cylinder.

o-Nitrophenylhydrazine

A modified procedure of Müller, Montigel and Reichstein (100) was used for the preparation of o-nitrophenylhydrazine. This material not only has the advantage of forming nicely crystalline derivatives with the carbohydrates but forming only hydrazones with the ketoses. In this way the sirupy ketoses can be obtained as crystalline derivatives, purified and regenerated to the original ketoses by treatment of the ketose o-nitrophenylhydrazones with an aldehyde, such as benzaldehyde. The water soluble free ketose can then be separated from contamination by all aromatic reagents merely by extraction with ether.

(100) H. Müller, C. Montigel and T. Reichstein, Helv. Chim. Acta, 20, 1468 (1937).

The Hydrolytic Stability of the Aldonamides

Since the aldonamides occupy an important position as intermediates in the syntheses of some of the ketoses via the

diazomethyl ketose route, it was considered important to observe their behavior with respect to hydrolytic stability in water at room temperature. In a recent report on the synthesis of L-manno-heptulose, the hydrolytic instability of an aqueous solution of L-mannonamide was noted (31). This is in contrast to the more drastic hydroxyl or hydronium ion catalysis employed for the hydrolysis of the amides of simple carboxylic acids. Although Weerman (101) prepared a number of the aldonamides and noted a

(101) R. A. Weerman, Rec. trav. chim., 37, 16 (1918).

change in specific rotation of their aqueous solutions with time, no rotation data or isolation of the ammonium salt was reported to substantiate a conclusion that the aldonamides were hydrolyzing in aqueous solution at room temperature. Irvine and co-workers (102)

(102) J. C. Irvine, R. F. Thomson and C. S. Garrett, J. Chem. Soc., 103, 238 (1913).

had previously prepared D-gluconamide in crude form but no indication of hydrolytic instability was reported. Even Hudson and Komatsu (103), who repeated Weerman's work in order to

(103) C. S. Hudson and S. Komatsu, J. Am. Chem. Soc., 41, 1141 (1919).

formulate his amide rule of rotation (104), did not record any

(104) C. S. Hudson, J. Am. Chem. Soc., 40, 813 (1918).

hydrolytic instability of these amides. Renfrew and Cretcher (105)

(105) A. G. Renfrew and L. H. Cretcher, J. Am. Chem. Soc., 54, 4402 (1932).

reported that an aqueous solution of D-talonamide shows a change in rotation from [α] D -13.1° to a slightly dextrorotatory value after several days.

The hydrolytic instability of several aldonamides had also been noted in this laboratory By Bennett (106) under neutral,

(106) R. B. Bennett, M. Sc. Thesis, The Ohio State University (1955).

acidic and basic conditions. It was therefore decided to obtain as pure a sample of D-gluconamide as possible in order to investigate whether the hydrolytic curve of D-gluconamide as obtained by Bennett could be reproduced. Upon repeating this work a hydrolytic curve was obtained (Figure 1) almost identical to that of Bennett. It was therefore decided to investigate the exact nature of the final hydrolytic product by the isolation of a definitive substance. That the final product of the reaction, which the polarimetric curve delineated, was solely the ammonium salt, was therefore established by the isolation of ammonium

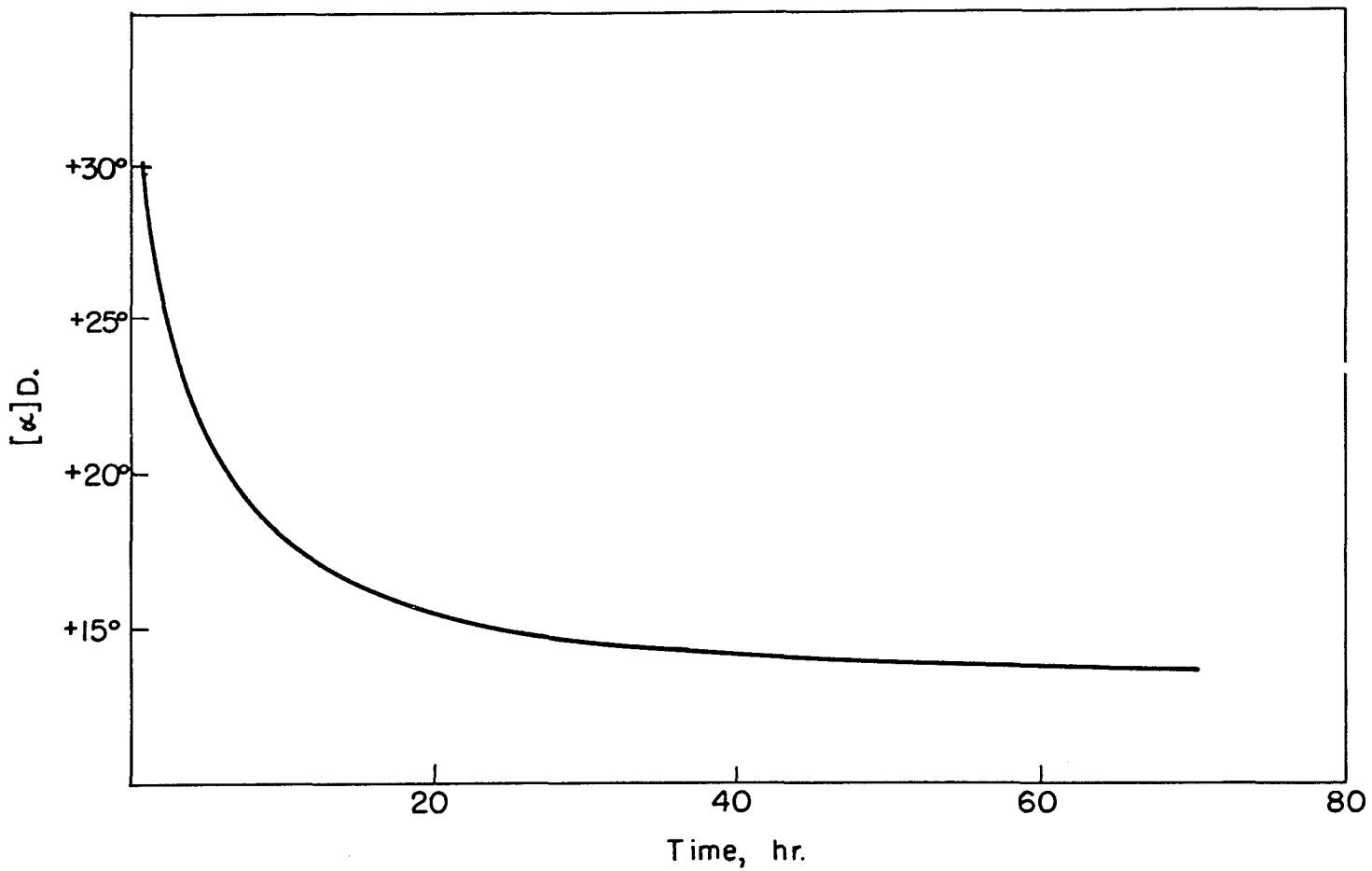

Figure 1. The Hydrolysis of D-Gluconamide

D-gluconate which compared in all ways to an authentic sample of the same substance prepared by the direct neutralization of D-gluconic acid with ammonium hydroxide.

The amides of the simple carboxylic acids, such as acetamide, are not as readily hydrolyzed as are the aldonamides. Therefore, the presence of hydroxyl groups would seem to be the accelerating factor. However, the stability of D-erythronamide to hydrolysis under apparently the same conditions, reported herein, makes a more extensive explanation necessary.

The Synthesis of 1,3,4,5-Tetra-O-benzoyl-keto-D-erythro-pentulose

As mentioned previously in the historical section (p. 22), with respect to the diazomethyl ketone ketose route, the synthesis of the diazomethyl ketone intermediate necessitates the prior isolation of the carbohydrate acid chloride. The latter, in turn must be obtained from an acid in which the sensitive hydroxyl groups have been blocked, usually as esters. The required D-erythronic acid triester cannot be obtained directly from the acid since D-erythronic acid exists as such only in aqueous solution.

The experimental approach for the synthesis of the ketose via the diazomethyl ketone was therefore to prepare a free D-erythronic acid tribenzoate from D-erythronamide tribenzoate by removal of the amide group. In this way, D-erythrono-1,4-lactone was dissolved in liquid ammonia to form D-erythronamide

according to the procedure of Glattfeld and Macmillan (107).

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(107) J. W. E. Glattfeld and D. Macmillan, J. Am. Chem. Soc., 56, 2481 (1934).

This method was easy to execute and produced D-erythronamide in good yield. However, D-erythronamide was very sensitive to heat and could not be crystallized effectively even from a nonpolar solvent such as 1,2-di-O-methylethanediol. For use as a starting material for the next step in the synthesis, the bulk of the amide did not require crystallization.

Now that a material was available in which the lactone ring had been held open by the amide function and the three free hydroxyl groups were now capable of being esterified, the amide was treated with benzoyl chloride in anhydrous pyridine in order to form 2,3,4-tri-O-benzoyl-D-erythronamide. The triester of the amide was thus obtained in practically quantitative yield as a white crystalline product. It now remained to remove the amide function in order to make available the desired 2,3,4-tri-O-benzoyl-D-erythronic acid as a compound possessing a free carboxyl group and with the three sensitive hydroxyl groups blocked as esters.

Removal of the amide function could not take place by either acidic or basic hydrolysis as the three ester functions would similarly undergo at least partial hydrolysis. Following the

procedure of Wolfrom, Konigsberg and Weisblat (108) nitrosyl

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(108) M. L. Wolfrom, M. Konigsberg and D. I. Weisblat, J. Am. Chem. Soc., 61, 574 (1939).

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chloride in dioxane (or benzene) was therefore used to effect an oxidative transformation of the amide function into the free acid without affecting the benzoate ester groups. Gaseous nitrous anhydride (109) has been used by other workers for related

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(109) C. D. Hurd and J. C. Sowden, J. Am. Chem. Soc., 60, 235 (1938).

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problems but nitrosyl chloride is much more desirable for this purpose because of its availability and easy handling as a reagent which can be measured out as a liquid and poured into the reaction system. From this reaction the desired 2,3,4-tri-O-benzoyl-D-erythronic acid was obtained in a colorless crystalline form.

The reaction of 2,3,4-tri-O-benzoyl-D-erythronic acid with phosphorus pentachloride in anhydrous ether gave a crystalline acid chloride in 81 per cent yield. Other workers have prepared sugar acid chlorides from the blocked acids and thionyl chloride (19,20,22) but the phosphorus pentachloride procedure can be used efficiently to prepare sugar acid chlorides when the product

is crystalline (110). In this way the acid chlorides can be

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(110) R. T. Major and E. W. Cook, J. Am. Chem. Soc., 58, 2477 (1936).

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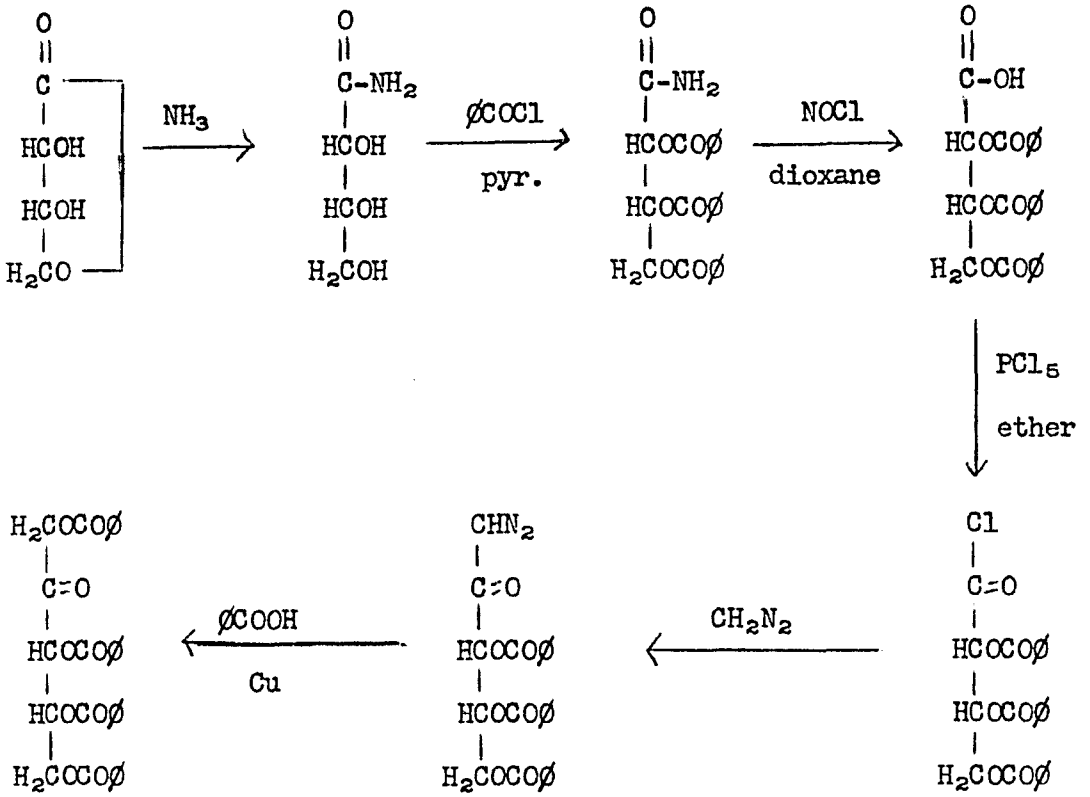
prepared efficiently without the required purification and distillations involved in the thionyl chloride method and the phosphorus by-products remain in the ether-petroleum ether solution.

The acid chloride, 2,3,4-tri-O-benzoyl-D-erythronyl chloride was reacted with two moles of diazomethane to produce an initially sirupy diazomethyl ketone. Purification of this crude 1-deoxy-1-diazo-3,4,5-tri-O-benzoyl-keto-D-erythro-pentulose by silicate column chromatography gave a light-yellow crystalline product which slowly evolved a gas on acidification.

The 1-deoxy-1-diazo-3,4,5-Tri-O-benzoyl-keto-D-erythro-pentulose was transformed into the ketopentose tetrabenzoate, 1,3,4,5-tetra-O-benzoyl-keto-D-erythro-pentulose, by heating the diazomethyl ketone with benzoic acid and copper bronze, as a catalyst, in an oil bath at 125° until the rapid evolution of gaseous nitrogen had ceased. The reaction product was crystallized from n-butyl ether to give the nicely crystalline acyclic ketopentose tetrabenzoate as the desired product.

The synthesis of 1,3,4,5-tetra-O-benzoyl-keto-D-erythro-pentulose from D-erythrono-1,4-lactone can be summarized as follows.

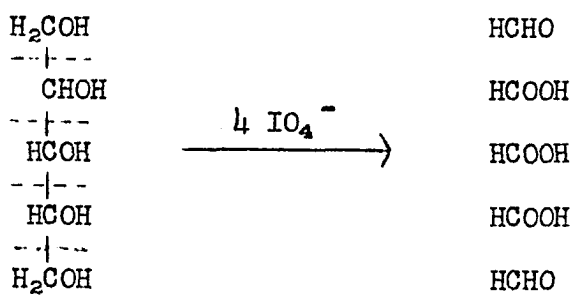


The Proof of Structure of 1,3,4,5-Tetra-O-benzoyl-keto-D-erythro-pentulose

It was next considered desirable to offer definite proof of the acyclic nature of the crystalline ketopentose tetrabenzoate. The keto-ester was found to consume 16.6 ml. (S.T.P.) of hydrogen under catalytic conditions. This corresponds to the addition of 13 moles of hydrogen per mole of ketopentose tetrabenzoate and is the expected value from the anticipated reduction of the four benzene rings present in the tetraester and the carbonyl group.

The ketopentose tetrabenzoate was then reduced with sodium borohydride in dioxane-water solution to reduce the carbonyl group

and subsequent hydrolysis of the ester groups gave a sirupy nonreducing pentitol mixture. A portion of the pentitol mixture was titrated with a standard solution of metaperiodate and was found to consume 1.33 millimoles of the standard oxidant in 2 hr. This sodium metaperiodate consumption corresponds to a ratio of 4.0 millimoles of oxidant per millimole of substrate. An aliquot of the reaction mixture was titrated for acid content and it was determined that 3.1 millimoles of acid had been produced per millimole of pentitol mixture. Treatment of a portion of the periodate reaction mixture with an aqueous solution of 5,5-dimethylcyclohexane-1,3-dione (dimedon) gave material which was identical with an authentic derivitive of formaldehyde dimedon and also indicated an equivalency of 1.8 millimoles of formaldehyde produced per millimole of pentitol substrate. These data are consistent with the amounts of the aldehyde and the acid products to be expected upon periodate oxidation of a pentitol system as illustrated.



A sample of the crystalline mixed pentitols obtained from the sodium borohydride reduction was treated with 2 N hydrochloric

acid in order to obtain products on a crystalline basis which would further establish the free keto-nature of the tetrabenzoate. Paper chromatography of the resultant product from the hydrochloric acid treatment, using 1-butanol saturated with ammonium hydroxide as developer and periodate-benzidine as indicator, revealed the presence of two zones of R_f 0.24 and 0.39. The top zone (R_f 0.24) was shown to be D-arabinitol by comparison with known D-arabinitol and also by the formation of and comparison with known D-arabinitol pentaacetate. The second zone (R_f 0.39) proved to be 1,4-anhydro-DL-ribitol and was identified by comparison with an authentic sample of the anhydro-alditol. Material from the second zone, upon treatment with benzoyl chloride in anhydrous pyridine, also gave a substance which was shown to be identical with an authentic sample of 2,3,5-tri-O-benzoyl-1,4-anhydro-DL-ribitol. For the preparation of the authentic 1,4-anhydro-DL-ribitol and 2,3,5-tri-O-benzoyl-1,4-anhydro-DL-ribitol it was necessary to prepare ribitol by the sodium borohydride reduction of D-ribose. This experiment represents the first recorded reduction of D-ribose to ribitol. "Synthetic ribitol has been prepared by the reduction of L-ribose with sodium amalgam (64). Oddly enough, whereas L-ribose is a synthetic pentose, ribitol does not appear to have been prepared from the naturally occurring D-ribose (111)." The periodate consumption of a sample of

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(111) R. L. Lohmar, V. The Polyols, W. Pigman's "The Carbohydrates," Academic Press, New York (1957).

1,4-anhydro-DL-ribitol revealed that one mole of periodate had been consumer and no acid or formaldehyde could be detected. As a result the position of the anhydro ring must be 1,4. After this work was completed, these ribitol derivatives were described by Baddiley, Buchanan and Carss (112).

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(112) J. Baddiley, J. G. Buchanan and B. Carss, J. Chem. Soc., 4058 (1957).

The free keto-structure for this tetrabenzoate has therefore been further demonstrated by the isolation of the two 2-epimeric pentitols.

The Synthesis of D-erythro-Pentulose

The approach to the transformation of an erythro-pentulose derivative into sirupy D-erythro-pentulose was initially attempted by the direct saponification of 1,3,4,5-tetra-O-benzoyl-keto-D-erythro-pentulose with aqueous barium hydroxide according to the procedure of Wolfrom, Thompson and Evans (25). This procedure is used to saponify sensitive keto-acetates but when applied to the ketopentose tetrabenzoate no positive results were obtained. The insolubility of carbohydrate benzoate esters as well as the extreme alkali sensitivity of the ketopentose probably explains the negative results obtained from these experiments.

A partly successful way in which to saponify the tetrabenzoate was found by dissolving the ketoester in anhydrous methanol and

treating the solution with a catalytic amount of sodium methoxide. In this way 1,3,4,5-tetra-O-benzoyl-keto-D-erythro-pentulose was converted to sirupy D-erythro-pentulose with a rotation of -15° in fair agreement with the reported value of +15.8° (71) for the pure enantiomorph. Attempts to increase the yield by increasing the methoxide content and the reaction time served only to increase the decomposition of the product as evidenced from the rotations of the resulting sirups.

Since the above method was so sensitive to reaction conditions a second method of obtaining the ketopentose was attempted. Other workers (19,20) have shown that diazomethyl ketones can be transformed into hydroxymethyl ketones by acid catalyzed hydrolysis. When this procedure was applied to a methanolic solution of 1-deoxy-1-diazo-3,4,5-tri-O-benzoyl-keto-D-erythro-pentulose, a sirupy reducing product was obtained in 40 per cent yield with a rotation comparable (-16°) to the previous procedure. Again, extended treatment of the diazomethyl ketone under hydrolyzing conditions only served to decrease the yield of the product.

Both samples of the sirupy free ketopentose when reacted with o-nitrophenylhydrazine gave crystalline D-erythro-pentulose o-nitrophenylhydrazone with a melting point agreeing closely with the value reported in the literature.

The Proof of Structure of Weisblat's D_{II} Resulting from the Action of Diazomethane upon aldehydo-D-Arabinose Tetraacetate

It became of interest during the course of this work to prove the structure of a compound obtained by Weisblat (113) and designated D_{II} by him. Analysis of the compound suggested that it possessed the structure of a dimethylene adduct to aldehydo-D (and L)-arabinose tetraacetate since the enantiomorphous compounds had been obtained from both D and L-arabinose.

(113) D. I. Weisblat, Ph. D. Dissertation, The Ohio State University (1941).

Chromatography of both enantiomorphous forms and a reexamination of the analysis gave results agreeing with the conclusion that two methylene groups had been added to aldehydo-D (and L)-arabinose tetraacetate. Ultraviolet absorption analysis gave $\log \varepsilon_{max}$ 1.60 (282 mμ, c 1.8×10^{-2} M) and $\log \varepsilon_{max}$ 1.63 (282 mμ, c 9×10^{-3} M) indicating an ethyl ketone (59,114).

(114) W. C. G. Baldwin, M. L. Wolfrom and T. M. Lowry, J. Chem. Soc., 696 (1935).

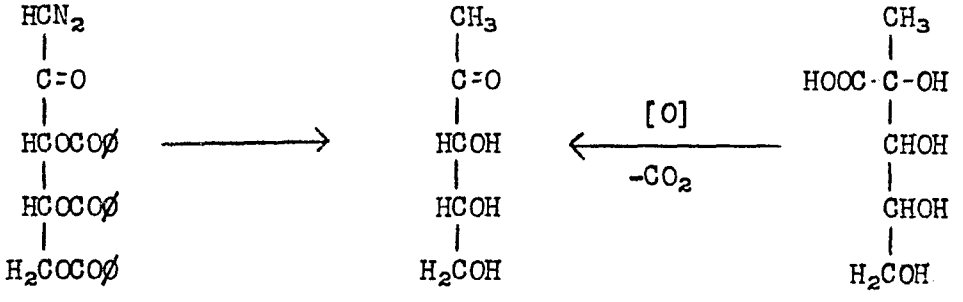
The unequivocable synthesis of the ethyl ketone, 1,2-dideoxy-3-keto-D-arabino-heptulose tetraacetate from diazoethane and tetra-O-acetyl-D-arabinonyl chloride, followed by the comparison of this synthetic compound by melting point, rotation and X-ray diffraction

powder patterns with Weisblat's original sample showed the unknown compounds to be indeed the ethyl ketones. Their formation during the reaction of diazomethane upon aldehydo-D (and L)-arabinose tetraacetate is consistent with the addition of two moles of diazomethane to each mole of the aldehydo-compounds, possibly with the methyl ketone acting as precursor. Similar ethyl ketone formation has been observed in this laboratory in the reaction of diazomethane upon aldehydo-D-glucose pentaacetate and aldehydo-D-galactose pentaacetate (59).

SUGGESTIONS FOR FURTHER WORK

1. A further extension of the diazomethyl ketone ketose synthesis, particularly with the use of benzoate esters, should be attempted for the synthesis of L-*threo*-pentulose ("L-Xylulose") using commercially available ascorbic acid as a starting material.

2. The transformation of 1-deoxy-1-diazo-3,4,5-tri-*O*-benzoyl-*keto*-D-*erythro*-pentulose into the 1-deoxy-D-*erythro*-



pentulose (or a suitable derivative) should be investigated as a method which might provide the long-sought proof of structure of the configuration of saccharinic acid.

3. 1-Deoxy-1-diazo-3,4,5-tri-*O*-benzoyl-*keto*-D-*erythro*-pentulose should be converted into the 1-iodo (or 1-bromo)-1-deoxy-3,4,5-tri-*O*-benzoyl-*keto*-D-*erythro*-pentulose in an attempt to displace the halogen with silver benzoate as a method of improving the yield of 1,3,4,5-tetra-*O*-benzoyl-*keto*-D-*erythro*-pentulose.

4. Now that relatively pure D-glyceraldehyde is easily available, a rapid synthetic route to free D-*erythro*-pentulose by the reaction of nitroethanol with D-glyceraldehyde via the Sowden nitroethanol (explosive!) synthesis should be attempted.

5. The transformation of 1-deoxy-1-diazo-3,4,5-tri-*O*-benzoyl-*keto*-D-*erythro*-pentulose into the five-carbon saccharinic acid, 2-deoxy-D-*erythro*-pentonic acid, via the Wolff rearrangement should be investigated.

6. The reduction of 1-deoxy-1-diazo-3,4,5-tri-*O*-benzoyl-*keto*-D-*erythro*-pentulose to the amine should be attempted with zinc and acetic acid with the possibility of obtaining a 1-amino-1-deoxy-*keto*-benzoate.

EXPERIMENTAL

The Preparation of D-Erythrono-1,4-lactone from D-Arabinose

The alkali-air oxidation procedure of Hardegger, Kreis and El Khadem (93) for the preparation of D-erythrose from D-ribose was modified and extended to D-arabinose.

To a precooled (0°) solution of 10 g. of D-arabinose (115)

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(115) Pfanstiehl Chemical Co., Waukegan, Illinois

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contained in 200 ml. of water was added a precooled (0°) solution of 10 g. of potassium hydroxide in 200 ml. of water. With the mixture being maintained at 0° by an ice-water bath contained in a Dewar flask, oxygen was bubbled through a fritted glass tube into the mixture until the solution failed to give a Benedict test for a reducing sugar. This reaction time was found to vary considerably from 30 to 80 hr. in the five runs attempted. The reaction mixture was passed through a column of IR-120 resin (116) to remove the sodium ions and the

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(116) A product of the Resinous Products and Chemical Co., Philadelphia, Pa.

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column eluate found to be acidic (pH 2) to test paper. The solution was evaporated to a thick sirup under reduced pressure and the resulting product was dissolved in ethanol and evaporated again to a thick sirup. The material was distilled under reduced

pressure at 140-160°(0.1 mm.) and the light-yellow sirupy product dissolved in the minimum amount of boiling ethyl acetate. After standing at ice box temperature for three days, a small amount of crystals had been deposited in the flask along with some sirupy material. The crystals of D-erythrono-1,4-lactone were suction filtered and dried in a vacuum desiccator at room temperature; yield 3.2 g. (41 per cent), m.p. 96-99°. Recrystallization from ethyl acetate yielded a product, m.p. 103-104°, which, after vacuum sublimation at 90° and 25 microns, gave material, m.p. 104-105° and $[\alpha]^{20}$ D -71° (c 1.0, water); X-ray powder diffraction data (117): 7.53m, 6.20s(2), 4.78m, 4.32s(1), 4.03m, 3.78w, 3.56w, 3.23w, 3.07m(3), 2.87w, 2.75w, 2.67w, 2.51m. These data are in agreement with the values (103° and -73°) cited by Ruff (118) and by Glattfeld and Forbrich (119).

(117) Interplanar spacing, Å., CuK radiation. Relative intensity, estimated visually: s, strong; m, medium; w, weak. Parenthetical numerals indicate the order of the three most intense lines: 1, most intense.

(118) O. Ruff, Ber., 32, 3679 (1899).
(119) J. W. E. Glattfeld and L. R. Forbrich, J. Am. Chem. Soc., 56, 1209 (1934).

In the five runs made of this preparation the yields were found to vary from 10 to 41 per cent.

Attempts to improve the yield of isolated product by reacting the distilled sirupy lactone with phenylhydrazine to form the

crystalline phenylhydrazide, did not improve the ease of isolation or the yield of D-erythrono-1,4 lactone.

The Preparation of D-Erythronic Phenylhydrazide

To 1.2 g. of D-erythrono-1,4-lactone in 5 ml. of absolute ethanol was added 1.6 g. (1.5 ml.) of phenylhydrazine. The mixture was refluxed for 4 hr. and the solvent removed under reduced pressure. The residue was crystallized from ethyl acetate; m.p. 128-129°. Recrystallization from the same solvent gave colorless material, m.p. 130-131°, $[\alpha]^{20}$ D +19° (c 4, water) in agreement with the values (129-130° and +19°) cited by Hardegger, Kreis and El Khadem (93).

The Preparation of Calcium D-Arabinonate Pentahydrate from D-Arabinose

The bromine oxidation procedure of Hudson and Isbell (120),

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(120) C. S. Hudson and H. S. Isbell, J. Am. Chem. Soc., 51, 2225 (1929).

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employing barium benzoate as a buffer, was applied to D-arabinose and the resulting D-arabinonic acid isolated as the crystalline calcium salt.

To a solution of 100 g. of D-arabinose in 8 l. of water was added 400 g. of barium benzoate and 40 ml. of bromine. The mixture was placed in the dark with occasional shaking and after 48 hr. was filtered and the excess bromine removed by aeration. A slight excess of 6 N sulfuric acid was added and the barium sulfate

removed by suction filtration. The filtrate was stirred with lead carbonate until free of sulfate ions and silver oxide added until free of bromide ions. The resulting filtrate was treated with hydrogen sulfide to remove lead and silver ions and, after filtering, the hydrogen sulfide was removed by aeration. The resulting aqueous solution was concentrated to 500 ml. and the benzoic acid removed by chloroform extraction. The clear solution was heated to boiling and a slight excess of calcium carbonate added. After boiling for 15 min., the mixture was suction filtered and evaporated under reduced pressure to a semi-solid mass. The calcium D-arabinonate pentahydrate was recrystallized from a minimum amount of hot water; yield 90 g. (53 per cent), m.p. 99-100°, $[\alpha]^{20}D$ -6.5° (c 2.5 water), in agreement with (99-101° and -6.8°) reported by Overend, Stacey and Wiggins (94).

The Preparation of D-Erythrose from Calcium D-Arabinonate

For the preparation of this tetrose, the Ruff procedure as modified by Hockett and Hudson (95) for the preparation of D-arabinose was used.

To 500 ml. of water was added slowly, with stirring, equal portions each of solutions of 5.0 g. of barium acetate in 15 ml. of water and 2.7 g. of ferric acetate in 15 ml. of water. The mixture was heated to boiling and 40 g. of calcium D-arabinonate slowly added. The resultant mixture was boiled for 30 min. and, after clarification with carbon, was cooled to 40°. To the

cooled mixture was added 29 ml. of hydrogen peroxide (30 per cent) whereupon the mixture became dark in color and the temperature rose to 70°. After cooling the mixture to 40°, a second portion of 29 ml. of hydrogen peroxide was added. The mixture was allowed to stand overnight at room temperature, treated with carbon and evaporated under reduced pressure to 50 ml. Upon the addition of 300 ml. of methanol a solid material precipitated which was removed by suction filtration. After the addition of 200 ml. of ethyl ether, the product was filtered and evaporated under reduced pressure to a thick sirup; yield 10.3 g., $[\alpha]^{20}D$ -26° (c 1, water).

The Preparation of D-Erythrono-1,4-lactone from D-Erythrose

The oxidation of D-erythrose to its aldonic acid was accomplished in the presence of calcium carbonate according to the following modification of the general procedure of Gakhokidze (121).

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(121) A. M. Gakhokidze, J. Gen. Chem (U.S.S.R.), 15, 539 (1945); C.A., 40, 4674 (1946).

To a solution of 4.8 g. of crude sirupy D-erythrose dissolved in 50 ml. of water was added 10 g. of calcium carbonate and 2.5 ml. of bromine. The mixture was allowed to stand at room temperature in the dark for 2 days after which 9.0 g. of oxalic acid was added and the mixture boiled for 15 min. The cooled mixture was filtered by suction filtration to remove calcium oxalate and treated with

silver carbonate to remove halide ions. Filtration of the precipitated silver bromide and treatment with hydrogen sulfide gave a non-reducing aqueous solution which was evaporated to a thick sirup. Repeated evaporation of the dissolved sirup from small volumes of ethanol gave a colorless, thick sirup as a product. The sirup was dissolved in boiling ethyl acetate and, after nucleation with known D-erythrono-1,4-lactone and remaining overnight at room temperature, gave crystalline material; 2.9 g. (60 per cent), m.p. 103-104°. This material on admixture with known D-erythrono-1,4-lactone of like melting point gave no depression.

The Preparation of D-Erythrose from D-Glucose

The tetrose, D-erythrose, was prepared by the controlled oxidation of D-glucose with lead tetraacetate according to a modification of the procedure of Perlin and Brice (96).

A solution of 5.0 g. of D-glucose in 10 ml. of water was added to 500 ml. of glacial acetic acid. To this rapidly stirred solution was added slowly 25 g. of lead tetraacetate and after a reaction time of 10 min. the mixture was passed through a column of IR-120 resin (116) until free of lead ions. The solution was evaporated under reduced pressure to a thick sirup in order to remove the acetic acid and then dissolved in 50 ml. of 0.1 N hydrochloric acid and brought to the boiling point. The anions

were removed from the solution with Duolite A-4 resin (122) and

(122) A product of the Chemical Process Co., Redwood City, California.

evaporation to a thick sirup gave material; 2.6 g. (78 per cent), $[\alpha]^{25}D$ -28° (c 1, water) in agreement with the value (-30°) cited by Perlin and Brice (96).

This fairly pure erythrose was oxidized by bromine in the presence of calcium carbonate to D-erythrono-1,4-lactone by the procedure previously mentioned; yield 2.0 g. (60 per cent), m.p. 103-104°, with no depression on admixture with a known sample of D-erythrono-1,4-lactone of like melting point.

The Preparation of Amyl Nitrite

This alkyl ester was prepared according to the method of Noyes (123).

(123) W. A. Noyes, J. Am. Chem. Soc., 55, 3888 (1933).

A precooled solution (0°) of 14.5 ml. of concentrated sulfuric acid (sp. gr. 1.84) in 10 ml. of water was added slowly with stirring to 56.3 ml. of amyl alcohol. After this mixture was again cooled to 0° it was slowly introduced with rapid stirring below the surface of a cooled solution (0°) of 38 g. of sodium nitrite in 150 ml. of water. With the temperature being maintained at 0-5°, the reaction mixture was rapidly stirred for

15 min. and then placed in a separatory funnel where the three layers were separated. The bottom or salt layer and the middle or sodium sulfate aqueous layer were removed from the top ester layer and the product washed twice with 10 ml. of a solution of sodium chloride in 10 ml. of water. The product was then washed twice with 50 ml. of a solution of 1 g. of sodium bicarbonate in 50 ml. of water and dried by filtering through anhydrous magnesium sulfate. The product (yield 90 per cent) was light green in color and was kept refrigerated until used.

The Preparation of p-Toluene Diazonium Sulfate

This stable crystalline diazonium salt was prepared according to the old but still excellent procedure of E. Knoevenagel (124).

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(124) E. Knoevenagel, Ber., 28, 2048 (1895).

To 15 g. of p-toluidine dissolved in 225 ml. of ethanol (95 per cent) was added cautiously, with stirring, 16.3 ml. of concentrated sulfuric acid (sp. gr. 1.84) and the temperature of the mixture adjusted to 30°. After the slow addition of 24 ml. of amyl nitrite the temperature rose only slowly and upon standing the diazonium sulfate crystallized from the reaction mixture. The mixture was cooled to 0° and the white crystalline product removed by suction filtration. The solid diazonium salt, produced by this method in quantitative yield, could be recrystallized well from hot ethanol (95 per cent) but the product initially produced was considered to be sufficiently pure for this work.

The Preparation of D-Erythrono-1,4-lactone from D-erythro-2-Hexulosono-1,4-lactone 2,3-cis-enediol ("D-Araboascorbic Acid")

The desired lactone, D-erythrono-1,4-lactone, was conveniently prepared on a large scale from commercial "D-araboascorbic acid" ("isovitamin C", "isoascorbic acid") in this way by a modification of the procedure of Weidenhagen, Wegner, Lung and Nordström (97).

To a solution of 70.4 g. of D-erythro-2-hexulosono-1,4-lactone 2,3-cis-enediol ("D-araboascorbic acid") (125) in 350 ml.

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(125) Distillation Products Industries, Division of Eastman Kodak Company, Rochester 3, N. Y.

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of water was added a solution of 86.4 g. of p-toluene diazonium sulfate in 400 ml. of water. The mixture was allowed to stand at room temperature whereupon a solid material began to separate from the reaction mixture after about 10 min. The reaction was complete after 1 hr. and the resulting solid p-tolylhydrazidoxalyl-D-erythrono-1,4-lactone was suction filtered and washed with water; yield 108.2 g. (92 per cent), m.p. 172-175°. The color could be removed from the product by treating with boiling petroleum ether at this stage. Recrystallization of the product from absolute ethanol gave pure material, m.p. 177°.

The material from above (106 g.) was dissolved with heating in 1 l. of water and the mixture boiled for 5 min. The hot solution was clarified with carbon and filtered through a Celite

pad by suction filtration. After cooling overnight at ice-box temperature (0-3°), the aqueous solution had deposited a white crystalline material, oxalic acid p-tolylhydrazide; yield 55 g., m.p. 152-153°.

The filtrate was concentrated under reduced pressure and the remaining oxalic acid p-tolylhydrazide removed by suction filtration. The filtrate was evaporated under reduced pressure to a thick sirup and then further evaporated from several portions of absolute ethanol. The sirupy product was dissolved in a minimum amount of boiling ethyl acetate and allowed to stand overnight at ice box temperature (0-3°). D-Erythrono-1,4-lactone separated in beautiful long needles; yield 19.8 g., m.p. and mixed m.p. with known lactone, 103-104°.

The Preparation of D-Erythronamide

To 23.6 g. of sublimed D-erythrono-1,4-lactone contained in a 500 ml. Erlenmeyer flask, fitted with a drying tube, was added 200 ml. of anhydrous liquid ammonia. The lactone readily dissolved in the liquid ammonia and the mixture was placed in a vermiculite-filled box and allowed to stand overnight. The resulting sirupy material was then placed in a vacuum desiccator to remove the last traces of ammonia. No crystallization had occurred within three days.

The preparation was repeated on a 1.0 g. sample of D-erythrono-1,4-lactone as before but the resulting sirupy produce was dissolved in a minimum amount of hot di-O-methyl-1,2-ethanediol and allowed

to stand overnight at ice-box temperature (0-3°). Crystals were deposited which were filtered by suction; m.p. 95°, $[\alpha]^{20}D$ +28° (c 2.0, water) in agreement with the constants reported by Glattfeld and Macmillan (107); X-ray powder diffraction data (117): 5.21m, 4.26s(1), 3.84m, 3.63m(3), 3.39m, 3.28m(3), 3.07s(2), 2.92w, 2.85w, 2.73w, 2.63m, 2.45w, 241w.

The sirupy amide prepared previously was nucleated with the crystalline D-erythronamide and crystallization was instantaneous with the evolution of a considerable amount of ammonia. The crystalline mass was washed with di-O-methyl-1,2-ethanediol and the yield found to be practically quantitative. Since considerable D-erythronamide was lost during recrystallization, the bulk amide was carried on to the next step without further treatment.

The Attempted Hydrolysis of D-Erythronamide

An aqueous solution of D-erythronamide was prepared with ordinary distilled water in a concentration of 4 g. of D-erythronamide per 100 ml. of solution. The solution was placed in a 2 dm. glass polarimeter tube and was polarimetrically observed over a period of 80 hr. at 25° with the sodium D-line. No change in rotation was observed for the sample during this 80 hr. period.

The Preparation of D-Gluconamide

D-Gluconamide was prepared from D-glucono-1,5-lactone (115) by reaction with liquid ammonia as described for the preparation of D-erythronamide. Recrystallization from di-O-methyl-1,2-ethanediol gave white crystalline material; m.p. 142-143°, $[\alpha]^{25}D$ +31.4. Further crystallization failed to alter these constants.

The Preparation of Ammonium D-Gluconate

An amount of D-glucono-1,5-lactone (5.0 g.) (115) was dissolved in 100 ml. of water and the solution heated to boiling. Concentrated ammonium hydroxide was added dropwise to the solution until the solution was just basic to test paper. The solution was evaporated under reduced pressure to a solid mass, whereupon recrystallization from ethanol (95 per cent) gave crystalline material; m.p. 153-154°, $[\alpha]^{25}D$ +11.8° (c 3, water).

The Hydrolysis of D-Gluconamide

An aqueous solution of D-gluconamide was prepared with ordinary distilled water in exact concentration to that reported (1.50 g./50 ml.) by Bennett (106) in order to test the reproducibility of the polarimetric curve. The mutarotation was determined in a 4-dm. glass polarimeter tube at 25° with the sodium D-line. The data obtained are recorded in Table IV and Figure 1.

Table IV

The Hydrolysis of D-Gluconamide

Time, hr.	Observed Rotation in Degrees	Specific Rotation in Degrees
0.5	+3.56	+29.7
1.0	+3.42	+28.5
1.5	+3.22	+26.8
2.5	+2.96	+24.7
5.0	+2.54	+21.2
10.0	+2.13	+17.8
20.0	+1.86	+15.5
25.0	+1.77	+14.8
35.0	+1.72	+14.3
45.0	+1.68	+14.0
55.0	+1.67	+13.9
70.0	+1.63	+13.6

The Isolation of a Hydrolytic Product of D-Gluconamide and its Identity with Ammonium D-Gluconate

D-Gluconamide (1.500 g.) was dissolved in distilled water contained in a volumetric flask and the volume adjusted to 50.00 ml. The solution was transferred to a 4-dm. glass polarimeter tube and the rotation followed until it became constant (+30.7° → +13.6°, 70 hr.). The solution was removed from the polarimeter tube and evaporated to dryness under reduced pressure. Recrystallization of the crystalline residue from 95 per cent ethanol gave a quantitative yield of a white crystalline solid; m.p. 153-154°, $[\alpha]^{25}D$ +11.8° (c 3, water). Comparison of this compound with authentic ammonium D-gluconate, $[\alpha]^{25}D$ +11.2° (c 3, water), by melting point, melting point on admixture, and X-ray powder diffraction pattern showed them to be identical; X-ray powder diffraction data (117): 8.92m, 5.10s(3), 4.88m, 4.66m, 4.44s(3), 3.85s(1), 3.34s(1), 3.21m, 3.11m, 2.91m, 2.56w, 2.51w, 2.43w, 2.30w.

The Preparation of 2,3,4-Tri-O-benzoyl-D-erythronamide

To 27.0 g. of D-erythronamide dissolved in 300 ml. of anhydrous pyridine and cooled to 0° was added slowly, with agitation, 72 ml. of benzoyl chloride. After the addition was complete, the mixture was removed from the ice-bath and allowed to stand at room temperature for 48 hr. The semi-solid mass was poured into an ice-water mixture and stirred well. The fluffy solid material was washed with ice water and suction filtered.

Recrystallization from 95 per cent ethanol gave white crystalline material; 85 g. (95 per cent), m.p. 205-206°, $[\alpha]^{25}$ D +10° (c 0.8, chloroform), X-ray powder diffraction data (117): 9.41m, 8.91m, 5.51w, 5.30m(3), 5.10m(3), 4.77m, 4.42s(2), 4.04s(1), 3.77w, 3.41m, 3.22w, in agreement with the constants (205° and +10°) cited by Jelinek and Upson (126).

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(126) V. C. Jelinek and F. W. Upson, J. Am. Chem. Soc., 60, 355 (1938).

The Synthesis of Nitrosyl Chloride

To 46 g. of sodium nitrite was added 88 g. of aluminum chloride, the solid mixture stirred quickly, and placed in a filtering flask fitted with a solid stopper. A Tygon tube connected the side arm to a condensing trap cooled in a Dewar flask with an acetone and dry ice mixture. The solid mixture was heated slowly until the red vapor of nitrosyl chloride was produced at a rate sufficient for the nitrosyl chloride to be condensed in the trap. The red liquid nitrosyl chloride was then distilled by connecting the collecting trap to another dry ice cooled trap and allowing the collecting trap to warm to room temperature. In this way most of the aluminum chloride, which had sublimed into the product, was removed. The liquid nitrosyl chloride was maintained in the cooled collecting trap until used.

For later work in this problem industrial nitrosyl chloride available in large quantities (in cylinders) was used.

The Synthesis of 2,3,4-Tri-O-benzoyl-D-erythronic Acid

To 18.0 g. of 2,3,4-tri-O-benzoyl-D-erythronamide dissolved in 200 ml. of purified dioxane (127) and cooled to 0°, was added

(127) K. Hess and H. Frahm, Ber., 71, 2627 (1938).

slowly, with stirring, 30 ml. of nitrosyl chloride. The mixture was allowed to stand overnight at 0° and then was allowed to warm slowly to room temperature. The resulting semi-solid gum that formed upon pouring the reaction mixture into water, was dissolved in absolute ethanol, evaporated to a heavy sirup, and crystallized from 15 ml. of benzene to give a light-brown material; yield 14.3 g. (80 per cent), m.p. 133-135°. Recrystallization from benzene gave colorless 2,3,4-tri-O-benzoyl-D-erythronic acid; m.p. 138°-139°, $[\alpha]^{21}D$ +27° (c 0.5, chloroform), X-ray powder diffraction data (117): 9.22m(2), 5.22m(2), 4.80m, 4.44s(1), 3.99m(2), 3.75w, 3.53w, 3.22w.

Anal. Calcd. for $C_{25}H_{20}O_8$: C, 66.96; H, 4.50. Found: C, 67.19; H, 4.60.

The Synthesis of 2,3,4-Tri-O-benzoyl-D-erythronyl Chloride

To 9.0 g. of 2,3,4-tri-O-benzoyl-D-erythronic acid, dissolved in 100 ml. of anhydrous ether, was added 4.2 g. of phosphorus pentachloride. The reaction flask was fitted with a drying tube and stirred with a magnetic stirrer. After stirring the reaction mixture at room temperature for 4 hr., 250 ml. of petroleum ether (b.p. 30-60°) was added and the mixture placed in the ice-box

overnight. The resulting crystalline mass was rapidly suction filtered and placed in a vacuum desiccator; yield 7.5 g. (81 per cent), m.p. 94-95°, $[\alpha]^{21}D$ -14° (c 2.0, chloroform), X-ray powder diffraction data (117): 9.36s(2), 5.26s(2), 4.84m, 4.56m, 4.46m, 4.29w, 4.14s(1), 3.97w, 3,63w, 3.48w.

Anal. Calcd. for $C_{25}H_{29}ClO_7$: C, 64.33; H, 4.10; Cl, 7.59. Found: C, 64.40; H, 4.21; Cl, 7.47.

The Preparation of Diazomethane

The diazomethane used in this work was prepared by one of two methods. Early in this problem the method of Arndt (98) from nitrosomethylurea was used but in later work, diazomethane was produced by the more excellent method of De Boer (99) from N-methyl-N-nitroso-p-toluenesulfonamide.

a. Method of Arndt (98). In a liter round-bottomed flask were placed 120 ml. of 50 per cent aqueous potassium hydroxide solution and 400 ml. of ether. The mixture was cooled to 0° and 41.2 g. of nitrosomethylurea was added with shaking. The flask was fitted with a condenser set for distillation. The lower end of the condenser carried an adapter passing through a two-holed rubber stopper and dipping below the surface of 80 ml. of ether cooled in an ice bath. The exit gases were passed through a second 80 ml. portion of ether, likewise cooled to 0°. The reaction flask was placed in a water bath heated to 50° and brought to the boiling point of the ether, with occasional shaking. The ether was distilled until it came over colorless, which was usually the case

after two-thirds of the ether had been distilled. The solutions in the receivers were combined and dried over solid potassium hydroxide pellets. The solutions were then allowed to remain overnight with sodium wire.

The dried ether solutions were standardized as follows. Approximately 0.8 g. of pure benzoic acid was weighed accurately into a 125 ml. Erlenmeyer flask. After the addition of 10 ml. of ether, 10 ml. of the diazomethane solution to be standardized was added to the flask from a pipette followed by 40 ml. of absolute alcohol. The solution was then diluted with water and the excess benzoic acid determined by back-titration with 0.1 N sodium hydroxide, using phenolphthalein as the indicator. Solutions prepared as above usually contained approximately 0.02 g. of diazomethane per ml. of the ether solution.

b. Method of De Boer (99). To 35 ml. of 2-(2-ethoxyethoxy)-ethanol and 10 ml. of ether were added a solution of 6 g. of potassium hydroxide dissolved in 10 ml. of water. This solution was placed in a 100 ml. long-necked distilling flask fitted with a dropping funnel and an efficient condenser set downward for distillation. The condenser was connected to two receiving flasks in series, the second of which contained 20 ml. of ether. The inlet tube of the second receiver dipped below the surface of the ether and both receivers were cooled to 0°. The flask containing the alkali solution was heated in a water bath at 70° and a solution of 21.5 g. of N-methyl-N-nitroso-p-toluenesulfonamide in 130 ml. of

ether was added through the dropping funnel in about 25 min. During the distillation of the ether the reaction flask was agitated vigorously. When the dropping funnel was empty, 20 ml. of ether was added slowly and distillation continued until the ether was colorless. The combined ether distillate contained about 3 g. of diazomethane which was dried and standardized as in procedure a.

The Synthesis of 1-Deoxy-1-diazo-3,4,5-tri-O-benzoyl-keto-D-erythro-pentulose

A solution of 4.7 g. of 2,3,4-tri-O-benzoyl-D-erythronyl chloride in 50 ml. of anhydrous ether was added slowly, with stirring, to a solution of 1 g. of diazomethane in 50 ml. of dry ether. The mixture was maintained overnight at 10-15° whereupon the addition of petroleum ether (b.p. 30-60°) gave a crude yellow product; yield 3.8 g. (81 per cent), m.p. 79-81°.

One gram of the above product was dissolved in 10 ml. of benzene and chromatographed on a 230 x 35 mm. (diam.) (128) column

(128) Adsorbent dimensions.

of Magnesol (129)-Celite (130) (5:1 by wt.) by development with

(129) A synthetic magnesium silicate produced by the Wesvaco Chemical Division of the Food Machinery and Chemical Corp., South Charleston, W. Va.

(130) No. 535, a siliceous filter-aid produced by the Johns-Manville Co., New York, N. Y.

100 ml. of benzene-t-butyl alcohol (500:1 by vol.). An alkaline permanganate streak (131) showed a large zone near the bottom of

(131) W. H. McNeely, W. W. Binkley and M. L. Wolfrom, J. Am. Chem. Soc., 67, 527 (1945).

the extruded column. The sectioned bottom zone was extracted with acetone and the sirup obtained on solvent removal at reduced pressure was crystallized from ether (warming)-petroleum ether. The crystals possessed a slight yellow color; yield 0.64 g., m.p. 95-96°, $[\alpha]^{21}$ D -28° (c, 2.0, chloroform), X-ray powder diffraction data (117): 10.07m(2), 7.80w, 5.91w, 5.37s(1), 4.63w, 4.10s(1), 3.79m, 3.36m.

Anal. Calcd. for $C_{26}H_{20}N_2O_7$: C, 66.10; H, 4.27; N, 5.93. Found: C, 66.01; H, 4.19; N, 5.74.

The Synthesis of 1,3,4,5-Tetra-O-benzoyl-keto-D-erythro-pentulose

A mixture of 200 mg. of 1-deoxy-1-diazo-3,4,5-tri-O-benzoyl-keto-D-erythro-pentulose, 1 g. of benzoic acid and a trace of copper bronze were heated in an oil bath at 125° for 2 min. After the rapid evolution of gas had ceased, the mixture was cooled in an ice bath and the resulting material was dissolved in 25 ml. of chloroform. The chloroform solution was washed with 50 ml. each of N potassium carbonate, N sulfuric acid and water and, after drying over sodium sulfate, was evaporated under reduced pressure. Repeated evaporation at reduced pressure from methanol solution gave a crystalline product; yield 98.6 mg. (42 per cent), m.p. 139-140°.

Recrystallization was effected from 5 ml. of n-butyl ether; yield 88 mg., m.p. 142-143°, $[\alpha]^{20}$ D +31.5° (c 3.4, chloroform), X-ray powder diffraction data (117): 10.88s(2), 7.01m(3), 5.49m, 5.17m, 4.44s(1), 4.20w, 3.98m, 3.63m, 3.43m. This tetraester failed to give conclusive indication for the presence of a carbonyl group in both the ultraviolet and infrared regions due to the presence of the benzoate groups.

Anal. Calcd. for $C_{33}H_{26}O_9$: C, 70.0; H, 4.6. Found: C, 69.8; H, 4.7.

The Catalytic Reduction of 1,3,4,5-Tetra-O-benzoyl-keto-D-erythro-pentulose

For the determination of the catalytic consumption of hydrogen by the keto-ester, 32.9 mg. of 1,3,4,5-tetra-O-benzoyl-keto-D-erythro-pentulose was dissolved in 10 ml. of redistilled glacial acetic acid and 150 mg. of prereduced Adams catalyst (132) added.

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(132) "Organic Synthesis," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y. (1941), p. 463.

After 25 min. the sample consumed 16.6 ml. (S.T.P.) of hydrogen which agreed favorably with the calculated value of 16.9 ml.

The Sodium Borohydride Reduction of 1,3,4,5-Tetra-O-benzoyl-keto-D-erythro-pentulose

To 3.0 g. of 1,3,4,5-tetra-O-benzoyl-keto-D-erythro-pentulose dissolved in a mixture of purified dioxane (127) and 20 ml. of water

was added a solution of 200 mg. of sodium borohydride in 4 ml. of water and the whole was allowed to stand at room temperature for 1 hr. The solution was concentrated under reduced pressure at 50° and the resulting sirupy residue was dissolved in chloroform. The chloroform solution of the reduction products was washed with 50 ml. each of N sulfuric acid, saturated aqueous sodium bicarbonate and water. After drying over sodium sulfate, the chloroform solution was evaporated to dryness under reduced pressure. The residue was dissolved in 100 ml. of acetone, treated with 10 ml. of 5 N sodium hydroxide and allowed to stand at room temperature for 2 hr. The acetone was removed by evaporation at reduced pressure, the sodium ions were removed with Dowex (acid form) (133), and the

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(133) A product of the Dow Chemical Co., Midland, Michigan.

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benzoic acid by extraction with ether. Some of the benzoic acid crystallized in the ion-exchange resin but this did not interfere with the removal of the carbohydrate product from the resin. The resulting non-reducing solution was evaporated to dryness under reduced pressure and the residue was dissolved in methanol and decolorized with carbon. No crystals were obtained upon remaining for 2 hr. at 0-5°. Dry heptane (15 ml.) was added and the mixture maintained at 0-5° for 12 hr., whereupon, crystallization was effected; yield 366.5 mg. More product was formed on further addition of heptane; total yield 4.17 mg., m.p. 65-80°.

The Preparation of Formaldehyde Dimedon

To 2 ml. of formalin (134) and 10 ml. of 95 per cent ethanol

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(134) Baker Reagent Grade formaldehyde (36-38 per cent formaldehyde by wt.).

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was added 1 g. of 5,5-dimethyl-1,3-cyclohexanedione (dimedon) and 1 drop of piperidine. The mixture was refluxed for 10 min. and water added to incipient turbidity. After standing overnight at ice-box temperature (0-3°), the colorless product was suction filtered; yield 1 g., m.p. 189-190°. Recrystallization from ethanol-water gave pure material, m.p. 191-191.5°, in agreement with the value reported (135).

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(135) E. C. Horning and M. G. Horning, J. Org. Chem., 11, 95 (1946).

Periodate Oxidation of the Pentitol Mixture Obtained From the Sodium Borohydride Reduction of 1,3,4,5-Tetra-O-benzoyl-keto-D-erythro-pentulose

An aqueous solution of the previously prepared pentitol mixture (51.9 mg., 0.34 millimole) was titrated with a standard solution of sodium metaperiodate and was found to consume 1.33 millimole of the standard sodium metaperiodate in 2 hr. This sodium metaperiodate consumption corresponds to a ratio of 4.0 millimoles of oxidant per millimole of substrate and this value was unchanged upon allowing

the pentitol and sodium metaperiodate reaction mixture to remain at room temperature for 24 hr. An aliquot of the reaction mixture was titrated for the acid content and it was determined that 3.1 millimoles of acid had been produced per millimole of the pentitol mixture. Treatment of half of the reaction mixture with an aqueous solution of 5,5-dimethylcyclohexane-1,3-dione (dimedon) gave a crystalline product; yield 89 mg. Recrystallization of this derivative from methanol gave colorless material; yield 61 mg., m.p. 191-192°, unchanged on admixture with an authentic sample of formaldehyde dimedon. The isolation of 89 mg. of formaldehyde dimedon thus constitutes an isolation of 1.8 millimoles of formaldehyde produced per millimole of pentitol substrate in the sodium metaperiodate oxidation of the pentitol mixture.

The Synthesis of Ribitol (Adonitol) from D-Ribose

To a solution of 4.5 g. of D-ribose (115) contained in 50 ml. of water was added 1 g. of sodium borohydride and the mixture allowed to stand overnight at room temperature. The solution was then made slightly acid with concentrated hydrochloric acid and the mixture evaporated to dryness. Repeated evaporation under reduced pressure (5 times) of the residue from small volumes of methanol (20 ml.) served to remove the boric acid from the residue. The remaining residue was dissolved in 50 ml. of water and deionized by passing through a column of first IR-120 (116) then Duolite A-4 (122). The aqueous solution from the columns was evaporated to dryness under reduced pressure. Crystallization of the solid product from

ethanol gave a nearly quantitative yield of colorless material; m.p. 102°, $[\alpha]^{25}$ D 0° (c 3, water) in agreement with the values (102° and 0°) reported by Fischer (64).

The Synthesis of 1,4-Anhydro-DL-ribitol

A solution of 2 g. of ribitol in 100 ml. of 2.1 N hydrochloric acid was heated at 110° for 27 hr. The resulting solution was evaporated under reduced pressure to a sirup, whereupon, repeated vacuum evaporation (5 times) at reduced pressure from small volumes of water served to remove the hydrochloric acid. Paper chromatography, using 1-butanol saturated with ammonium hydroxide as developer and periodate-benzidine (136) as indicator, gave but a single spot and indicated that the resulting sirup contained only one component. Crystalline material was obtained by solution of the sirup in 20 ml. of hot 1-butanol followed by the addition of 4 ml. of hot hexane; yield 1.5 g., m.p. 76-77°. Recrystallization gave pure material; m.p. 76.5-77°.

(136) M. Viscontini, D. Hoch and P. Karrer, Helv. Chim. Acta, 38, 642 (1955).

Anal. Calcd. for $C_5H_{10}O_4$: C, 44.7; H, 7.5. Found: C, 44.6; H, 7.3.

An aqueous solution of the product was titrated with a standard solution of sodium metaperiodate and was found to consume one millimole of the standard sodium metaperiodate per millimole of

substrate, with no further consumption of oxidant after 24 hr. No acid could be detected by titration of an aliquot of the reaction mixture and no formaldehyde was produced as determined with an aqueous 5,5-dimethylcyclohexane-1,3-dione (dimedon) solution.

The Synthesis of 2,3,5-Tri-O-benzoyl-1,4-anhydro-DL-ribitol

To a solution of 100 mg. of 1,4-anhydro-DL-ribitol dissolved in 5 ml. of anhydrous pyridine was added, at 0°, 0.25 ml. of benzoyl chloride and the mixture allowed to remain overnight at room temperature. After the addition of ice and 25 ml. of chloroform, the chloroform layer was washed with 50 ml. each of N sulfuric acid, saturated aqeuous sodium bicarbonate, and water. The solvent was removed under reduced pressure from the dried extract and the residual sirup was dissolved in 10 ml. of hot 1-butanol, decolorized with carbon and filtered. Crystals were obtained on cooling; yield 300 mg. (89 per cent), m.p. 115-116°. Three recrystallizations from the same solvent gave pure material; m.p. 116-117°.

Anal. Calcd. for $C_{26}H_{22}O_7$: C, 69.9; H, 4.9. Found: C, 69.6; H, 4.9.

The Preparation of D-Arabinitol

D-arabinitol was prepared from D-arabinose by reduction with sodium borohydride by the same procedure as was used for the production of ribitol from D-ribose. Crystallization from ethanol gave a colorless product; m.p. 102° in good agreement with the value (103°) reported by Ruff (137).

(137) O. Ruff, Ber., 32, 550 (1899).

The Treatment of D-Arabinitol with 2.1 N Hydrochloric Acid

A sample of D-arabinitol (1.0 g.) was heated at 110° for 27 hr. in the manner which was previously described for ribitol. The sugar alcohol was recovered unchanged; yield 0.85 g., m.p. 102°, undepressed on admixture with authentic D-arabinitol of like melting point. Paper chromatography, as described previously for 1,4-anhydro-DL-ribitol, of the crystalline substance, as well as the mother liquor material, showed only one component.

The Preparation of Penta-O-acetyl-D-arabinitol

To 1 g. of D-arabinitol dissolved in 20 ml. of anhydrous pyridine was added 10 ml. of acetic anhydride. The reaction mixture was allowed to stand overnight and excess ice and 50 ml. of chloroform was added. The chloroform layer was washed with 50 ml. each of N sulfuric acid, saturated aqueous sodium bicarbonate solution and water. After drying over sodium sulfate, the chloroform solution was evaporated to dryness under reduced pressure. The sirup obtained on solvent removal was dissolved in 15 ml. of dry ether and 30 ml. of dry heptane added. Crystals were obtained on standing overnight at 0-5°; yield 680 mg., m.p. 74-75° in agreement with the value (76°) reported by Asahina and Yanagita (138).

(138) Y. Asahina and M. Yanagita, Ber., 67, 799 (1934).

The Separation and Characterization of the Pentitol Mixture Obtained from the Sodium Borohydride Reduction of 1,3,4,5-Tetra-O-benzoyl-keto-D-erythro-pentulose

To 300 mg. of the crystalline mixed pentitols was added 30 ml. of 2 N hydrochloric acid and the mixture was heated at 100° for 28 hr. The solution was evaporated to dryness under reduced pressure and the hydrochloric acid was removed by repeated evaporation at reduced pressure from small volumes of water. The remaining sirup was dissolved in a small volume of water and the solution applied in horizontal streaks onto large sheets of Whatman 3 MM paper (46.4 x 58.2 cm.). The paper chromatograms were developed using 1-butanol saturated with ammonium hydroxide as developer and the bands (R_f 0.24 and 0.39) indicated by spraying vertical strips, cut from the edges and middle of each paper, with periodate-benzidine spray (136). The two bands containing the bulk of the material were eluted with water and the eluates were concentrated under reduced pressure.

The residue from the top band (R_f 0.24) was dissolved in 1 ml. of absolute ethanol and 2 ml. of 1-butanol added. After remaining overnight at 0-3°, the solution deposited crystals; yield 41 mg., m.p. 94-96°. Recrystallization from the same solvent gave pure material; m.p. 102°, unchanged on admixture with authentic D-arabinitol of like melting point.

The mother liquor from the first crop of crystals was evaporated to dryness under reduced pressure and the sirupy residue treated with 5 ml. of dry pyridine and 2 ml. of acetic anhydride. After remaining 5 hr. at room temperature, excess ice and 25 ml. of chloroform were added. The chloroform layer was washed with 50 ml. each of N sulfuric acid, saturated aqueous sodium bicarbonate solution and water. The chloroform solution was dried over sodium sulfate and the mixture evaporated to dryness under reduced pressure. The sirup thus obtained was dissolved in 5 ml. of dry ethyl ether and 15 ml. of dry heptane added. Crystals were obtained after remaining overnight at 0-5°; yield 107 mg., m.p. 74-75°, unchanged on admixture with authentic penta-O-acetyl-D-arabinitol of like melting point.

The presence of D-arabinitol in the original pentitol mixture could also be shown by the marked increase in rotation of the sample on the addition of ammonium molybdate and sulfuric acid (139). In this manner, it was estimated that the pentitol

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(139) M. Frèrejacque, Compt. rend., 200, 1410 (1935); 208, 1123 (1939).

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mixture was about 45 per cent D-arabinitol.

The residue from the second band (R_f 0.39) was dissolved in 1 ml. of 1-butanol and dry heptane added to incipient turbidity. A crop of rather gummy crystals were obtained which were recrystallized in the same manner; yield 32 mg. Recrystallization

(twice) gave pure material; m.p. 75-76° and m.p. 76-77° on admixture with the authentic 1,4-anhydro-DL-ribitol (m.p. 76.5-77°) prepared previously.

The combined mother liquors from the crystallizations were evaporated to dryness under reduced pressure and the residue treated with 3 ml. of benzoyl chloride in 10 ml. of anhydrous pyridine. After 0.5 hr., ice was added and the product was extracted with chloroform, washed twice with 50 ml. each of N sulfuric acid, saturated aqueous sodium bicarbonate solution and water. The dried chloroform layer was evaporated under reduced pressure and the resultant sirup was dissolved in 2 ml. of hot 1-butanol. Crystals were obtained on cooling; yield 160 mg., m.p. 114-116°. Pure material was formed on recrystallization from 1-butanol-heptane; m.p. 116-116.5° and m.p. 115-116° on admixture with authentic 2,3,5-tri-O-benzoyl-1,4-anhydro-DL-ribitol of like melting point.

The Preparation of o-Nitrophenylhydrazine

For the preparation of this reagent, a modified procedure of Müller, Montigel and Reichstein (100) was used.

To 50 g. of o-nitroaniline dissolved in 125 ml. of concentrated hydrochloric acid and cooled to 0° was added a precooled solution (0°) of 30 g. of sodium nitrite in 50 ml. of water. The mixture was maintained at 0° for 15 min. by cooling in an ice-salt bath. The resulting solution was filtered and neutralized to turbidity with 0.1 N sodium hydroxide solution. A solution of 50 g. of potassium hydroxide in 250 ml. of water saturated with sulfur dioxide was

added slowly, with stirring, to the diazotization solution. Potassium carbonate (90 g.) was added to the mixture and the temperature was maintained at 0-5°. The reaction solution was stirred with a magnetic stirrer for 1 hr. and acidified with concentrated hydrochloric acid. The crystalline product was removed by suction filtration and then dissolved in a minimum amount of hot water. Upon the addition of sodium acetate the free hydrazine base precipitated and was washed with cold water; yield 44 g., m.p. 90°.

The Preparation of D-erythro-Pentulose o-Nitrophenylhydrazone from D-Arabinose

A solution of 100 g. of D-arabinose in 1000 ml. of anhydrous pyridine was heated at reflux temperature for 4 hr. The solvent was removed by evaporation at reduced pressure and the last traces of pyridine removed by repeated evaporation at reduced pressure from small volumes of water. The resulting sirup was dissolved in hot absolute ethanol and allowed to remain overnight at 0-3°. The D-arabinose which had crystallized from the ethanol solution was removed by suction filtration and the solvent concentrated under reduced pressure. The concentrated solution was allowed to remain at 0-3° for 2 days and the D-arabinose which crystallized from the solution was removed; total yield of recovered D-arabinose, 80 g.

The remaining ethanol solution was concentrated to 200 ml. and 11 g. of o-nitrophenylhydrazine added. After boiling the mixture for 15 min., the solution was allowed to remain at 0-3° for two days.

The red-orange crystals which resulted were removed by suction filtration and crystallized from a minimum amount of hot absolute ethanol; yield 21 g., m.p. 150°. Repeated crystallization of the hydrazone from absolute ethanol gave pure D-erythro-pentulose o-nitrophenylhydrazone; yield 6 g., m.p. 168-169°, $[\alpha]^{20}$ D +48.1 (c 4, methanol), in agreement with the values (168-169.5° and +48.3°) reported by Glatthaar and Reichstein (72).

The Synthesis of D-erythro-Pentulose and D-erythro-Pentulose o-Nitrophenylhydrazone from 1-Deoxy-1-diazo-3,4,5-tri-O-benzoyl-keto-D-erythro-pentulose

To 470 mg. of 1-deoxy-1-diazo-3,4,5-tri-O-benzoyl-keto-D-erythro-pentulose, dissolved in 20 ml. of methanol, was added 20 ml. of a 5 per cent sulfuric acid solution of methanol-water (1:1 by volume). The mixture was refluxed for 30 min. and cooled to room temperature. The addition of Duolite A-4 resin (122), until the neutral point, was followed by the evaporation to a thick sirup at reduced pressure.

To the resulting sirup, dissolved in 20 ml. of methanol and cooled in a dry ice-chloroform bath, was added a catalytic amount of sodium methoxide in anhydrous methanol. The mixture was allowed to stand for 2 days and upon warming to room temperature was adjusted to the neutral point with IR-120 resin (116). Evaporation under reduced pressure of the resulting solution gave a light-yellow sirup which was dissolved in water and extracted with ethyl ether. Clarification with carbon, followed by solvent removal under reduced

pressure, gave a light-yellow sirup which was reducing to Fehling solution; yield 61 mg. (40 per cent), $[\alpha]^{21}$ D -16° (c 1.8, water), in agreement (opposite sign) with the value $[\alpha]^{27}$ D +16.6 (c 1.442, water) reported by Levene and Tipson (73) for the enantiomorph. Paper electrophoresis of the product gave only a single spot (140).

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(140) A. B. Foster, Chemistry and Industry, 828, 1050 (1952); J. Chem. Soc., 982 (1953).

Anal. Calcd. for $C_5H_1O_5$: C, 40.00; H, 6.71. Found: C, 39.92; H, 6.63.

To 30 mg. of the above sirup dissolved in 5 ml. of absolute ethanol was added a solution of 30 mg. of o-nitrophenylhydrazine dissolved in 5 ml. of absolute ethanol. The reaction mixture was refluxed for 15 min. and reduced in volume to approximately 5 ml. by a stream of dry air. After standing overnight at 0-3°, the crystals were suction filtered; yield 35 mg., m.p. 155-156° and m.p. 156-157° on admixture with authentic D-erythro-pentulose o-nitrophenylhydrazone prepared from the pyridine interconversion of D-arabinose.

The Synthesis of D-erythro-Pentulose and D-erythro-Pentulose o-Nitrophenylhydrazone from 1,3,4,5-Tetra-O-benzoyl-keto-D-erythro-pentulose

To 470 mg. of 1,3,4,5-tetra-O-benzoyl-keto-D-erythro-pentulose dissolved in 20 ml. of anhydrous methanol and cooled

in a dry ice-chloroform bath, was added a catalytic amount of sodium methoxide in anhydrous methanol. After standing for 2 days, the solution was adjusted to the neutral point with IR-120 resin (116) and evaporated under reduced pressure to a sirup. The sirup was dissolved in 10 ml. of water, clarified with carbon, and extracted with ethyl ether. Solvent removal under reduced pressure gave a yellow reducing sirup; yield 50 mg., $[\alpha]^{20}$ D -15° (c 2.0, water).

The sirupy D-erythro-pentulose was treated with an equivalent amount of o-nitrophenylhydrazine and the o-nitrophenylhydrazone isolated as in the previous section; yield 25 mg., m.p. 156-157°, with no depression in m.p. on admixture with authentic D-erythro-pentulose o-nitrophenylhydrazone obtained from the pyridine interconversion of D-arabinose.

The Preparation of D-Arabinonyl Chloride Tetraacetate from D-Arabinose

D-Arabinose was oxidized with bromine as described earlier for the preparation of D-arabinonic acid but neutralized with potassium carbonate instead of calcium carbonate to produce potassium D-arabinonate. D-Arabinonic acid was prepared from the potassium salt by recrystallization from acetic acid and acetylation with zinc chloride and acetic anhydride according to the procedure of Robbins and Upson (141,142) gave D-arabinonic acid tetraacetate. D-Arabinonyl

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(141) G. B. Robbins and F. W. Upson, J. Am. Chem. Soc., 62, 1074 (1940).

(142) J. M. Brakenburg and F. Upson, J. Am. Chem. Soc., 55, 2512 (1933).

chloride tetraacetate was prepared from D-arabinonic acid tetraacetate by treatment with phosphorus pentachloride in anhydrous ether by the method of Wolfrom, Brown and Evans (23). Pure material was obtained on crystallization from dry ether by the addition of petroleum ether; m.p. 74-75°, $[\alpha]^{20}$ D +46° (c 2.5, abs. chloroform).

The Synthesis of 1,2-Dideoxy-3-keto-D-arabino-heptulose Tetraacetate

N-Ethyl-N-nitrosourea was prepared according to the procedure for the preparation of the homologous N-methyl-N-nitrosourea (143).

(143) "Organic Synthesis," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y. (1943), p. 461.

An ethereal solution of the urea derivative gave diazoethane on treatment with a solution of potassium hydroxide in 2-(2-ethoxy-ethoxy)-ethanol (8 per cent yield).

A solution of 700 mg. of diazoethane in 80 ml. of ether was cooled in an alcohol-dry ice-bath. To this solution was added slowly, with stirring, a solution of 1.8 g. of tetra-O-acetyl-D-arabinonyl chloride in 50 ml. of ether. The mixture was allowed to stand for 30 min. and was then evaporated to dryness under reduced pressure. The resulting sirup was dissolved in 20 ml. of benzene and chromatographed in 10-ml. portions on two Magnesol (129)-Celite (130) (5:1 by wt.) columns (4.4 x 21.5 cm.) using 500 ml. of benzene: t-butyl alcohol (100:1 by vol.) as developer. Alkaline permanganate streaking (131) revealed the presence of a

zone located 6-9 cm. from the column top. The sectioned zones from the two columns were combined, eluted with acetone, and the eluate was evaporated to a thick sirup which effevesced on acidification and showed absorption at 4.77, 6.1 and 7.2 μ (7).

This sirupy 1,2-dideoxy-2-diazo-3-keto-D-arabino-heptulose tetraacetate was dissolved in 40 ml. of chloroform and 10 ml. of 47 per cent hydriodic acid was added. The mixture was shaken until nitrogen evolution ceased (about 5 min.). The dark-red chloroform solution was washed with water, sodium thiosulfate solution and again with water. The chloroform solution was dried with sodium sulfate and the solvent removed under reduced pressure to yield a yellow sirup. The sirup was dissolved in 20 ml. of benzene, the benzene solution divided in half, and each half chromatographed on Magnesol (129)-Celite (130) (5:1 by wt.) columns (4.4 x 20.5 cm.) using 500 ml. of benzene: t-butyl alcohol (100:1 by vol.) as developer. On streaking with alkaline permanganate (131), three zones were observed at 0-3 cm., 8-12 cm., and 15-16 cm., from the column top.

The middle zones from both columns were combined, eluted with acetone, and the eluate evaporated under reduced pressure to yield a light-yellow sirup of 1,2-dideoxy-3-keto-D-arabino-heptulose tetraacetate which crystallized from ether-petroleum ether (b.p. 30-60°); yield 160 mg., m.p. 86-88°. Recrystallization was effected from the same solvent, $[\alpha]^{20}$ D +54.4° (c 2.6, U.S.P. chloroform), m.p. 93-94°. X-ray powder diffraction

data (117): 9.88m(2), 7.25s(1), 5.29s(1), 4.68m(2), 4.20m(2), 4.01w, 3.80m(2), 3.58w, 3.47w, 3.33w, 2.78w.

The Identification of Weisblat's D_{II} as 1,2-Dideoxy-3-keto-D-arabino-heptulose Tetraacetate

A sample of the substance, m.p. 93-94°, $[\alpha]$ D +53.4, obtained by Weisblat (113) from aldehydo-D-arabinose tetraacetate was found to give no depression in m.p. on admixture with the authentic sample of 1,2-dideoxy-3-keto-D-arabino-heptulose tetraacetate prepared in this work. The X-ray diffraction powder patterns of both substances were identical; ultra-violet absorption spectrum in 1,2-di-O-methyl-ethanediol: $\log \varepsilon_{max}$ 1.60 (282 mμ, c 1.8 x 10^{-2} M), and $\log \varepsilon_{max}$ 1.63 (282 mμ, c 9 x 10^{-3} M).

SUMMARY

1. D-Erythronamide has been shown to be hydrolytically stable in water at room temperature for 80 hours.

2. Ammonium D-gluconate has been identified as a hydrolytic product in the hydrolysis of D-gluconamide at room temperature.

3. A laboratory preparation for the small scale synthesis of nitrosyl chloride is described.

4. 2,3,4-Tri-O-benzoyl-D-erythronic acid was synthesized from 2,3,4-tri-O-benzoyl-D-erythronamide by the action of nitrosyl chloride in either dioxane or benzene.

5. 2,3,4-Tri-O-benzoyl-D-erythronyl chloride was synthesized from the reaction of 2,3,4-tri-O-benzoyl-D-erythronic acid with phosphorus pentachloride in anhydrous ether.

6. 1-Deoxy-1-diazo-3,4,5-tri-O-benzoyl-keto-D-erythro-pentulose was synthesized by the action of diazomethane upon 2,3,4-tri-O-benzoyl-D-erythronyl chloride.

7. 1-Deoxy-1-diazo-3,4,5-tri-O-benzoyl-keto-D-erythro-pentulose was transformed by acid hydrolysis in a methanol-water solution into sirupy D-erythro-pentulose, characterized as its crystalline o-nitrophenylhydrazone.

8. 1,3,4,5-Tetra-O-benzoyl-keto-D-erythro-pentulose was synthesized by the action of benzoic acid and copper bronze on 1-deoxy-1-diazo-3,4,5-tri-O-benzoyl-keto-D-erythro-pentulose.

9. 1,3,4,5-Tetra-O-benzoyl-keto-D-erythro-pentulose was transformed by treatment with a catalytic amount of methoxide

ion in methanol solution into sirupy D-*erythro*-pentulose, characterized as its crystalline *o*-nitrophenylhydrazone.

10. 1,3,4,5-Tetra-*O*-benzoyl-*keto*-D-*erythro*-pentulose has been shown to have a free carbonyl group by catalytic reduction with hydrogen.

11. 1,3,4,5-Tetra-*O*-benzoyl-*keto*-D-*erythro*-pentulose has been reduced with sodium borohydride in a dioxane-water solution to the corresponding diastereoisomeric pentitol tetrabenzoate intermediates which, after saponification with aqueous sodium hydroxide and treatment with hydrochloric acid, were separated by paper chromatography and identified as D-arabinitol (and D-arabinitol pentaacetate) and 1,4-anhydro-DL-ribitol (and 2,3,5-tri-*O*-benzoyl-1,4-anhydro-DL-ribitol). The isolation of the two 2-epimeric pentitols thus establishes the free *keto*-nature of the second carbon atom in the ketopentose tetrabenzoate.

12. Ribitol has been produced by the sodium borohydride reduction of D-ribose for the first time.

13. A preparative procedure for the synthesis of 1,4-anhydro-DL-ribitol from ribitol is described.

14. A preparative procedure for the synthesis of 2,3,5-tri-*O*-benzoyl-1,4-anhydro-DL-ribitol from 1,4-anhydro-DL-ribitol is described.

15. D-Arabinitol has been shown to be stable to refluxing 2.1 *N* hydrochloric acid for 27 hr., under which conditions ribitol is converted to 1,4-anhydro-DL-ribitol.

16. The paper chromatographic conditions, using 1-butanol saturated with ammonium hydroxide as developer, are described for the separation of 1,4-anhydro-DL-ribitol and D-arabinitol. In this system the former compound has a R_f of 0.24 and the latter compound a R_f of 0.39.

17. 1,2-Dideoxy-3-keto-D-arabino-heptulose tetraacetate was prepared from diazoethane and D-arabinonyl chloride tetraacetate.

18. The identity of Weisblat's D_{II} has been established as 1,2-dideoxy-3-keto-D-arabino-heptulose tetraacetate by comparison with the synthetic material prepared from the reaction of D-arabinonyl chloride tetraacetate with diazoethane.

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AUTOBIOGRAPHY

I, James Davidson Crum, the son of Walter James Crum and Frances Louise Davidson Crum, was born in Ironton, Ohio, on July 29, 1930. I received my primary education at Lombard Elementary School and graduated from Ironton High School in 1948, the recipient of the Bausch and Lomb Honor Science Award. During this latter period of time it was indeed a privilege and pleasure to have been the student of Miss Lillian E. Humphrey, whose instruction in biology and chemistry provided the basis for my early interest in the sciences. My undergraduate training was received at Miami University, Oxford, Ohio, from 1948 to 1950, where I served as an undergraduate assistant in the Freshmen Chemistry Laboratory, and from 1950 to 1952 at The Ohio State University where I graduated in June, 1952, with a Bachelor of Science Degree in chemistry. During the summers of 1948 to 1952, I partially supported my undergraduate education by serving in the capacity of chemist for the Barrett Division of the Allied Chemical and Dye Corporation, Ironton, Ohio. In September, 1952, I became an assistant in the Department of Chemistry at Marshall College, Huntington, West Virginia, where, as a student of Professor J. Holland Hoback, I received a Master of Science Degree in August, 1953, with the thesis entitled "The Synthesis of Some Aminocarbonyl- and Aminothiocarbonylsalicylamides." I matriculated in September, 1953, in the Graduate School of The Ohio

State University as a candidate for the degree of Doctor of Philosophy in Chemistry and served as an assistant in the Freshmen Chemistry Division for three quarters. In September 1954 I became an assistant in the Organic Chemistry Division and, subsequently, as assistant instructor in March 1955, where I was special assistant in the Organic Division. After serving in this capacity for two years, I was awarded a Charles F. Kettering Foundation Fellowship which I held during my remaining residence at The Ohio State University. While at the University, one of my most memorable student associations was with an art student, Anne Crane Kanode, who became my wife on September 2, 1956.