

INVESTIGATION OF THE ACTION OF
SELECTED OXIDIZING AGENTS ON
D-MANNITOL-1,2,3,5,6-PENTANITRATE

BY

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A C K N O W L E D G E M E N T

I would like to express my thanks and appreciation to Doctor L.D. Hayward for help and encouragement during the course of this work.

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ABSTRACT

The oxidation of D-Mannitol-1,2,3,5,6-pentanitrate by a selection of non-specific oxidants was investigated under acidic, basic and neutral conditions.

Results of preliminary experiments led to further study of the action of chromium trioxide in acetone solution on the pentanitrate. Short term oxidation with this mixture yielded a syrupy product which on hydrogenation gave a further, optically inactive syrup which did not give a positive test with Pacsu's ketose reagent or with Fehling's solution. When the reaction was allowed to go to completion, a white crystalline compound, which did not reduce Fehlings solution was isolated from the oxidation mixture. This compound, which was not identified, yielded D-mannitol on hydrogenation but differed in physical properties and infra-red spectra from D-Mannitol-1,2,3,5,6,-pentanitrate, D-Mannitol hexanitrate and isomannide dinitrate.

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INTRODUCTION

A number of the possible aldo- and 2-ketohexoses have been found widely distributed in nature. They and their non-naturally occurring isomers have all been synthesized and extensively studied. Such has not been the case with the 3-ketohexose isomers. Although their existence has been postulated, and has been the subject of controversy, as yet no 3-ketose has been isolated from natural sources.

For many years, two substances, 'glutose' and 'galtose', were believed to be 3-ketoses. Despite the fact that their identity was later disproved, the great amount of speculation which was aroused concerning the formation and biological activity of 3-ketoses led to study of possible unequivocal synthetic routes to authentic samples of these sugars. The present work describes an attempt to prepare D-arabino-3-hexulose which has the structure to which Lobry de Bruyn and Alberda van Ekenstein assigned the name α -glutose.

Oxidation of a suitably substituted hexitol would lead to a 3-hexulose. Normally, oxidation of an unsubstituted sugar alcohol occurs at the ends of the carbon chain to yield aldohexoses or hydroxy acids (1,2), although it is possible by some methods, to obtain 2-ketohexoses (3,4). No oxidants

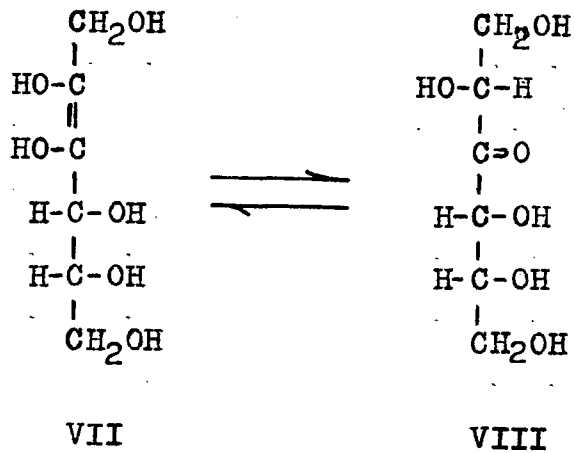
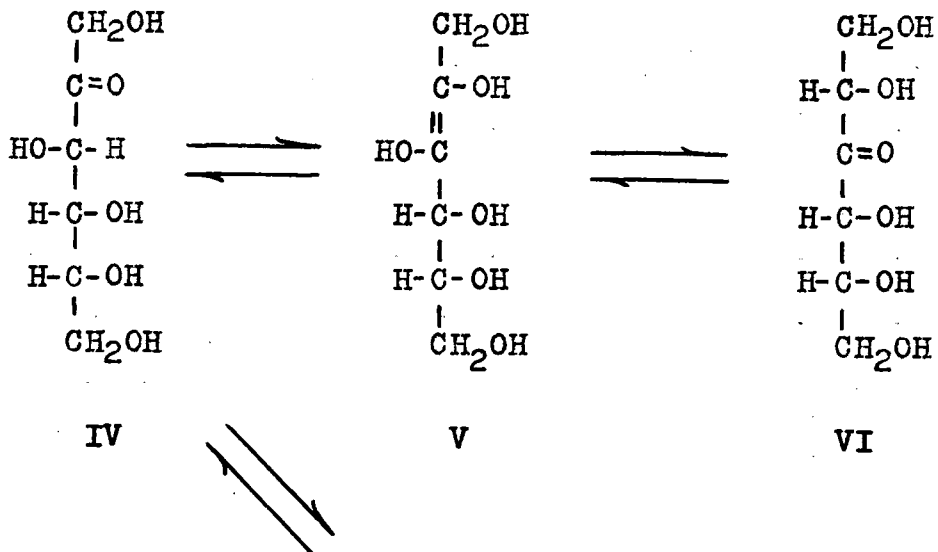
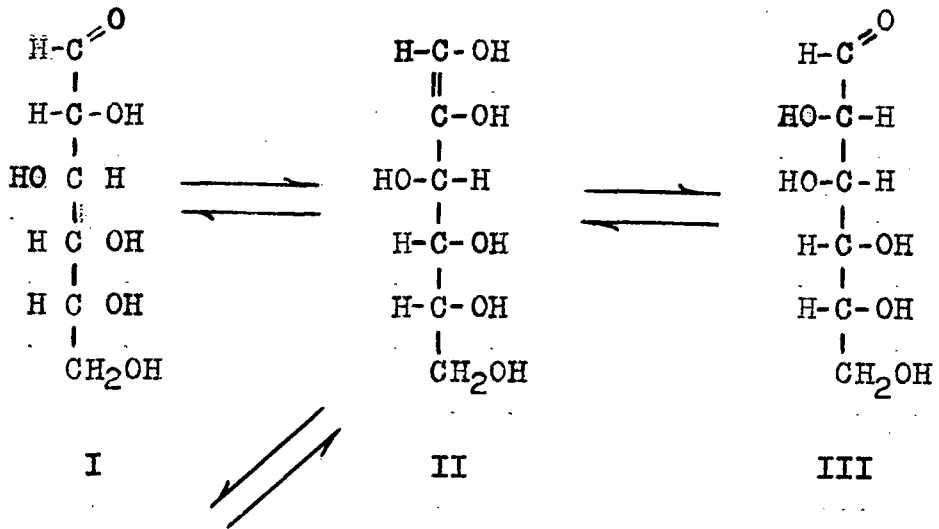
specific for the hydroxyl at carbon three of the unsubstituted polyol have so far been discovered. If, however, all other hydroxyl groups could be blocked, by suitable substituents, oxidation might be induced at position three on the carbon chain with the formation of a ketonic group at this site. Removal of the blocking substituents should yield a compound isomeric with the known hexoses.

Since it possessed a free hydroxyl group at the desired position, D-mannitol-1,2,4,5,6-pentanitrate appeared to provide a suitable starting material for the oxidation. The nitrate ester groups were known to be relatively stable to neutral and acid conditions (5) and to oxidation, yet could be easily and quantitatively removed when desired by catalytic hydrogenation (6). It was therefore postulated that selective oxidation of the free hydroxyl group with a suitable oxidizing agent, followed by removal of the nitrate ester groups, would complete the synthesis of D-arabino-3-hexulose.

HISTORICAL INTRODUCTION

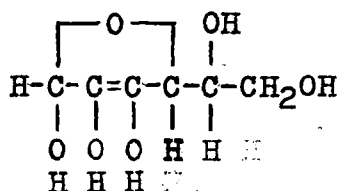
GLUTOSE

In their study of the interconversion of D-glucose (I), fructose (IV) and D-mannose (III) in aqueous solutions under the influence of inorganic bases (potassium, sodium, calcium and lead hydroxides, sodium acetate and sodium carbonate), Lobry de Bruyn and Alberda van Ekenstein (7) found that a non-fermentable, apparently homogeneous syrup could be obtained in yields varying from one to twenty percent. This syrup, which could be neither crystallized nor resolved, was tentatively identified as a hexulose 'glutose' (VI, VIII), in which the carbonyl group was in position three on the carbon chain. They postulated that a 3-hexulose could be formed by a continuation down the carbon chain of the epimeric shifts which resulted in the conversion of aldoses to 2-ketoses through enediol forms (II, V, VII). Though either I, III, or IV could be used as starting materials for the preparation of "glutose", Lobry de Bruyn and van Ekenstein found that the best yields could be obtained by heating an aqueous solution of IV with lead hydroxide (8). The conversion to 'glutose', however, appeared to be irreversible. Further treatment of the product with alkali failed to yield any trace of I, III or IV.



'Galtose', another non-fermentable syrup, also thought to be a 3-hexulose, was prepared in a similar manner from D-galactose (9). From the residue which remained as a by-product of the commercial production of alcohol from cane molasses by fermentation, up to six percent of a syrup apparently identical to 'glucose' could be isolated (10).

Nef (11) questioned the identity of this 'glucose', suggesting that it was, in fact, a partial oxidation product of D-glucose (I), D-glucosone (IX). IX could not be reconverted to hexoses, but would yield organic acid salts on further



IX

treatment with base in the presence of atmospheric oxygen. Nef then prepared another syrup which he termed 'authentic glucose', by treatment of I with aqueous calcium hydroxide in the cold with the exclusion of air.

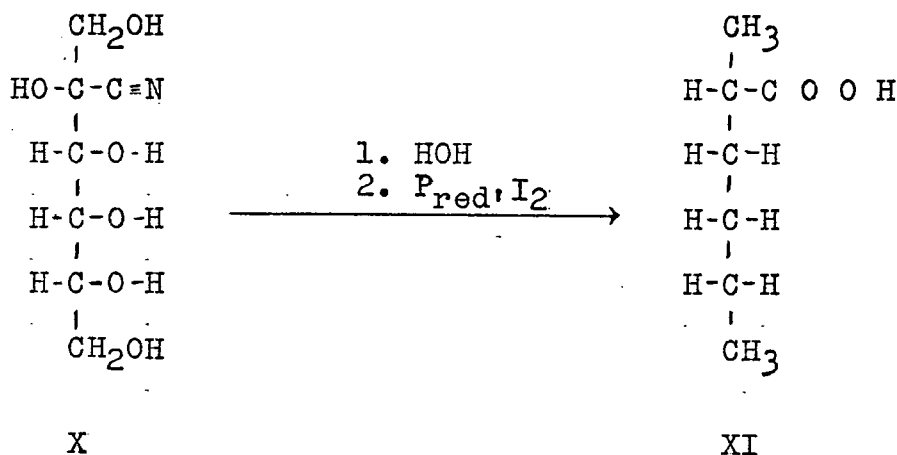
Later, Spoehre and Wilbur (12), in 1924, claimed that I and IV were interconvertible at 38° in the presence of disodium acid phosphate. Formation of some 'glucose' was reported. None of the products were isolated, conclusions being based on reducing power, optical rotation, alkalinity and susceptibility to fermentation.

Benedict, Dakin and West (13), reported a thirty-eight

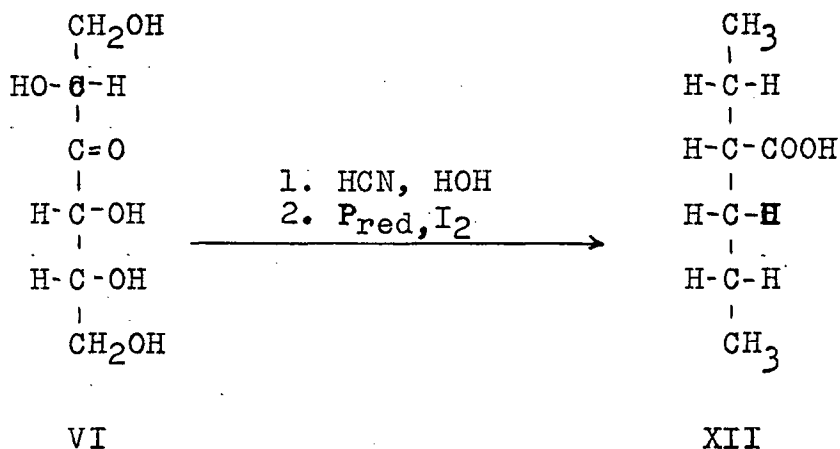
percent yield of 'glucose' prepared by shaking a solution of invert sugar with calcium hydroxide for several hours. With regard to physiological actions, they noted that their glucose, in contrast to the other hexoses, was neither absorbed nor utilized by the human body.

Spoehr and Strain (14) believed that the 'glucoses' prepared by different methods were not identical, however, they attributed the variations in reactivity to the presence of impurities which varied with the method of preparation. They found that the reported 'glucose phenylosazone' could be separated into several components by solvent extraction and that there was no evidence for the presence of a 3-hexulose.

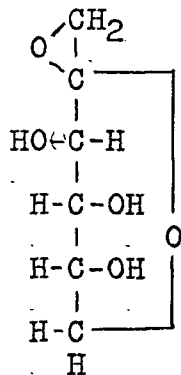
Spoehr and Strain then obtained evidence that 'glucose' could not be a 3-hexulose. 'Glucose' formed a cyanohydrin (X) which by hydrolysis and reduction could be converted to 2-methylcaproic acid (XI); this acid must have been derived from a 2 hexulose, since a true 3-keto-hexose



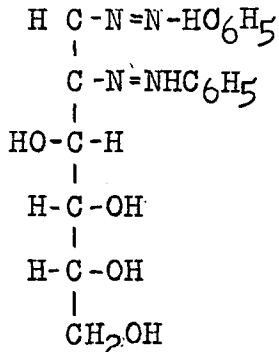
would yield 2-ethylvaleric acid (XII).



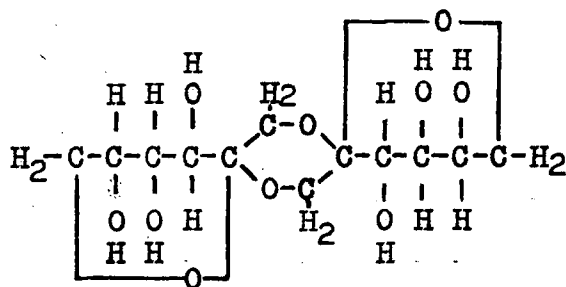
Sattler and Zerban (15, 16) in 1945, isolated the unfermentable reducing substances in cane molasses and proved them identical to the heterolevulosan (XIII), probably 1,2-anhydro-D-fructopyranose, and the diheterolevulosan (XIV) reported by Pictet and Chavan (17). The latter was shown to be a difructose anhydride by Schulbache and Behre (18). Sattler and Zerban also demonstrated that the 'glutosazone' reported by previous workers was identical to D-glucosazone (XV).



XIII

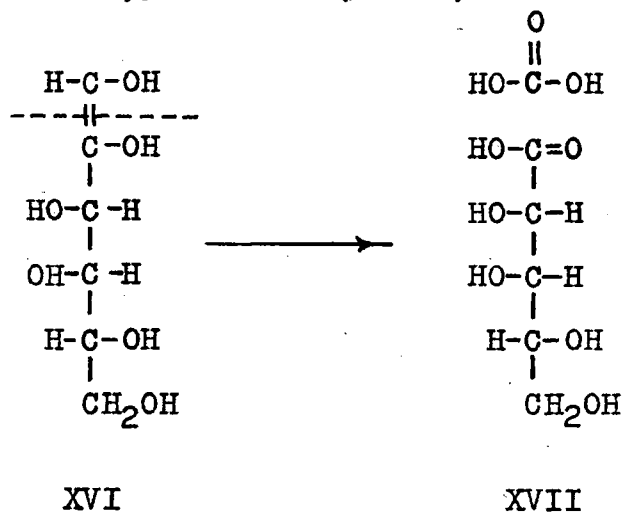


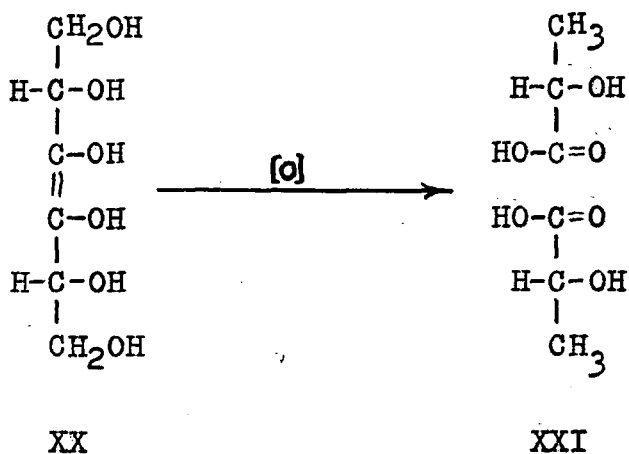
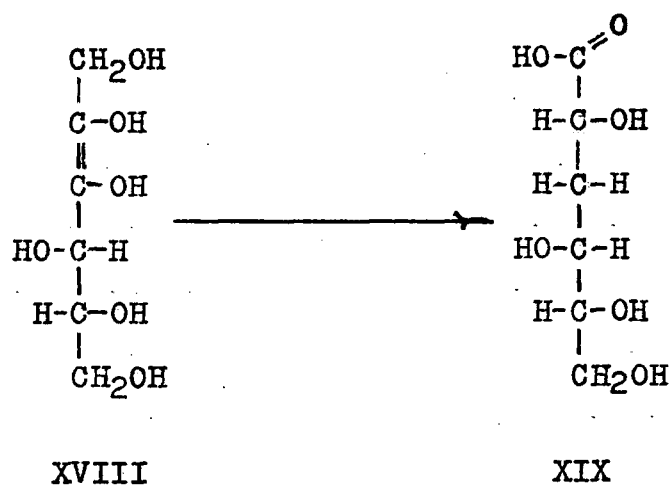
XV



XIV

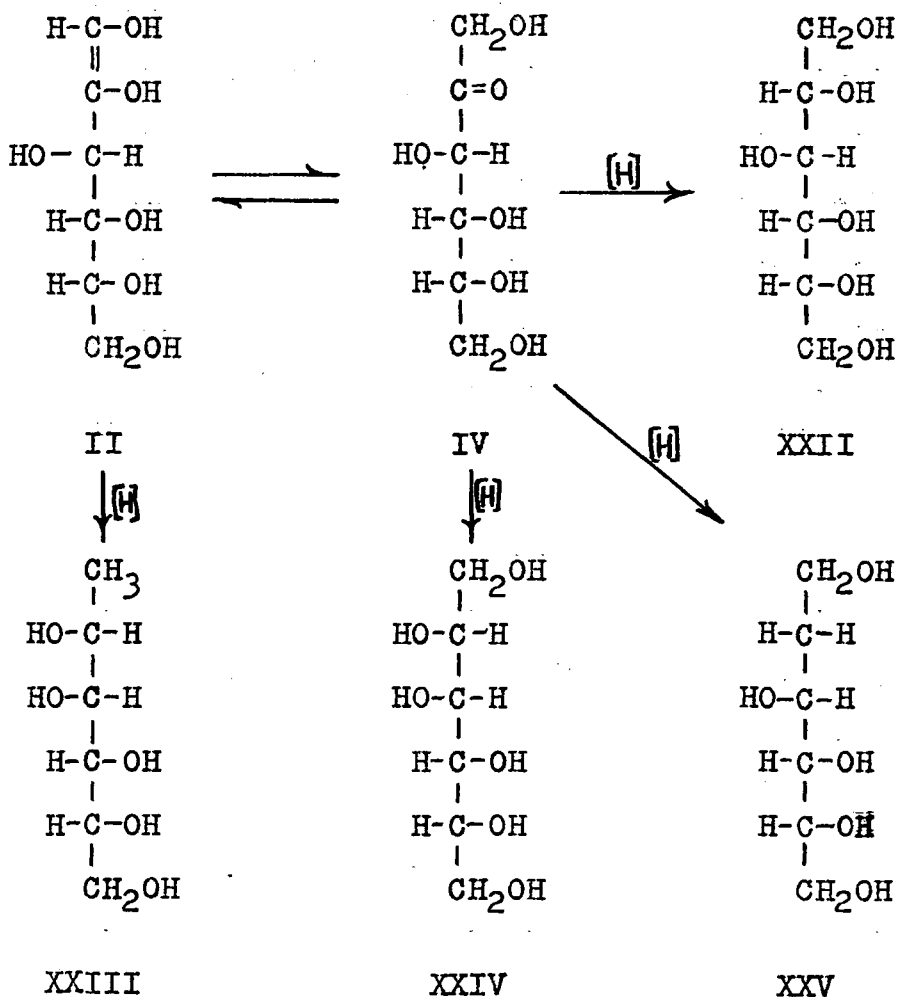
Evans and coworkers (19), nevertheless, showed that 2,3-enediols were actually formed in the course of a reaction by isolating formic acid (XVII), lactic acid (XXI) and the lactone of D-galacto- α -metasaccharinic acid (XIX) from an alkaline solution of galactose. They postulated that formic and lactic acids were formed through air-oxidative cleavage of the double bonds of the 1,2- and 3,4-enediols respectively (XVI, XX), while the lactone was formed, by a series of steps, from the 2,3-enediol (XVIII).

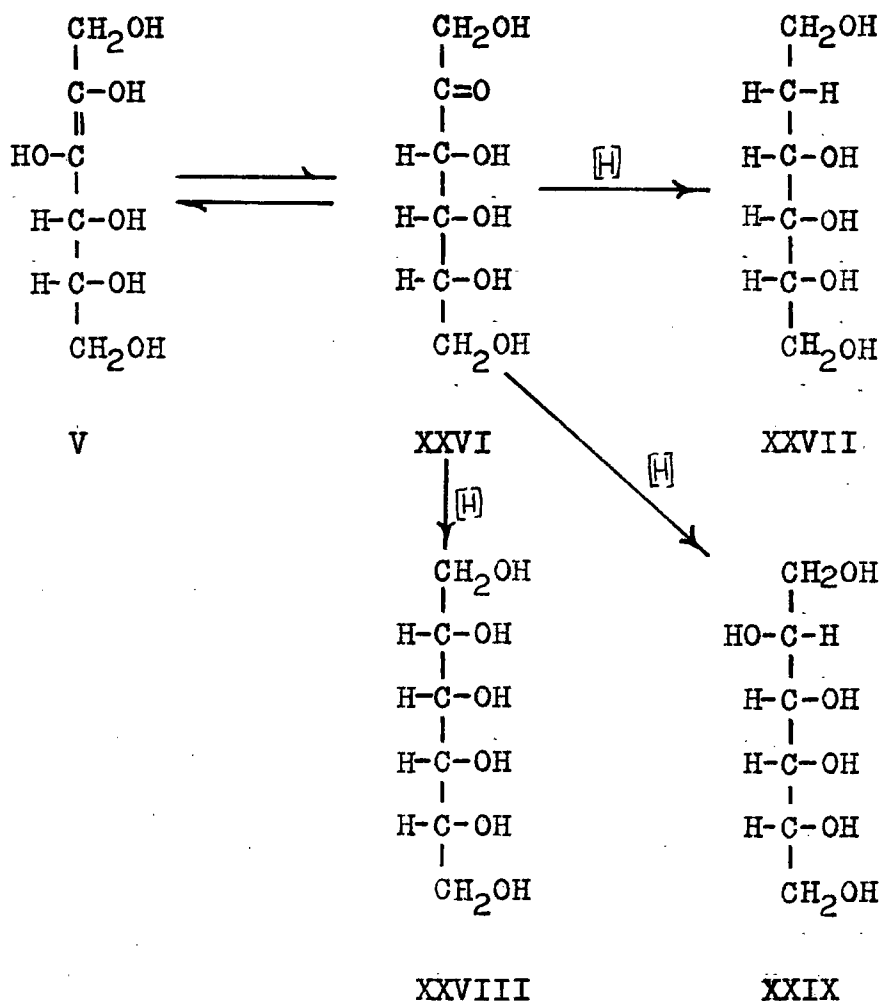




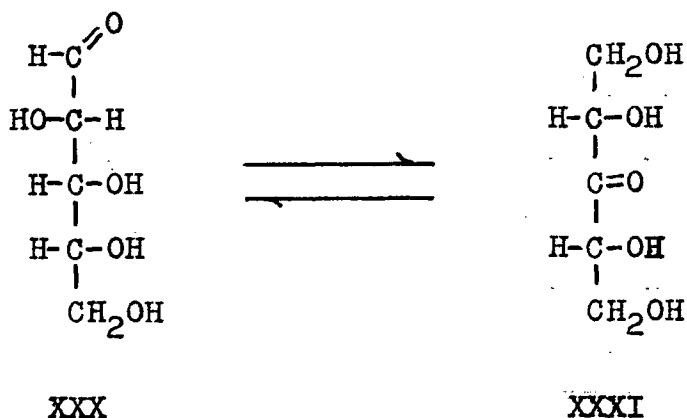
The existence of a 2,3-enediol gained further support from the findings of Wolfrom and coworkers (20), who in 1946 obtained evidence that V must have been present in a glucose solution at pH 10 to 13. From the products of electrolytic reduction of D-glucose in basic solution they isolated D-sorbital (XXII) the expected product, in thirty percent yield, but also found 2-desoxy-D-sorbitol (XXV), (0.34%); D-mannitol (XXIV), (2.27%); and 1-desoxy-D-mannitol, (XXIII), (0.95%); formed from the 1,2-enediol shift (II, IV).

D-allitol (XXVIII), (0.5% yield), and an unknown 2-desoxy hexose thought to be 2-desoxy-D-allitol (XXVII), (0.4% yield), which were also isolated, could have formed only as a result of a 2,3-enediol shift (V,XXVI). D-talitol (XXIX), which could also have been formed, was not obtained.

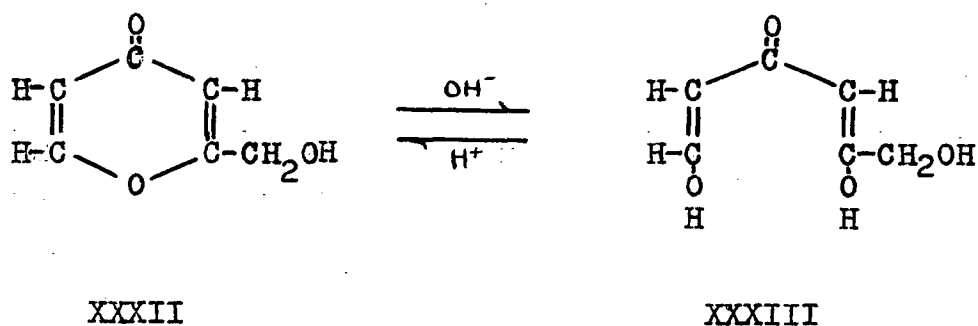




Only one 3-pentulose has been described in the literature. Ashwell and Hickman (21) in 1954 isolated from spleen extracts a micromolar quantity of a compound which they tentatively identified as erythro-3-ketopentose (XXXI). They postulated that the compound was formed from ribose (XXX) through an enediol intermediate.

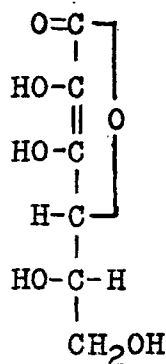


Other compounds related to the sugars which contain the 3-keto group are kojic acid (XXXII and XXXIII) (22), the ascorbic acids (23,24) and 2,3-diketo-D-gluconic acid (25). Kojic acid is produced by the action of certain molds on hexoses and various saccharides. Its structure is that of an unsaturated 3-hexulose anhydride. Beelik and Purves (26) postulated that the acid assumes an open chain structure (XXXIII) in basic solutions as a 3-keto-enediol which cyclized almost quantitatively on acidification.

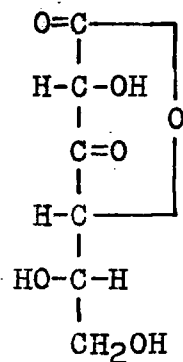


L-ascorbic acid (XXXIV) (Vitamin C), an enediol, was found to exist in an equilibrium mixture with a 3-keto-acid (XXXV), which was isolated only as a hydrazone deriva-

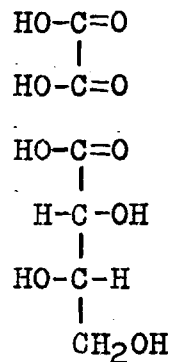
tive. The equilibrium mixture itself was unstable, suffering rapid oxidation to oxalic acid and L-threonic acids (XXXVI).



XXXIV



XXXV



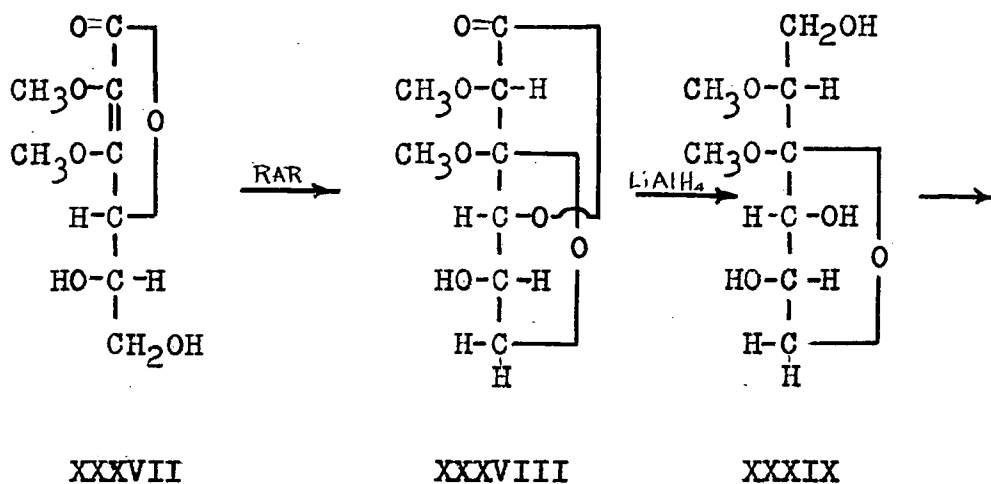
XXXVI

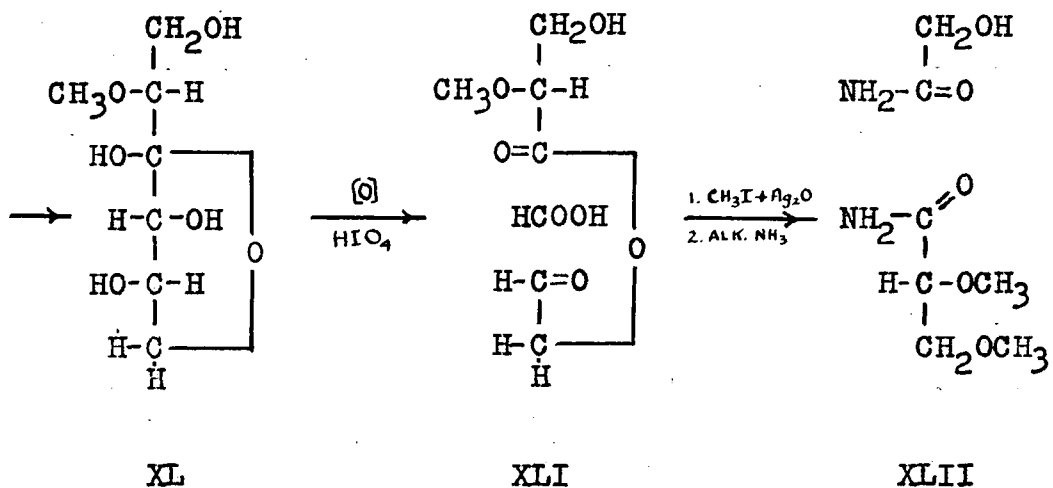
2,3-Diketo-D-gluconic acid was reported as a product of low temperature oxidation of D-glucose with hydrogen peroxide in the presence of ferrous sulphate (25). The compound decomposed readily on heating yielding carbon dioxide, oxalic acid and trihydroxybutyric acid.

A 3-keto-D-gluconic acid has also been postulated to occur at one stage of the Warburg-Dickens-Harecker biological cycle (27). Wilson and Calvin (28) have postulated the existence of a 3-pentulose as an intermediate in the biological fixation of carbon dioxide.

Recently, J.K.N. Jones (29) has reported the preparation of 2-O-methyl-L-xylo-3-hexulose (XL) from L-ascorbic acid (XXXV). By rearrangement of the 2-3-di-O-methyl ether (XXXVII), of L-ascorbic acid, he prepared the methyl glycoside of a 3-

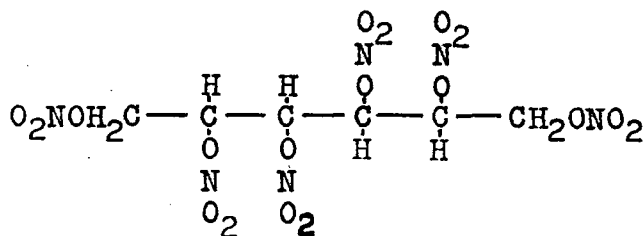
hexulonic acid, isolated as the amide. The reduction of the lactone of this acid (XXXVIII) with lithium aluminum hydride yielded a glycoside of the 3-hexulose (XXXIX). Upon acid hydrolysis the free sugar (XL) was obtained, and was characterized as the crystalline 2,5-dichlorophenylhydrazone. Oxidation of the sugar with periodic acid yielded one mole of formic acid and an ester (XLI). Since glycolamide and 2,3-di-O-methyl-D-glyceronic acid amide (XLII) were obtained through treatment of the ester with methyl iodide and silver oxide, followed by alcoholic ammonia, the structure of the sugar was confirmed as XL, probably in the alpha form. Jones also reported that 3-hexuloses as yet uncharacterized, may be obtained from D-arabo-ascorbic acid and D-gluco-ascorbic acid.





D-MANNITOL PENTANITRATE

The nitration of D-mannitol to the hexanitrate (XLIII) was first accomplished in 1847 by Domante and Menard (30). No Products of lower degree of nitration were isolated.

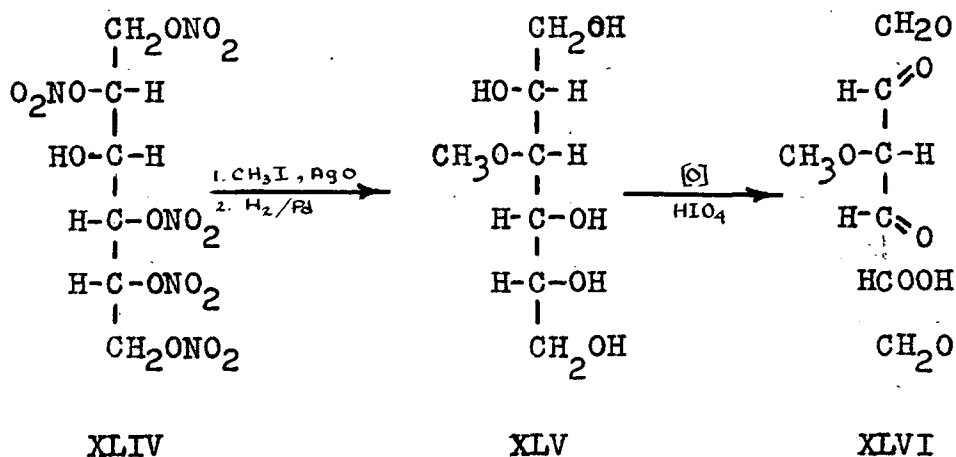


XLIII

It was not until 1864 when Tichanowich (31), investigating the action of anhydrous ammonia on an ethereal solution of the hexanitate, isolated a D-mannitol pentanitate as a white crystalline compound, soluble in alcohol and ether and insoluble in water.

Marshall and Wigner (32), in 1902, prepared the same D-mannitol pentanitate in good yield by the action of cold dry pyridine on the corresponding hexanitate. Wigner (33) also obtained the same pentanitate by careful nitration of D-mannitol. Although the main product of his reaction was D-mannitol hexanitate, a small quantity of the lower nitrate was isolated by concentration of the mother liquors.

The structure of Wigner's pentanitate was not determined until 1952 when Hayward (34) proved that the unesterified hydroxyl was located on the third (or equivalent fourth) carbon of the hexitol chain. Methylation and subsequent denitration of D-mannitol pentanitate yielded a monomethyl D-mannitol and periodate oxidation of this compound, resulting in the formation of two moles of formaldehyde and one of formic acid (XLVI), indicated the position of the methyl substituent (XLV), and hence of the original free hydroxyl group. Tichanowich's compound was therefore correctly termed D-mannitol-1,2,3,5,6-pentanitate (XLIV).



Recently, Elrick, Marans and Preckel (35) prepared (XLIV) in seventy percent yield by treatment of the corresponding hexanitrate in acetone solution with solid ammonium carbonate.

DENITRATION OF NITRIC ACID ESTERS

Complete removal of nitrate groups from D-mannitol hexanitrate has been accomplished by alkaline hydrolysis. Tichanowich (31) found that treatment of the nitrated compound with alcoholic potassium hydroxide regenerated the parent alcohol, but also yielded an anhydride, D-mannitan (1,4-anhydro-D-mannitol). He also observed that the action of sodium amalgam on the hexanitrate caused mannitan formation, whereas magnesium and zinc oxides gave 'nitromannitan',

apparently a mannitan tetranitrate. D-mannitol could also be regenerated by treatment of the nitrate with the weak base ammonium sulphide.

Mills (36), regenerated D-mannitol in undetermined yield by warming the nitrated derivative with hydriodic acid.

Vignon and Bray (5), in 1902, studied the action of 'metaphenylenediamine', aniline, water and five percent sulphuric acid on D-mannitol, D-dulcitol and D-erythritol nitrates. They found that both nitrate and nitrite ions were produced, while the alcohols were completely decomposed by the basic reagents. Boiling water had no effect though de-esterification occurred upon heating the nitrates with water in a sealed tube. Removal of the ester groups could be accomplished by refluxing the nitrated polyols with dilute sulphuric acid, but some decomposition of the alcohol resulted.

Oldham (37) denitrated carbohydrate nitrate esters with iron powder in glacial acetic acid. The parent carbohydrates were recovered from the reaction mixtures in approximately thirty percent yield.

A satisfactory method for removal of nitrate ester groups, high pressure hydrogenation of the nitrates with a palladium catalyst, was developed by Kuhn (6) who obtained almost quantitative yields of the parent alcohols. This method was modified by Hayward (34) who obtained low hydrogen pressures in a Parrhydrogenator. Kuhn (38) also proposed

the use of methanolic hydrazine with a palladized charcoal catalyst as a denitrating agent for alkyl nitrates, since the reagent would not reduce carbonyl groups or double bonds. However, it was found (39) that the use of hydrazine was not successful for carbohydrate nitrates because, due to its basic character, the reagent caused decomposition of the sensitive sugars.

EXPERIMENTAL

Special Precautions

Due to the explosive nature of the hexitol nitrates, no more than seven grams were handled or stored in the dry state.

A. MATERIALS

D-Mannitol Hexanitrate

D-Mannitol was nitrated by the method of Sokoloff (40), in 82% yield. The product was recrystallized from aqueous ethanol. M.p. 112-113°C. (uncorr.) $[\alpha]_D^{25} = +42.9^\circ$ (c 1.027, Ethanol, l=1).

D-Mannitol 1,2,3,5,6-pentanitrate

1. Method of Marshall and Wigner (32,34,41). D-mannitol-pentanitrate was prepared by the method of Marshall and Wigner in 68.5% yield.

2. Method of Elrick, Marans and Preckel (35). D-mannitol hexanitrate (7.50 gm.) was dissolved in acetone (35 ml.) at 22°C. in a 100 ml. flask fitted with a condenser and a thermometer. Ammonium carbonate (2.17 gm.) was washed into the colourless acetone solution with water (5 ml.) and acetone (8 ml.). Within fifteen minutes after the addition of the carbonate, the colour of the solution darkened to a bright orange. The temperature of the reacting mixture rose to

34°C., then fell to 25°C. over a period of two hours. Rapid evolution of gases from the warm solution was observed. Initially, the gas turned moist litmus paper blue and possessed the characteristic odour of ammonia. After one hour, the gas evolved turned blue litmus red, and possessed the odour of oxides of nitrogen. The quantity of solid material in the flask decreased slowly. After one and one-half hours, a flocculent precipitate which slowly increased in bulk, was observed. Evolution of gases continued at decreasing rate for sixteen hours. When evolution ceased, the solution was evaporated at room temperature and decreased pressure to a volume of 10 ml., causing the separation of a red oily liquid and the precipitation of some solid material. The mixture was poured into cold water (300 ml.), causing the separation of an orange oil which rapidly solidified. The solidified product was dried to a constant weight of 5.47 gm. The yield after one recrystallization was 4.5 gm. (67%). The product was recrystallized to a constant melting point of 80-81°C. A mixed melting point with a sample of mannitol pentanitrate prepared by the method of Marshall and Wigner gave a value of 80-81°C. $[\alpha]_D^{25} = +46.5^\circ$ (C 1.084, Ethanol, $l=1$). Brown(41) reported $[\alpha]_D$ 47.7° (C 4.426).

Nitric Acid

Red fuming nitric acid was obtained from Baker and Adams, s.g. 1.59-1.50.

Chromium trioxide

Analytical reagent grade chromium trioxide was obtained from the British Drug Houses limited, London, England.

Acetone

Acetone was dried by refluxing over anhydrous magnesium sulphate, then was distilled from potassium permanganate to remove traces of readily oxidized impurities.

Pyridine

Pyridine was dried by refluxing over two successive portions of Barium oxide.

B. ANALYTICAL METHODS

Nitrogen

Nitrogen was determined by a modified Kjeldahl method as described by Brown and Purves (42).

Chromium

Chromium VI was determined as barium chromate by the method described by Vogel (43). Chromium III was precipitated as green chromic hydroxide from a solution just basic with ammonia, and 0.125 molar in ammonium nitrate. The precipitate was filtered out, ignited, and weighed as Chromic oxide.

Ketose Test

A qualitative test for ketoses has been described by Pacsu (44). Addition of sodium hydroxide to an acetone solution of a ketose yielded a bright yellow solution. The

colour was discharged on acidification with sulphuric acid. The resulting solution decolourized aqueous permanganate.

Diphenylamine Reagent

The diphenylamine reagent for nitrates was prepared as described in the "Manual of the Identification of Organic Compounds" (45).

Refractive Index

The refractive index was determined in an Abbe refractometer connected to a thermostatically controlled constant temperature bath. Readings were taken at 21°C.

C. NITRATION OF D-MANNITOL-1,2,3,5,6-PENTANITRATE

D-Mannitol-1,2,3,5,6-pentanitrate (0.5000 gm.) was nitrated by the method of Sokoloff (40). The crude yield of the dried white crystalline product was 0.5407 gm. (96%). The product was recrystallized from water to a constant melting point of 112-113°C. A mixed melting point with D-Mannitol hexanitrate gave 112-113°C.

D. INVESTIGATION OF OXIDANTS FOR D-MANNITOL-1,2,3,5,6-PENTANITRATE.

I. Potassium Permanganate in Acetone Solution

D-Mannitol-1,2,3,5,6-pentranitrate (0.50 gm.) was dissolved in acetone (10 ml.) at room temperature. To the clear colourless solution was added a suspension of potassium permanganate (0.38 gm.) in acetone (25 ml.). The purple colour of the

permanganate was discharged after refluxing the solution in a hot water bath for fifteen minutes. A dark brown precipitate formed. The mixture was cooled in an ice bath, filtered and the colourless filtrate obtained evaporated to dryness. A white, odourless crystalline material (0.35 gm.) melting at 78.5 - 79.5°C. was obtained. Mixed melting point with D-mannitol 1,2,3,5,6-pentanitrate was 78.5 - 80.0°C.

The crystalline product (0.242 gm.) was dissolved in 20% aqueous ethanol (25 ml.) and the solution was shaken with hydrogen for sixteen hours in a Parr hydrogenator in the presence of palladized-charcoal catalyst (0.05 gm.) at an initial pressure of 41.7 p.s.i. The final pressure was 41.4 p.s.i. The catalyst was removed by filtration and the solution evaporated to a pale yellow residue (0.0198 gm.). The product gave negative tests with the diphenylamine reagent, Pacsu's reagent and Fehlings solution. After one recrystallization, the product melted at 160 - 163°C. A mixed melting point with D-mannitol gave 160 - 165°C.

II. Potassium Permanganate in Pyridine Solution

To a solution of D-mannitol-1,2,3,5,6-pentanitrate (0.50 gm.) in anhydrous pyridine (10 ml.) at room temperature was added potassium permanganate (0.3 gm.) dissolved in pyridine (20 ml.). The dark purple solution rapidly changed colour to dark greenish brown. After thirty minutes the brown solution was poured into water (100 ml.) and the pyridine neutralized with dilute hydrochloric acid. A dark brown residue precipitated.

The mixture was filtered and the clear colourless filtrate was extracted with ether. Evaporation of the dried ethereal solution yielded a yellow oily residue (0.05 gm.) having the odour of mould. The dark brown precipitate from the oxidation was also extracted with ether. The ethereal solution thus obtained was evaporated leaving a pale cream crystalline residue (0.3 gm.) M.p. 68 - 74°C. After one recrystallization from aqueous-ethanol the melting point was 78 - 80°C. A mixed melting point with D-mannitol-1,2,3,5,6-pentanitrate gave 78 - 80°C.

The crystalline product (0.2608 gm.) was hydrogenated by the method described in section D(I). The yellow semi-crystalline solid hydrogenation product (0.1637 gm.) gave negative reactions with the diphenylamine reagent, Pacsu's reagent and Fehlings solution. The product recrystallized from aqueous ethanol melted at 161 - 164°C. A mixed melting point with D-mannitol gave 161 - 165°C. The yellow syrup (0.030 gm.) isolated from the oxidation mixture was hydrogenated by the procedure described in section D (I). The syrupy hydrogenation product (0.0134 gm.) gave negative tests with diphenylamine reagent, Pacsu's reagent and Fehlings solution.

III. Sodium Bismuthate in Acetone Solution

D-mannitol-1,2,3,5,6-pentanitrate (0.50 gm.) was dissolved in a mixture of acetone (10 ml.) and acetic acid (1 ml.). To this solution was added a suspension of sodium bismuthate (0.50 gm.) in acetone (15 ml.). The mixture was allowed to stand overnight at room temperature, then was filtered through a Whatman No. 50 filter paper. Some white, finely divided

material still remained in suspension. The mixture was evaporated to dryness and the dried solid extracted with ether. Evaporation of the ethereal solution yielded a pale yellow odourless crystalline compound (0.37 gm.) melting at 79 - 81°C. A mixed melting point with D-mannitol-1,2,3,5,6-pentanitrate gave 78 - 81°C.

The crystalline product (0.3137 gm.) was hydrogenated by the method described in section D (I). A yellow semi-crystalline solid (0.2004 gm.) was isolated from the reaction mixture. The hydrogenation product gave negative tests with diphenylamine reagent and Pacsu's reagent and a doubtful Fehling's test. After two recrystallizations from aqueous ethanol the product melted at 161 - 163°C. A mixed melting point with mannitol gave 161 - 163°C.

IV. Hydrogen Peroxide in Acetic Acid

D-mannitol-1,2,3,5,6-pentanitrate (0.28 gm.) was dissolved in glacial acetic acid (1.5 ml.) at room temperature. To this solution was added a mixture of 30% hydrogen peroxide (1.3 ml.) in glacial acetic acid (2 ml.). After standing overnight at room temperature, the clear colourless solution was shaken with a few grains of palladium charcoal catalyst to remove the excess peroxide. The catalyst was then filtered out and the solution evaporated to dryness. A white crystalline compound (0.028 gm.), having a melting point of 81 - 82°C. was obtained. A mixed melting point with D-mannitol 1,2,3,5,6-pentanitrate gave 81 - 82°C.

V. Chromium Trioxide in Glacial Acetic Acid - Acetic Anhydride - Sulphuric Acid Solution

A mixture of acetic acid (5 ml.), sulphuric acid (5 ml.) and acetic anhydride (15 ml.) was cooled in an ice-salt bath. D-mannitol-1,2,3,5,6-pentanitrate (1.00 gm.) was dissolved in 5 ml. of the acid mixture in a 100 ml. flask fitted with a dropping funnel, a condenser and a thermometer. The flask was cooled in an ice-salt bath. Chromium trioxide (1.00 gm.) dissolved in the remainder of the acid mixture (20 ml.) was added slowly through the dropping funnel over a period of one hour. On standing overnight in the refrigerator, the colour of the resulting oxidation mixture changed from dark red to dark green. The dark green solution was poured into water (300 ml.) and the acid neutralized with sodium bicarbonate. The neutral solution was extracted with ether, then with chloroform. Evaporation of the dried ethereal extract yielded 29.5 mg. of pale cream crystalline material. The substance gave a negative test with diphenylamine reagent and when ashed left a white residue which turned red litmus paper blue. The residue from evaporation of the chloroform extract was extracted with carbon tetrachloride, with ethanol, then again with carbon tetrachloride. Evaporation of the ethanol extract yielded 26.9 mg. of cream coloured crystalline material. Evaporation of the two carbon tetrachloride extracts yielded 49.6 mg. and 25.2 mg. respectively of brown semi crystalline residues. The brown syrupy chloroform residue, after extraction, weighed 39.4 mg. The residue gave a negative test with diphenylamine reagent. Positive tests were

obtained for the ethanol and carbon tetrachloride fractions.

Analyses

Ethanol extract	Found: %N = 11.5, 11.0
First carbon tetrachloride extract	%N = 9.05, 5.9
Second carbon tetrachloride extract	%N = 14.05, 14.05

VI. Chromium Trioxide in Glacial Acetic Acid-Acetic Anhydride

D-Mannitol-1,2,3,5,6-pentanitrate (0.50 gm.) was dissolved in acetic acid (10 ml.) at room temperature. To this solution was added chromium trioxide (0.2 gm.) in acetic acid (15 ml.) and acetic anhydride (10 ml.). The resulting dark orange-red solution slowly changed colour to a dark green on standing for one and one-half hours at room temperature.

This green solution was poured into cold water (50 ml.) and solid sodium bicarbonate was added slowly with vigorous stirring to neutralize the acid. The neutral solution was extracted with ether, which was then dried and evaporated, leaving a brown oily residue (0.088 gm.)

Analysis: Found %N = 14.3, 14.6

Treatment of D-Mannitol-1,2,3,5,6-pentanitrate with Acetic-Acid-Acetic Anhydride Sulphuric Acid Mixture

D-Mannitol-1,2,3,5,6-pentanitrate (0.20 gm.) was dissolved in a mixture of chilled acetic acid (1 ml.) sulphuric acid (1 ml.) and acetic anhydride (5 ml.). This solution was allowed to sit in an ice-salt bath for three hours, the temperature of the mixture rising slowly. After three hours, the solution, smelling of oxides of nitrogen was poured into ice water (50 ml.). The white feathery crystals which precipi-

tated slowly from the aqueous solution were collected on a filter and dried to a constant weight of 0.14 gm. The melting point after one recrystallization from ethanol was 119.5 - 120.5°C. A mixed melting point with an authentic sample of D-mannitol-hexaacetate was 119.5 - 120.5°C.

VII. Chromium Trioxide in Pyridine Solution

D-mannitol-1,2,3,5,6-pentanitrate (0.50 gm.) was dissolved in anhydrous pyridine (10 ml.) at room temperature. Chromium trioxide (0.2 gm.) in dry pyridine (15 ml.) was added slowly to the pentanitrate solution. The dark orange oxidation mixture was allowed to stand overnight, then was poured into cold water (150 ml.) and the solution acidified with dilute hydrochloric acid. A dark brown oil which separated on acidification, was extracted in ether and combined with the ether extracts of the aqueous layer. Evaporation of the dried ethereal solution yielded a pale cream crystalline residue (0.27 gm.) M.p. 75 - 77°C. A mixed melting point with a sample of D-mannitol-1,2,3,5,6-pentanitrate was 75 - 79°C. The oxidation product (0.2015 gm.) was hydrogenated by the method described in section D(I). A white crystalline product (0.1024 gm.) which gave negative tests with diphenylamine reagent, Fiacsu's reagent and Fehlings solution, was obtained. After one recrystallization from aqueous ethanol the product melted at 164 - 166°C. A mixed melting point with D-mannitol gave 164 - 166°C.

VIII. Chromium Trioxide in Acetone Solution

a. D-mannitol-1,2,3,5,6-pentanitrate (0.50 gm. $.00112\overset{\text{moles}}{\text{M.}}$) was dissolved in dry acetone (10 ml.) and a solution of chromium trioxide (0.2 gm. $.002\text{ M.}$) in dry acetone (15 ml.) was added. (Caution: Chromium trioxide must be added to the acetone slowly. Acetone should not be added to Chromium trioxide). The resulting dark brown solution was allowed to stand overnight at room temperature, then was poured into cold water (200 ml.) with the formation of a pale yellow precipitate. After filtration of the mixture, the precipitate was dissolved in ether and the aqueous filtrate extracted several times with ether. The combined ethereal solutions were dried and evaporated to yield a pale cream semi-crystalline residue (0.4437 gm.) M.p. 70 - 80 °C. A mixed melting point with D-mannitol-1,2,3,5,6-pentanitrate gave 64 - 75°C.

Analysis: Found: %N. = 16.3, 16.3

The oxidation product 0.2985 gm. was hydrogenated by the usual method yielding 0.1867 gm. of a yellowish syrupy compound. The hydrogenated product gave negative tests with diphenylamine reagent, Pacsu's reagent and Fehlings solution.

b. The previous procedure was repeated using D-mannitol-1,2,3,5,6-pentanitrate (6.100 gm., $0.015\overset{\text{moles}}{\text{M.}}$) and chromium trioxide (1.100 gm., $0.011\overset{\text{moles}}{\text{M.}}$) in a total volume of 130 ml. acetone. The precipitate which formed in this aqueous

solution was dried to a constant weight of 3.6645 gm. Evaporation of the ether extract yielded a light brown syrup (0.4591 gm.). Repeated crystallization of the precipitate yielded 3.4660 gm. of a white crystalline material melting at 80 - 81°C. A mixed melting point with a sample of D-mannitol-1,2,3,5,6-pentanitrate gave 80 - 81°C. The mother liquor was combined with the syrupy product. In attempted recrystallization, the product continually oiled out, partially solidifying only on standing. $[\alpha]_D^{23} = +43.2^\circ$ (C 1.266, Ethanol, $l=1$). The compound did not reduce Fehlings solution.

Analysis Found: %N = 16.8, 16.9

Analysis of aqueous solution:

Found: N 24.6, 24.4 meq.

Required: 24.4 meq.

Cr.III 0.0236, 0.0245 gm.

Cr.IV 0.0218, 0.0236 gm.

Infra red analysis showed very little as the sample would not mull satisfactorily in Nujol and an attempt to deposit the substance directly on the prism was unsuccessful.

The syrup (0.4545 gm.) was hydrogenated as described in section D (I). A diphenylamine test of the resulting solution indicated that nitrate groups were still present. The solution was filtered and returned to the hydrogenator with platinum oxide catalyst (0.1 gm.). After shaking with hydrogen overnight, the solution gave no reaction with the

diphenylamine reagent. The solution was filtered and evaporated to a slightly greenish syrup (0.0533 gm.) which did not crystallize on standing. The observed optical rotation was $[\alpha]_D^{23} = 0^\circ$. (C 0.529, H₂O, $l = 1$).

$[\eta]_D^{21} = 1.4673$. The syrup did not reduce Fehlings solution nor did it give a positive test with Pagsu's reagent.

c. D-mannitol-1,2,3,5,6-pentanitrate (0.50 gm., $.00112 \text{ M.}^{\text{moles}}$) was dissolved in acetone (30 ml.) contained in a stoppered flask, fitted with a dropping funnel, connected by glass tubing to a pneumatic trough arranged for collecting gas samples over water. To the pentanitrate solution was added slowly from the funnel Chromium trioxide (0.088 gm., $0.00088 \text{ M.}^{\text{moles}}$) in acetone (10 ml.). The solution was allowed to stand at room temperature until the colour changed to pale green and indicated that most of the hexavalent chromium had been reduced (16 days). No evolution of gas was observed, and the water in the collecting tube remained neutral to litmus. The reaction mixture contained a dark greenish-brown precipitate deposited on the walls of the flask. The clear, pale green acetone solution was decanted into water (200 ml.) causing the formation of a bulky precipitate resembling cotton wool. The aqueous mixture was extracted directly with ether and the dried ethereal extract was evaporated to dryness in a rotary evaporator, leaving 0.4083 gm. of orange-brown solid resi-

due. After several recrystallizations from ethanol-carbon tetrachloride, a white crystalline product (0.1143 gm.) melting at 73.5 - 74.5°C. was obtained. $[\alpha]_D^{25} = +49.6$ (C 4.82, ethanol $l=1$). Further recrystallization failed to alter the melting point or the optical rotation. A mixed melting point with D-mannitol-1,2,3,5,6-pentanitrate gave 71 - 78°C. Reworking of the mother liquors yielded a further 0.1331 gm. of product and 0.1539 gm. of brown semi-crystalline residue. No mannitol pentanitrate was recovered.

Analysis: Found: %N = 19.0, 18.2, 18.6, 18.0
(av. 18.4)

The infra red spectrum of this compound showed the characteristic peaks for nitrate groups, but did not show the peak at 3620 cm^{-1} for the hydroxyl group of mannitol pentanitrate. There was however a small peak at 3520 cm^{-1} . There was no absorption at 1740 cm^{-1} where the carbonyl stretching band would appear.

In a blank experiment to determine the action of chromium trioxide in acetone, there was no apparent evolution of gas, and ether extraction of the aqueous solution yielded only 2.8mg. of clear syrupy residue.

In a similar experiment D-mannitol hexanitrate (0.40 gm.) was treated in acetone solution (40 ml.) with chromium trioxide (.088 gm.). There was no apparent evolution of gas. When the solution was poured into water, precipitation occurred. The pale, creamy-white precipitate was filtered

out and dried to a constant weight of 0.3678 gm. M.p. 107 - 110°C. The filtrate was extracted several times with ether which was then dried and evaporated. Yield of crystalline material 0.034 gm. M.p. 105 - 110°C. Total crude yield was 0.4036 gm. (101%). After two recrystallizations the substance melted at 111.5 - 113°C. A mixed melting point with D-mannitol hexanitrate gave 111.5 - 113°C.

Hydrogenation of the Crystalline Oxidation Product from Section VIII c.

The crystalline material (0.0525 gm.) was hydrogenated in the usual manner. No pressure drop was observed but after nine hours, a negative diphenylamine test showed the absence of nitrate nitrogen. The hydrogenation mixture contained a suspension of fine colourless crystals. The solution was filtered and the solids were washed with water. The combined filtrate and washings were evaporated to dryness below 50°C. bath temperature. The colourless syrupy residue (0.0223 gm.) crystallized on standing overnight in a vacuum desiccator and the crude product melted at 140 - 155°C. After two recrystallizations from aqueous ethanol the melting point was 164 - 165.5°C. A mixed melting point with authentic D-mannitol was 164 - 165°C. The observed specific rotation was $[\alpha]_D^{23} = \pm 0.00$ (C .046, water, $l = \frac{1}{2}$). The infra red spectrum of the hydrogenated product corresponded closely to that of D-mannitol.

TABLE 1
Results of Oxidations

Oxidant	Solvent	Time	Mannitol Pentanitrate Recovered	Other Products
I KMnO_4	Acetone	15 min.	70%	-
II KMnO_4	Pyridine	30 min.	60%	Oil
III NaBiO_3	Acetone-Acetic acid	14 hrs.	74%	-
IV H_2O_2	Acetic Acid	14 hrs.	100%	-
V CrO_3	Glacial Acetic acid Acetic Anhydride Sulphuric Acid	24 hrs.	-	Oil, loss of Nitrogen
VI CrO_3	Glacial Acetic acid Acetic anhydride	$1\frac{1}{2}$ hrs.	-	Oil, loss of Nitrogen
VII CrO_3	Pyridine	14 hrs.	54%	-
VIIIa CrO_3	Acetone	14 hrs.	-	Syrup, slight loss of nitro- gen
b CrO_3	Acetone	14 hrs.	55%	Syrup, slight loss of nitro- gen.
c CrO_3	Acetone	16 days	-	White crystalline compound.

Preparation of Isomannide (1:4, 3:6 - Dianhydromannitol)

Isomannide was prepared by the method of Wiggins (46). D-mannitol (50 gm.) was dissolved in concentrated hydrochloric acid (300 ml.) in a one liter two-necked flask fitted with a gas bubbler and a condenser protected by a drying tube. Dry hydrogen chloride gas was introduced from a cylinder until evolution of gas indicated that the solution was saturated. The bubbler was then removed and the solution was refluxed for 72 hours. Hydrogen chloride fumes were evolved for several hours while the colour of the solution gradually darkened. The solution was evaporated to a syrup under reduced pressure, water (50 ml.) was added and the solution again evaporated to a syrup. The crude syrup (42.5 gm.) was distilled under vacuum. A clear colourless fraction (10.8 gm.) was collected boiling at 117 - 125°C. at a pressure of 2 mm. Both fractions crystallized on standing overnight. Fraction one was re-crystallized from ethyl acetate - ethanol to a constant melting point 85 - 86°C. $[\alpha]_D^{25} = +91.0^\circ$ Wiggins (46) reported $[\alpha]_D = +91.0^\circ$ and m.p. 86-87°C.

Nitration of Isomannide

Isomannide (2.0 gm.) was dissolved in cold red fuming nitric acid (20 ml.) in an ice bath. To the solution was added slowly, with stirring, cold concentrated sulphuric acid (40 ml.). After standing for fifteen minutes, the syrupy reddish-orange solution was poured into ice-water (500 ml.). No precipitate formed immediately, however fine

colourless needles were deposited when the solution was allowed to stand at room temperature for two hours. The product was recovered on a filter, washed with water and dried in a vacuum desiccator to a constant weight of 1.4 gm. (46%). The melting point after two recrystallizations from carbon-tetrachloride water was 64 - 65.5°C. $[\alpha]_D^{26} = + 319.2^\circ$ (C. 1.213, H₂O, $l = 1$). Krantz (47) reported a melting point of 65.5°C.

Analyses:	Found: %N	11.4, 12.0 (av. 11.7)
	Required:	11.85

Hydrogenation of Isomannide

Isomannide (0.1285 gm.) was hydrogenated as described in section D (I), using platinum oxide catalyst (0.1 gm.) at an initial pressure of 35.4 p.s.i. There was no detectable pressure drop during the reaction period. After removal from the hydrogenator, the solution was filtered and evaporated in a rotary evaporator to a clear syrup (0.1275 gm.) which did not crystallize on standing in a vacuum desiccator. Crystallization occurred immediately when the syrup was seeded with a crystal of isomannide. After one recrystallization from ethanol-ethylacetate the melting point of the product was 85 - 86°C. The mixed melting point with an authentic sample of isomannide was 85 - 86°C.

Hydrogenation of Isomannide Dinitrate

Isomannide dinitrate (0.1213 gm.) was hydrogenated

by the procedure given in Section D (I), using platinum oxide catalyst (0.1 gm.) at an initial pressure of 39.5 p.s.i. There was no apparent pressure drop, but at the end of the hydrogenation period a test for nitrate with the diphenylamine reagent was negative. The solution was filtered and evaporated to a colourless syrup (0.0505 gm.) The syrup crystallized after seeding with a crystal of isomannide. After one recrystallization from ethanol-ethyl acetate the product melted at 85 - 86°C. The mixed melting point with isomannide was 85 - 86°C.

D I S C U S S I O N

CHOICE OF OXIDANT

The reactions of hexoses and their derivatives with a number of oxidizing agents had previously been studied (48). Several of the reagents had been shown to be specific for oxidation at the ends of the carbon chain, or at the penultimate positions. However, investigation has not revealed an oxidant which acts specifically on a hydroxyl group at the third position. It is thus evident that to introduce a carbonyl group at the third carbon only of a hexitol molecule it is necessary to form suitable inert derivatives of all the other hydroxyl groups.

Bacterial oxidation was not indicated because it had been shown that 1:2, 5:6 - diisopropylidene-D-glucose, which

possessed an unsubstituted hydroxyl group at position three, was untouched by bacterial action (49).

Oxidation of the same compound with aqueous permanganate was also attempted (50), however the only product isolated from the reaction was the potassium salt of 1:2 - isopropylidene-xyluronic acid. This indicated that reaction occurred preferentially at C₆.

Oppenauer oxidation of 1,3-dibenzoyl glycerol was unsuccessfully attempted by White (49), however he was able to prepare 1,3-dibenzoyldihydroxyacetone by treatment of the disubstituted glycerol with chromium trioxide in acetic acid.

Sullivan (52) also using chromium trioxide and glacial acetic acid prepared an L-sorbosæ derivative from a D-sorbitol. Oxidation of 6 - tosyl - 1:3, 2:4-diethylidene-D-sorbitol yielded 1-tosyl-3:5, 4:6 - diethylidene-keto-L-sorbose.

Chromium trioxide thus appeared to be a suitable oxidant for hydroxyl groups in substituted polyols. The action of chromium trioxide and other unspecific oxidants; e.g. potassium permanganate, hydrogen peroxide and sodium bisulfate were investigated in various solvents. Alkaline solvents were not considered since nitrate groups were known to be hydrolyzed under basic conditions (5).

Pyridine, known to be an organic base which is capable of removing the nitrate ester from position three of

D-mannitol hexanitrate (34), produces a pentanitrate that is relatively stable to further attack by pyridine (41). Thus despite its basic character, pyridine appeared to be a suitable solvent. To provide acid conditions, acetic acid-acetic anhydride mixtures, comparatively stable to oxidation, were used.

In the remainder of the oxidations, acetone was used as the most convenient neutral solvent. Acetone is known to be susceptible to attack by chromium trioxide in the hot solution (53), however, at room temperature experiment failed to indicate evolution of gas or the formation of a significant quantity of polymeric material, when acetone was allowed to stand in the presence of chromium trioxide.

RESULTS OF OXIDATIONS

The results of the application of the various oxidizing solutions to D-mannitol-1,2,3,5,6-pentanitrate are summarized in Table I. Hydrogen peroxide in acetic acid solution was apparently ineffective as an oxidant for D-mannitol pentanitrate, since the starting material could be recovered quantitatively.

In all the other attempts, it was noted that some interaction had occurred, since the original pentanitrate could not be recovered in high yields (Table I).

When chromium trioxide was used in acetic acid-acetic anhydride mixtures, non crystalline products were

TABLE II
Nitrogen Contents of Some Polyol Nitrates

<u>COMPOUND</u>	<u>FORMULA</u>	<u>%NITROGEN</u>
1. D-mannitol hexanitrate	$ \begin{array}{c} \text{O}_2\text{O}_2 \\ \text{N N} \\ \text{H H H O O H} \\ \\ \text{O}_2\text{NO}-\text{C}-\text{C}-\text{C}-\text{C}-\text{C}-\text{C}-\text{ONO}_2 \\ \quad \quad \quad \quad \\ \text{H O O H H H} \\ \text{N N} \\ \text{O}_2\text{O}_2 \end{array} $	18.6%
2. D-mannitol-1,2,3, 5,6-pentanitrate	$ \begin{array}{c} \text{O}_2\text{O}_2 \\ \text{N N} \\ \text{H H H O O H} \\ \\ \text{O}_2\text{NO}-\text{C}-\text{C}-\text{C}-\text{C}-\text{C}-\text{ONO}_2 \\ \\ \text{H O O H H H} \\ \text{N H} \\ \text{O}_2 \end{array} $	17.3%
3. D-mannitan tetramitrate	$ \begin{array}{c} \text{O} \\ \text{H H} \\ \\ \text{H}_2\text{C}-\text{C}-\text{C}-\text{C}-\text{C}-\text{ONO}_2 \\ \\ \text{O O H H H} \\ \text{N N} \\ \text{O}_2\text{O}_2 \end{array} $	15.5%
4. Isomannide dinitrate	$ \begin{array}{c} \text{O} \\ \text{H H} \\ \\ \text{H}_2\text{C}-\text{C}-\text{C}-\text{C}-\text{C}-\text{H}_2 \\ \quad \\ \text{O} \quad \text{H H} \\ \text{N} \quad \\ \text{O}_2 \quad \text{O} \end{array} $	14.8%
5. Dimer	<p>Mannitol pentanitrate</p> <p style="text-align: center;"> </p> <p style="text-align: center;">O</p> <p style="text-align: center;"> </p> <p>Mannitol pentanitrate</p>	17.6%

obtained. Kjeldahl analyses showed that the nitrogen content was considerably lower than that required for a hexitol pentanitrate on the corresponding carbonyl derivative. This could probably be accounted for by the formation of acetylated products, as it was also shown that mannitol pentanitrate could be converted to mannitol hexaacetate in an acetic acid - acetic anhydride - sulphuric acid mixture.

A similar solvent mixture had been previously proposed by Wolfrom (54) for acetylation and denitration.

In most other cases the crystalline material isolated was unaltered mannitol pentanitrate. Only with the use of a chromium trioxide-acetone oxidation mixture was a product obtained which lowered the melting point of the original pentanitrate. Treatment of mannitol pentanitrate with a slight excess of chromium trioxide in acetone for a short period of time yielded a small quantity of semi-crystalline material; 55% of the pentanitrate was recovered unchanged. Chromium VI was present in excess of that required by the reaction

$$3 \text{ } \text{>CHOH} + 2 \text{ CrO}_3 \rightarrow 3 \text{ } \text{>C=O} + 2 \text{ Cr}_2\text{O}_3^{\text{III}} + 3 \text{ H}_2\text{O}.$$

More chromium (52%) was reduced to the trivalent state than was accounted for by the oxidation of the non-recovered pentanitrate to a hexulose derivative. Detection of nitrogen in the aqueous solution suggested that a portion of the pentanitrate was decomposed to water soluble products. Since mannitol hexanitrate could be recovered unchanged from treatment in a similar oxidation medium, it seemed

that attack on the pentanitate molecule occurred first at the site of the free hydroxyl group. The Nitrogen content of the syrupy product was lower than that required for the desired hexulose. The infra red spectra, which was admittedly poor, showed no trace of absorption at or near 1740 cm^{-1} , the characteristic carbonyl stretching frequency. Denitration of the material yielded a syrup which gave a negative test with Pacus's reagent and did not reduce Fehlings solution.

The treatment of mannitol pentanitate with the chromium trioxide acetone mixture for sixteen days produced quite different results. A white crystalline compound was obtained, the nitrogen content of which, as determined by the Kjeldahl method was higher than that of the desired hexulose and of the starting material. The compound showed no infra-red absorption at or near 1740 cm^{-1} , indicating that it was not a carbonyl derivative. The spectrum also showed differences from those of the mannitol penta- and hexanitrites and from isomannide dinitrite.

Hydrogenation of the compound yielded a crystalline product apparently identical to D-mannitol, therefore the material isolated from the reaction mixture could not have resulted from chain degradation of mannitol pentanitate.

Mannitol hexanitrate (see Table II) contains a percentage of nitrogen agreeing with that found experimentally for the crystalline oxidation product, however, since the physical properties and infra-red spectra are substantially different, it is doubtful that the compound is mannitol hexanitrate.

Since chromium trioxide is a dehydrating agent as well as an oxidant, it was considered possible that anhydride formation could occur to give manniton tetranitrate or isomannide dinitrate. Tichanowich (31) obtained some mannitan tetranitrate from treatment of mannitol pentanitrate with anhydrous ammonia, although manniton was not prepared, isomannide was synthesized (46) and nitrated. The unusually high optical rotation of isomannide dinitrate is reported for the first time in this work. Although the preparation of the compound had been reported in the literature (47), the physical constants quoted were limited to the melting point and solubility. The infra-red spectrum of isomannide dinitrate showed absorption at 1030 cm.^{-1} probably due to the presence of the strained cyclic ether linkage (55). This peak was not present in the spectrum of the unknown. A similar peak, probably near 1076 cm.^{-1} from the tetrahydrofuran structure would be expected in mannitan tetranitrate. The unknown showed no absorption in this region. It was also determined that

treatment of isomannide and its dinitrate under conditions similar to those used in hydrogenation of the unknown yielded only isomannide in both cases. Since the ether linkage was preserved in these compounds, it is doubtful that hydrogenolysis of similar materials would yield mannitol. It is therefore considered improbable that the compound is an intramolecular anhydride.

Though the nitrogen analysis fails to confirm the postulate, the possibility of formation of an intermolecular anhydride, combining two molecules of pentanitrate joined through an ether linkage at the three positions, would not be incompatible with other data obtained. Such a compound might conceivably yield mannitol in hydrogenation.

Another possibility, though also in disagreement with the nitrogen analysis, is the conversion of mannitol pentanitrate into a different molecular form. A structure having more internal hydrogen bonding would have a lower melting point and the spectral bands could exhibit slight shifts.

No satisfactory structure has been postulated.

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