## THE SYNTHESIS OF ALLITOL HEXANITRATE

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#### ABSTRACT

Two methods for the synthesis of D-allose from D-ribose, the nitromethane condensation and the cyanohydrin synthesis, were investigated. The nitromethane condensation was first tested with D-arabinose and crystalline derivatives of D-mannose and D-glucose were obtained. In the nitromethane condensation with D-ribose, it was found that a considerable portion of the D-ribose did not react. A partial separation of the resulting nitroalcohols from the unreacted D-ribose was achieved on an adsorption chromatography column.

Application of the cyanohydrin synthesis to D-ribose yielded  $\gamma$ -D-allonolactone which was reduced to D-allose and then to allitol by sodium amalgam and Raney nickel, respectively. The pure allitol which was obtained in crystalline form was characterized by the melting point, analysis, and acetylation to the known, crystalline hexaacetate derivative.

Crystalline allitol hexanitrate was prepared by the nitration of allitol with a mixture of fuming nitric and sulfuric acids or with a mixture of fuming nitric acid and acetic anhydride, and is now reported for the first time. A qualitative experiment indicated that allitol hexanitrate reacted more slowly with dry pyridine at room temperature than the corresponding D-mannitol derivative and produced no gaseous product.

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#### INTRODUCTION

The purpose of this research was to prepare allitol hexanitrate, which has not previously been synthesized in order that its reaction with pyridine might be studied. The denitrating action of pyridine on the stereoisomeric hexanitrates of D-mannitol (14), (22) and dulcitol (39) has been proven to be selective for the nitrate group on  $C_3$ (or the equivalent  $C_4$ ) of the hexitol chain. A similar study of allitol hexanitrate with pyridine would further test the specificity of this unusual selective reaction, and might also give some information of the relationship between conformation and configuration of these open-chain, polyol derivatives.

The synthesis of allitol hexanitrate required the synthesis of the corresponding hexitol, allitol, which is not found in nature. Hence, a considerable portion of this research was concerned with the preparation of D-allose and allitol.

The hexitols have been reviewed by Lohmar and Goepp (38), by Lespieau (32), and by Pigman and Goepp (44).

Allitol (I), which is also known as allodulcitol, is one of the meso forms of the hexitols. It has the projection-configurational formula I.



(I)

#### HISTORICAL INTRODUCTION

The first synthesis of allitol (I) (33) was related to an earlier investigation made by Griner in 1892.

Griner (20), in hydrogenating acrolein (II) by means of a zinc-copper couple and acetic acid, obtained a liquid corresponding in properties and analysis to the reduction product, divinylglycol (III). The yield was very low since no polymerization inhibitors were available, and the acrolein resinified very rapidly. Griner knew that divinylglycol could exist in optically active (d or l), meso, or racemic (dl) forms. If the dlmixture were present, and one of the isomers was preferentially attacked by a suitable mould, optical activity might appear. LeBel, at Griner's request, carried out such cultures which were successful, but optical activity did not appear. From these results, Griner concluded that only the meso form was present. It has since been found, however, that divinylglycol prepared according to Griner's method exists in both the meso and racemic forms. Thus, Griner's conclusion was erroneous (32).

A vinyl group may be oxidized to the corresponding diol by the action of dilute potassium permanganate solution, and Griner applied this reagent to the divinylglycol from which, theoretically, the hexitol should have been obtained. However, in spite of all his attempts to moderate the conditions, he was unable to arrest the reaction at the desired polyol stage.

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To another portion of the divinylglycol, Griner added two moles of hypochlorous acid, and obtained the two stereoisomeric forms of divinylglycoldichlorohydrin (IV). From one of these isomers, Griner obtained mannitol (V), but he reported that he was unable to obtain a hexitol from the other isomer.

 $CH_2 = CH - CHO$ (II)  $\int Zn - Cu$  HOAc  $CH_2 = CH - CHOH - CHOH - CH = CH_2$ (III)  $\int HOC1$   $CH_2C1 - CHOH - CHOH - CHOH - CH_2C1$ (IV)

In 1932 (33), (34) Lespieau and Wiemann synthesised

allitol for the first time by adding four hydroxyl groups to divinylglycol (III) by using a solution of silver chlorate containing a small amount of osmic acid. Their product also contained dl-mannitol (V).

Lespieau and Wiemann also made use of another synthetic method to obtain allitol. They reacted chloroacetaldehyde (VII) with the Grignard reagent (VI) derived from acetylene to give the meso-divinylacetylenedichlorohydrin (VIII) (31), from which the corresponding hexynetetrol (IX) was obtained. This was then reduced to the hexenetetrol (X) using Bourguel's catalyst (13), a dispersion of colloidal palladium on starch, and hydrogen. The hexenetetrol was then hydroxylated with silver chlorate and osmic acid yielding the two meso hexitols, allitol (I) and dulcitol (XI) (36), (35).



For the purposes of identification, Wiemann (67) prepared two crystalline derivatives of allitol; the hexaacetate and the dibenzylidene acetal.

Another method of synthesis which was available was the reduction of the corresponding hexose, D-allose, to allitol. D-Allose is a rare monosaccharide not found in nature, which has, however, been prepared from the pentose, D-ribose, by a Kiliani cyanohydrin synthesis (26).



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In 1910, Levene and Jacobs (37) reacted D-ribose (XII) with hydrogen cyanide, and on hydrolysis of the resulting isomeric cyanohydrins, they obtained the isomeric D-allonic (XIII) and D-altronic (XIV) acids, which they were able to separate. Calcium-D-altronate crystallized from the solution first, and after removal of the calcium from the calcium-D-allonate in the mother liquor,  $\gamma$  -D-allonolactone (XV) was obtained upon evaporation. This lactone was reduced by sodium amalgam to D-allose (XVI). In a similar manner, D-altrose (XVII) was obtained from calcium-D-altronate. However, Levene and Jacobs were unable to obtain either of the two hexoses in a crystalline state.

Austin and Humoller, by application of the cyanohydrin synthesis to L-ribose, obtained crystalline L-allose (3), (4) in 1933. This was immediately followed by the work of Phelps and Bates, in 1934, in which they prepared crystalline D-allose from D-ribose by the Kiliani cyanohydrin synthesis (42).

An improved application of the cyanohydrin synthesis to the preparation of D-allose from D-ribose was reported by Pratt and Richtmeyer (45) during the course of the present investigation.

The reduction of D-allose to allitol was first accomplished by Steiger and Reichstein, in 1936 (61). After synthesising D-allose from D-ribose by the cyanohydrin synthesis, they reduced the D-allose with hydrogen under pressure over a nickel-silica gel catalyst. The resulting crystalline product was shown to be identical with the one obtained earlier by Lespieau and Wiemann.

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. · · · · ·	СООН	COOH
H-C=O	н-С-он	НО-С-Н
H-C-OH	 н-с-он	 Н-С-ОН
$H-C-OH + HCN + H_2O \longrightarrow$	H-C-OH	+ H-C-OH
H-C-OH	H-C-OH	H-C-OH
CH_OH	снон	CH <sub>2</sub> OH
(XII)	(XIII)	(XIV)
(XIII)	(	(XIV)
- H <sub>2</sub> O		– H <sub>2</sub> O
o=c	0=	=c1
н-с-он	нс	р-С-н
́н-с-он	H	н-с-он
H-C	F	I-C
н-с-он	F	н-с-он
і сн <sub>2</sub> он		і сн <sub>2</sub> он
(XV)		
Na/Hg		Na/Hg
H-C=O	F	I-C=O
н-с-он	HC	-С-Н
H-C-OH	F	I I-C-OH
н-с-он	ŀ	I-C-OH
I н-с-он	ŀ	I-C-OH
I СН <sub>2</sub> ОН		I Сн <sub>2</sub> Он
(XVI)		(XVII)

.

<u>-</u>.8 -

In 1946, Wolfrom and co-workers prepared allitol from keto-D-psicose (71). They reduced keto-D-psicose pentaacetate with hydrogen under pressure over a kieselguhr-supported nickel catalyst at an elevated temperature. The resulting product was deacetylated with barium hydroxide to yield syrupy allitol which was then converted to a crystalline methylene derivative.

The above investigation was connected with a study of the reduction of alkaline glucose solutions (69), (70) under conditions known to cause sugar interconversions. Wolfrom and co-workers also isolated a very small amount of allitol from the electrolytic reduction at amalgamated lead cathodes of glucose in mild alkaline solution and at a temperature below 30° C. (71). The appearance of allitol was accounted for by the postulation of several ene-diol type shifts.

The same workers also prepared four new crystalline derivatives of allitol; monomethylene allitol, dimethylene allitol and the diacetate and dilaurate of the latter (71).

The foregoing methods of synthesis of allitol are the only ones which have been reported. However, a new procedure for the addition of one carbon atom to the carbon chain of an aldose was developed by Sowden and Fischer. This method consisted of a base-catalysed condensation between an aldose and nitromethane. The method has been reviewed by Sowden (52).

The only previously recorded application (53) of the nitroparaffin-aldehyde condensation reaction to the sugar series was that

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reported in 1921 by Pictet and Barbier (43). These workers treated glycolaldehyde, glyceraldehyde, L-arabinose, and D-glucose with nitromethane and potassium bicarbonate. They made no attempt, however, to isolate the expected nitroalcohols. It was in 1944, that Sowden and Fischer on application of this procedure to an acetylated cyanohydrin were the first to isolate the nitroalcohols (53). In 1945, they treated 2, 4-benzylidene-L-xylopyranose with nitromethane, and isolated the nitroalcohol (only one isomer was obtained) from which they obtained L-gulose (54) by means of the Nef reaction (40).

Nef (40), in 1894, treated the sodium salt of simple primary nitroparaffins with an excess of mineral acid causing oxidation of the nitroparaffin with the subsequent production of nitrous oxide (hyponitrous acid) and an aldehyde.

Sowden and Fischer reported nitromethane condensations with other substituted sugars (55), (56). In 1947, glucose and mannose were prepared by a condensation of nitromethane with arabinose (57). From D-arabinose (XVII), the isomeric nitroalcohols, 1-nitro-1-desoxy-D-mannitol (XIX) and 1-nitro-1-desoxy-D-glucitol (XX), were formed in the condensation reaction, and then converted on treatment with sulfuric acid to D-mannose (XXI), and D-glucose (XXII) respectively. In a similar series, the rare L- forms of these aldohexoses were prepared from L-arabinose as starting material.

Sowden and Fischer reported a condensation between D-ribose and nitromethane (56), however, they did not mention obtaining any crystal-

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line condensation products or the preparation of D-allose. The procedure has since been used as a preparative method for other sugars (48), (51), (58), and has also been used in the preparation of D-glucose with a labelled glycosidic carbon atom (49), (50).

HO-C-H $ $ H-C-OH + CH <sub>3</sub> NO <sub>2</sub> $\xrightarrow{\text{NaOCH}_3}$   H-C-OH   CH <sub>2</sub> OH (XVIII)	H-C=0		
$  H-C-OH + CH_3NO_2 - \frac{NaOCH_3}{I} + CH_2OH - CH_2OH - CH_2OH - CN_2OH -$	НО-С-Н		
H-C-OH + CH <sub>3</sub> NO <sub>2</sub>   H-C-OH   CH <sub>2</sub> OH (XVШ)			NaOCH <sub>2</sub>
- С-ОН   СН <sub>2</sub> ОН (XVШ)	H-C-OH +	CH <sub>3</sub> NO <sub>2</sub>	<del>````````````````````````````````</del>
н-с-он   сн <sub>2</sub> он (XVШ)	l l	J 1	
 Сн <sub>2</sub> он (XVШ)	H-C-OH		
Сн <sub>2</sub> он (XVШ)		•	
(XVIII)	Сн <sub>2</sub> ОН		
	(XVIII)		

CH <sub>2</sub> NO <sub>2</sub>	CH <sub>2</sub> NO <sub>2</sub>
HO-C-H	H-C-OH
но-с-н	но-С-н
H-C-OH +	н-с-он
н-С-он	H-C-OH
сн <sub>2</sub> он	сн <sub>2</sub> он
(XIX)	(XX)
H <sub>2</sub> SO <sub>4</sub>	HaSO
$\downarrow$ 2 4	↓ 2 4
H-C=0	H-C=O
HO-C-H	H-C-OH
НО-С-Н	HO-C-H
H-C-OH	H-C-OH
н-с-он	H-C-OH
і Сн <sub>2</sub> он	। Сн <sub>2</sub> он
(XXI)	(XXII)

The use of either the cyanohydrin synthesis or the nitromethane condensation with D-ribose would lead to the production of D-allose which could then be reduced to allitol. Several methods have been used for reductions of this type.

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As previously mentioned, Steiger and Reichstein reduced D-allose to allitol with hydrogen under 120 atmospheres pressure using a nickel-silica gel catalyst and a temperature of 140°C. (61). Catalytic hydrogenation has also been applied to the reduction of other aldoses. D-Altrose, the 2-epimer of D-allose, was reduced to D-altritol (D-talitol) by Hann, Haskins, and Hudson (21) using a Raney nickel catalyst and 127 atmospheres pressure. The corresponding L- isomer was hydrogenated using 135 atmospheres pressure and a nickel kieselguhr-supported catalyst by Humoller, Wolfrom, Lew, and Goepp (27). Glattfeld and Schimpff (19) have prepared various sugar alcohols from the corresponding aldose with hydrogen under pressure and a platinum catalyst.

The well-known sodium amalgam reduction of E. Fischer has been applied to the conversion of an aldose to the sugar alcohol.

A more recent method for the reduction of an aldose has made use of sodium borohydride (1) which has also been used in the direct reduction of a sugar lactone to the alcohol (72).

Karabinos and Ballun have recently reported the reduction of aldoses and ketoses to the polyols by refluxing in aqueous ethanol with Raney nickel (29).

The synthesis of the hexanitrate of allitol has not been reported, but the nitric acid esters of several other hexitols have been obtained in a crystalline state. In 1847, Domonte and Menard reacted mannitol with fuming nitric acid and sulfuric acid (16) and obtained a crystalline nitro compound which apparently was the hexanitrate although the analytical results were not too clear.

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The hexanitrate of mannitol was definitely obtained by Sokoloff, in 1879, by using nitric and sulfuric acids (47), and this preparation was repeated in 1929, by Patterson and Todd (41). The hexanitrate of dulcitol was prepared by the nitric and sulfuric acid method by Wigner, in 1903 (68).

In 1889, Vincent and Delachanal reported the nitration of sorbitol by a mixture of fuming nitric and sulfuric acids. They did not, however, obtain a crystalline product (64). Bergeim (9) reported having obtained crystalline sorbitol hexanitrate by nitration with nitric and sulfuric acids in 1930. This was later confirmed by Tettamanzi and Arnaldi (62). Urbanski and Kwiatkowska (63) investigated the possibility that the syrupy product obtained originally from sorbitol was a mixture of partially nitrated compounds. They found that depending on the temperature at which the nitration was carried out, a mixture of penta- and hexanitrate or only the hexanitrate of sorbitol was produced. The nitration was achieved by the usual nitric-sulfuric acid mixture.

An alternative method of nitration has been used by Honeyman and Morgan in the nitration of certain glucose derivatives (25). They applied a mixture of fuming nitric acid and acetic anhydride to a suspension of the sugar in acetic anhydride at 0° C., and obtained nearly quantitative yields of the fully-nitrated derivatives.

#### DISCUSSION

## A. The Nitromethane Condensation

The nitromethane condensation has been applied to the synthesis of several sugars by Sowden and co-workers. Sowden and Fischer reported a condensation with D-ribose (56). However, they did not obtain the nitroalcohol in a crystalline form and did not separate the two isomers. Furthermore, they did not convert the syrupy nitroalcohols to the corresponding hexoses. It was decided to attempt a synthesis of allitol from the pentose, D-ribose, by application of this method, since Lohmar and Goepp (38) had stated that this method would make the synthesis of some hexitols much simpler than the older cyanohydrin synthesis. Before attempting the synthesis from D-ribose, the method was tried on D-arabinose. This was done in order to become familiar with the technique (57), since D-ribose was a relatively expensive starting material. D-Arabinose was expected to yield D-glucose and D-mannose which have been the most thoroughly investigated of the hexoses.

A sample of D-arabinose was condensed with nitromethane in the presence of sodium methoxide in a methanol solution, and the resulting mixture of sodium salts of the isomeric nitroalcohols was isolated in a crude yield of 122.3%. When this mixture was treated with sulfuric acid to oxidize the nitro group, the two hexoses, D-mannose and D-glucose, were obtained in solution. D-Mannose was separated from the solution as the water-insoluble D-mannose phenylhydrazone, and the phenylhydrazino residue was removed by treatment with benzaldehyde and benzoic acid in aqueous ethanol solution. The crude, syrupy D-mannose which could not be crystallized was obtained in a yield of 42.6%, and was reduced with sodium borohydride in aqueous solution.

The solution containing the D-glucose phenylhydrazone was divided into two equal portions; one part was treated with phenylhydrazine again, and the insoluble D-glucose phenylosazone was isolated in a crude yield of 24.2%. The other portion of the D-glucose phenylhydrazone solution was treated in the same manner as for D-mannose phenylhydrazone in order to obtain D-glucose. The resulting solution gave a positive Fehling's test, but no crystalline D-glucose could be isolated; a considerable amount of sodium acetate was present. The syrupy product was acetylated by the method of Gattermann (18), but no crystalline  $\beta$ -pentaacetyl-D-glucose has been obtained.

A sample of D-ribose was condensed with nitromethane in the same manner as for D-arabinose. The resulting, insoluble sodium salts (76.4% of theory) were dissolved in water, and the sodium ion removed with an ion exchange column. A crude, syrupy material, presumed to be the mixture of the two isomeric nitroalcohols, was obtained in a yield of 53.1%.

Extraction of this syrupy mixture with absolute ethanol at 50°C. gave a syrupy fraction A and extraction with absolute ethanol at reflux temperature gave a similar fraction B which also could not be crystallized. The ethanol insoluble residue (C) amounted to 20.7% of the

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total material before extraction and was soluble in water. Paper chromatograms were run on fractions A and B and compared to D-ribose as a standard. It was found that both fractions contained unreacted D-ribose. Also in each case a second spot appeared which was assumed to be the two nitroalcohols. From the density of the spots it appeared that the concentration of the nitroalcohols was greater than that of D-ribose in fraction A, but that in fraction B, the opposite was true. On the basis of both fractions A and B together, D-ribose and the nitroalcohols appeared to be present in approximately equal amounts. Hence, the approximate yield of both nitroalcohols was 20%. Residue C gave no spot at all when compared to D-ribose as standard on a paper chromatogram.

Attempts were then made to separate the D-ribose from the nitroalcohols in fraction A on an adsorption chromatography column using a mixture of celite and silicic acid. After many trials, in which the composition of the developer was varied, a partial separation was achieved. A paper chromatogram was run on the ethanol extracts of the column and compared to a standard solution of D-ribose. The first two sections contained only D-ribose, but the last two contained D-ribose as well as some other material which gave a spot very near to the solvent front. This spot was in a considerably different position to the one that was assumed to be the nitroalcohols on the paper chromatograms of the fractions A and B.

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The work, at this point, was discontinued since the yields from this method appeared to be rather low and also since the separation of the two isomeric nitroalcohols appeared to be difficult.

The nitromethane condensation may be expressed by the following equilibrium:

 $RCHO + CH_3NO_2 \longrightarrow R-CHOH - CH_2NO_2$ 

The reaction was catalysed by a base which when applied especially to reducing sugars had to be mild since strong alkali in the presence of oxygen resulted in fragmentation of the carbon chain and complex isomerization reactions. Furthermore, it has been found that strong alkali shifts the equilibrium to the left. Hence in these condensations sodium methoxide and an excess of nitromethane were used in order to displace the equilibrium to the right.

However, the most important factor was the solubility relationships between the reaction medium, the aldose, and the sodium nitroalcohols. The optimum conditions for maximum yield were those in which the aldose was quite soluble and the sodium nitroalcohols relatively insoluble in the reaction medium. The results of various condensations have been summarized in Table I.

The benzylidene group which was stable to base was used effectively in the case of D-glucose to improve the solubility relationships. In a paper by Sowden and Thompson (59) which appeared during the course of the present investigation, they stated that an alcoholic medium had not been very satisfactory for the nitromethane condensation with some sugars and that the use of an aqueous solution of sodium hydroxide was being investigated. They found that with D-arabinose in aqueous solution, the reaction proceeded rapidly with comparable yields.

#### TABLE I

## YIELDS OF NITROALCOHOLS FROM THE NITROMETHANE CONDENSATION WITH ALDOSES

Reacting Aldose	% Yields of Nitroalcohols	Reference
2, 4-benzylidene-L-xylopyranose 4, 6-benzylidene-D-glucose L-xylose D-ribose D-glucose D-erythrose 2, 4-benzylidene-D-erythrose D-mannose D-arabinose	$50.4^{a}$ 21.0 a 21.0 c 35.0 c 21.0 c 5.0 b 40.0 d 64.0 e 55.0 e 69.0 e	54 55 56 56 56 56 51 51 51 58 57

a - Isolated only one isomer

- b Isolated as acetylated nitroolefin
- c Nitroalcohols are syrupy isolated as acetylated nitroolefin
- d Nitroalcohols are partially crystalline isolated as acetylated nitroolefin
- e Crystalline nitroalcohols separated by fractional crystallization

Sowden and Fischer reported a condensation with D-ribose (56) which gave syrupy nitroalcohols which were converted to the crystalline acetylated nitroolefin (21%). They stated that D-ribose dissolved readily in the reaction medium. From the results of the present investigation, it did not appear that D-ribose did dissolve readily as the resulting nitroalcohols contained a large portion of unreacted D-ribose. This was probably the main reason for the poor yields of nitroalcohols.

The separation of the two isomeric nitroalcohols was the second difficult feature of the method. In most of the cases where the nitromethane condensation has been successfully applied to the synthesis of higher sugars, the nitroalcohols have been crystalline and were separated from each other by fractional crystallization but in the present case the nitroalcohols were obtained only as a crude syrup. The paper chromatograms gave no evidence that two isomeric nitroalcohols were present. However, as the structural difference between the two isomers was rather small, it would be anticipated that such a separation would be difficult. The work on the adsorption chromatography columns tended to support this assumption.

# B. The Cyanohydrin Synthesis

The cyanohydrin synthesis has been the conventional method for the preparation of higher sugars since the work of E. Fischer. Recourse was taken to this method when the nitromethane condensation proved to be unsatisfactory. A modified procedure (45) of the synthesis was followed.

An aqueous solution of D-ribose was treated with an aqueous solution of sodium cyanide for 24 hours at 5°C. This solution, after boiling to hydrolyze the nitriles and expell the ammonia, was passed while still hot through an ion exchange column containing Amberlite IR 120 resin in the calcium cycle. Passage through the column converted the two

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isomeric acids, D-allonic and D-altronic, to the calcium salt form. On concentration of the solution, the calcium salt of D-altronic acid crystallized out first and in this manner, the isomers were separated. The mother liquor containing calcium-D-allonate was then passed through the ion exchange column in the hydrogen cycle in order to remove the calcium and leave the free acid. On subsequent evaporation solid  $\gamma$ -D-allonolactone (m. p. 98-123° C.). was obtained. However, examination of this material under the microscope indicated that it was not crystalline. In the literature this compound has been reported as being crystalline with a melting point of 97-120° C. (7). The yields from three runs have been summarized in Table II and compared with those obtained by other workers.

#### TABLE II

Run	% Yield of Calcium-D-Altronate	% Yield of $\pmb{\sim}$ -D-Allonolactone	Reference
1 2 3	$34.2^{a}$ $41.6$ $10.9$ $40.0^{a,c}$ $31.0^{a}$ $52.3^{a}$	37.8 34.6 31.7 <sup>b</sup> 34.0 <sup>c</sup> 46.9 not available	This work This work This work 45 42 37

#### YIELDS IN THE CYANOHYDRIN SYNTHESIS FROM D-RIBOSE

a - Isolated as the hemiheptahydrate

b - Appeared to contain some D-altronolactone

c - Average of seven runs

The yields summarized in Table II indicate that the two isomers were produced in approximately equal amounts. With other sugars a preference for one isomer has been reported; for example, D-manno-D-gala-heptose was obtained from D-mannose in almost theoretical yield and the epimer was not detected (26). In two runs the ion exchange column used was contaminated with a small amount of iron which complexed with the cyanide ion forming a colloidal solution of Prussian blue,  $Fe_4$  (Fe (CN)<sub>6</sub>)<sub>3</sub>. On concentration of the eluate, the blue material coagulated and was removed by filtration. On the third run, apparently most of the iron on the resin had been removed and no Prussian blue was encountered.

During the recrystallization of the calcium-D-altronate hemiheptahydrate prepared in one run, some mould began to grow in the solution which might account for the comparatively low yield obtained in this case.

#### C. The Sodium Amalgam Reduction

The sodium amalgam reduction of sugar lactones to aldoses has been used in the synthesis of sugars since it was first discovered by Fischer in 1889, even though it was not investigated in a quantitative manner until 1947 (60). The procedure followed here was that outlined in Polarimetry, Saccharimetry, and the Sugars (7). The solid  $\gamma$ -Dallonolactone was reduced to syrupy D-allose as indicated by the positive Fehling's test, and has resisted all attempts at crystallization. A yield of 44.0% was obtained. The specific rotation of the syrupy D-allose was several degrees lower than the reported value indicating the presence of

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impurities.\*

According to Sperber, Zaugg, and Sandstrom (60), the pH of the reaction medium was the most important single factor for maximum yields in the lactone reduction. They found that a pH range of 3.0-3.5 and a temperature not greater than  $15^{\circ}$  C. were the optimum conditions. A pH of 2-3 gave approximately the same yields but the reaction proceeded at a much faster rate and hence the pH was more difficult to control. At a pH of 4-5, however, the yields were 10-15% lower. The yields varied from 82-84% for  $\gamma$ -D-galactonolactone to 50-57% for D-arabonolactone.

In this investigation the pH of the solution was controlled using Congo red indicator paper. This was a rather crude method and a pH meter would give a more accurate control. This relatively poor control of the pH was probably the main cause of the poor yield since L-allonolactone has been reduced to L-allose with sodium amalgam in a yield of 77% (4).

The control of the pH has been simplified by a modification to the standard procedure (28). In place of the addition of the sulfuric acid, a relatively insoluble solid acid such as oxalic acid was added to the mixture. As the sodium amalgam reacted, the acid dissolved and maintained an approximately constant pH. Yields of the order of 70-90%

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<sup>\*</sup> Seed crystals of authentic D-allose have recently been received from Dr. H.S.Isbell to whom we are grateful. The use of this material in the crystallization of our syrupy sample is still under investigation.

have been obtained.  $\Upsilon$ -D-Allonolactone has been reduced in this manner to D-allose in a yield of 71% (45).

#### D. The Raney Nickel Reduction

Refluxing with Raney nickel in aqueous ethanol solution has been applied to the reduction of several aldoses to the corresponding sugar alcohols and yields of 74-90% have been obtained (29). Attempts were made to apply this simple method to the reduction of a sugar lactone directly to the sugar alcohol. With  $\Upsilon$ -D-galactonolactone yields of the order of 5% of crystalline dulcitol were obtained. Since the yield was low, sodium amalgam reduction was preferred for converting the  $\Upsilon$ -Dallonolactone to D-allose and the Raney nickel method was used for the reduction of the D-allose to allitol. The method was tested on D-mannose and recrystallized D-mannitol was obtained in a yield of 47.2%.

One portion of syrupy D-allose was subjected to low pressure hydrogenation with a platinum dioxide catalyst. The product which was not hydrogenated as indicated by the reducing power was then completely reduced to allitol by refluxing in aqueous ethanol with Raney nickel.

A sample of allitol obtained from the reduction of crude, syrupy  $\Upsilon$ -D-allonolactone partially crystallized on standing <u>in vacuo</u> over phosphorus pentoxide but when it was allowed to stand in the open air it became syrupy within several minutes. D-Altritol has been reported as being hygroscopic (10), (11) and therefore the sample of  $\Upsilon$ -D-allonolactone was probably contaminated with a lactone of D-altronic acid.

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Allitol has been obtained in a yield of 69.1% (crude) from D-allose with reduction by the Raney nickel procedure. On concentration of the reaction mixture after the reduction, a green colour was obtained which was shown to be due to nickelous nickel.

Pure allitol was obtained as long, slender needles after repeated recrystallization from aqueous ethanol, was optically inactive, and showed the correct analysis. The melting point of  $151.0 - 151.5^{\circ}$  C. agreed with the reported value and acetylation to the known allitol hexaacetate completed the characterization.

## E. The Sodium Borohydride Reduction

Sodium borohydride has been used for the reduction of sugar lactones (72) and aldoses (1) to the sugar alcohols. Previously, the reduction of the lactone to the aldose was performed using sodium amalgam. This method of reduction was difficult to control and unless the technique had been well studied, the yields were low. The reduction of the aldose to the sugar alcohol has been done by sodium amalgam or by high pressure hydrogenation with Raney nickel catalyst. The use of sodium borohydride was a more convenient method than the latter, although the yields were somewhat lower.

In the borohydride reduction, the sugar alcohol complexed with the boric acid, and formerly the sugar alcohol was isolated as the polyacetate which was then converted back to the sugar alcohol or the reduction mixture was refluxed with dilute hydrochloric acid in order to destroy the complex. A newer method in which the borate was removed as the volatile methyl ester has been reported (6).

The borohydride reduction was first tested on  $\Upsilon$ -D-galactonolactone and crystalline dulcitol was isolated in a yield of 48.0%. The mother liquor gave a positive test for reducing sugar which indicated that a longer reduction period might have increased the yield. In a similar manner, D-galactose was converted in a yield of 33.9% to crystalline dulcitol; in this case also, reduction was incomplete.

In an attempt to simplify the synthesis of allitol,  $\Upsilon$ -D-allonolactone was treated with sodium borohydride, and a syrupy, non-reducing product was obtained. This material has not yet been thoroughly worked up but probably contains allitol.

#### F. The Nitration of Allitol

D-Mannitol has been nitrated with a mixture of fuming nitric and sulfuric acids by Patterson and Todd (41) in a yield of 75%. McKeown and Hayward (39) nitrated dulcitol by the same method in a yield of 92%. Sorbitol hexanitrate was prepared in a yield of 60% by Urbanski and Kwiatkowska (63) and in 97% yield by Tettamanzi and Arnaldi (62).

Allitol was nitrated with the nitric-sulfuric acid mixture and the crystalline hexanitrate was obtained in a yield of 36.3%. A syrupy by-product was obtained which may possibly be partially nitrated allitol. Urbanski and Kwiatkowska (63) found that the temperature at which the nitration was carried out influenced the degree of nitration of sorbitol. In the first nitration of allitol, the temperature was not rigidly controlled.

The second method of nitration which was used was that of Morgan and Honeyman who treated methyl-4, 6-O-ethylidene- $\beta$ -Dglucoside with a mixture of fuming nitric acid and acetic anhydride and obtained the 2, 3- dinitrate of the above compound in a yield of 89% (25). Crystalline allitol hexanitrate was prepared by this method in a yield of 59.1%. The crude product was obtained in approximately 90% yield. In this case, also, some syrupy material was obtained from the nitration mixture which did not crystallize and may possibly be partially nitrated allitol. The pure allitol hexanitrate which had the correct nitrogen content melted at 59.0 - 59.5° C. A sample of the prismatic crystals slowly decomposed with the evolution of nitrogen dioxide after standing in a glass vial at room temperature for about six weeks.

#### G. The Reaction of Pyridine with Allitol Hexanitrate

The reaction of pyridine with D-mannitol hexanitrate has been investigated and the resulting pentanitrate shown to be D-mannitol-1, 2, 3, 5, 6-pentanitrate by Hayward (22). Some features of the mechanism of this denitration reaction and some of the by-products were investigated by Brown and Hayward (14). Dulcitol hexanitrate was known to react in a similar manner with pyridine and the resulting pentanitrate was shown to be D, L-galactitol-1, 2, 4, 5, 6-pentanitrate by McKeown and Hayward (39).

The reaction of pyridine with allitol hexanitrate was investigated only in a qualitative manner. That some reaction occurred was

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indicated since the solution changed from colourless to amber and crystals which were apparently pyridinium nitrate appeared on the walls of the testtube above the surface of the solution. No gas evolution was observed during the reaction and in this respect the behavior of allitol hexanitrate differed from that of D-mannitol hexanitrate which was treated with pyridine at the same time for comparison. A colourless syrup was recovered from the allitol reaction mixture by dilution with water. This syrup did not crystallize when seeded with allitol hexanitrate, or on long standing in a vacuum desiccator, and slowly turned yellow after several days. The crystalline mannitol pentanitrate was recovered in good yield from the control when worked up in a similar manner.

### H. The Preparation of Allitol Hexaacetate

The preparation of acetates with acetic anhydride in the presence of a basic catalyst such as pyridine is quite general in the carbohydrate field. D-Mannitol hexaacetate was prepared by this method in a yield of 86.7% (5). Allitol hexaacetate was obtained by this procedure in the form of long, thin, needle-like crystals in a yield of 58.0% and melted at 62.0-62.5° C. (reported values were 61° C. (44) and 61 - 62° C. (71) ). The analysis and molecular weight determination confirmed the identity of this compound.

The drastic acetylation method of Wiemann (67) using acetic anhydride under reflux for 12 hours gave no crystalline allitol hexaacetate. Darkening of the reaction mixture indicated that some degradation had taken place.

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#### EXPERIMENTAL

#### A. Special Precautions

In view of the sensitivity of carbohydrates, especially reducing sugars, to heat, all concentrations were carried out under reduced pressure at a temperature not exceeding 50° C. Bumping of the solutions was prevented by introducing a fine stream of bubbles of nitrogen gas from a "bleeder", or by the use of a rotary Craig-type evaporator (15).

#### B. Materials

## D-Arabinose

D-Arabinose as supplied by the Pfanstiehl Chemical Company was dried over phosphorus pentoxide <u>in vacuo</u>; m.p. 160-161° C.;  $\left[\alpha\right]_{D}^{18.6} - 104.6^{\circ}$  (c, 0.53; l, l; H<sub>2</sub>O) (constant). The reported constants were m.p. 160° C.;  $\left[\alpha\right]_{D}^{20} - 104.5^{\circ}$  (H<sub>2</sub>O) (equilibrium) (44).

#### **D-Ribose**

D-Ribose purchased from the Pfanstiehl Chemical Company was dried <u>in vacuo</u> over phosphorus pentoxide; m. p.  $85 - 87^{\circ}$  C.;  $[\alpha]_{D}^{18.6} - 22.6^{\circ}$  (c, 1.06; 1,1; H<sub>2</sub>O) (constant). A sample of D-ribose purchased from the Nutritional Biochemicals Corporation when similarly dried did not differ significantly in melting point and specific rotation. Pigman and Goepp reported a m. p. of  $87^{\circ}$  C. and specific rotation

 $\left[\alpha\right]_{D}^{1}$  - 23.1 to -23.7° (c, 4; H<sub>2</sub>O) for pure D-ribose (44) which showed complex mutarotation. The L-ribose had

$$\left[ \varkappa \right]_{D}^{20}$$
 +20.3 to +20.7° (c, 4; H<sub>2</sub>O) (44).

# $\gamma$ -D-Galactonolactone

A sample of  $\gamma$ -D-galactonolactone (Pfanstiehl Chemical Company) after drying <u>in vacuo</u> over phosphorus pentoxide had m.p. 134.0-135.5° C. and specific rotation  $[\alpha]_D^{21.5}$  -80.0° (c, 0.54; l, 1; H<sub>2</sub>O) (constant). The reported values were m.p. 133-135° C.,  $[\alpha]_D$  -77.40° (7).

## Nitromethane

Nitromethane supplied by Eastman Organic Chemicals (white label) was distilled in an all-glass apparatus under reduced pressure in an atmosphere of nitrogen. The distillate was colourless.

## Organic Solvents

Methanol, ethanol, benzene, pyridine, toluene, ether, and n-pentane were purified as recommended by Fieser (17), and distilled in an all-glass apparatus.

#### Acetic Anhydride

Reagent grade acetic anhydride purchased from May and Baker Ltd. was distilled in an all-glass apparatus, and the fraction distilling at 136.5° C. collected.

### Raney Nickel Catalyst

The nickel-aluminum alloy (technical grade) was obtained from the Raney Catalyst Company. The catalyst was prepared according to the procedure outlined by Vogel (65).

A solution of 190 gm. of sodium hydroxide in 750 ml. of water was magnetically stirred in a two litre beaker, and cooled in an ice-bath while 150 gm. of nickel-aluminum alloy was added in small portions. Hydrogen gas was evolved in copious quantities, and the solution temperature was kept below 25°C. during the additon which required about two hours. The solution was allowed to come to room temperature overnight, and was then heated on the steam-bath until the evolution of hydrogen again became slow (12 hours). The supernatant liquid was decanted, and the black, finely-divided Raney nickel was washed with distilled water, 50% sodium hydroxide solution, and again with distilled water until the wash liquid showed no basicity to litmus paper. The catalyst was then washed an additional ten times with water, three times with 100 ml. portions of 95% ethanol and three times with 100 ml. portions of absolute ethanol. The nickel catalyst was stored under absolute ethanol in a glass-stoppered bottle. Approximately one ml. of catalyst weighed 0.6 gm.

#### Sodium Amalgam (2.5%) (65)

Sodium (19.0 gm.) was placed in a 500 ml. Erlenmeyer flask, and 20 ml. of dry toluene was added. The sodium was melted with a free flame, and 350 gm. of mercury was then added dropwise. At first several flashes of flame occurred, but this was followed by the evolution of dense white fumes. The toluene continued to boil even after the removal of the flame. The toluene remaining after the additon of the mercury was decanted, and the amalgam was poured into a mortar and pulverized.

## Permanganate-Periodate Spray Reagent for Chromatograms (30)

A 2% aqueous solution of sodium metaperiodate and a 1% potassium permanganate in a 2% aqueous sodium carbonate soution were prepared. These two solutions were mixed immediately before use in the

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ratio of four parts of the periodate solution to one part of the permanganate solution, and sprayed on the chromatogram. After the brown spots indicating the location of the sugar had appeared, the purple colour of the permanganate was removed by washing the chromatogram with water.

#### Alkaline Permanganate Reagent (12)

A 1% solution of potassium permanganate in 2.5 N sodium hydroxide was prepared, and used as a reagent for detection of sugars on adsorption column chromatograms.

#### Red Tetrazolium

Red Tetrazolium (2, 3, 5-triphenyltetrazolium chloride) was purchased from the Nutritional Biochemicals Corporation. One ml. of a 0.5% aqueous solution of the dye was treated with one drop of sugar solution. The mixture was heated on a water-bath, and a red precipitate, or colour, indicated the presence of reducing sugar (17).

### Preparation of the Ion Exchange Column

The ion exchange column containing about 400 gm. of Amberlite IR 120 resin was converted to the calcium cycle by passing through a 10% calcium chloride solution until the eluate gave a test for calcium. The column was then washed with water until evaporation of an aliquot (10 ml.) of the eluate gave a negligible amount of residue.

The resin was converted to the hydrogen cycle by washing with 3N hydrochloric acid until the eluate gave no test for calcium. The column was then washed with water until an aliquot of the eluate gave a negligible amount of residue on evaporation.

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## C. The Nitromethane Condensation

#### 1. The Condensation of Nitromethane with D-Arabinose

D-Arabinose (10.00 gm.) was suspended in a mixture of 40 ml. of nitromethane and 50 ml. of methanol, and a solution of 2.3 gm. of sodium in 70 ml. of methanol was added. The resulting mixture became noticeably cooler immediately. The container was wrapped in aluminum foil to avoid photochemical decompositon, and shaken for 18 hours at room temperature. The precipitated sodium salts were removed by suction filtration, and washed with cold methanol, ether, and petroleum ether. The light brown, amorphous salts were dried <u>in vacuo</u> over phosphorus pentoxide for several days. Yield 19.0 gm. (122.3%).

The salts were dissolved in 70 ml. of water, and the dark red solution was added dropwise with constant stirring and external cooling to a solution of 13 ml. of concentrated sulfuric acid in 19 ml. of water. A gas was evolved during the additon, and the final, pale yellow solution was neutralized to Congo red (pH 5) with solid sodium carbonate, then treated with charcoal, and filtered by suction through a bed of celite. The filtrate was then treated with solid sodium bicarbonate until just alkaline to litmus paper, and then made just acid with acetic acid. Fehling's solution gave a positive test for reducing sugars.

Phenylhydrazine (7 ml.) in 13 ml. of 25% acetic acid was added to the sugar solution. A precipitate of D-mannose phenylhydrazone appeared within several minutes. After standing overnight, the orangebrown precipitate was removed by suction filtration, and the filtrate which

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contained the soluble D-glucose phenylhydrazone was set aside to be worked up as described below. The crude D-mannose phenylhydrazone was washed successively with water, 60% ethanol, absolute ethanol, and acetone, which removed much of the original colour leaving a final product which was only slightly yellow. After drying <u>in vacuo</u> over phosphorus pentoxide, 7.3 gm. (40.6%) of D-mannose phenylhydrazone with a melting point of 176° C. was obtained. The reported melting point was 199 - 200° C. (7).

The D-mannose phenylhydrazone (7.3 gm.) was refluxed for 2.5 hours with 100 ml. of water, 20 ml of ethanol, 10 ml. of benzaldehyde, and 1 gm. of benzoic acid. A dark brown oil separated out from the solution, and the supernatant liquor was decanted and extracted three times with chloroform. The aqueous solution was decolourized with charcoal, and concentrated to a syrup which after drying <u>in vacuo</u> over phosphorus pentoxide weighed 5.11 gm. (42.6% yield calculated as D-mannose), and could not be induced to crystallize although numerous attempts were made over a period of 18 months.

The syrupy D-mannose was dissolved in 90 ml. of water and a solution of sodium borohydride (1.0 gm.) in 10 ml of water was added dropwise with stirring. The resulting solution had a pH of 8, and was kept at room temperature for 2 hours. At the end of that time, the evolution of hydrogen had almost completely stopped, and two or three drops of the solution gave a negative Fehling's test after acidification with acetic acid to destroy the excess borohydride. The bulk of the solution was then acidified with acetic acid, and concentrated to a syrup. The

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syrup was successively diluted, and concentrated six times with methanol to destroy the borate complex, and remove the borate as the volatile methyl ester (6). The white, amorphous residue was dissolved in water, and the filtered, aqueous solution gave a negative test for reducing sugar with red tetrazolium reagent. The solution was made just turbid by the addition of ethanol, and allowed to stand. A syrupy product was obtained.

One half of the filtrate containing D-glucose phenylosazone (150 ml.) was treated in the same manner as for the D-mannose phenylhydrazone in order to remove the phenylhydrazino residue. The aqueous solution after extraction with chloroform, and treatment with charcoal was pale yellow in colour, and was concentrated to approximately 50 ml. whereupon solid, inorganic material began to precipitate. Sufficient water was added to redissolve the precipitate, and the solution was neutralized to Congo red with warm, saturated barium hydroxide solution. The precipitated barium sulfate was removed by centrifugation. The centrifugate was treated with barium acetate solution to remove any remaining sulfate ion (pH 5-6), and passed through the ion exchange column in the hydrogen cycle (eluate pH 5-6). The column was washed with about 500 ml. of water, and the total eluate concentrated until solid material began to precipitate. Further drying in a vacuum desiccator over phosphorus pentoxide for several days gave 9.20 gm. of brown, solid material.

The solid residue was refluxed with 35 ml. of ethanol for one hour giving a dark brown extract. The extraction was repeated with

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a further 35 ml. of ethanol, and the two extracts were combined, and allowed to stand. The extract gave a positive test with Fehling's solution. Some crystalline material was obtained from the extract which after drying <u>in vacuo</u> over phosphorus pentoxide melted at 323 - 327° C. Anhydrous sodium acetate was reported to melt at 324° C. (24).

The solid residue remaining from the extractions was dissolved in water giving a brown coloured solution which was treated with charcoal. The solution gave a positive test with Fehling's solution. On standing some crystalline material was removed which after air-drying had a melting point of 57° C. The reported melting point of hydrated sodium acetate was 58°C. (24). The aqueous mother liquor was added to the ethanol extract, and after standing, more crystalline, hydrated sodium acetate was obtained. The presence of reducing sugar was indicated by the Fehling's test, but none was isolated in a crystalline state.

The above crude material was dried <u>in vacuo</u>, and pulverized in a mortar with 3 gm. of anhydrous sodium acetate. This mixture was heated in a water-bath for 2 hours with 30 ml. of acetic anhydride, and the resulting brown solution was poured into about 150 ml. of ice-water, and allowed to stand in the refrigerator for two days. A brown syrup separated which was extracted three times with chloroform. The chloroform was removed, and the resulting brown syrup dissolved in ethanol and allowed to stand. Many attempts to obtain crystalline  $\beta$ -pentaacetyl-D-glucose from ethanol and aqueous ethanol have all failed. The syrup had the same odour as charred sugar.

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The brown oils obtained in the removal of the phenylhydrazino residue from D-mannose and D-glucose phenylhydrazones were crystallized from aqueous ethanol. The crystalline material had a melting point of 154 - 158°C. The two isomeric forms of benzaldehyde phenylhydrazone were reported to melt at 154 - 155°C. and 157 - 158°C. (23).

The remaining portion (150 ml.) of the solution containing D-glucose phenylhydrazone was heated in a boiling water-bath with 90 ml. of freshly prepared phenylhydrazine raagent for 20 minutes after which it was allowed to stand overnight. The phenylhydrazine reagent was prepared in the following manner (2): phenylhydrazine hydrochloride (10 gm.) was dissolved in 90 ml. of water; 15 gm. of sodium acetate and three or four drops of glacial acetic acid were added, and the resulting solution was treated with charcoal and filtered.

The orange-brown precipitate of D-glucose phenylosazone was removed by suction filtration, and dissolved in 50% aqueous ethanol. This solution on treatment with charcoal gave a dark red coloured solution. Crude material (1.86 gm.) with a melting point of  $180 - 185^{\circ}$  C. was obtained on standing. This was recrystallized from anisole, and gave a melting point of  $186 - 189^{\circ}$  C. A further 1.04 gm. of crude D-glucose phenylosazone was obtained from the original solution giving a total yield of 2.9 gm. (24.2%). This material was recrystallized fromaqueous ethanol, and after drying <u>in vacuo</u> over phosphorus pentoxide had a melting point (decomposition point) of  $199 - 203^{\circ}$  C. The reported

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melting point of D-glucose phenylosazone was  $208^{\circ}$  C. (7).

## 2. The Condensation of Nitromethane with D-Ribose

D-Ribose (23.68 gm.) was treated with 50 ml. of methanol, 90 ml. of nitromethane, and a solution of 5.3 gm. of sodium in 175 ml. of methanol, by the procedure described for D<sub>7</sub>arabinose. The yield of dried, amorphous, sodium salts of the mixed nitroalcohols was 28.09 gm. (76.4%). The salts were dissolved in 700 ml. of water, and the solution (pH 10) was passed through the ion exchange column in the hydrogen cycle. The red eluate (pH 5-6) was darker after passing through the column, and treatment with charcoal removed a considerable amount of the colour. The column was washed with water until a 10 ml. aliquot of the eluate on evaporation yielded a negligible amount of residue.

The total eluate was concentrated to a dark brown syrup which was dried <u>in vacuo</u> over phosphorus pentoxide for several days. Yield of the supposed mixture of crude nitroalcohols was 17.68 gm. (53.1%).

The dried syrup was extracted with 50 ml. of absolute ethanol for 2 hours at 50° C. with protection against moist air, and the orange-yellow absolute ethanol extract was filtered through a fritted glass funnel, and allowed to stand at room temperature. Three more similar absolute ethanol extractions were carried out on the syrup.

A descending paper chromatogram was run in a n-butanol, glacial acetic acid, and water system (5:1:2) on Whatman No. 1 paper on the first absolute ethanol extract. The chromatogram was sprayed with Lemieux's periodate solution (30) and two spots were obtained with  $R_f$  values of 0.33 and 0.43; the latter spot being larger and darker. Slow evaporation of the combined ethanol extracts left a dark brown syrup (A) which reduced Fehling's solution, but could not be crystallized. A paper chromatogram of A compared to a D-ribose standard gave two spots; one corresponded to the D-ribose standard, and the other which was darker had a larger  $R_f$  value.

The solid residue remaining from the warm ethanol extractions was further extracted with 50 ml. of absolute ethanol at reflux temperature for 2 hours, and the orange-coloured solution was removed by filtration through a fritted glass funnel. The extraction was repeated twice, and the three extracts combined, and allowed to evaporate to a brown syrup (B) which reduced Fehling's solution. A paper chromatogram of syrup B compared to D-ribose as standard gave two spots; the larger and darker of the two corresponded to the spot obtained from the D-ribose standard.

The ethanol insoluble, dark residue (C) remaining from these extractions weighed 3.56 gm., and was completely water soluble. It failed to give a spot on a paper chromatogram when compared with D-ribose.

In an adsorption chromatography column, 0.85 x 13 cm., was placed 2 gm. of a mixture of silicic acid and celite (2:1), and this column was washed with a solution of ethanol-benzene (1:4  $^{v}/v$ ), and 2.1 mgm. of A in dilute ethanol (0.2 ml.) was placed on the column, and the chromatogram was developed with 2.5 ml. of the ethanol-benzene mixture.

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The column, on extrusion, was streaked with Lemieux's periodate reagent (30), and the first brown band extended for 2.9 cm. from the top of the column. The second band began 3.6 cm. from the top, and was 1.1 cm. wide. The total column length was 5.9 cm.

A similar column was sliced into sections corresponding to these bands, and each of these sections was extracted with warm ethanol. The extracts were run on a paper chromatogram, and compared to a D-ribose standard. From these chromatograms, the first section (first brown band) and the second section both contained D-ribose. The third section (second brown band) and the fourth section both contained D-ribose as well as some other material which appeared very close to the solvent front.

#### D. The Cyanohydrin Synthesis of $\Upsilon$ -D-Allonolactone

D-Ribose (45.00 gm.) was dissolved in 325 ml. of water and the solution cooled to 3° C. in an ice-salt-bath. To this was added a solution containing 19.6 gm. of sodium cyanide in 135 ml. of water. also cooled to 3°C. The resulting solution was allowed to stand at 5°C. for 24 hours. The clear, pale yellow solution (pH 11) then gave a negative test with Fehling's solution, and was heated on the steam-bath for 2 hours, and then boiled gently under reflux for 6 hours during which ammonia was evolved. While still hot, the solution was passed through the ion exchange column in the calcium cycle. The pH of the eluate was about 5. The column was thoroughly washed with water, and the total

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eluate was concentrated until calcium-D-altronate hemiheptahydrate began to crystallize. The recovered calcium-D-altronate hemiheptahydrate was recrystallized, and air-dried; yield 25.30 gm. (34.2%).

The amber filtrate containing the calcium-D-allonate (pH 5) was passed through the ion exchange column in the hydrogen cycle to remove the calcium. The eluate and washings were concentrated to a brown syrup which solidified on drying <u>in vacuo</u> over phosphorus pentoxide. This solid material was then dissolved in water, treated with charcoal, filtered, and allowed to stand. Solid  $\Upsilon$ -D-allonolactone with a melting range of 98 - 123° C. separated in a yield of 20.19 gm. (37.8%). Examination of this material under the microscope indicated that it was not crystalline. From a second run starting with 50.00 gm. of D-ribose, 29.79 gm. (41.6%) of calcium-D-altronate, and 20.51 gm. (34.6%) of  $\Upsilon$ -D-allonolactone were obtained. The lactone melted at 68 - 91° C.

In a third experiment, D-ribose (8.20 gm.) was treated with 3.68 gm. of sodium cyanide in a similar manner to that described above. The solution on passage through the ion exchange column became blue-green in colour, and on subsequent concentration, a flocculent, blue precipitate was obtained which was removed by filtration. Evaporation of the filtrate gave 7.23 gm. of crude, wet calcium-D-altronate hemiheptahydrate. Recrystallization from water, and drying over phosphorus pentoxide, <u>in vacuo</u>, converted this to 1.28 gm. (10.9%) of calcium-D-altronate. During this recrystallization a mould began to grow in the solution.

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When the mother liquor containing the calcium-D-allonate came into contact with the ion exchange resin, the blue colour was obtained again. Concentration of the eluate resulted in the precipitation of this material which was removed by filtration. Crude, syrupy  $\Upsilon$ -D-allonolactone was obtained in a yield of 3.08 gm. (31.7%) which solidified on drying. Many attempts to crystallize this crude material from aqueous and aqueous ethanol solutions failed. The material was twice precipitated from ethanol solution by the addition of ligroin to give 0. 37 gm. of solid  $\Upsilon$ -D-allonolactone with a melting point of 95 - 129° C. (7). Examination under the microscope indicated that this material was not crystalline. The mother liquors when concentrated, and dried <u>in vacuo</u> over phosphorus pentoxide yielded 1.42 gm. of crude syrupy  $\Upsilon$ -D-allonolactone.

The blue solid material was soluble in oxalic acid solution, and, in sodium hydroxide gave a brown precipitate which on the addition of hydrochloric acid to the solution reverted to the blue colour. The addition of concentrated acid to the blue coloured solution gave a faint odour of hydrogen cyanide. A small sample of the resin was treated with a solution of sodium cyanide, but no blue colour was obtained. On the addition of either calcium chloride or hydrochloric acid to this mixture, the blue colour developed. A second sample of resin was ignited in a crucible, and the residue dissolved in concentrated hydrochloric acid. This solution, when treated with potassium thiocyanate gave a red colouration typical of iron (66).

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# E. The Reduction of $\Upsilon$ -D-Allonolactone with Sodium Amalgam

Solid  $\Upsilon$ -D-allonolactone (20.51 gm.) (m. p. 68-91° C.) was dissolved in 200 ml. of water in a 600 ml. beaker, and the solution stirred magnetically. The solution was cooled in an ice-salt-bath, and after ice had begun to form in the solution 1.6 ml. of 10% sulfuric acid were added. During one hour, four 100 gm. portions of 2.5% sodium amalgam were added to the solution with continuous stirring. The solution was kept just acid to Congo red by the addition of 10% sulfuric acid from a burette. A greenish-yellow solid substance which appeared to be sulfur floated to the surface of the solution during the reduction. The solution was kept in the ice-salt-bath throughout the entire reduction period.

The solution was decanted from the mercury and treated with sufficient solid sodium carbonate such that the solution after standing for one-half hour in the cold, was just alkaline to litmus. The solution was then made just acid to litmus by the additon of 10% sulfuric acid, and the fine precipitate was removed by suction filtration through a bed of celite. The almost colourless filtrate was concentrated to a volume of about 75 ml. Ethanol was added until no further precipitation occurred, and the white precipitate was removed by filtration. The filtrate was concentrated to a pale-yellow syrup which was refluxed with 25 ml. of absolute ethanol for one-half hour. All of the syrup dissolved, and the resulting solution which gave a positive test with Fehling's solution was slowly evaporated in the presence of anhydrous calcium chloride. There was thus obtained 13.94 gm. (25.8%) of crude, semi-crystalline D-allose. Attempts to recrystallize this material were fruitless.

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An aqueous solution of the crude D-allose was clarified with charcoal, and made up to 50 ml., and an aliquot of this solution contained 0.1941 gm. of dry, syrupy D-allose. On this basis, the total yield of syrupy D-allose was 9.12 gm. (16.9%). The specific rotation was  $\left[\alpha\right]_{D}^{21}$  + 9.79° (c, 3.88; 1; 1; H<sub>2</sub>O) (constant). The reported specific rotation of  $\beta$ -D-allose was  $\left[\alpha\right]_{D}^{+14.4°}$  (c, 5; H<sub>2</sub>O)(constant)(7).

#### F. The Reduction of D-Allose with Raney Nickel

Crude, syrupy D-allose (8.73 gm.) was refluxed for 1.5 hours in 450 ml. of 70% aqueous ethanol with approximately 100 gm. of Raney nickel catalyst. The catalyst was removed by filtration, and the filtrate concentrated to a green syrup. On drying overnight <u>in vacuo</u> over phosphorus pentoxide, 6.1 gm. of crude syrupy allitol was obtained. The green solution was tested with dimethylglyoxime, and a positive test for nickel was obtained (66).

The crude allitol was crystallized from aqueous ethanol to give 0.38 gm. of clear, needle-shaped crystals which after air-drying melted at 147-148° C. This product was recrystallized to a constant melting point from aqueous ethanol, and after drying over phosphorus pentoxide <u>in vacuo</u> melted at 151.0-151.5° C. The reported melting point was 150-151° C. (44). A total of 1.41 gm. (2.6%) of crystalline allitol was isolated in four crops. The crystals were long, slender needles, about 2 - 3 mm. in length. The specific rotation was observed to be  $\left[\alpha\right]_{D}^{16.5}$  0° (c, 1.92; 1, 0.5; H<sub>2</sub>O). The reported specific

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rotation was  $\begin{bmatrix} \alpha \end{bmatrix}_D 0^\circ$  (44). Found: C, 39.46%; H, 7.62%. Calc. for C<sub>6</sub> H<sub>14</sub> O<sub>6</sub>: C, 39.55%; H, 7.76%.

# G. The Reduction of $\sqrt{D-Allonolactone}$ with Sodium Borohydride

Solid  $\gamma$ -D-allonolactone (20.19 gm.) (m.p. 98-123° C.) was dissolved in 40 ml. of water, and added dropwise to a solution containing 5.0 gm. of sodium borohydride in 65 ml. of water which was cooled in an ice-bath, and magnetically stirred. Throughout the reaction period of 145 minutes, the temperature was kept below 20° C. The rate of evolution of hydrogen was quite rapid at first, but gradually diminished. The initial pH of the solution was 7, and the final 8. The excess borohydride was then destroyed by the dropwise addition of 6 N sulfuric acid after which the solution gave a positive reducing sugar test with red tetrazolium. The treatment with sodium borohydride was repeated. Tests with red tetrazolium and Fehling's solution after the second reduction were negative. The solution was then concentrated to a heavy syrup which contained some crystalline material. This syrup was concentrated to dryness eight times with methanol to remove the boric acid, and then dissolved in warm water, and allowed to stand over phosphorus pentoxide in a vacuum desiccator.

## H. The Nitration of Allitol

# 1. Nitration with Fuming Nitric and Sulfuric Acids

Allitol (0.097 gm.) was pulverized to a white powder with a stirring rod, and added in small portions to 0.33 ml. of fuming nitric

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acid (d. 1.49 - 1.50) previously cooled in an ice-salt-bath. The mixture was stirred after each addition until all of the allitol was in solution. The reaction test-tube was kept in the ice-salt-bath throughout the procedure. Concentrated sulfuric acid (0.55 ml.) was then added dropwise with stirring to the mixture, and at this point, the solution became opaque. The mixture was allowed to stand in the ice-salt-bath for 15 minutes after which an additional 0.05 ml. of concentrated sulfuric acid were added. It appeared that the nitrate had separated as a syrup. The mixture was poured with stirring into 30 ml. of ice-water, and a heavy, viscous, colourless syrup separated, which did not crystallize after scratching with a glass rod for several minutes.

The aqueous mixture was then extracted with three 12 ml. portions of chloroform. The chloroform extract was washed with water, 10% sodium bicarbonate solution, and again with water, and dried over anhydrous magnesium sulfate. The dried chloroform solution was evaporated to give 0.156 gm. of dry, crude, syrupy material. After standing for several days, the syrup became very slightly yellow in colour; no odour of oxides of nitrogen could be detected. The syrup was dissolved in cold ether, and allowed to stand in an ice-salt-bath. n-Pentane which had been cooled in the ice-salt-bath was added to the ether solution dropwise until a cloudiness just persisted. The solution was then allowed to stand at room temperature, and, after several days, no crystallization had occurred. The syrup was redissolved in ether, and n-pentane added until turbid, but this time at room temperature. The solution on standing in the

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refrigerator for several hours deposited prismatic crystals. These were removed by suction filtration, and air-dried. They melted at 57.5-58.0° C., and were obtained in a yield of 0.087 gm. (36.3%). After several recrystallizations from aqueous ethanol, a constant melting point of 59.0-59.5° C. was obtained. From the mother liquor of the original crystallization, some syrupy material was obtained which has resisted all attempts at crystallization. A nitrogen analysis of the pure allitol hexanitrate by the Dumas method (8) gave the following result: Found: N, 18.5, 17.8, 19.7, 18.8%. Calc. for hexitol hexanitrate, C<sub>6</sub> H<sub>8</sub> N<sub>6</sub> O<sub>18</sub>: N, 18.6%. Calc. for hexitol pentanitrate, C<sub>6</sub> H<sub>9</sub> N<sub>5</sub> O<sub>16</sub>: N, 17.2%.

# 2. Nitration with Fuming Nitric Acid and Acetic Anhydride

Powdered allitol (0.199 gm.) was placed in a 15 ml. testtube with 1.82 ml. of acetic anhydride, and cooled to a temperature below  $0^{\circ}$  C. in an ice-salt-bath. A mixture of 1.82 ml. of acetic anhydride and 0.73 ml. of fuming nitric acid (d. 1.49-1.50) was prepared, and cooled to a temperature below  $0^{\circ}$  C., and then added to the above suspension of allitol, and the resulting mixture kept at about  $0^{\circ}$  C. in the ice-salt-bath for one hour with occasional agitation. The test-tube was then removed, and allowed to come to room temperature over a period of 15 minutes. At the bottom of the test-tube, there was a small amount of white crystalline material. The mixture was then poured into approximately 75 ml. of ice-water with stirring. A syrup immediately separated, and the mixture was allowed to stand overnight in the refrigerator.

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The aqueous mixture was extracted three times with 25 ml. of ether; the ether extract was washed with 50 ml. of water, 50 ml. of 10% sodium bicarbonate solution, a final 50 ml. of water, and was dried for 3.5 hours over anhydrous magnesium sulfate which was subsequently removed by filtration. The ether solution was concentrated to 0.448 gm. of syrup which partially crystallized on drying <u>in vacuo</u> over phosphorus pentoxide. The partially crystalline product was recrystallized from alcohol, and pure allitol hexanitrate was obtained in a yield of 0.292 gm. (59.1%), melting at 59.0-59.5° C. The mother liquors, on evaporation, left a syrupy residue which has not been obtained in crystalline form.

The sample of allitol hexanitrate was stored in a glass vial with a polyethylene cap at room temperature. After it had been standing for six weeks, it slowly decomposed with the evolution of dense, red-brown fumes of nitrogen dioxide. A sample of D-mannitol hexanitrate standing beside the allitol hexanitrate sample showed no signs of decomposition.

# I. The Reaction of Pyridine with Allitol Hexanitrate

A sample of crystalline allitol hexanitrate (0.047 gm.) was powdered with a stirring rod in a test-tube, and 0.34 ml. of dry pyridine was added. Within two minutes all of the allitol hexanitrate had dissolved forming a clear, colourless solution at room temperature ( $27^{\circ}$  C.). Within five minutes the solution began to take on a yellow colour, and after standing for twenty minutes, long, fine, needle-like crystals of pyridinium nitrate had formed on the inner walls of the test-tube above the surface of

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the solution. Throughout the reaction, no temperature increase could be detected, and no bubbles of gas were observed. After standing overnight, the colour of the solution had darkened considerably, and was now amber.

Water (5.0 ml.) was added with stirring to the solution, and a syrup separated which could not be induced to crystallize by scratching with a glass rod. After standing several hours, a seed of allitol hexanitrate was added, and the aqueous mixture was allowed to stand overnight, but crystallization did not occur. The aqueous mixture was extracted with three 10 ml. portions of ether. The ether extract was washed with 10 ml. of 10% hydrochloric acid, 10 ml. of water, and evaporated, and the resulting syrup dried <u>in vacuo</u> over phosphorus pentoxide. There resulted 0.032 gm. (76.2%) of yellow syrup which may possibly be allitol pentanitrate.

In a parallel reaction a powdered sample of D-mannitol hexanitrate (0.052 gm.) was treated with 0.37 ml. of pyridine, and a clear, colourless solution was obtained immediately. Within two minutes, the solution took on a yellow colour, and the evolution of gas bubbles was observed. Within fourteen minutes crystals of pyridinium nitrate had appeared on the inner walls of the test-tube above the surface of the solution. After standing overnight, the colour of the solution had darkened considerably, and was slightly darker than that of the allitol hexanitrate.

Water (5.0 ml.) was added with stirring to the solution, and a white precipitate was immediately obtained which was removed by suction filtration, and dried <u>in vacuo</u> over phosphorus pentoxide. There was obtained 0.029 gm. (61.7%) of crude, crystalline D-mannitol pentanitrate

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with a melting point of 77.5 - 80.5° C. The reported melting point was  $81 - 82^{\circ}$  C. (22).

# J. The Preparation of Allitol Hexaacetate

Pyridine (0.6 ml.) and 0.6 ml. of acetic anhydride were added to 0.060 gm. of pure crystalline allitol, and the mixture was heated in a water-bath at 65° C. for ten minutes. Since the allitol had not completely dissolved, pyridine and acetic anhydride were added in equal volumes, and the temperature of the water-bath increased to 70° C. until all of the allitol had dissolved. This required a total heating period of forty minutes and a total volume of 1.0 ml. of pyridine and 1.0 ml. of acetic anhydride. The flask was fitted with a calcium chloride drying-tube, and allowed to stand for 24 hours at room temperature.

The solution was then poured into 125 ml. of ice-water with constant stirring, and the resulting mixture allowed to stand in the refrigerator for two days. At the end of this period, solid material had deposited on the inner walls of the beaker. The aqueous mixture was extracted three times with chloroform, and the extract after drying over anhydrous magnesium sulfate was concentrated to a syrup which on drying over phosphorus pentoxide <u>in vacuo</u> partially crystallized, yielding 0.144 gm. of crude allitol hexaacetate. After several attempts this material was recrystallized from aqueous ethanol. Long, thin needles of allitol hexaacetate with a melting point of 62.0 - 62.5° C. were obtained in a yield of 0.083 gm. (58.0%). The melting point was reported as 61° C. (44) and 61 - 62°C. (71). Found: C, 50.77%; H, 6.23%. Calc. for  $C_{18}$  H<sub>26</sub>Q<sub>2</sub>:

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C, 49.76%; H, 6.04%. The molecular weight was determined by the Rast method (8) using the lactam of <u>p</u>-aminohexahydrobenzoic acid as the solvent. Found: 437,446. Calc. for  $C_{18}$  H<sub>26</sub> O<sub>12</sub>: 434.

From a sample of crude allitol, 0.20 gm. of crude allitol hexaacetate was obtained in the same manner as described above. This material was recrystallized from aqueous ethanol and melted at 60-61° C. A second sample of crude allitol (0.49 gm.) was reluxed with 3.5 ml. of acetic anhydride for 12 hours. Within a few minutes, the solution became orange-brown in colour, and at the end of the reflux period some dark brown, solid material was present. The reaction mixture was poured into 50 ml. of ice-water, and allowed to stand in the refrigerator for two days. A dark brown syrup separated, and the aqueous mixture was extracted three times with chloroform. The dried chloroform solution was concentrated to a brown syrup which after repeated attempts has not crystallized from aqueous ethanol.

#### K. The Preparation of D-Altritol

The specific rotation of the pure calcium-D-altronate was observed to be  $\left[\alpha\right]_{D}^{19}$  - 2.02° (c, 1.79; l, 1; H<sub>2</sub>O). The reported specific rotation for calcium-D-altronate hemiheptahydrate was  $\left[\alpha\right]_{D}^{20}$  - 2.4° (c, 1.8; H<sub>2</sub>O) (46).

Calcium-D-Altronate (29.79 gm.) was dissolved in 400 ml. of hot water, and passed through the ion exchange column in the hydrogen cycle. The column was washed with 500 ml. of hot water to remove any

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material which might have crystallized in the column, and then with cold water. The total eluate was concentrated to a syrup which was dried <u>in vacuo</u> over phosphorus pentoxide. There was obtained 22.33 gm. (164.5%) of crude, yellow, syrupy D-altronic acid which probably contained some of the corresponding lactone (37).

A sample of the above product (1.01 gm.) was treated for 20 minutes with 0.2 gm. of sodium borohydride as previously described for  $\sqrt{-D}$ -allonolactone. A white amorphous material was obtained after concentration and treatment with methanol, which did not become syrupy on standing in the open air. D-Altritol has been reported to be hygroscopic (10), (11). This material was then dissolved in aqueous ethanol, and this solution gave a positive reducing test with Fehling's solution and with red tetrazolium reagent. The treatment with sodium borohydride was repeated, and this time the solution exhibited no reducing power, and was allowed to stand <u>in vacuo</u> over anhydrous calcium chloride. Some crystalline inorganic material has been removed, but the syrupy material has not crystallized.

# L. The Reduction of $\sqrt{-D-Galactonolactone}$ with Raney Nickel

 $\gamma$ -D-Galactonolactone (1.0 gm.) in aqueous ethanol solution was treated as described for D-allose with 10 gm. of Raney nickel. There was obtained 0.028 gm. (2.7%) of dulcitol with a melting point of 184-185° C. after two recrystallizations from aqueous ethanol. The reported melting point of dulcitol was 188.5-189.0° C. (44). The product was chromato-

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graphed on paper as described previously, and gave a single spot identical to that displayed by dulcitol.

In a second run with 2.0 gm. of  $\sqrt{-D}$ -galactonolactone, dulcitol was obtained in a yield of 0.110 gm. (5.4%). After recrystallization from aqueous ethanol, the material melted at 179-181° C. A mixed melting point with  $\sqrt{-D}$ -galactonolactone was about 135° C. whereas with an authentic sample of dulcitol, the mixted melting point was 181-185° C.

In a third run with a 1.5 gm. sample of  $\gamma$ -D-galactonolactone, the reflux period was 6 hours, and crystalline material was obtained in a yield of 0.068 gm. (4.4%) with a melting point of 187.5 - 188.0° C.

### M. The Reduction of D-Mannose with Raney Nickel

D-Mannose (0.65 gm.) was treated with approximately 5 gm. of Raney nickel as described for D-allose. A crude yield of 0.96 gm. of D-mannitol was obtained. This was recrystallized from aqueous ethanol and 0.31 gm. (47.2%) of material melting at 163 - 164° C. was obtained. A second recrystallization increased the melting point to 166 - 167° C. The reported melting point of D-mannitol was 165 - 166° C. (44).

# N. The Reduction of $\sqrt{-D}$ -Galactonolactone with Sodium Borohydride

 $\gamma$ -D-Galactonolactone (1.00 gm.) was treated with sodium borohydride in the manner previously described. Recrystallized dulcitol with a melting point of 183 - 187°C. was obtained in a yield of 0.49 gm. (48.0%). The mother liquors gave a positive test for reducing sugar with red tetrazolium.

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D-Galactose (1.0 gm.) was treated with sodium borohydride in the manner described by Abdel-Akher, Hamilton and Smith (1). Crystalline dulcitol was obtained in a yield of 0.34 gm. (33.9%). On recrystallization from ethanol, this material melted at 187.5 - 188.5° C. The mother liquors gave a positive reducing sugar test with red tetrazolium.

## P. The Preparation of D-Mannitol Hexanitrate

D-Mannitol (0.100 gm.) was nitrated according to the procedure of Patterson and Todd (41). Recrystallization from aqueous ethanol yielded 0.174 gm. (70.4%) of crystalline D-mannitol hexanitrate with a melting point of 109 - 110° C. The reported melting point was 111 - 112° C. (22).

#### CLAIMS TO ORIGINAL RESEARCH

- 1. Two routes for the synthesis of allitol from D-ribose have been investigated and pure crystalline allitol was obtained and characterized.
- 2. Crystalline allitol hexanitrate was synthesized for the first time by the nitration of allitol with fuming nitric and sulfuric acids, or with fuming nitric acid and acetic anhydride.
- 3. Preliminary experiments indicated that allitol hexanitrate reacted slowly at room temperature with dry pyridine, possibly suffering partial denitration.
- 4. The Raney nickel method of reduction of aldoses to alditols was extended to the reduction of D-allose to allitol.
- 5. The nitromethane condensation with D-ribose was reinvestigated and it was found that a considerable portion of the D-ribose did not react. A partial separation of the components of the reaction mixture was obtained on adsorption chromatography columns.
- 6. Some studies were made of the reduction of aldoses and aldonolactones with sodium borohydride in aqueous solution.

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