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The ring structure in some derivatives of sorbose

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THE RING STRUCTURE IN SOME DERIVATIVES OF SORBOSE

By

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Approved

Signature was redacted for privacy.

In charge of Major work

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Dean of the Graduate College

Iowa State College

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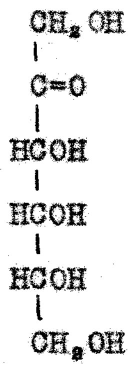
HISTORY OF THE KETOSES

It is reasonable that in the realm of the simple saccharides the ketose sugars should hold the same high esteem as do the aldose sugars. Knowledge of the aldose sugars has been far advanced and their chemistry well established. Of the ketose sugars only one, fructose, a ketohexose, has been studied to any extent. This hiatus in the understanding of the simple saccharides can be attributed to the unavailability of the ketoses. Little by little, however, the ketoses are being studied and their characterization is now beginning to supplement aldose chemistry and to produce a more complete understanding of the simple saccharides. Such a complete understanding of monosaccharides is needful for on such knowledge rests the true structural interpretation of the complex polysaccharides, and of still higher importance, an understanding of the ultimate biologic processes.

Structurally the ketose sugars differ from the aldose sugars by the submergence of the carbonyl group from an end position to an internal position in the carbon chain. Generally, the carbonyl group accedes to a penultimate location in the carbon chain giving rise to the usual structures commonly ascribed to ketose sugars. Such structures will be the only ones dealt with in this dissertation.

As evidenced from the number of assymetric carbon atoms, there are possible eight ketohexoses, four ketopentoses, two ketotetroses and one ketotriose. These monosaccharides have the configurations shown below.



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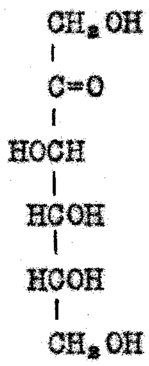

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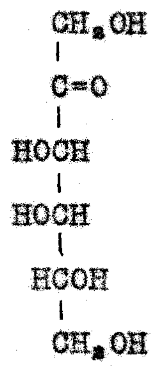

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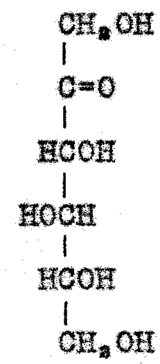

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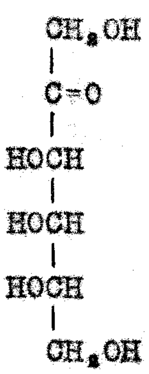

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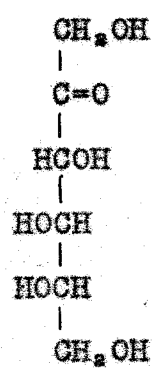

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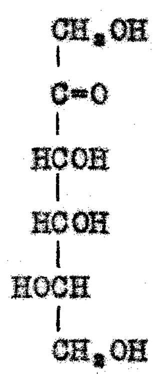

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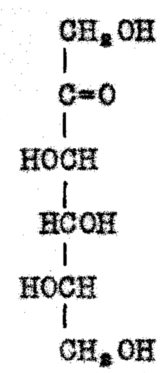

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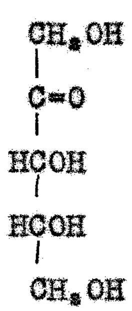
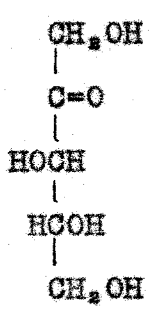


d-Araboketose



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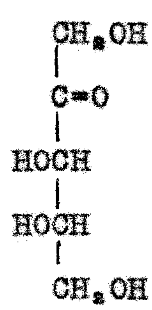

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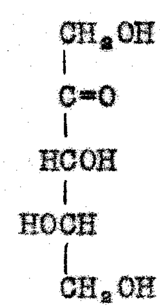


l-Xyloketose

d-Erythrulose	l-Erythrulose	Dihydroxyacetone
CH_2OH	CH_2OH	CH_2OH
|	|	|
C=O	C=O	C=O
|	|	|
HCOH	HOCH	CH_2OH
|	|	
CH_2OH	CH_2OH	

d-Erythrulose is not known. l-Erythrulose (described as d-erythrulose in the older literature) has been obtained as a sirup showing a specific rotation in water of $[\alpha]$ +11.4°.(1) It is not attacked by yeast. The ketose can be prepared through the use of Bacterium xylinum (2,3,4) or acetobacter (5) acting on a 4% solution of l-erythitol. The sugar quickly reduces Fehling's solution. It can be precipitated with sodium bisulfite giving the addition compound. This reaction definitely shows open chain structure for the addition compound and indicates little or no tendency for the sugar to be stabilized as a lactol ring.

No ketopentoses are known in a pure crystalline form. Those recorded in the literature are probably mixtures of isomeric forms. Bacterium xylinum oxidizes arabitol (6) to araboketose. l-Xyloketose has been found in urine during pentosuria (7-10). This sugar in water shows a specific rotation of +34.8°. It reduces Fehling's solution more rapidly than does glucose. d-Xyloketose has been produced lately (11) by heating d-xylose in dry pyridine and shows a specific rotation of -33.2° in water solution.

d-Tagatose has been prepared by the rearrangement of d-galactose through treatment with 6% calcium hydroxide (12-14). More recently d-tagatose has been prepared by the epimerization of β-d-galactose (15) in dry pyridine with subsequent fermentation of the remaining galactose to alcohol. The crystalline sugar has a melting point of 162° and an optical rotation of $[\alpha]^{20}_{578}$ - 3.9° in water and shows a mutarotation (in 25 minutes) of +0.37° in the negative direction; thereby indicating an alpha configuration for the crystalline sugar. The diacetone derivative has been prepared (16). Methylation of tagatose (17) by Fischer's method yields α-Methyl tagatoside which has a melting point of 128° and a rotation in water of $[\alpha]^{70}_{578}$ + 56.8. Complete methylation gives a poor yield of pentamethyl tagatose $[\alpha]^{20}_{578}$+21.4° (in methanol) which can be hydrolyzed to a tetramethyl tagatose $[\alpha]^{20}_{578}$-3.4° (in methanol). Acetylation of the sugar, employing the usual procedures of acetylation, yields a pentaacetate of melting point 132° and rotation $[\alpha]^{20}_{578}$+20.2° when dissolved in chloroform, or -25° when dissolved in methanol (18). This pentaacetate is not reduced by Raney's catalyst and is believed to be a ring form, although no proof of ring structure for tagatose or its derivatives has yet been given. l-Tagatose is reported as being formed by the action of alkali on l-sorbose (19). Recently, Glatthaar and Reichstein (20) by means of an ingenius series of reactions, have converted d-galacturonic acid into l-tagatose.

Two other presumably ketose sugars, glutose (21, 22) and galtose (23) have been recorded but are of doubtful nature. One of these may be the missing ketoallose, psicose, or perhaps one may be a ketose wherein the ketone group is on carbon atom three.

Fructose, the only ketose monosaccharide occurring in nature, will not be considered here. This sugar has been well studied. In fact, practically all of our knowledge of ketose reactivity has arisen from a study of fructose. Yet such interpretation of ketose chemistry must be held with some reserve since it is doubtful if fructose is truly representative of these sugars. Certain isolated facts arising out of the evolutionary study of other ketoses would tend to show fructose as an exception to general ketose chemistry rather than as a possessor of the representative properties of the family. With these facts in mind, it is well to proceed with a study of the history and chemistry of the ketose sorbose.

HISTORY AND CHEMISTRY OF SORBOSE

Sorbose is not commonly found in nature. It is produced as the result of controlled fermentation processes from the naturally occurring alcohol sorbitol. Pelouze (24, 25) in 1852 analyzed the juice of the mountain ash berries and found them to contain malic acid, calcium malate, glucose and a sugar differing in properties from those previously known. The juice of the berries was left in earthen vessels for thirteen to fourteen months. The clear supernatent liquid remaining was decanted and evaporated by gentle heat to a thick sirup. From this sirup brown crystals were deposited which were decolorized by bone black. Upon repeated recrystallization Pelouze obtained what he believed to be a pure crystalline sugar which he called sorbine (sorbose). This sugar possessed the molecular formula $C_6H_{12}O_6$ and, hence, was a monosaccharide. It could not be fermented by yeast and was not attacked by dilute acid although it turned brown and was decomposed by alkali. It rapidly reduced Fehling's solution. The optical rotation was recorded as $[\alpha]_R$ - 35.97°. The crystals were rectangular octohedrons belonging to the right prismatic system and had a density at 15° of 1.654.

Long heating at 150-180° gave an amorphous acid substance of deep red color, which was called sorbic acid. Sorbose in fermented mountain ash berries was later observed by Byschl (26) and Berthelot (27). Delffs (28) in 1871 concluded that sorbose is not present in the original juice but is formed during the fermentation. However, since Delffs believed that sorbine belonged to the same group as mannitol, quercitol, dulcitol and persitol, it may be that he did not find sorbose but was dealing with sorbitol. Boussengault (29) found sorbitol in the freshly expressed juice, thereby demonstrating that this alcohol was not a product of fermentation. Through the use of zymitic processes, sorbose has been obtained by many workers using several bacteria but mainly <u>Bacterium xylinum</u> and <u>Acetobacter</u> (30-43). Kiliani and Schreibler (44) studied the constitution of sorbose and recognized it as a ketose. Vincent and Delachanal (45) obtained sorbitol by the reduction of sorbose with the use of sodium amalgam as the reducing agent. From this reaction it appeared possible to produce sorbose through oxidation of sorbitol.

Freund (46) also concluded sorbose to be formed by the fermentation of sorbitol in the juice of the mountain ash berry. This viewpoint has been contested by Lippman (47) who claimed that the gum over wounds in the mountain ash could be hydrolyzed to yield sorbose. These findings would suggest the natural occurrence of sorbose, but they cannot be interpreted as presenting facts antagonistic to the beliefs that sorbose may result from the fermentation of sorbitol in the juice of the mountain ash berries.

In 1904 Bertrand (48-50) published a lengthy review in which he drew several conclusions in regard to the known chemistry of sorbose.

1. Sorbose does not pre-exist in mountain ash berries but is formed by the oxidation of sorbitol under the influence of sorbose bacterium.
2. The structure of sorbose is $CH_2OHCHOHCHOHCHOHCOCH_2OH$
3. Since ketoses can be transformed by reduction to a mixture of two stereoisomeric alcohols of which one is identical with the original alcohol from which the ketose is derived, a method is at hand for transforming certain polyhydric alcohols into <u>d</u>-iditol.
4. The bacterium together with reduction may be employed as a means of going from an aldose to a ketose.

Schlubach and Vorwerk (41) using Bertrand's method, greatly increased the yield of sorbose. They obtained between 50 and 75 per cent conversion of sorbitol. The sugar was obtained in the form of large rhombohedral crystals melting at 159-161° and had a specific rotation of $[\alpha]^{18}_{D}$ - 43.1° in water.

A special study of sorbose production by means of bacteria was made by Fulmer (51) and his co-workers, wherein it was found that a fifteen per cent concentration of sorbitol was optimum; the conversion to sorbose being about eighty per cent. In this work the use of Acetobacter suboxydans proved to be more expedient than Acetobacter xylinum, since the purification and separation of the sugar was more easily effected when the former bacteria were used. Employing the methods of Fulmer the U. S. Agricultural By-Products Laboratory (52) has studied the large scale production of sorbose and has successfully prepared this sugar in large quantities.

Of theoretical significance is the preparation of l-sorbose through the oxidative action of bromine water (53, 54) and of formaldehyde (55,56) on d-sorbitol.

Dilute alkali converts l-sorbose to l-galactose, l-gulose, and l-idose (57). Reduction of the sugar by the use of sodium-amalgam produces the expected mixture of d-sorbitol and l-iditol (57). The phenylosazone (58, 59) of l-sorbose is identical with the osazones of l-gulose and l-idose (melting point 164°). Nitric acid oxidation of the sugar yields xylotrihydroxyglutaric acid (44). On heating with acid there is produced laevulinic acid, humic material, and furfural (60, 61). l-sorbose is said to be converted to glycocollic acid on treatment with chlorine and silver oxide (62). Yeast does not attack the pure sugar (62). l-sorbose gives the fructose-reaction with resorcinol and hydrochloric acid (60, 61) and is colored a purple red with an ether-bromine-water mixture (63). The p-bromophenylosazone (64) and the o-nitrophenylosazone (65) have been prepared in the crystalline form. Tables have been prepared (66) for the quantitative determination of l-sorbose by means of Fehling's solution.

Mutarotation of l-sorbose was not observed by the earlier workers (14, 41, 67). Smith and Tollens (61) found that the rotation increased with increasing concentration; the specific rotation being -42.4° at five per cent concentration and -44.8° at forty per cent concentration in water at room temperature. They further observed a decrease in specific rotation with rise in temperature; the rotations as compared to those above being

-39.1° at five per cent concentration and -40.6° at forty per cent concentration in water at 80°C. Recently a careful study of sorbose rotational values was undertaken by the U. S. Bureau of Standards (68). Through the use of concentrated solutions of pure sorbose in water it was found that the rotation increased slightly and then decreased so that the initial and final rotations were not widely different; the change being about 0.7° S. Mutarotation was found to be essentially complete in one hundred and twenty minutes. Exact specific rotations were found to be $[\alpha]_D^{0.4}$ - 43.3° and $[\alpha]_D^{20}$ - 43.4° at a concentration corresponding to twelve grams of sorbose in one hundred cubic centimeters of solution.

α-Methyl-l-sorboside was early prepared by Emil Fischer (69) using his versital method of shaking the pure sugar with a one-half to one per cent solution of dry hydrochloric acid gas dissolved in methanol. This sorboside had a melting point of 120-122° C. and a rotation of $[\alpha]_D^{20}$ - 88.7° in water. This compound was later studied by Arragon (70). It is not attacked by yeast or emulsin. Recently the stereoismeric β-methyl-l-sorboside (71) which has a melting point of 106.2° C. and a specific rotation of $[\alpha]_D^{20}$ - 39° (in water) has been prepared through the deacetylation of the β-methyl-l-sorboside tetraacetate of melting point 75° C. and rotation $[\alpha]_D^{20}$ - 79.8° (in chloroform). The last compound was prepared through the action of methanol, silver carbonate and silver nitrate on α-acetochlorosorbose of melting point 67°C. and rotation of $[\alpha]_D^{20}$ - 83.8° in chloroform. The α-acetochlorosorbose was prepared by treating α-sorbose tetraacetate (72, 73) with liquid hydrochloric acid for two hours at 0°C. in a glass bomb.

Through the direct acetylation of sorbose, Schluback and Vorwerk (41) obtained a crystalline pentaacetate having a melting point of 97.5°C. and a specific rotation of $[\alpha]_D^{18}$ - 2.9° in chloroform. This acetate was later obtained by Arragon (72) and was believed to be the α-pentaacetate. However, in opposition to fructose and other sugars this compound did not form the expected halogenose. The compound further showed strong reduction to Fehling's solution. Thus it appeared possible that the acetate was a derivative of the open-chain form of sorbose. That such was the case has lately been proven by Cramer and Pacsu (74) when they were able to hydrogenate this acetate using platinum suspended in ether solution, and then, after acetylation of the products, to obtain the hexaacetates of <u>d</u>-sorbitol and <u>l</u>-iditol. What is thought to be the true α-sorbose pentaacetate (75) has been prepared through the further acetylation of sorbose tetraacetate using acetic anhydride and two per cent sulfuric acid at 5° C. The substance showed a melting point of 95° C. and a rotation of $[\alpha]^{20}_{5780}$ - 52.4° . The α- sorbose pentaacetate (71) was prepared through the action of acetic anhydride and silver acetate on α- acetochlorosorbose. This pentaacetate showed a melting point of 113.8° C. and a rotation of $[\alpha]^{20}_{D}$ - 74.4° in chloroform.

α-Methyl-l-sorbose tetraacetate of melting point 88° C. and rotation of $[\alpha]_{D}$ -31.8° has been prepared both by the methylation of α-sorbose tetraacetate and by the acetylation of α-methyl-l-sorboside (70).

Using the general procedures for methylation Arragon (76) has methylated α-methyl-l-sorboside to a pentamethyl derivative showing the following constants; N_{19} 1.4475, D_{19} 1.108, $[\alpha]^{20}_{5780}$ - 31.5°(in methanol). This compound could be hydrolyzed to a α- tetramethyl sorbose $[\alpha]^{70}_{5780}$ - 4.9° (in methanol) and an β-tetramethyl derivative $[\alpha]^{20}_{5780}$ - 3.6°(in methanol). Methylation of the β-tetramethyl sorbose formed a second pentamethyl sorbose $[\alpha]^{20}_{5780}$ - 11.8° (in methanol).

4-Methoxy-l-sorbose (77) has been recorded. Trioxymethylene reacting on sorbose produces a monomethylene compound (78) of melting point 54° C. and rotation of $[\alpha]_{D}$ - 25°

in water. Compounds of sorbose with bromal (79), resorcinol (80) and phloroglucinol (81) have been reported. Sorbose also takes up hydrocyanic acid to produce a crystalline product (44). A trinitrate of sorbose anhydride has been reported (82).

As an intermediate in the synthesis of vitamin C, Reichstein and Grüssner have prepared 2,3,4,6-diacetone sorbose (42).

d-Sorbose in the older literature was designated l-sorbose. The d-modification has been prepared (57) through the rearrangement of d-galactose in alkali. When the products were dissolved in methanol-analine solution d-sorbose was the first to crystallize. It showed a melting point of 164°C. and a rotation of $[\alpha]_D^{20}$ + 42.9° (in water). The sugar has also been obtained through the rearrangement of d-gulose or d-iodose (39). Reduction of d-sorbose by sodium-amalgam produced d-iditol and d-sorbitol. The α-methyl-d-sorboside showed a melting point of 119°C and a rotation of $[\alpha]_D$ + 88.5° (in water). Monomethylene d-sorbose of melting point 81°C. and rotation of $[\alpha]_D$ + 25° has been produced. The phenylosazone of melting point 168° C. is identical with that of gulosazone and d-idosazone.

STATEMENT OF THE PROBLEM; DISCUSSION OF RESULTS.

With the sole exceptions of diacetone sorbose and the open-chain pentaacetate, the ring structures for l-sorbose and its derivatives have remained undetermined. It has been the purpose of the work herein discussed to supply a precise structural background to this field. This has, in part, been done through theoretical considerations and through exact chemical methods.

Among the central compounds of the simple sugars are the glycosides, and any precise development of monosaccharide chemistry based upon strict constitutional assignment must in general be referred to these compounds. Thus, the assertion of their structure is of first importance. The recent development of sorbose chemistry has excluded such structural assignment, although methyl-l-sorboside (69) was one of the earliest known derivatives of sorbose. The high negative rotation (-88.7°) compared with that for pure sorbose (-43.4°) indicates that this glycoside is an alpha modification (83).

Since ethylene oxide rings have never been known to form under the usual conditions for glycoside formation, and since the molecular length of a ketohexose molecule does not permit the production of a septanoid ring, the structure of α-methyl-l-sorboside must contain either a furanoid or pyranoid ring. Wherever a sugar is found to produce glycosides containing six membered rings and also glycosides containing five membered rings, the glycosides possessing the smaller rings have shown, in every case, higher rates of hydrolysis when compared to those possessing the larger or pyranoid ring. To be strictly comparable the aglucon must be the same for the two compared rings in the same sugar, and, moreover, the glycosides must be of the same alpha or beta isomeric types. Rates of hydrolysis are then valuable in serving to distinguish glycosides containing the stable pyranoid ring from those containing the unstable furanoid ring. Rates of hydrolysis, however, do not remain the same as one passes from sugar to sugar. That is to say, α-methyl-d-mannoside does not hydrolyze at the same rate as does α-methyl-d-glucoside. This is reasonable since the contribution toward reactivity by the assymmetric centers will have different values in the different sugars. No definite conclusion concerning ring structure could, therefore, be drawn unless there existed two α-methyl-l-sorbosides showing among their other properties different rates of hydrolysis. The occurrence of only one α-methyl-l-sorboside excluded any exact interpretation of hydrolysis data as regarded the assignment of ring structure. The information was, however, not without some value and so the hydrolysis of the known crystalline α-methyl-l-sorboside was studied.

When pure crystalline α-methyl-l-sorboside was dissolved in distilled water it gave no reduction with Fehling's solution even after standing for five days. Neither was reduction toward Fehling's solution evidenced when the sorboside was allowed to stand with hundredth normal hydrochloric acid for six hours. However, a copious precipitate of cuprous oxide occurred when the glycoside was boiled one minute in tenth normal hydrochloric acid and then tested with Fehling's solution. At a temperature of 30°C. and a concentration of eight-tenths of one per cent it was found that α-methyl-l-sorboside was completely hydrolyzed in 1.75 normal hydrochloric acid in less than one day. In 0.102 normal hydrochloric acid the hydrolysis was completed in nine to ten days. In 0.017 normal acid completion of hydrolysis occurred in about thirty days. The true end point of this latter hydrolysis was indefinite due to mold growth which became noticeable after twenty-eight days. The general shape of the hydrolysis curve for this last case is shown in Figure 1. This curve suggested that the hydrolysis was a first order reaction. The velocity constant was calculated to be 0.049, when time was taken in days. This gave a half period of fourteen and two-tenths days.

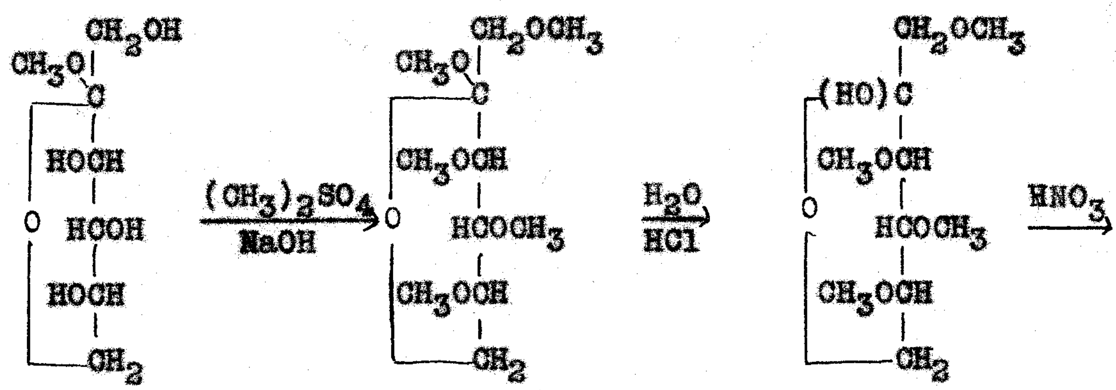
Menzies' (84) examination of methyl-d-fructofuranoside showed that this sugar exhibited perceptible reduction toward Fehling's solution after standing in distilled water for six hours. On standing six hours in one-hundredth normal hydrochloric acid, marked evidence of hydrolysis was shown when tested with Fehling's solution. At a concentration of nine-tenths of one per cent in 0.011 normal sulfuric acid and at a temperature of 20°C. methyl-d-fructofuranoside was completely hydrolyzed in less than twenty-seven days. Although complete data concerning the hydrolysis of methyl-d-fructopyranoside do not seem to have been published, yet it is known that this glycoside is quite stable toward hydrolysis even against relatively high acid concentrations.

This data indicated that whereas δ-methyl-l-sorboside did not show the extreme stability of methyl-d-fructopuranoside, it was evidently more stable to hydrolysis than methyl-d-fructofuranoside. Although the number of days required for the complete hydrolysis of methyl-d-fructofuranoside and of α-methyl-l-sorboside did not differ greatly, it must be noted that the hydrolysis of the sorboside was carried out at 30°C. in contrast to the lower temperature of 20°C. used for methyl-d-fructofuranoside. Had the hydrolysis of α-methyl-l-sorboside been carried out at 20°C. the time for completion of the reaction would have been greatly extended.

These comparisons might possibly point to α-methyl-l-sorboside as containing the more stable or pyranoid ring. Yet, such data cannot be relied upon because of the previously stated reason that hydrolytic studies are not strictly comparable between the various sugars. For exact constitutional proof of the ring structure recourse was made to the well established methods of oxidative degradation. For this purpose pure crystalline α-methyl-l-sorboside (I or VI) was methylated to produce a liquid pentamethyl sorbose (II or VII). This completely methylated sugar was hydrolyzed by hot two per cent hydrochloric acid to produce a tetramethyl derivative (III or VIII).*

*At the time of these preparations the pentamethyl-l-sorbose and the tetramethyl-l-sorbose were the first methylated derivatives of sorbose known. The optical rotations were taken in chloroform. A paper by Arragon (76) soon appeared announcing the preparation of these same derivatives but with rotations recorded in methanol. For comparison with Arrogon's work the optical rotations of the penta-methyl and tetramethyl sorbose were repeated in methanol. Confirmation of Arragon's rotations was obtained.

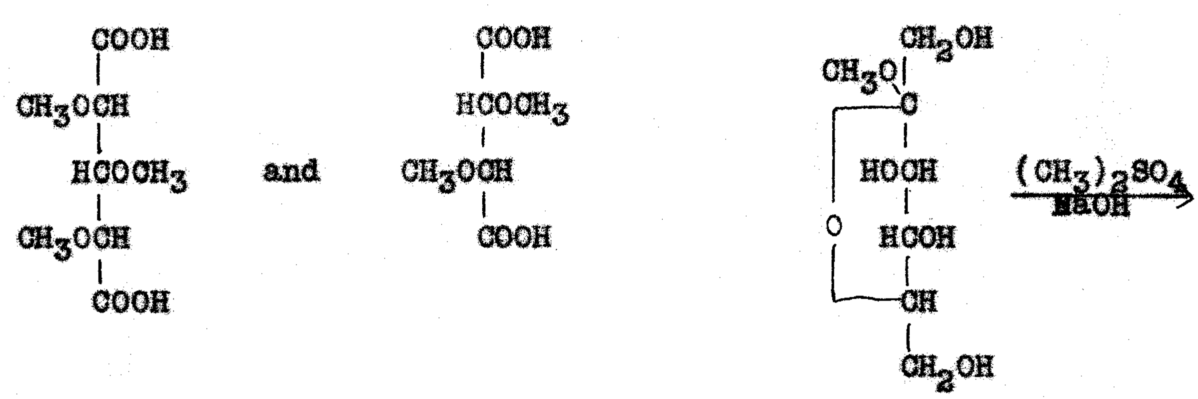
Since it is known (85) that in such a series of reactions the ring form remains unaltered, the tetramethyl sugar must have contained a ring identical with that possessed by δ-methyl-l-sorboside.



δ-Methyl-l-sorbopyranoside (I)

1:2:3:4:5. Penta-methyl-l-sorbose (II)

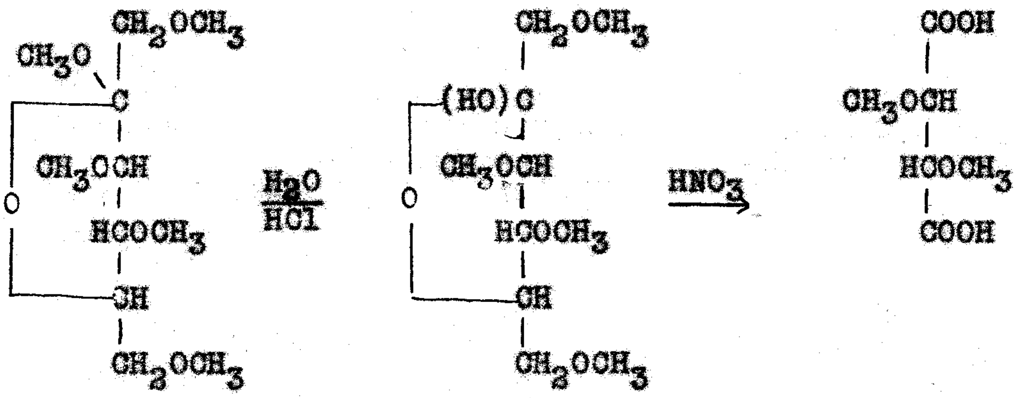
1:3:4:5. Tetra-methyl-l-sorbose (III)



Xytolrimethoxy-glutaric acid (IV)

Dextro-Dimethoxy-succinic acid (V)

δ-Methyl-l-sorbofuranoside (VI)



1:2:3:4:6. Pentamethyl-l-sorbose (VII) | 1:3:4:6. Tetramethyl-l-sorbose (VIII) | Levo-Dimethoxysuccinic acid (IX)

The tetramethyl-l-sorbose was oxidized by concentrated nitric acid to dextro-dimethoxysuccinic acid. The latter product was obtained in good yield. No intermediate products of oxidation corresponding to those of fructose (86) were isolated. However, the presence of dextro-dimethoxysuccinic acid alone sufficed for the certain allocation of the lactol ring if consideration of an ethylene oxide structure were forgone.

If the oxygen bridge engaged carbon atom five (VIII) a large yield of levo-dimethoxysuccinic acid (IX) would be expected in the oxidation products of 1:3:4:6.-tetramethyl sorbose. No levo-dimethoxysuccinic acid could be obtained. If the oxygen bridge engaged carbon atom six (III) the oxidation products would be expected to yield xylotrimethoxyglutaric acid (IV) and dextro-dimethoxysuccinic acid (V). Probably due to an insufficient amount of material no trimethoxyglutaric acid could be separated. Dextro-dimethoxysuccinic acid was, however, isolated in good yields. It was seen at once that the isolation of this product, since it asserted methylation of carbon atom five, alone sufficed for the elimination of the furanose structure. Dextro-dimethoxysuccinic acid must have contained carbon atoms four and five, since no other adjacent carbon atoms in the tetramethyl sorbose could have given rise to an acid of this configuration.

The presence of dextro-dimethoxysuccinic acid was proved definitely by the preparation of its amide and methyl amide. These are well defined crystalline derivatives prepared by Haworth (87) as reference compounds in the sugar series.

This evidence conclusively demonstrated a normal pyranoid configuration for tetramethyl sorbose ($[\alpha]^{28}_{D}$ + 4.95°) and, hence, also for the glycoside, α-methyl-l-sorboside, which may now be called α-methyl-l-sorbopyranoside. Simultaneously, with this proof of ring structure for α-methyl-l-sorbopyranoside there logically appeared the proof of ring configuration for all the derivatives of this glycoside, as for example: sorbose tetraacetate, α-ethyl-l-sorboside, α-ethyl-l-sorboside tetraacetate, α-methyl-l-sorboside tetrabenzoate, pentamethyl sorbose, tetramethyl sorbose, β-methyl-l-sorboside, and α-chloroacetosorbose. All of these products can now be assumed to possess a normal pyranoid ring structure. The relationship of some of these compounds to α-methyl-l-sorboside will be discussed later.

In the further characterization of α-methyl-l-sorbopyranoside the tetraacetate (76) was prepared. The glycosidic methyl group seemed to be extremely stable in this derivative for even on standing over night in acetyl chloride saturated with hydrochloric acid gas only the starting material was recovered. α-Methyl-l-sorbopyranoside tetrabenzoate was prepared for the first time. In this derivative also the glycosidic methyl group showed great stability. Neither of the above two derivatives showed replacement of the methoxyl group by chlorine when they were treated with several reagents designed to produce halogeno sugars. These conclusions were verified by later workers (71).

During the study of Fischer's method for glycoside formation with regard to l-sorbose it was observed that a solution of this sugar in ethanol underwent an optical rotary change analogous to the change occuring during the formation of α-methyl-l-sorbopyranoside in methanol (Figure 1). The close similarity in the optical changes indicated a reaction between sorbose and the ethanol solution with formation of an ethyl-*l*-sorboside, which like the methyl-*l*-sorboside would be expected to be of the *alpha* configuration. The reaction was essentially complete in four hours at room temperature.

A small quantity of *l*-sorbose was subjected to the action of a one per cent solution of hydrogen chloride in dry ethanol with recovery, at the end of four hours, of fine colorless needles having a melting point of 116° C, and an optical rotation of $[\alpha]^{26}_{D}$ - 73.9° when dissolved in water. The strong negative rotation as compared to *l*-sorbose indicated an α-glycoside. On solution in dilute hydrochloric acid the hydrolysis curve followed closely that found for α-methyl-*l*-sorbopyranoside. Ten days were required for complete hydrolysis in tenth normal acid and approximately thirty days in 0.015 normal acid (Figure 1). The velocity constant for hydrolysis in the 0.015 normal acid was calculated to be 0.043, when time was taken in days. From this constant the half period for hydrolysis was calculated as sixteen days.

The close similarities of the rate of formation and of the rate of hydrolysis with the corresponding rates for α-methyl-*l*-sorbopyranoside suggested that α-ethyl-*l*-sorboside might contain a stable pyranoid ring. The truth of this assumption was proved by methods which permitted the direct chemical linkage of α-ethyl-*l*-sorboside with

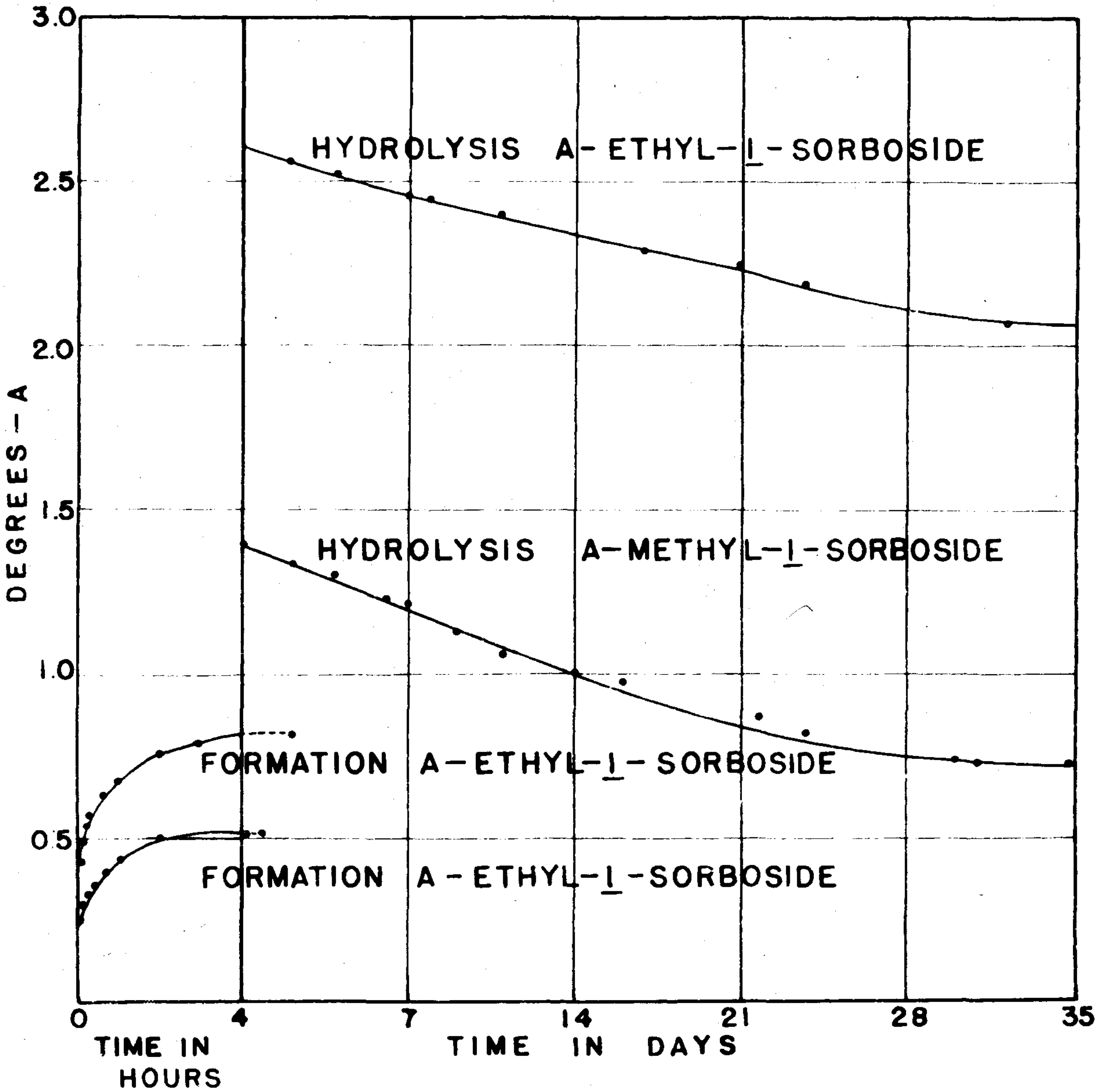

3.0
2.5
2.0
1.5
1.0
0.5
DEGREES - A
HYDROLYSIS A-ETHYL-l-SORBOSIDE
HYDROLYSIS A-METHYL-l-SORBOSIDE
FORMATION A-ETHYL-l-SORBOSIDE
FORMATION A-ETHYL-l-SORBOSIDE
0
4
7
14
21
28
35
TIME IN HOURS
TIME IN DAYS

Figure 1.

β-methyl-l-sorbopyranoside.

Acetylation of the α-ethyl-l-sorboside produced an β-ethyl-l-sorboside tetraacetate which was identical with the compound obtained through the ethylation of sorbose tetraacetate. The structure of sorbose tetraacetate (72, 73) was established through the fact that acetylation of α-methyl-l-sorbopyranoside yielded an α-methyl-l-sorbopyranoside tetraacetate (70) identical with the compound obtained through the methylation of sorbose tetraacetate. It is evident that in this series of reactions the ring structure did not change. Hence, α-ethyl-l-sorboside and its tetraacetate also possess a normal pyranoid ring structure.

Through the expedient of hydrogenation and acetylation followed by subsequent isolation of the hexaacetates of d-sorbitol and l-iditol, Cramer and Pacsu (74) have proven that the common pentaacetate of l-sorbose is a derivative of the open chain sugar. This conclusion might have further been substantiated if it could have been shown that sorbose pentaacetate were capable of mercaptalization to yield l-sorbose ethyl thioacetal pentaacetate. With this in mind the mercaptalization of the keto sorbose pentaacetate was undertaken. To prevent the loss of the easily hydrolysable acetyl groups, mild conditions and strictly anhydrous solutions were employed. Following the methods advanced by Wolfrom (88), for the mercaptalization of fructose, zinc chloride was used as the catalyst. When a solution of keto sorbose pentaacetate was treated with dry ethyl mercaptan containing zinc chloride and a reaction insoluble dehydrating agent, a substance was produced which did not reduce Fehling's solution. The sirup distilled in a high vacuum but with some decomposition. A specific optical rotation of $[\alpha]^{30}_{D}$ - 13.1° in chloroform and a refractive index of N^{24}_{D} 1.5050 were found. The compound could be further demercaptalated to produce keto sorbose pentaacetate. From this evidence, it might be assumed that the compound was indeed the l-sorbose thioacetal pentaacetate and, hence, a derivative of the open chain sugar. The material could not be obtained crystalline. Lack of time made impossible any further attempts to crystallize this compound. It is interesting, in this connection, that the non-crystalline character of the entiomorphic compound, d-sorbose ethyl thioacetal pentaacetate, has been noted by Wolfrom (89).

For the further study of ring structure in derivatives of l-sorbose the monotosyl (mono-p-toluenesulfonyl) derivative was especially desired. The monotosylation of l-sorbose was of interest because the reaction implied a study of the rates of reactivity for the various hydroxyl groups in the sugar. Compeditive esterification had up to this time never been studied in the ketose series. The unimolecular acylation of aldose derivatives containing both primary and secondary hydroxyl groups led to the preferential esterification of the former (90). Among the secondary hydroxyl groups that could be present, the one adjacent to the carbonyl group, or position two in the aldose sugars, was usually the most reactive. With these considerations in mind the speculation was made that in sorbose the hydroxyl group on carbon atom one as well as the hydroxyl group on carbon atom six would show high reactivity. The hydroxyl on carbon atom three, since it is adjacent to the carbonyl group, was expected to be reactive. Since the hydroxyl group on carbon atom one was both primary and adjacent to the carbonyl group it was expected to show a very high reactivity.

Early in this work a monotrityl-l-sorbose (monotriphenyl-methyl-l-sorbose) was prepared. This compound did not form an osazone nor give a precipitate with phenyl hydrazine. It, however, showed strong Fehling's reduction. These facts suggested that the compound was a derivative of l-sorbose in which carbon atom one was blocked.

When a solution of l-sorbose in dry pyridine was treated with a molecular equivalent of tosyl chloride there was formed a compound which, though it did not react with phenyl hydrazine, showed a strong Fehling's reaction. Again these reactions suggested that carbon atom one was blocked, while the potentially reducing carbon atom two remained open. In the time that was had this compound could not be obtained in the pure crystalline state. While first observation indicated that the monotosylation of l-sorbose produced 1-tosyl-l-sorbose, no conclusions can be drawn until further work has been accomplished.

OPTICAL ROTATORY CONSIDERATIONS

Hudson (91) has observed a number of interesting generalizations pertinent to the optical rotations in the sugars. In his speculations on sorbose he calculated the specific rotation to be $[(b_{sorbose} - a_{Me}) + (a_{Me} - a_{OH})] \div$ mol. wt. = $(-17,200 + 18,500 - 8,500) \div 180 = -40$, a value quite near the observed rotation of sorbose. He believed that this result was a sufficient indication for regarding $-43°$ as the true rotation of α-l-sorbose, and that such a value was not an equilibrium rotation such as the value $+52°$ for glucose. This conclusion he believed justified because the equilibrium rotations of the many rotating sugars are in all cases widely different from the rotations of their alpha and beta forms. As sorbose was later shown to be the first exception to this latter statement, it was well that Hudson limited his remarks by saying that they should be regarded as indications only, and not proofs. At this time only two crystalline ketoses, fructose and perseulose, had been observed to undergo mutarotation. Mutarotation had not been detected for tagatose, manno-ketoheptose or sorbose. The reasons for this unusual lack of isomerization in solution were unexplainable, although spatial interference in ring formation was partly indicated (92).

Since that time mutarotation was observed in sorbose (68). As indicated in the historical section, the mutarotation was very slight. Pigman and Isbell believed the smallness of the mutarotation was due either to the fact (a) that the equilibrium was established between isomers having only slightly different optical values, in which case the solution contained considerable quantities of each isomer; or (b) that the known modification greatly predominated when the sugar was dissolved. These theories Pigman and Isbell tested by means of two solubility measurements. In the first case an excess of sorbose was shaken with ice water for three minutes and the specific rotation observed. In the second case the specific rotation of the solution was taken after equilibrium had been established between the sugar and the ice water. It was found that the two specific rotations differed from each other by less than one per cent, thereby indicating that the equilibrium solution of sorbose was composed almost exclusively of the isomer known in the crystalline state. This logical conclusion made no claim as to what isomeric form of sorbose composed the crystalline sugar. The agreement of Hudson's calculated value for α-l-sorbose with the value observed, and the higher negative rotation of the methyl-l-sorboside were the only suggestions that the crystalline sugar was an alpha modification. The ease with which l-sorbose produced an open chain pentaacetate might have been claimed as evidence for postulating a free keto structure for the crystalline sugar. The extreme doubtfulness that any free sugar could exist, crystalline, in open chain form did not exclude this theory from postulation. The relative high negative rotation of sorbose compared to the very small or nil rotations of open chain sugar derivatives, however, did much to discourage any conceptions of open chain structure. The isolation of derivatives of the unknown beta form or better still the isolation of the beta form of the sugar itself would have permitted a more certain assumption of ring structure for the common crystalline sugar.

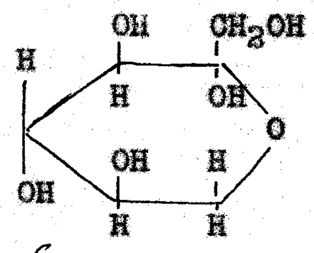
With these considerations in mind various attempts were made to prepare the beta modification. There are four general methods used for preparing the beta modifications of several of the sugars, but developed mainly for β-d-glucose. These methods are the acetic acid method of Hudson and Dale (93), the pyridine process of Behrend (94, 95), the ammonia-alcohol method of Levene (96), and an extension of Tanret's (97-99) original procedure. Each of these methods when applied to sorbose produced no new form of this sugar.

Certain salts have been known to influence the stability of one or the other isomeric forms of a dissolved sugar.

Recently several sugars have been known to form nicely crystalline double compounds with calcium chloride (100-104). All of these compounds undergo mutarotation; the rotatory changes in most cases follow closely the changes exhibited by the pure sugar components. Such changes show that the sugars in the calcium chloride addition compounds have been stabilized in one of their alpha or beta modifications. When l-sorbose was treated with calcium chloride there resulted a nicely crystalline addition compound, containing two molecules of water of hydration. This compound showed a rapid but small upward mutarotation thus resembling the rotatory changes exhibited by pure sorbose. The observed initial rotation was that calculated assuming the sugar component to be unaltered structurally and to possess the same specific rotation as pure sorbose. On acetylating the addition compound by the general procedures for acetylation, the keto sorbose pentaacetate was obtained. Hence, the property of sorbose to form preferentially an open chain pentaacetate is also exhibited by the calcium chloride addition compound. Acetylation using the special method (73) designed to give sorbose tetraacetate produced this acetate in good yield. These facts indicated that the calcium chloride addition compound did not stabilize sorbose in a new form.

Since the very mild acetylation of the calcium chloride addition compound produced sorbose tetraacetate, known to be a derivative of sorbopyranose, added weight was given to the suggestion that crystalline sorbose was α-l-sorbose. At about this time also Shlubach (71) announced the preparation of a positive rotating methyl sorboside, thereby further indicating that crystalline sorbose was an alpha modification.

If it was assumed, then, that common crystalline sorbose was indeed α-l-sorbose, it followed according to Pigman's and Isbell's conclusions that a solution of sorbose in water consisted almost entirely of α-l-sorbose. This, along with the data previously mentioned, showed a strong tendency for sorbose to remain in the alpha modification, which must be the stable modification for this sugar. It was known that in water solutions the equilibrium constants (ratio of beta to alpha forms) for the different sugars varied from 0.4 to 2.3. For most of the sugars the value was 1.7 showing the predomination of the beta isomer. For certain sugars as mannose, lyxose, and rhamnose the equilibrium constant was less than one, showing that the alpha form of these compounds was predominant in the solution. Reviewing this data it appeared that in practically every case the most abundant isomer in the equilibrium solution was that in which a trans arrangement was present between the hydroxyl group on the potentially reducing carbon and the hydroxyl on the adjacent asymmetric carbon atom. When the structure of α-l-sorbose was observed it was seen that such a trans arrangement existed between the hydroxyl groups.



α-l-Sorbose

In this respect sorbose was seen to conform to the known steric phenomena of the other sugars. Indeed, sorbose showed even greater tendency than other sugars to remain in the stable trans (alpha) form; since, according to Pigman and Isbell, almost the whole amount was retained in this form when the sugar was dissolved in water.

If Hudson's rules were assumed to hold for sorbose as for the other sugars, then the rotation of the unknown beta form could be predicted. Hudson found that the difference in molecular rotations of alpha-beta isomeric pairs was a constant value for all aldoses considered. If the same generalization were assumed to hold for the ketoses then the difference in the specific rotations between alpha and beta fructose should also be equal to the difference in specific rotation between alpha and beta sorbose. This difference for fructose was found to be

-63.3 - (-133.5) = + 69.9. If now this value were added to the value -43, for α-l-sorbose, the value + 26.9 would be obtained as the predicted rotation for the unknown β-l-sorbose.*

At the time evidence was found for the existence of α-ethyl-l-sorboside it was desired to predict the optical rotation for the substance in advance of its preparation. This prediction could easily be made through an extension of Hudson's generalizations. As mentioned above, Hudson showed that $A_{\alpha Me} + A_{\beta Me}$ = constant, and likewise $A_{\alpha Et} + A_{\beta Et}$ = constant. Without making further assumptions $A_{\alpha Et} - A_{\alpha Me}$ = constant, might have been expected to hold true. If this value were found to be constant then its addition to the molecular optical rotation of a methyl-glycoside would yield the molecular optical rotation of the corresponding ethyl glycoside.

When all of the available data were collected (Table I) it was seen that in reality this difference, $A_{\alpha Et} - A_{\alpha Me}$, was roughly a constant; but that the signs of the differences were not uniform. Thus, it could not be predicted whether the difference was to be added or subtracted from the molecular rotation of a methyl glycoside in order to obtain the value for the corresponding ethyl

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* Since sorbose was a member of an l-series the beta sugar had to be more positive in rotational value than the alpha form. Hence, the addition of 69.9 was required.

glycoside.

Under these circumstances it was decided to take the value for fructose exclusively, for the prediction of optical rotation. The difference, $A_{Et} - A_{Me}$, in the case of fructose was +1,120, which indicated that the molecular rotation of the ethyl fructoside was greater than that of the methyl fructoside. If this value were added to the molecular optical rotation for α-methyl-l-sorboside the molecular optical rotation of α-ethyl-l-sorboside should have been obtained. Thus, -17,200 (molecular rotation for α-methyl-l-sorboside) + 1,120 = -16,080, the predicted molecular optical rotation for α-ethyl-l-sorboside, and $-16,080 \div 208 = -77.3°$, which is the predicted specific optical rotation for α-ethyl-l-sorboside. The true optical rotation as found was $[\alpha]_D^{26} - 73.9°$.

When an attempt was made to predict the optical rotation of α-ethyl-l-sorboside tetraacetate, the literature afforded data which, though small in extent, were consistent with themselves (Table II). In each case the ethyl glycoside tetraacetate was seen to have a numerically higher molecular rotation than the corresponding methyl compound. In the calculation with this data the average value of $A_{Et} - A_{Me}$ could be used with impunity. If to the molecular optical rotation of α-methyl-l-sorboside tetraacetate, -18,820, was added the average of the differences $A_{Et} - A_{Me}$ (-2,790) and the molecular optical rotation thereby otained (-21,610) was divided by the molecular weight of α-ethyl-l-sorboside tetraacetate, its specific rotation was calculated to be -57.5. The actual value found after preparing the compound was $[\alpha]_D$ - 54.6°.

Table I

Rotations were taken with the D-line of sodium

when the solvent was water

Substance	Specific Rotation	Molecular Rotation	Difference
α-Ethyl-d-glucoside	+150.6	+31,320	+ 670
α-Methyl-d-glucoside	+158.0	+30,650	
β-Ethyl-d-glucoside	- 33.9	+ 6,950	- 740
β-Methyl-d-glucoside	- 32.0	+ 6,210	
α-Ethyl-d-galactoside	+ 186.8	+38,810	+ 610
α-Methyl-d-galactoside	+ 196.6	+38,200	
β-Ethyl-d-galactoside	- 6.7	- 1,393	
β-Methyl-d-galactoside	- 4.2	- 81.5	-1,310
α-Ethyl-l-arabinoside	+ 9.95	+ 2,070	-1,290
α-Methyl-l-arabinoside	+ 17.3	+ 3,360	
β-Ethyl-d-fructoside	- 155.3	- 32,380	+1,120
β-Methyl-d-fructoside	- 172.1	- 33,500	
β-Ethyl maltoside	+ 79.2	+ 29,300	+1,220
β-Methyl maltoside	+ 78.8	+ 28,060	
Average			(±) 994

Table II

Rotations were taken with the D-line of sodium

when the solvent was chloroform

Substance	Specific Rotation	Molecular Rotation	Difference
α-Ethyl-d-glucoside tetraacetate	+132	+49,630	+2,210
α-Methyl-d-glucoside tetraacetate	+131	+47,420	
β-Ethyl-d-glucoside tetraacetate	- 27.1	-10,150	-3,630
β-Methyl-d-glucoside tetraacetate	- 18.2	- 6,520	
β-Ethyl-d-galactoside tetraacetate	- 29.8	-11,280	-2,230
β-Methyl-d-galactoside tetraacetate	- 25.3	- 9,050	
β-Ethyl-d-fructoside tetraacetate	-127.6	-48,130	-3,100
β-Methyl-d-fructoside tetraacetate	-124.4	-45,030	
Average			2,790

EXPERIMENTAL

Preparation of l-Sorbose

The l-sorbose used in these researches was obtained in part as a gift from Dr. E. I. Fulmer and in part as a gift from the United States By-Products Laboratory in Ames. A further quantity of l-sorbose was prepared according to the methods of Fulmer (51) for the bacterial oxidation of sorbitol. This sugar was purified by dissolving it in the least amount of hot distilled water required for complete solution and then adding an equal volume of 95% ethyl alcohol. The pure colorless crystals had a melting point of 164° and showed a specific optical rotation of $[\alpha]_D^{25} - 43.4°$.

Preparation of α-Methyl-l-Sorboside

This substance was prepared after the method of Fischer (69). Fifty grams of powdered sorbose were placed in two liters of methanol, which had previously been dried over sodium carbonate and to which had been added 10 grams of dry hydrogen chloride. The mixture, in a gallon bottle, was shaken for two days. Then 50 grams of lead carbonate were added and the mixture shaken again for two hours. The methanol was distilled off under reduced pressure. The residual sirup was extracted repeatedly with acetone. From the acetone solution were obtained 43 grams of α-methyl-l-sorboside. This material melted at 118°.

Preparation of
Tetramethyl-α-methyl-l-sorboside

In a three necked round bottom flask, equipped with a glass stirrer in the central neck and a dropping funnel in each of the two side necks, were placed 25 grams of α-methyl-l-sorboside and 15cc of water. The mixture was heated to 70°. Dimethyl sulfate was allowed to drop at the rate of one drop per second from one of the dropping funnels. Through the other funnel 60% potassium hydroxide was admitted at a rate such that the mixture in the flask was at all times slightly alkaline. In three hours 400cc of alkali and 250cc of dimethyl sulfate had been added to the reaction. The temperature was then raised to 100° and the solution maintained at this temperature for one hour. Vigorous stirring was employed. At this time the solution was cooled and extracted with three 100cc portions of chloroform. The combined extract was washed with water and then dried over sodium sulfate. The chloroform was removed under diminished pressure. The 16 grams of remaining sirup were distilled at a pressure less than one millimeter. The liquid boiled at 90 - 95° with the bath at a temperature of 100 - 110°. This sirup was remethylated according to the above method. After isolating the sirup from this second methylation a third methylation was applied. For this purpose the sirup was dissolved in 25 grams of methyl iodide and 13.5 grams of freshly prepared silver oxide added in small portions. After addition of all of the silver oxide the mixture was refluxed for 16 hours. The methyl iodide was then distilled off and the residue extracted with three 100 cc portions of ether. After removal of the ether the remaining sirup was distilled at a pressure of less than one millimeter. Most of the liquid distilled at 85° with the bath at 100°. The distillate was a clear and very mobile liquid; yield 3 grams. The specific rotation in chloroform was $[\alpha]_D^{22} = \frac{-0.25 \times 100}{2 \times 4 \times 0.3316} = -18.8°$. In methanol the rotation was $[\alpha]_D^{25} = \frac{-0.55 \times 100}{2 \times 4 \times 0.2131} = -32.1°$. Arragon recorded $[\alpha]_D^{20}$ - 31.5° in methanol (76).

Preparation of Tetramethyl-l-sorbose

Thirty grams of tetramethyl-α-methyl-l-sorboside at 10% concentration were hydrolyzed for one and one-half hours in 2% hydrochloric acid; the temperature being maintained at 95°. On completion of the hydrolysis the solution was neutralized with lead carbonate, filtered and extracted with three 75 cc portions of chloroform. On evaporation of the chloroform under reduced pressure the remaining sirup was distilled at a pressure of approximately one millimeter. The sirup distilled at a bath temperature of 125° to produce a light yellow sirup of rather thick consistency. This sirup showed a rotation of $[\alpha]_D^{28} = \frac{-0.20x100}{2x4x0.246} = -10.2°$ in chloroform and $[\alpha]_D^{27}$ + 4.95° in methanol. Arragon recorded (76) a specific rotation of $[\alpha]_D^{30}$ + 4.9° in methanol.

Oxidation of Tetramethyl-l-sorbose

To 5 grams of tetramethyl-l-sorbose were added 38.5 cc of concentrated nitric acid (density, 1.42). The solution was heated carefully to 70°. At this temperature vigorous oxidation set in and the solution was removed from the heating bath for a few minutes to prevent the reaction from becoming too violent. After the initial reaction had subsided the solution was replaced in the heating bath and the temperature raised carefully to 95°, and the solution kept at this temperature for two hours. At the end of this time reaction had ceased and a clear light yellow solution remained. The mixture was poured into three times its volume of water and the excess nitric acid removed by distilling at 40° under 20 millimeters pressure. Water was added from time to time and the distillation continued for six hours. The evaporation was further continued, replacing water by methanol until one liter had distilled, after which the liquid was taken to dryness. The product was esterified by gently refluxing in methanol for six hours, enough nitric acid remaining to catalyze the reaction. When esterification was complete the nitric acid was neutralized by silver carbonate. The solution was evaporated to dryness and the residue extracted with ether. On evaporation of the ether a light yellow sirup remained which was distilled at about one millimeter pressure to give two fractions. The first fraction distilled at 120-125° and weighed 2.1 grams; the second fraction distilled at 125-135° and weighed 0.4 grams. The first fraction showed a specific rotation in chloroform of $[\alpha]_D^{24} = \frac{0.21 \times 100}{2 \times 4 \times 0.084} = +31.4°$. A micro rotation of some prepared authentic dimethyl-dextro-dimethoxysuccinic ester gave $[\alpha]_D^{32} + 39.1°$ in chloroform.

Preparation of *Dextro*-

Dimethoxysuccinamide and *Dextro*-

Dimethoxysuccinomethylamide from Nitric Acid Oxidation Products

A 5.9 mg. sample of the light yellow sirup from the first fraction was dissolved in 3 cc of dry methanol saturated at 0° with ammonia gas. On standing in the ice box over night, long needles weighing 3.7 mg. precipitated from the solution. These crystals melted at 270° and showed specific rotation of $[\alpha]_D^{29} = \frac{0.15 \times 100}{(100\ 0.97) \times 0.001504} = +96°$ in water. On concentration of the alcoholic solution another milligram of crystal of <u>dextro</u>-dimethoxysuccinamide was obtained.

<u>Analysis</u>. Calcd. for $C_6H_{12}O_4N_2$: N, 15.92.

Sample: 3.114 mg.; N_2, 0.464 cc.; Press., 739 mm.;

Temp., 27°. Found: N, 16.13.

A further small quantity of the first fraction was dissolved in 10 cc. of dry methanol which had been saturated at 0°, with methyl amine. The solution was allowed to stand over night in the ice box and was then slowly concentrated. During the evaporation burr-like clusters of crystals appeared. These crystals, when recrystallized from ethyl acetate, showed a melting point of 204° and a specific optical rotation of $[\alpha]_D^{35} = \frac{+0.80 \times 100}{(100\ 0.9706) \times 0.005967} = +130.3°$ in water. The average yield of <u>dextro</u>-dimethoxysuccinomethylamide in these preparations was 60%.

<u>Analysis</u>. Calcd. for $C_8H_{10}O_4N_2$: N, 13.73.

Sample: 3.763 mg.; N_2, 0.496 cc.; Press., 736 mm.;

Temp., 35°. Found: N, 13.84.

The second fraction of the distillate, from the nitric acid oxidation, contained some dimethyl <u>dextro</u>-dimethoxysuccinate and a small quantity of unidentifiable material.

Preparation of
α-Methyl-l-sorbopyranoside Tetraacetate

To 4 grams of α-methyl-l-sorboside dissolved in 25 cc. of dry pyridine were added 13 cc. of acetic anhydride. After standing over night the mixture was poured into 500 cc. of ice water and extracted twice with 75 cc. portions of chloroform. The combined extract was washed successively with sodium bisulfate solution, sodium bicarbonate solution, and water. The chloroform extract was dried over sodium sulfate and the chloroform removed under diminished pressure. The sirup was crystallized from alcohol; yield 2.9 grams. The melting point was 88° and the specific optical rotation in chloroform was $[\alpha]^{22}_{D} = \frac{-4.19x100}{2x4x1.005} = -52.4°$. Arragon reported (70) for this compound a melting point of 88° and a specific optical rotation of $[\alpha]^{20}_{D}$ - 51.8 in methanol.

Preparation of
α-Methyl-l-sorbopyranoside Tetrabenzoate

Eight grams of α-methyl-l-sorboside were dissolved in 30 cc. of dry pyridine and to the cold solution were carefully added with stirring 24 cc. of benzoyl chloride with 60 cc. of dry chloroform. The mixture was cooled in ice for one hour and then allowed to stand at room temperature over night. The mixture was poured into 500 cc. of ice water and the solution extracted with two 60 cc. portions of chloroform. The chloroform extracts were combined and washed with cold 5% hydrochloric acid, sodium bicarbonate solution and water. The chloroform was dried over sodium sulfate and then evaporated at reduced pressure. The remaining sirup was taken up in hot ethanol. On cooling in ice a thick light yellow sirup separated. This sirup was washed with cold ethanol and then ice water. On stirring in ice water the sirup crystallized yielding 14 grams of crystals which were not very pure. These crystals did not reduce Fehling's solution and showed an optical rotation of $[\alpha]_D^{28}$ + 6.96° in chloroform. The crystals were taken up in alcohol and the solution evaporated. After a time crystals separated. These, after being washed well with alcohol and dried, melted at 127° and showed an optical rotation of $[\alpha]_D^{27} = \frac{+0.22 \times 100}{2 \times 4 \times 0.1813} = +15.2°$ in chloroform.

<u>Analysis</u>: Calcd. for $C_{34}H_{37}O_9(OCH_3)$: OCH_3, 5.08.
Sample: 10.044 mg., 0.960 cc. of 0.1000 N. $Na_2S_2O_3$.
Found: OCH_3, 4.95.

Attempted Demethylation of
α-Methyl-l-sorbopyranoside Tetraacetate

One gram of α-methyl-l-sorbopyranoside was dissolved in 50 cc. of cold acetyl chloride which had been previously saturated with dry hydrogen chloride. The solution was allowed to stand in the ice box over night and was then evaporated under reduced pressure. A sirup remained which crystallized after a few minutes. The crystals were taken up in benzene and the solution washed with a water suspension of silver oxide. The benzene solution was then evaporated to a sirup under reduced pressure. The sirup was taken up in ether. From the ether solution 0.5 gram of crystals separated. Their melting point was 86° and the optical rotation in chloroform was $[\alpha]_D^{25}$ - 52.7°. Hence, the α-methyl-l-sorbopyranoside tetraacetate was recovered unchanged.

Attempted Preparation of Acetochlorosorbose

Five grams of α-methyl-l-sorbopyranoside tetraacetate were dissolved in 20 cc. of dry chloroform. The mixture was contained in a glass stoppered erlenmeyer flask. To this solution were added 2 grams of aluminum chloride and 4 grams of phosphorus pentachloride. The mixture was shaken with occasional warming for 25 minutes. The solution was then poured into ice water and quickly extracted with chloroform and the chloroform solution washed with water. After drying and evaporating the chloroform solution an amber sirup remained. The sirup was taken up in ether and filtered from norite. On evaporation 2 grams of crystals separated. These, after one recrystallization from alcohol, melted at 81° and showed an optical rotation of $[\alpha]_D^{25}$ - 50.5°. Hence, α-methyl-l-sorbopyranoside tetraacetate was recovered.

Rate of Formation of α-Methyl-l-sorbopyranoside

When the rate of formation of α-methyl-l-sorboside in methanol solution was studied, it was found that glycoside formation proceeded much faster than was expected.

A quantity of sorbose was shaken for several minutes with dry methanol. After some of the sugar had been dissolved 12.5 cc. of the methanol solution were placed in a 25 cc. volumetric flask. The flask was then filled to the mark with dry methanol containing 1% hydrogen chloride. The flask was shaken vigorously and a portion of the solution placed in a two decimeter polarimetric tube. The rotary changes observed are recorded in Table III. The graphic illustration of the mutarotation is shown in Figure 1. The reaction was essentially complete in four hours.

Table III

Rate of Formation of α-Methyl-l-sorbopyranoside

Zero time taken at the point of mixing the sorbose solution with the methanol containing 1% hydrogen chloride.

Time	-α Observed
2 min.	0.25
4 "	0.28
5 "	0.30
6 "	0.32
8 "	0.34
10 "	0.35
15 "	0.37
20 "	0.38
27 "	0.40
55 "	0.42
90 "	0.45
2 hrs.	0.50
5.5 "	0.54
6.5 "	0.55
24 "	0.56

Rate of Hydrolysis of α-Methyl-l-sorbopyranoside

In order to test the resistance of α-methyl-l-sorboside toward hydrolysis, a 1% solution of the pure glycoside in water was prepared and allowed to stand. In six hours 1 cc. of the solution was tested with Fehling's solution. No reduction of the Fehling's solution occured. In 24 hours a second 1 cc. portion tested with Fehling's solution showed no reduction. After standing five days the compound was still intact, as evidenced by the lack of reaction when 1 cc. of the solution was tested with Fehling's solution. A 1% solution of α-methyl-l-sorboside in 0.01 N hydrochloric acid, likewise, showed no reduction toward Fehling's upon standing for 24 hours. If, however, the solution of α-methyl-l-sorboside in 0.01 N acid was boiled for one minute, a precipitate of cuprous oxide was obtained on testing with Fehling's solution.

In order to make a more exact determination of the hydrolsis rate of α-methyl-l-sorboside tests were made in three different acid concentrations. Hydrolysis rates were followed polarimetrically. The concentration of α-methyl-l-sorboside in each case was 0.8 grams per 100 cc. of solution. In the first test a solution of 1.75 normal hydrochloric acid was used. The acid concentration in this case proved to be too high for accurate measurement; the hydrolysis being completed in less than 24 hours. In the second test an acid concentration 0.102 normal in hydrochloric acid was employed. As evidenced from Table IV the hydrolysis was complete in 9-10 days. In the third test 0.015 normal acid was employed. The hydrolysis apparently required 30-31 days for completion (Table IV). The plot of this curve is shown in Figure 1. The end point was made somewhat indefinite due to mold growth which became noticeable after 28 days. Assuming the hydrolysis to be a first order reaction the velocity constant K for this last case was calculated by means of the well-known kinetic equation $K = \frac{2.303}{t} \log \frac{\alpha_0 - \alpha_\infty}{\alpha - \alpha_\infty}$. The average velocity constant K was found to be 0.049 when time was taken in days. The period for half hydrolysis was then calculated to be $t_{\frac{1}{2}} = \frac{0.693}{0.049} = 14.2$ days.

Rate of Formation of α-Ethyl-l-sorbopyranoside

During the study of Fischer's method (69) for glycoside formation with relation to l-sorbose it was observed that a solution of this sugar in ethanol underwent an optical rotary change analogous to the change occuring during the formation of α-methyl-l-sorboside in methanol.

A quantity of ethanol which had previously been dried over sodium and distilled was saturated with pure l-sorbose. To 12.5 cc. of this solution were added 12.5 cc. of a 1%

Table IV

Rate of Hydrolysis of α-Methyl-l-sorbopyranoside

in Hydrochloric Acid

Concentration of sorboside was 0.8 grams per 100 cc. of solution. Average temperature 30°.

Time	Acid Normality 0.102		Acid Normality 0.015	
in days	α Tube 5	α Tube 6	α Tube 3	α Tube 4
0	1.40	1.32	1.40	1.25
1	1.20	1.15	1.39	1.30
2	1.10	1.09	1.34	1.22
3	0.96	0.95	1.32	1.21
4	0.89	0.89	1.30	1.20
6	0.72	0.71	1.22	1.17
8	0.71	0.70	1.15	0.94
9	0.67	0.63	1.12	1.02
11	0.66	0.63	1.05	0.93
13	0.65		1.02	0.88
15	0.64		0.98	0.88
17	0.64		0.95	0.86
21			0.94	0.79
24			0.82	0.72
27			0.80	0.68
30			0.74	0.60
31			0.72	0.60
44			0.71	

solution of hydrogen chloride in dry ethanol. The solutions were thoroughly mixed and the optical rotation observed two minutes after mixing. The mutarotation is shown in table V and illustrated graphically in Figure 1. The reaction was essentially complete in four hours. The close similarity of these changes as compared with the changes occuring during the formation of α-methyl-l-sorboside suggested the formation of an ethyl sorboside which would be of the alpha configuration.

Rate of Hydrolysis of α-Ethyl-l-sorbopyranoside

In order to further compare α-ethyl-l-sorboside with the corresponding methyl derivative, the rate of hydrolysis in acid solution was studied. These optical changes were followed polarimetrically when the solution was contained in a two decimeter tube. In the first case measurements were made on a solution containing 0.270 grams of α-ethyl-l-sorboside per 100 cc. of 0.1 normal hydrochloric acid. The results are recorded in Table VI where it is observed that the hydrolysis was essentially complete in 10 days.

In the second case measurements were made on a solution containing 0.442 grams of α-ethyl-l-sorboside per 100 cc. of 0.01 normal hydrochloric acid. The results as recorded in Table VI indicated the reaction to be complete in about 30

Table V

Rate of Formation of α-Ethyl-l-sorbopyranoside

Zero time taken at the point of mixing the sorbose solution with the ethanol containing hydrogen chloride.

Time in Minutes	$-\alpha$ Observed
2	0.43
3	0.44
4	0.47
5	0.49
6	0.48
8	0.51
10	0.53
12	0.54
14	0.56
17	0.56
18	0.58
21	0.60
23	0.61
29	0.63
50	0.67
87	0.72
130	0.76
180	0.78
320	0.82
2,880	0.82

Table VI

Rate of Hydrolysis of α-Ethyl-l-sorbopyranoside in Hydrochloric Acid

Time in Days	Acid Normality 0.1 $-\alpha$	Acid Normality 0.01 $-\alpha$
0	1.60	2.61
1	1.45	2.57
2	1.40	2.56
4	1.16	2.52
6	1.00	2.46
7	0.93	2.45
8	0.92	2.44
9	0.92	2.43
11		2.41
14		2.34
17		2.30
21		2.26
24		2.20
30		2.07
31		2.07
32		2.07

days. The true end point of the hydrolysis in this case was somewhat uncertain due to mold growth which became noticeable after 26-28 days. The data for the last case is shown graphically in Figure 1. The average velocity constant K for this case was calculated to be 0.043 when time was taken in days. This gave a half period for hydrolysis of 16.1 days. It was seen at once that the rate of hydrolysis of α-ethyl-l-sorboside was comparable to that for α-methyl-l-sorboside.

Preparation of α-Ethyl-l-sorbopyranoside

Twenty grams of finely powdered dry sorbose were dissolved with shaking in 1500 cc. of ethanol which previously had been dried with sodium and distilled. To this solution were added 250 cc. of dry ethanol containing 20 grams of dry hydrogen chloride. The mixture at once became a light pink in color. After standing for four hours the solution was light amber in shade. A solution of 13 grams of sodium dissolved in dry ethanol was added and this mixture shaken for five minutes. Then carbon dioxide was passed through the solution for one hour. The solution was distilled under reduced pressure at a temperature no higher than 50°. The residue was extracted repeatedly with boiling ethyl acetate and ethanol. The solvents were removed from the combined extracts by distilling under reduced pressure at 50°. The red sirupy residue was extracted with boiling ethyl acetate until only a brittle red gum remained. From the ethyl acetate extracts there separated on cooling a flocculent white precipitate which did not reduce Fehling's solution; yield 10 grams. This material was dissolved in hot acetone and filtered from norite. On cooling long needles separated, which had a melting point of 114-115°. One recrystallization from ethyl acetate raised the melting point to 115-116°. The specific optical rotation in water was $[\alpha]_D^{26} = \frac{-3.40 \times 100}{2 \times 4 \times 0.5755} = -73.9°$. The solution showed no mutarotation on standing for twenty-four hours.

<u>Analysis</u>. Calcd. for $C_6H_{11}O_5(OC_2H_5)$: C, 46.15; H 7.69; OC_2H_5, 21.63. Sample: 3.850 mg.; CO_2, 6.492 mg.; H_2O, 2.664 mg. Sample: 4.808 mg.; cc. of 0.0996 N $Na_2S_2O_3$, 1.40. Found: C, 45.98; H, 7.70; OC_2H_5, 21.77.

Preparation of α-Ethyl-l-sorbopyranoside Tetraacetate

<u>First Method</u>

To 4 grams of α-ethyl-l-sorbopyranoside dissolved in 25 cc. of dry pyridine were added 13 cc. of acetic anlydride. After standing over night the mixture was poured into 500 cc. of ice water and extracted twice with 75-cc. portions of chloroform. The combined extract was washed successively with sodium bisulfate solution, sodium bicarbonate solution, and water. The chloroform extract was dried over anlydrous sodium sulfate, filtered and the chloroform removed under diminished pressure. The sirup crystallized from 45% ethanol. The yield was 3 grams. The crystals had a melting point of 74-75° and showed an optical rotation in chloroform of $[\alpha]_D^{26} = \frac{-3.50x100}{2x4x0.8016} = -54.6°$.

Analysis. Calcd. for $C_{14}H_{19}O_9(OC_2H_5)$: C, 51.06; H 6.38; OC_2H_5, 11.96. Sample: 4.577 mg.; CO_2, 8.560 mg.; H_2O, 2.626 mg. Sample: 6.476 mg.; cc. of 0.0996 N $Na_2S_2O_3$, 1.034. Found: C, 50.94; H, 6.375; OC_2H_5, 11.95.

Second Method

Twenty grams of powdered $\mathcal{L}$-sorbose tetraacetate, 75 grams of freshly prepared silver oxide and 128 grams of ethyl iodide were heated under reflux until reaction began, enough heat being generated after the reaction started to maintain the solution at the boiling point. When the reaction subsided the solution was boiled for two and one-half hours longer under reflux. At this time the ethyl iodide was distilled off and the residue extracted with ether. The ether was removed under diminished pressure and the residue taken up in hot petroleum ether (B.P. 30-49°). From this solution long needles crystallized. The yield was 14 grams. Recrystallization from 45% ethanol produced fine, soft needles having a melting point of 74° and a specific optical rotation of $[\alpha]_D^{26}$ - 54.6° in chloroform. No lowering in melting point was shown when some of these crystals were mixed with crystals obtained by the first method.

Study of the Crystallization of l-Sorbose

In an attempt to isolate α-l-sorbose the crystallization of sorbose from various solvents was studied.

Ten grams of sorbose were dissolved in 12 cc. of warm concentrated ammonium hydroxide. When complete solution of the sugar was attained 100 cc. of absolute ethanol were added. In a short time crystals appeared. The solution was then filtered by suction and the crystals washed with absolute alcohol and dried. The yield was 6 grams. The optical rotation of $[\alpha]_D^{33}$ - 42.5° (c, 2 in water) showed the recovery of α-l-sorbose.

To 5 grams of sorbose dissolved in 15 cc. of hot pyridine were added 55 cc. of absolute alcohol. In four hours the precipitated crystals were filtered, washed with absolute alcohol and dried; yield 2.5 grams. Rotation $[\alpha]_D^{33}$ - 43.1° (c, 4 in water).

To 5 grams of sorbose dissolved in 5 cc. of water and cooled to 0° were added 10 cc. of glacial acetic acid. On standing a short time crystallization occured. The crystals after washing with absolute ethanol and drying weighed 3 grams. The rotation was $[\alpha]_D^{33}$ - 43.4 (c, 2 in water).

A solution of 5 grams of sorbose dissolved in 5 cc. of hot water was heated to 100° c. Then 10 cc. of glacial acetic acid which had been heated to 100° were added with vigorous stirring to the sorbose sirup. On cooling the solution deposited 3 grams of crystals having an optical rotation of $[\alpha]_D^{33}$ - 43.4 (c, 2 in water).

A small quantity of pure sorbose contained in a test tube was placed in an oil bath at 165-175°. In seven minutes the sugar melted completely to form an amber liquid. The test tube was then removed from the bath and rotated in such a way as to run the melted sugar up on the walls of the tube. It was then quickly cooled in an air blast and a portion taken for an optical rotatory measurement. The rotation two minutes after solution in water was $[\alpha]_D^{26}$ - 39.6°; in 24 hours the reading became $[\alpha]_D^{26}$- 42°. This change in optical rotation was not sufficient to warrant any general assumption regarding mutarotation. The change might have indicated the production of a small quantity of α-l-sorbose, or it might have been caused by traces of decomposition material.

Preparation of a Calcium Chloride Compound of α-l-Sorbose

Twenty grams of l-sorbose were dissolved in 25 cc. of warm water and 18 grams of calcium chloride slowly added with stirring. After effecting complete solution by stirring and heating on a hot-plate, the solution was placed in a desiccator over phosphorus pentoxide. In three weeks the solution had turned to a thick mush of crystals. These were stirred with absolute ethanol, filtered and washed free from sirup with absolute ethanol. The yield of dry crystals was 15 grams. The melting point was 157° or 159° corrected. The substance melted with decomposition. Recrystallization by dissolving in water and slow concentration of the sirup in a desiccator produced fine crystals melting at 159° (corrected). The specific optical rotation in water two minutes after solution was $[\alpha]_D^{29} = \frac{-1.80x100}{2x4x0.9293} = -24.2°$. The compound underwent a small upward motarotation of about 0.3°. The mutarotation was complete in 15 minutes producing a final rotation of $[\alpha]_D^{29}$ - 23.9° as shown in Table VII.

If it were assumed that the sugar component in the compound $C_6H_{12}O_6$. $CaCl_2$. $2H_2O$ was unaltered structurally and possessed the same specific rotation as pure sorbose, then the value α could have been caldulated. Making this assumption the value of α as -2.50° was calculated for 1.3029 grams

Table VII

Mutarotation of Sorbose-Calcium Chloride

Addition Compound in Water

Run	Initial $[\alpha]_D^{29}$	Final $[\alpha]_D^{29}$	Change $[\alpha]_D^{29}$
1	- 24.15°	- 23.8°	0.3°
2	- 24.2 °	- 23.9°	0.3°
3	- 24.2 °	- 23.8°	0.4°
4	- 24.3 °	- 24.01°	0.3°
Mean	- 24.2 °	- 23.9°	0.3°

of the compound, containing 0.719 grams of sorbose. This value was in good agreement with the observed value of which was 2.52°.

Analysis. Calcd. for $C_6H_{12}O_6 \cdot CaCl_2 \cdot 2H_2O$: Ca, 12.25; Cl, 21.72. Sample: 0.2229 g.; 16.75 cc. of 0.08 N $KMnO_4$. Sample: 0.2100 g.; 0.1844 g. of AgCl. Found: Ca, 12.10; Cl, 21.74.

A second and faster method was found for the preparation of the calcium chloride addition compound of l-sorbose. In this method a sirup was prepared by dissolving 20 grams of sorbose in 25 c. of hot water and adding 18 grams of calcium chloride. The sirup was then diluted with three times its volume of absolute ethanol and the mixture placed in the ice box. On the addition of ether in small quantities a good precipitation of the addition compound soon appeared. The yield was 8 grams. The first crop of this material showed a melting point of 159° (corrected). No change in melting point was observed on mixing this substance with the addition compound prepared by the first method. The optical rotation was $[\alpha]_D^{27} = \frac{-2.30 \times 100}{2 \times 4 \times 1.188} = - 24.2°$.

Acetylation of the Calcium Chloride Addition Compound of α-l-Sorbose

First Method

To 4 grams of α-l-sorbose-calcium chloride addition compound dissolved in 80 cc. of pyridine were added 60 cc. of acetic anhydride. The mixture was cooled in ice and then placed in the ice box for two days. At the end of this time the mixture was poured, with stirring, into one liter of ice water and extracted three times with 75 cc. portions of chloroform. The combined extract was washed successively with 5% hydrochloric acid, sodium bicarbonate solution, and water. The chloroform extract was dried over anhydrous sodium sulfate and the chloroform removed under diminished pressure. The sirup was crystallized from ethanol. The yield was 1 gram. The melting point was 99° and no depression of melting point occured when the compound was mixed with authentic keto sorbose pentaacetate. Thus, this type of acetylation led to an open chain derivative.

Second Method

Four grams of the sorbose-calcium chloride double compound were dissolved in 150 cc. of acetic anhydride containing 1.5 grams of freshly fused zinc chloride. After cooling in ice this solution was placed in the ice box for two days.

The solution was then poured into a liter of ice water and extracted with three 75 cc. portions of chloroform. The combined extracts were washed with sodium bicarbonate and then water. After drying over sodium sulfate the chloroform was removed under reduced pressure. The remaining sirup crystallized from ethanol yielding about one gram of crystals. The melting point was 98-99° and showed no depression when the crystals were mixed with crystals of authentic keto sorbose pentaacetate. Thus, this method of acetylation also led to the formation of an open chain derivative.

Third Method

To 3 grams of the α-l-sorbose-calcium chloride addition compound dissolved in 30 cc. of cold pyridine there were added at intervals and with constant stirring a total of 30 cc. of acetic anlydride. The mixture was stirred in an ice bath for four hours and then poured into a liter of water and extracted with three 75 cc. portions of chloroform. The chloroform extracts were combined and washed with sodium bicarbonate solution and water. After drying over sodium sulfate the chloroform was removed under diminished pressure. The sirup was taken up in ethanol. On standing 0.036 grams of crystals appeared. Combined with authentic keto sorbose pentaacetate some of these crystals showed a mixed melting point of 97°. The specific rotation was $[\alpha]_D^{25}$ +1.6.

Hence, this material was keto sorbose pentaacetate. The remaining sirup was taken up in chloroform and filtered from norite. On the addition of ether and petroleum ether (BP 30-40°) 1.404 grams of crystals were obtained. Their melting point was 97°. Mixed with authentic keto sorbose pentaacetate a melting point of 80° was found. When the crystals were mixed with authentic α-l-sorbose tetraacetate the melting point of the mixture was 97°. The specific optical rotation was $[\alpha]_D^{27}$ - 19.1°. Hence, by this process of acetylation a good yield of α-l-sorbose tetraacetate was obtained.

Preparation of l-Sorbose Thioacetal Pentaacetate

In 60 cc. of ethyl mercaptan dried over drierite were dissolved 8 grams of freshly fused zinc chloride. To this solution were added 15 grams of fresh drierite and 15 grams of anhydrous sodium sulfate. Then 13 grams of dry keto sorbose pentaacetate were added and the solution cooled in ice. The mixture was allowed to stand in the ice box for one day. The solution was poured into 200 cc. of a saturated solution of sodium bicarbonate and the precipitate filtered off. The filtrate was extracted with three 50 cc. portions of chloroform. The precipitate was removed to a beaker and extracted twice with 500 cc. portions of chloroform. The combined chloroform extracts were dried over sodium sulfate, filtered, and the chloroform removed under diminished pressure. To the 13 grams of residual sirup petroleum ether (B.P. 30-40°) was repeatedly added and distilled to remove all traces of chloroform. The light yellow viscous sirup could not be made to crystallize. It showed no reduction to Fehling's solution. The refractive index was N_D^{24} 1.5030 and the specific optical rotation was $[\alpha]_D^{27} = \frac{-3.53 \times 100}{2 \times 4 \times 3.612} = -12.2^\circ$ in chloroform. Mutarotation was not observed. The sirup distilled in a pressure of less than one millimeter and at a temperature of 200°. The distillate was colored a light yellow evidencing some decomposition. After dissolving in ether and filtering from norite the almost colorless distillate showed a refractive index of N_D^{24} 1.5050 and a specific optical rotation of $[\alpha]_D^{30} = \frac{-0.35 \times 100}{2 \times 4 \times 0.3323} = -13.15^\circ$.

Analysis. Calcd. for $(C_2H_5S)_2$ $C_{16}H_{22}O_{10}$: S, 12.98. Sample: 0.00410 g.; 2.34 cc. of 0.015 N NaOH. Found: S, 13.7.

Demercaptalization

Five grams of the above mercaptalated sirup were dissolved in 20 cc. of acetone and 10 g. of cadmium carbonate were added. The mixture was stirred in a three necked flask by a strongly driven glass stirrer. Then 10 grams of mercuric chloride dissolved in 14 cc. of acetone were slowly added. While the mixture was continually stirred small quantities of cadmium carbonate were added from time to time. After one and a half hours the temperature of the solution was raised to 40° for fifteen minutes. Then the mixture was filtered and the precipitate washed with acetone. The acetone filtrates were combined. After the addition of fresh cadmium carbonate, the acetone was removed under diminished pressure. The dry residue was extracted with chloroform and the chloroform extract evaporated under reduced pressure. On the addition of ether to the residue, white crystals melting at 98° were obtained. On mixing some of these crystals with crystals of authentic keto sorbose pentaacetate the melting point remained at 98°.

Preparation of Monotrityl-l-sorbose

To 5 grams of sorbose dissolved in 30 cc. of dry pyridine were added 8 grams of trityl chloride. The mixture was allowed to stand at room temperature over night. It was then poured into a liter of ice water. After decanting the water from the precipitated sirup, the sirup was dissolved in 75 cc. of chloroform and the chloroform solution washed with 5% hydrochloric acid, sodium bicarbonate and water. The chloroform solution was dried over sodium sulfate and filtered from norite. On adding alcohol and evaporating

6 grams of crystals were obtained. The crystals gave no precipitate when treated with phenyl hydrazine. The impure crystals melted at 87° and showed an optical rotation of $[\alpha]_D^{26} - 21.7°$ in chloroform.

Preparation of Monotosyl-l-sorbose

To 5 grams of l-sorbose dissolved in 100 cc. of cold, dry pyridine were added 5.2 grams of tosyl chloride. The mixture was allowed to stand over night in the ice box. Then an equal volume of petroleum ether (B.P. 30-40°) was added and the top layer removed. The sirupy bottom layer was dissolved in hot ethyl acetate and filtered from norite. Lead carbonate was added to remove any remaining hydrogen chloride. After filtering and cooling the solution deposited 2 grams of crystals having a melting point of 140° and an optical rotation in water of $[\alpha]_D^{27} = \frac{-.60 \times 100}{4 \times 4 \times 0.2095} = -35.9°$. The crystalline material did not form an osazone when treated with phenyl hydrazine. The crystals did not seem to be completely pure. Lack of time prevented the purification of this substance.

SUMMARY

1. α-Methyl-*l*-sorboside was completely methylated to a pentamethyl derivative, which on hydrolysis of the glycosidic methyl group yielded a tetramethyl-*l*-sorbose ($[\alpha]^{28}_{D}$ + 4.95°). The oxidation of this latter compound by means of nitric acid resulted in the production of *dextro*-dimethoxysuccinic acid. The isolation of this acid was taken as sufficient evidence for the assumption of a normal pyranose structure in the tetramethyl-*l*-sorbose and, hence, also in the parent compound α-methyl-*l*-sorboside and its derivatives.

2. α-Methyl-*l*-sorbopyranoside tetrabenzoate was prepared.

3. α-Ethyl-*l*-sorbopyranoside and α-ethyl-*l*-sorbopyranoside tetraacetate were prepared and characterized. By means of a series of well established reactions these compounds were linked definitely to α-methyl-*l*-sorbopyranoside, thus proving the presence of a pyranoid ring in their structures.

4. The rates of formation and the rates of hydrolysis for α-methyl-*l*-sorbopyranoside and α-ethyl-*l*-sorbopyranoside were determined.

5. A calcium chloride addition compound of α-l-sorbose was prepared and characterized.

6. A sirupy l-sorbose thioacetal pentaacetate was prepared from keto sorbose pentaacetate.

7. A monotrityl and a monotosyl derivative of l-sorbose were prepared.

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