insoluble material through coarse fritted glass covered with a layer of Celite, concentrated to about 300 ml. under reduced pressure and freeze-dried. The polymer had a limiting viscosity number, $[\eta]$, of 410 in water.

Polymerization with benzoyl peroxide and α,α′-azoisobutyronitrile (AIBN). Sixteen 18 × 150 mm. test tubes were charged with monomer as follows: Tubes 1, 5, 9, 13: 235 mg. (10^{-3} mole) of *N*-acryloyl-D-glucamine. Tubes 2, 6, 10, 14: 1175 mg. (5×10^{-3} mole) of *N*-acryloyl-D-glucamine. Tubes 3, 7, 11, 15: 249 mg. (10^{-3} mole) of *N*-methacryloyl-D-glucamine. Tubes 4, 8, 12, 16: 1245 mg. (5×10^{-3} mole) of *N*-methacryloyl-D-glucamine.

Air was replaced with nitrogen by flushing as described above, 9 ml. of dimethylformamide (DMF) was added to each tube, and the tubes were stoppered. The *N*-acryloyl-D-glucamine dissolved readily but the methacryloyl compound was less soluble. Tubes 1–4 and 9–12 were placed in an oven at 60° for 30 min. Solution was still incomplete in tubes 4 and 12. Initiator was added to each of these eight tubes as follows: Tubes 1–4: 1 ml. of 2.4% (10^{-4} mole) benzoyl peroxide in dimethylformamide. Tubes 9–12: 1 ml. of 1.6% (10^{-4} mole) α,α′-azoisobutyronitrile in dimethylformamide. The stoppered tubes were then heated at 60° for 48 hr. Complete solution of the methacryloyl compound in tubes 4 and 12 did not occur. Initiator was added to the remaining eight tubes in a like manner: Tubes 5–8 received 1 ml. of 2.4% benzoyl peroxide in dimethylformamide. Tubes 13–16 received 1 ml. of 1.6% α,α′-azoisobutyronitrile in dimethylformamide. These tubes were immersed in a boiling water bath for 30 min. during which time the methacryloyl compound in tubes 8 and 16 did not completely dissolve. After 30 min. the tubes were chilled in cold water.

The polymers were only slightly soluble in dimethylformamide and usually precipitated as a sticky mass. They were triturated with methanol, collected on filters, dissolved in water, and dialyzed. The resultant solutions were concentrated under reduced pressure to a volume of about 30 ml. for measurement of viscosity. Yields were calculated as described above.

Measurement of viscosity. Viscosities were determined in aqueous solution at 25.0° using an Ubbelohde viscometer in which dilutions of 25:30, 25:35, 25:40, and 25:45 were made by the successive addition of 5-ml. portions of water to a 25-ml. aliquot of the original solution. The concentrations of the undiluted polymer solution were determined by drying on Celite at 100° in a vacuum oven. Limiting viscosity numbers,[15] $[\eta] = \lim_{C \to 0} \eta - \eta_0/\eta_0 C$, were calculated without application of density or kinetic energy corrections, which were negligible.

Measurement of molecular weight. The osmotic molecular weight of one of the polymers was determined in 0.1 molar sodium chloride solution using the Stabin-Immergut modification[16] of the Zimm-Myerson[17] osmometer with gel-cellophane membranes[18] and redistilled toluene as the manometric liquid. A value of 3.1×10^6 was found.

Electrolyte tolerance of poly(N-acryloyl-D-glucamine). To 10 g. of electrolyte solution 2–3 drops of a 2% solution of poly(*N*-acryloyl-D-glucamine) were added, and the solution was observed for precipitation of the polymer.

Acknowledgment. The authors thank the National Science Foundation and the Corn Industries Research Foundation for grants in partial support of this work.

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(16) J. V. Stabin and E. H. Immergut, *J. Polymer Sci.*, **14**, 209 (1954).

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[CONTRIBUTION FROM THE CHEMICAL RESEARCH DEPARTMENT, ATLAS POWDER CO.]

Catalytic Isomerization of the Hexitols; D-Glucitol, D-Mannitol, L-Iditol, and Galactitol

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A study has been made of the catalytic isomerization, in aqueous solution, of D-glucitol, D-mannitol, and L-iditol over the temperature range 130° to 190°. At 170° and 1900 p.s.i.g. hydrogen the quasi-equilibrium 2 D-glucitol ⇌ D-mannitol + L-iditol is established after three to four hours in the presence of nickel-kieselguhr catalyst. To a first approximation, the equilibrium concentrations of the hexitols are: 41.4 ± 2.5 wt. % D-glucitol, 31.5 ± 2.4 wt. % D-mannitol, and 26.5 ± 2.3 wt. % L-iditol. The presence of hydrogen is necessary for isomerization to occur; however, the extent of isomerization is virtually independent of hydrogen pressure over the range 650 to 2600 p.s.i.g. This may be a surface saturation (completion of a monolayer) effect. Isomerization occurs in alkaline solution, but is inhibited in mildly acid solutions. A mechanism is proposed, involving catalytic dehydrogenation of a hexitol followed by alkali catalyzed isomerization of the related aldo- and ketohexoses *via* 1,2-enediol intermediates. Hydrogenation of the hexose mixture completes the reaction scheme. A small amount of secondary isomerization of D-glucitol to galactitol (1–2%) and of D-mannitol and L-iditol to DL-talitol (2%) occurs under these conditions. Catalytic isomerization of galactitol at 170° and 1900 p.s.i.g. hydrogen yields two major products, DL-glucitol and DL-talitol, and two minor products, allitol and DL-mannitol. During this work the hexaacetyl derivatives of DL-talitol and DL-mannitol, and the tribenzylidene derivative of DL-talitol were prepared for the first time.

In recent years, the catalytic isomerization of polyhydric alcohols has been reported by several investigators.[1-8]

A series of papers on the hydrogenolysis of carbohydrates by von Rudloff, Tulloch, Perlin, Francis, and Gorin[1-6] is of particular interest in that

(1) E. von Rudloff and A. P. Tulloch, *Can. J. Chem.*, **35**, 1504 (1957).

(2) P. A. Gorin and A. S. Perlin, *Can. J. Chem.*, **36**, 661 (1958).

these authors are the first to point out that isomerization occurs frequently when carbohydrates are subjected to catalytic hydrogenation and/or hydrogenolysis conditions. Thus, these authors have shown that methyl β-D-glucopyranoside[1] isomerizes to a D-altrose derivative, that 1,2-*O*-isopropylidene-D-glucofuranoside[2] isomerizes to 1,2-*O*-isopropylidene-L-idofuranoside, and that methyl β-L-arabopyranoside[3] isomerizes to products from which D-xylose, D-ribose, and D-, and L-xylose can be obtained. From hydrogenolysis studies of methyl β-L-arabopyranoside-1-C^{14} at 250° Francis and Perlin[4] concluded that hydrogenolysis of the methoxyl group occurs initially, accompanied by isomerization. The isomerization of 1,2-*O*-isopropylidene-D-xylofuranoside[5] to 1,2-*O*-isopropylidene-D-ribofuranoside in 42% yield has been recently reported. Finally, comparative studies on the isomerization of α- and β-methyl glycopyranosides have been reported.[6]

Fletcher and Goepp[7] established quite a few years ago that when the dianhydride of either D-glucitol or D-mannitol is treated with Raney nickel at 200° under 250 atmospheres of hydrogen, isomerization to the dianhydride of L-iditol occurs.

Wicker[8] found that *cis-trans* isomerization of 3,3,5-trimethylcyclohexanol over nickel and platinum catalysts occurs only in alkaline solution.

The isomerization reaction appears to constitute an important synthetic path to rare sugars and sugar alcohols that have been hitherto available only in small quantities after multistep syntheses. For this reason, it seems desirable to report the results of a study of the isomerization of the hexitols, D-glucitol, D-mannitol, and L-iditol. When either D-glucitol or an equimolar mixture of D-mannitol and L-iditol is subjected to catalytic hydrogenation conditions, an equilibrium mixture of the three hexitols is obtained after three to four hours at 170°. During the course of this work, the effects of (a) temperature, (b) catalyst concentration, (c) hydrogen pressure, (d) hexitol structure, and (e) hydrogen ion concentration (in the *p*H range 5 to 9) on the equilibrium concentrations of D-glucitol, D-mannitol, and L-iditol were studied.

The *meso*-hexitol, galactitol, was selected as a substrate for further isomerization studies. We chose galactitol because it was readily available and because application of the 1,2-enediol mechanism predicted that we should obtain only one product, DL-talitol, thus simplifying the separation problems.

(3) A. S. Perlin, E. von Rudloff, and A. P. Tulloch, *Can. J. Chem.*, **36**, 921 (1958).

(4) T. Francis and A. S. Perlin, *Can. J. Chem.*, **37**, 1229 (1959).

(5) P. A. Gorin, *J. Org. Chem.*, **24**, 49–53 (1959).

(6) P. A. Gorin, *Can. J. Chem.*, **38**, 641–51 (1960).

(7) H. G. Fletcher and R. M. Goepp, *J. Am. Chem. Soc.*, **68**, 938 (1946).

(8) R. J. Wicker, *J. Chem. Soc.*, 2165 (1956).

EXPERIMENTAL

Materials. D-Glucitol (sorbitol) was obtained as a 70% aqueous solution (Atlas SORBO®) containing not more than 0.1% reducing sugar. Atlas reagent grade D-mannitol, m.p. 166–167°, was used without further purification. Galactitol, m.p. 187–188°, was prepared by the hydrogenation of D-galactose over nickel-kieselguhr catalyst at 160°. L-Iditol was prepared by the hydrogenation of technical grade L-sorbose (Merck). The co-produced D-glucitol was separated as the relatively insoluble pyridine complex[9] and the residual L-iditol crystallized from methanol, m.p. 73–73.5°.

The nickel-kieselguhr catalyst employed was a conventional supported nickel catalyst of the type described by Adkins.[10] The experiments reported here were made with several large batches of catalyst exhibiting no significant change in activity from batch to batch. Surface area measurements by the BET method indicated that the surface area of the catalyst used in this study varied only from 128 to 133 $m.^2/g.$, prior to reduction.

Electrolytic hydrogen was obtained from the Liquid Carbonic Company and was used without further treatment.

Pyridine, reagent grade, was obtained from the Allied Chemical and Dye Corporation as a water-white liquid and was used as received.

Apparatus. All high pressure experiments were carried out in a 1-l. stainless steel autoclave obtained from Pressure Products Industries, Hatboro, Pa. Agitation is supplied by a turbine, driven by a $^1/_{12}$ h.p. induction motor, the rotor of which operates under autoclave pressure at 1750 r.p.m. The turbine is a rotating impeller type, capable of providing internal gas recirculation without relying on vortex motion. This gas-pumping impeller was recently described by Snyder *et al.*[11]

The autoclave was equipped with a pressure recorder (0 to 3000 p.s.i.g.) and a Dynamaster electric proportional input temperature controller both supplied by the Bristol Company, Waterbury, Conn.

Provision was made for obtaining samples during the course of an experiment. A dip-tube extending to the bottom of the autoclave was connected to an external 20 μ line filter (Poroloy Company) and then to a high pressure valve.

Procedure. The general experimental procedure for an isomerization experiment was as follows: 286 g. (1.1 moles) or 592 g. (2.2 moles) of 70% D-glucitol solution was mixed with a sufficient quantity of nickel-kieselguhr catalyst under nitrogen to obtain a nickel content of 2.0%. The slurry (*p*H 8.8) was added to the autoclave, purged with nitrogen, and pressurized with hydrogen to 1300 p.s.i.g. at room temperature. The autoclave was then heated with agitation to reaction temperature, usually 170°, over a 35–38 min. period. After various time periods, liquid samples were taken for analysis by adsorption column chromatography.[12] Hexitol analyses were determined by periodate oxidation as described by Jackson.[13]

Characterization of D-glucitol isomerization products; general scheme. Chromatographic analysis of a typical D-glucitol isomerization product (Run 2, Table 5) indicated the presence of at least three hexitols, corresponding in their migration rates down the column to iditol, glucitol, and mannitol in order of increasing rate.[12]

(9) H. H. Strain, *J. Am. Chem. Soc.*, **56**, 1756 (1934).

(10) H. Adkins, *Reactions of Hydrogen with Organic Compounds Over Copper Chromium Oxide and Nickel Catalysts*, University of Wisconsin Press, Madison, Wis. (1937), pp. 14–19.

(11) J. R. Snyder, P. F. Hagerty, and M. C. Molstad, *Ind. Eng. Chem.*, **49**, 689 (1957).

(12) The method is based on the work of B. W. Lew, M. L. Wolfrom, and R. M. Goepp, *J. Am. Chem. Soc.*, **68**, 1449 (1946).

(13) E. L. Jackson, *Org. Reactions*, II, 341 (1944).

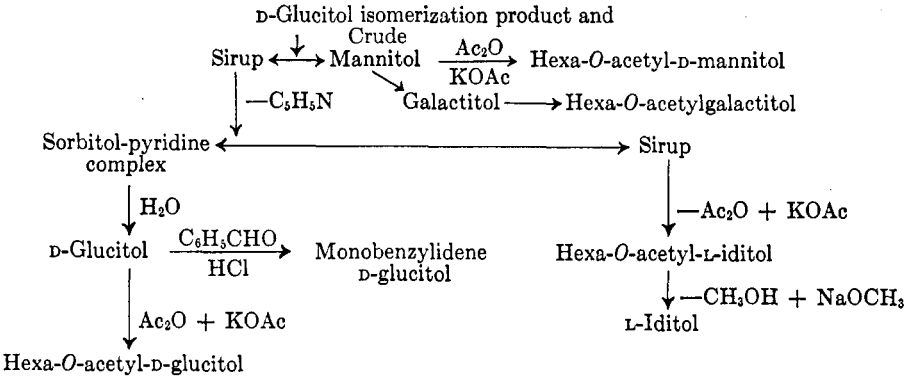

Fig. 1. Separation flow sheet

In order to identify the constituents of the isomerization product, a macro-scale separation was undertaken (Fig. 1).

All melting points are uncorrected.

A. Separation of D-*mannitol and galactitol.* Methanol, 75 ml., was added to 420 g. of aqueous hexitol solution containing 240 g. of hexitol (42.9% H_2O) (Run 2, Table 5) and crystallization allowed to proceed for 48 hr. at 0°. The crystallized hexitol was separated by filtration and washed with cold methanol; yield after drying *in vacuo*, 30.0 g. (12.5%), m.p. 148–159°. Recrystallization of a 5.0-g. sample from methanol-water yielded two fractions; (1) 0.5 g. (10%) of undissolved hexitol, m.p. 183–186°. This hexitol was identified as galactitol, m.p. 188–189°,[14] by conversion to the hexacetyl derivative,[15] m.p. and mixed m.p. with an authentic sample of hexa-*O*-acetylgalactitol, 169–170°.[14]

(2) The filtrate from the separation of galactitol was allowed to stand 16 hr. at room temperature and the crystallized hexitol filtered; yield: 2.9 g. (58%) crude mannitol, m.p. 157–159°. This hexitol was identified as mannitol by conversion to the hexacetyl derivative, m.p. and mixed m.p. with an authentic sample of hexa-*O*-acetyl-D-mannitol, 124–125°.[14] $[\alpha]_D^{26}$ +25.7° (*c* 10.6, chloroform). (Lit.[14] +25.0°).

B. Separation of D-*glucitol.* The filtrate from the mannitol crystallization was concentrated to a thick sirup under reduced pressure; yield, 220.7 g. The dried sirup was dissolved in 450 ml. of hot pyridine and then cooled. Crystallization of the sorbitol-pyridine complex[9] was initiated by seeding. The crystalline material was filtered, washed with cold pyridine and air-dried for 24 hr.; yield, 173.3 g., m.p. 58–74°. A 100.0-g. sample of the sorbitol-pyridine complex was taken up in 150 ml. of water and the solution concentrated under reduced pressure. A 3.5-g. sample of the sirupy hexitol product was diluted with 7 ml. of methanol. Benzaldehyde, 1 ml., and 1 ml. of concd. hydrochloric acid were added. After standing 16 hr. at room temperature, the sample was stirred until gelation occurred. The product crystallized and was filtered and washed with methanol-water (1:1); yield, 2.0 g. Recrystallization from water containing 1 g. of sodium bicarbonate yielded 1.0 g., m.p. 173–175°. The 2,4-*O*-monobenzylidene derivative of D-glucitol melts at 176–177°.[16] A 10.0-g. sample of the sirupy hexitol was acetylated[15] to complete its identification; yield, 21.6 g. (91%) of crude hexa-*O*-acetyl-D-glucitol, m.p. and mixed m.p. with an authentic sample of hexa-*O*-acetyl-D-glucitol, 98–99°.[14]

C. Separation of L-*iditol.* The pyridine filtrate was evaporated *in vacuo;* yield, 72.4 g. of sirupy hexitol. A 69.3-g. sample of sirup (which could not be crystallized) upon acetylation and quenching in water yielded 120.3 g. (72.8%) of crude hexaacetyl derivative. Recrystallization from ethanol yielded 63 g. (52%), m.p. and mixed m.p. with an authentic sample of hexa-*O*-acetyl-L-iditol, 121–122°. $[\alpha]_D^{26}$ −25.2° (*c* 14.0, chloroform), (lit.[14] −25.3°).

D. Recovery and crystallization of L-*iditol.* A 50.0-g. sample of hexaacetyl-L-iditol was mixed with 200 ml. of methanol and 0.25 g. of sodium methoxide. The mixture was stirred vigorously at room temperature. After 10 min., the system became homogeneous and was allowed to stand overnight. The solvent was removed under vacuum; yield of sirupy hexitol, 21.7 g. (quantitative). The sirupy hexitol was dissolved in 100 ml. of hot methanol and allowed to crystallize at 0°. After 24 hr., large crystals appeared. The crystalline L-iditol was filtered and dried in a vacuum desiccator; yield, 17.4 g. (80.2%), m.p. 71–73°. This material did not depress the melting point of L-iditol prepared by the hydrogenation of L-sorbose.

E. Separation of DL-*talitol.* The aqueous quench solution, obtained as a filtrate after removal of crude hexaacetyl-L-iditol, yielded after several weeks of slow evaporation at room temperature, a low melting hexaacetyl derivative. Two recrystallizations from ethanol gave a crystalline hexaacetyl derivative in 2% yield, based on D-glucitol charged, m.p. and mixed m.p. with a sample of hexa-*O*-acetyl-DL-talitol, 81–83°. $[\alpha]_D^{25}$ −0.6° (*c* 15.7, chloroform, 2-dm. tube).

Characterization of D-*mannitol isomerization products.* A 70% aqueous slurry of D-mannitol containing 151 g. of mannitol and sufficient catalyst to give a 2.0 wt. % nickel content was isomerized at 180° and 2000 p.s.i.g. hydrogen pressure for 2 hr. After removal of the catalyst by filtration, crystallization of the products from aqueous ethanol solution gave 41.8 g. (28%) hexitol, m.p. 149–160°. Recrystallization from ethanol in 80% yield gave crude mannitol, m.p. 159–162°. Acetylation yielded a hexaacetyl derivative, m.p. and mixed m.p. with an authentic sample of hexa-*O*-acetyl-D-mannitol, 124–125°. $[\alpha]_D^{26}$ +23.4° (*c* 14.0, chloroform).

The ethanol water filtrate was evaporated *in vacuo* and the resulting sirupy hexitol (yield: 134 g.) taken up in hot pyridine (2:1 pyridine:hexitol). A 57.3-g. sample of the sorbitol-pyridine complex, m.p. 71–73°, was separated by crystallization. This is equivalent to 27% D-*glucitol on a* 1:1 pyridine:D-glucitol basis.

The pyridine filtrate was evaporated *in vacuo* and the sirupy hexitol, 71.3 g., acetylated in 51% yield. Fractional crystallization yielded three fractions. (1) m.p. 162–165° in 2% yield based on mannitol, (2) m.p. 121–122° in 3% yield, and (3) m.p. 78–79° in 4% yield. Recrystallization of fraction 1 from ethanol raised the m.p. to 169–170°. A mixture of fraction 1 and hexa-*O*-acetylgalactitol melted

(14) R. H. Lohmar, Jr., in *The Carbohydrates*, W. Pigman, ed., Academic Press, N. Y., 1957, p. 247.

(15) R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, John Wiley & Sons, N. Y. (1948), p. 165 Procedure A.

(16) S. J. Angyal and J. V. Lawler, *J. Am. Chem. Soc.*, **66**, 837 (1944).

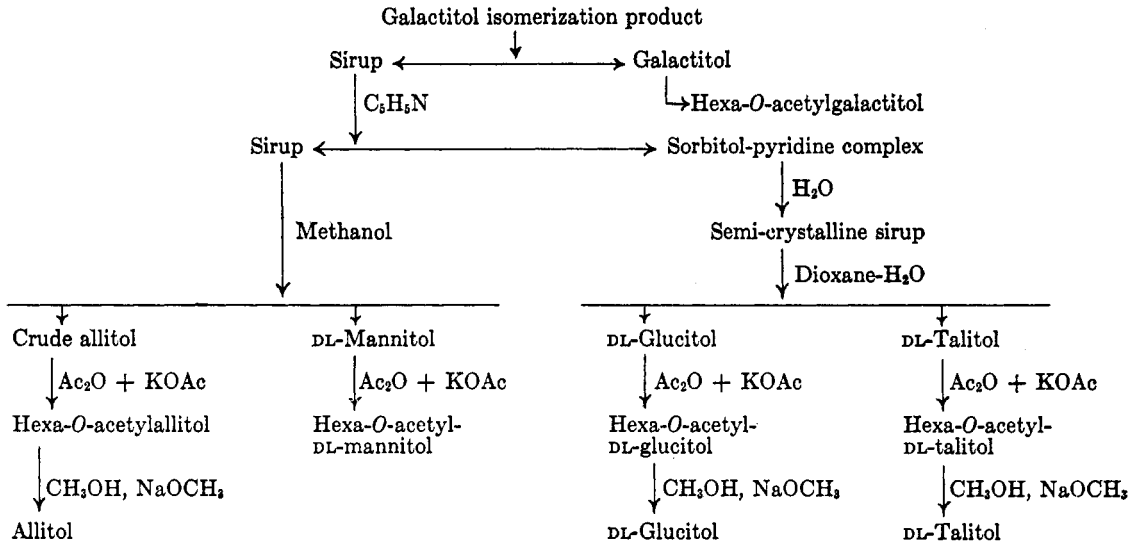

Fig. 2. Separation flow sheet

at 169–170°. Fraction two gave m.p. and mixed m.p. with an authentic sample of hexa-*O*-acetyl-L-iditol, 121–122°.[14] $[\alpha]_D^{26}$ −24.2° (*c* 14.0, chloroform). Fraction 3, $[\alpha]_D^{25}$ +0.2° (*c* 14.2, chloroform, 2-dm. tube), appears to be a hexaacetyl derivative of DL-talitol as suggested by comparison of the infrared spectrum of fraction 3 with that of the spectrum of a sample of hexa-*O*-acetyl-DL-talitol obtained from other sources.

Characterization of L-*iditol isomerization products.* A 70% solution of L-iditol (100 g. of L-iditol) was isomerized at 170° for 2 hr. at a 4.0% nickel concentration and 1900 p.s.i.g. hydrogen pressure. The products were worked up in the usual manner. No mannitol or galactitol crystallized after storing in aqueous ethanol (1:1) solution of the products at 0° for 72 hr.

The solution was evaporated *in vacuo*, the residual hexitols (96.0 g.) taken up in hot pyridine (192 ml.) and 49.2 g. of sorbitol-pyridine complex, m.p. 70–73°, crystallized after standing 24 hr. at 0°. This amount of sorbitol-pyridine complex is equivalent to 34 g. of D-glucitol (34% yield).

The pyridine filtrate was evaporated *in vacuo*; yield, 63.3 g. of sirupy hexitol. Acetylation gave hexa-*O*-acetyl-L-iditol, in 55% yield, m.p. and mixed m.p. 121–122°, equivalent to 35 g. (35%) of L-iditol. No other hexitols were found.

Characterization of galactitol isomerization products; general scheme. A preliminary isomerization experiment under isomerization conditions used for D-glucitol resulted in a rather low degree of isomerization of galactitol. After crystallization of much galactitol from the product a low melting hexitol fraction, m.p. 88–90°, was obtained in 12% yield. Comparison of the infrared spectrum of this material with that of D-talitol and D-glucitol suggested that this material was a mixture of glucitol and possibly talitol. Having established that the products contained glucitol, a method of separation based on the methods used for the separation of D-glucitol isomerization products was adopted. This separation involved cystallization of the majority of the unconverted galactitol from ethanol-water solution, separation of DL-glucitol as the relatively insoluble pyridine complex, and characterization of the residual hexitols by derivatization, (*cf.* Fig. 2).

More severe isomerization conditions were needed to isomerize galactitol than had been found suitable for the isomerization of D-glucitol. Thus, 4.0 hr. at 6.0% nickel, 1900 p.s.i.g. hydrogen pressure and 170° gave a satisfactory conversion level.

A. Separation of galactitol. A 35% aqueous slurry of galactitol (400 g. of galactitol) (*p*H 8.9) was isomerized for 4 hr. at 170°, 1900 p.s.i.g. hydrogen, and 6% nickel. After filtration of the products to remove catalyst, 400 ml. of 95% ethanol was added and crystallization allowed to proceed for 48 hr. at 0°. A 120.2-g. sample (30%) of crude galactitol, m.p. 170–172°, was obtained by filtration. Recrystallization of a 10-g. sample in 84% yield gave crude galactitol, m.p. 180–181°. Acetylation of a 3.0-g. sample of this material yielded 7.0 g. of hexa-*O*-acetylgalactitol which, after recrystallization from ethanol, had m.p. and mixed m.p. 169–170° with an authentic sample of hexa-*O*-acetylgalactitol.

B. Separation of DL-*glucitol.* The filtrate, after removal of most of the galactitol, was evaporated *in vacuo*; yield, 258.7 g. of sirupy hexitol which was taken up in 560 ml. of hot pyridine, seeded with a crystal of sorbitol-pyridine complex, and allowed to crystallize at 0° for 24 hr.; yield, 263.9 g. (46%) air dried sorbitol-pyridine complex (equivalent to 184 g., 46% sorbitol).

A 263.9-g. sample of the sorbitol-pyridine complex were taken up in 500 ml. of distilled water and the solution evaporated *in vacuo*; ethanol was added to facilitate the dehydration of the hexitol; yield, 184.3 g. of sirupy semi-solid product. Considerable DL-talitol coprecipitated with the sorbitol-pyridine complex during this separation of galactitol isomerization products. Recrystallization of the sirupy hexitol mixture from dioxane-water yielded 56.0 g. (14% based on galactitol) of crude crystalline DL-glucitol, m.p. 118–124°. The crude DL-glucitol was further purified by acetylation with potassium acetate and acetic anhydride and the product fractionally crystallized from ethanol. Two fractions were obtained: (1) 70.5 g., m.p. 115–116°, (7.3% based on galactitol) was hexa-*O*-acetyl-DL-glucitol.[17] (2) 28.6 g. (3.0% based on galactitol) of hexaacetyl derivative, m.p. 97–100°. The melting point was not depressed by mixing with a sample of hexa-*O*-acetyl-D-glucitol, m.p. 97–99°.

Since the measured specific rotation of fraction 2 is close to zero and yet has the proper melting point for D- or L-

(17) M. L. Wolfrom, B. W. Lew, R. A. Hales, and R. Max Goepp, Jr., *J. Am. Chem. Soc.*, **68**, 2342 (1946), obtained a melting point of 116–117° for a sample of synthetic hexa-*O*-acetyl-DL-glucitol prepared by recrystallizing a 1:1 mixture of the enantiomorphous forms of sorbitol hexaacetate.

glucitol hexaacetate, this material is believed to be a mechanical mixture of hexaacetyl-D- and L-glucitols. The infrared spectrum of fraction 2 was closely similar to that of fraction 1. Attempts to recrystallize this material to convert it into hexa-*O*-acetyl-DL-glucitol were not successful. However, when fractions 1 and 2 were separately subjected to methanolysis at room temperature in the presence of a trace of sodium methoxide, DL-glucitol was obtained from both fractions, yield: 26.6 g. (6.7% based on galactitol), m.p. 129–133°. Two recrystallizations from dioxane-water raised the melting point to 134–135°.[17]

C. Separation of DL-*talitol.* The dioxane-water filtrate, after separation of DL-glucitol, was evaporated *in vacuo;* yield, 133.4 g. of sirupy hexitol. The sirupy hexitol was taken up in ethanol and 98.9 g. (24.8%) of hexitol, m.p. 88° to 90°, separated by crystallization. Acetylation of the crude hexitol yielded 85.8 g. (8.9% based on galactitol) of crude hexa-*O*-acetyl-DL-talitol, m.p. 82–83°. Methanolysis yielded 15.4 g. (3.8% based on galactitol) of DL-talitol, m.p. 93–95°.[18] Acetylation of a 3.0-g. sample of DL-talitol yielded hexa-*O*-acetyl-DL-talitol, m.p. 85–86°, previously unreported in the literature.

Anal. Calcd. for $C_6H_8O_6(COCH_3)_6$: C, 49.77; H, 6.03. Found: C, 50.23; H, 6.04.

D. Tribenzylidene derivative of DL-*talitol.* A 1.0-g. sample of DL-talitol was dissolved in 2 ml. of 50% sulfuric acid, 2 ml. of benzaldehyde was added, and the mixture was shaken frequently. Crystallization occurred gradually over a 1-week period. The derivative was filtered and washed with ethanol; yield 0.67 g., m.p. 156.5–158.5°, after two recrystallizations from ethanol. The absence of free hydroxyl groups, as determined by a hydroxy number of zero, establishes the derivative as tribenzylidene-DL-talitol.[19]

Anal. Calcd. for $C_6H_8O_6(HCC_6H_5)_3$: C, 72.85; H, 5.83. Found: C, 72.89; H, 5.82.

E. Separation of DL-*mannitol and allitol.* The pyridine filtrate (after removal of the majority of the galactitol, glucitol, and talitol) was evaporated *in vacuo*; yield, 90.7 g. (23%) sirup. The dried sirup was taken up in methanol yielding 30.8 g. (7.7% based on galactitol) of crude hexitol, m.p. 108–110°, and 2.8 g. (0.7%) of a second crop, m.p. 143–154°. Recrystallization of the latter fraction from ethanol yielded 1.4 g. (0.35%) of a crystalline hexitol, m.p. 168–169°, probably DL-mannitol (lit.[14] m.p. 168–169°). Acetylation yielded hexa-*O*-acetyl-DL-mannitol, m.p. 107–109°, previously unreported, the infrared spectrum of which matched the infrared spectrum of hexa-*O*-acetyl-D-mannitol.

Anal. Calcd. for $C_6H_8O_6(COCH_3)_6$: C, 49.77; H, 6.03. Found: C, 49.75; H, 5.91.

The first crop of hexitol, 30.8 g., m.p. 108–110°, was acetylated yielding considerable hexa-*O*-acetylgalactitol and, from the aqueous quench solution, 23.5 g. (2.4% based on galactitol) of hexa-*O*-acetylallitol, m.p.[14] 58–60°. Methanolysis of a 13.0-g. sample of hexa-*O*-acetylallitol in methanol containing a trace of sodium methoxide yielded 2.2 g. (41%) allitol, m.p.[14] 146–148°. Acetylation of the noncrystallizable portion (from methanol) of the residual hexitols, 61.3 g., gave additional quantities of crude hexa-*O*-acetylgalactitol, 49.4 g. (5.1%), and hexa-*O*-acetyl-DL-talitol, 12.6 g. (1.3%).

(18) F. L. Humoller, M. L. Wolfrom, B. W. Lew, and R. M. Goepp, Jr., *J. Am. Chem. Soc.*, **67**, 1226 (1945) obtained a melting point of 95–96° for a sample of DL-talitol prepared by recrystallizing a 1:1 mixture of the enantiomorphous D- and L-talitol.

(19) E. Fisher, *Ber.*, **27**, 1528 (1894) obtained a melting point of 205–206° for the tribenzylidene derivative; however, as Lohmar points out (Ref. 14, p. 256), it is probable that Fisher's product was impure. His DL-talitol melted at 66–67° in contrast to our value of 95–96° (also, *cf.* Ref. 18).

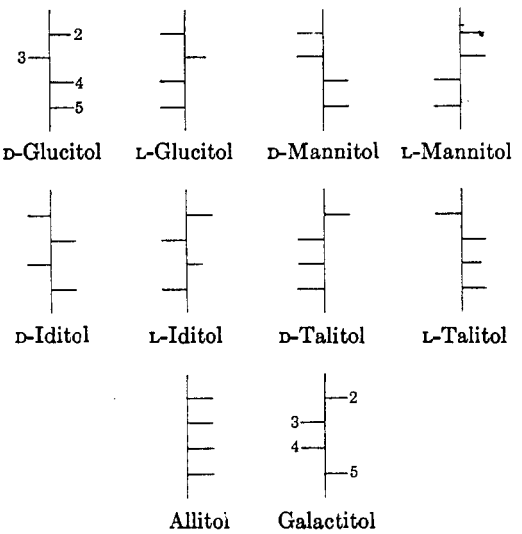

Fig. 3. Fischer projections

RESULTS AND DISCUSSION

In the experimental part of this paper, a description was given of the isolation and identification of D-mannitol and L-iditol as the major isomerization products of D-glucitol. It was also shown that D-glucitol is the major isomerization product of the isomerization of either D-mannitol or L-iditol.

In order to obtain information that would lead to a better understanding of the isomerization reaction, a study was made of the effect of the following reaction variables on the isomerization of D-glucitol: (a) catalyst concentration, (b) contact time, (c) temperature, (d) hydrogen pressure, and (e) hydrogen ion concentration. Some equilibrium studies were also carried out with 1:1 mixtures of D-mannitol and L-iditol and with a 4:3:3 mixture of D-glucitol, D-mannitol, and L-iditol.

Catalyst concentration. The effect of catalyst concentration on the rate of isomerization of D-glucitol was studied at 160° and 170°. At both temperatures the extent of conversion of D-glucitol to D-mannitol and L-iditol is proportional to the amount of nickel catalyst used. The results of this study at 170° and 1.0 to 4.0% nickel are given in Table I. The data also indicate, to a first approximation, that the rates of formation of D-mannitol and L-iditol are equal. Control runs in the absence of nickel catalyst, in both neutral and alkaline solu-

TABLE I

ISOMERIZATION OF D-GLUCITOL.[a] EFFECT OF CATALYST CONCENTRATION

Nickel, Wt. %	Product Analysis,[b] Wt. %		
	Glucitol	Mannitol	Iditol
1.0	68.8	14.6	16.7
2.0	50.9	22.5	24.2
4.0	40.1	29.5	27.8

[a] 170°, 3.0 hr., 1900 p.s.i.g. hydrogen, 70% D-glucitol solution. [b] Analysis by column chromatography.[12]

tion, did not result in measurable isomerization of D-glucitol.

Contact time. The effect of contact time on the isomerization of D-glucitol was studied at 170°, 2.0 and 4.0% nickel, and 1 to 6 hours contact time. The data in Table II show that a close approach to an apparent equilibrium is obtained in 3.0 hours at 2.0% nickel and in two to three hours at 4.0% nickel. These data suggest that an equilibrium is attained with approximately 40% D-glucitol, 30% D-mannitol, and 30% L-iditol being present in the equilibrium mixture. It is also possible that the glucitol zone contains a small amount of galactitol (see Experimental) since Lew, Wolfrom, and Goepp[12] have shown that glucitol and galactitol are not readily separated on a chromatographic column of the type used in analysis of these mixtures.

TABLE II

ISOMERIZATION OF D-GLUCITOL.[a] EFFECT OF CONTACT TIME

Nickel, %	Time, Hr.	Product Analysis,[b] Wt. % Glucitol	Mannitol	Iditol
2.0	1.0	85.1	11.4	1.4[c]
2.0	1.5	63.1	14.7	20.9
2.0	2.0	52.4	17.7	24.9
2.0	3.0	50.9	22.5	24.2
4.0	2.0	45.6	26.8	26.1
4.0	3.0	40.1	29.5	27.8
4.0	6.0	40.9	30.1	19.6

[a] 170°, 1900 p.s.i.g. hydrogen, 70% D-glucitol solution. [b] Analysis by column chromatography.[12] [c] Small amounts of iditol are difficult to separate from glucitol on an adsorption column. This value is probably low.

Equilibrium studies. After having established that an apparent equilibrium existed between glucitol, mannitol, and iditol, an attempt was made to approach equilibrium from the mannitol-iditol side of the equilibrium. Accordingly, a series of 1:1 mixtures of D-mannitol and L-iditol were isomerized at 170° and 4.0% nickel as a function of time. The results of this study are given in Table III. It is clear that the D-glucitol concentration of the reaction products increases with time up to about the same value, 35–45% obtained when starting with glucitol. The mannitol and iditol contents of the reaction products decrease regularly with increasing time to values in the neighborhood of 25–30%. These results suggest that an equilibrium exists between D-glucitol, D-mannitol, and L-iditol the composition of which is approximately 40% glucitol, 30% mannitol, and 30% iditol.

TABLE III

ISOMERIZATION OF A 1:1 MIXTURE[a] OF D-MANNITOL AND L-IDITOL.[b] EFFECT OF CONTACT TIME

Time, Hr.	Product Analysis,[c] Wt. % Glucitol	Mannitol	Iditol
0.5	18.3	39.6	38.8
1.0	27.6	36.6	33.6
2.0	35.1	34.1	30.3
3.0	43.6	34.0	22.6

[a] 50.0% D-mannitol, 50.0% L-iditol by weight. [b] 170°, 4.0% nickel, 50% hexitol solution, 1900 p.s.i.g. hydrogen. [c] Analysis by column chromatography.[12]

One limitation imposed on studies of the equilibrium composition of glucitol isomerization products is that hydrogenolysis of the carbon-carbon chain begins to occur if one attempts to study the reaction at contact times much longer than six hours at 170°. In order to circumvent this difficulty, an experiment was carried out in which the approximate equilibrium mixture was subjected to the usual isomerization conditions of 170° and 1900 p.s.i.g. hydrogen. Samples were taken as a function of time. The results of this study are given in Table IV. It is clear from these results, that, within a rather large experimental error, little change occurs in the concentration of D-glucitol, D-mannitol, and L-iditol over a four-hour period. If one averages the values of the concentrations of glucitol, mannitol, and iditol in Tables III and IV, eliminating those values that are clearly far from equilibrium one obtains the following equilibrium concentrations: D-glucitol 41.4 ± 2.5 (seven results), D-mannitol 31.5 ± 2.4 (seven results), L-iditol 26.5 ± 2.3 (seven results).

TABLE IV

ISOMERIZATION OF AN EQUILIBRIUM MIXTURE[a] OF D-GLUCITOL, D-MANNITOL, AND L-IDITOL.[b] EFFECT OF CONTACT TIME

Time, Hr.	Product Analysis,[c] Wt. % Glucitol	Mannitol	Iditol
0.5	44.4	28.7	26.2
1.0	40.6	29.8	31.3
2.0	43.3	27.8	25.0
3.0	43.0	31.9	24.4
4.0	39.9	34.3	25.6

[a] 40.0% D-glucitol, 30.0% D-mannitol, 30.0% L-iditol by weight. [b] 170°, 2.0% nickel, 50% hexitol solution, 1900 p.s.i.g. hydrogen. [c] Analysis by column chromatography.[12]

Temperature. The effect of temperature on the isomerization of D-glucitol was studied over the range 130° to 190°. The data are given in Table V. At 180° and 190° equilibrium is approached in 1.0 hour at 2.0% nickel concentration. At lower temperatures, larger amounts of catalyst and longer contact times are necessary to obtain comparable degrees of conversion. Thus, at 170° and 2.0% nickel a comparable isomerization level is achieved in two hours. At 160° and two hours time it is necessary to use 4.0% nickel to obtain a comparable conversion level. At 150°, four hours contact time are needed to achieve the same level. At 140°, still smaller amounts of isomerization occur in four hours and 4.0% nickel. At 130°, the isomerization is measurable but 6.0% nickel is necessary to obtain significant isomerization in four hours time.

TABLE V

ISOMERIZATION OF D-GLUCITOL.[a] EFFECT OF TEMPERATURE

Temp.	Time, Hr.	Nickel, Wt. %	Product Analysis,[b] Wt. % Glucitol	Mannitol	Iditol
190	1.0	2.0	53.3	20.3	26.4
180	1.0	2.0	54.4	17.8	23.5
170	1.0	2.0	85.1	11.4	1.4
170	2.0	2.0	52.4	17.7	24.9
160	2.0	2.0	84.8	10.5	1.5
160	2.0	4.0	56.5	18.6	19.2
150	4.0	4.0	59.5	19.1	21.1
140	4.0	4.0	72 0	12.3	12.2
130	4.0	6.0	71.9	8:0	10.3

[a] 70% D-glucitol solution, 1300 p.s.i.g. hydrogen at room temperature. [b] Analysis by column chromatography.[12]

Hydrogen pressure. The isomerization of D-glucitol was studied over a range of hydrogen pressure from 0 p.s.i.g. (no hydrogen added) to 2600 p.s.i.g. Run 59, Table 6, demonstrates that some hydrogen is necessary for measurable isomerization to occur in two hours at 170°. Comparison of runs 65 to 92, Table VI, indicates that isomerization increases with increasing hydrogen pressure over the range 210 to 650 p.s.i.g. This effect has been confirmed by duplicate runs. At higher pressures, a comparison of runs 92, 93, 89, and 66 indicates that the extent of isomerization is virtually independent of hydrogen pressure over the range 650 to 2600 p.s.i.g. Isomerization runs at 210 p.s.i.g. and six hours contact time show that mannitol and iditol are formed in essentially equal amounts. Thus, the low iditol content of run 65 is probably due to the difficulty of analyzing for small amounts (up to say 10%) of iditol in the presence of large amounts (60 to 85%) of glucitol.

TABLE VI

ISOMERIZATION OF D-GLUCITOL.[a] EFFECT OF HYDROGEN PRESSURE

Run	H_2 Pressure, P.s.i.g.	Product Analysis,[b] Wt. % Glucitol	Mannitol	Iditol
59	0.0[c]	90.3	3.0[d]	0.0
65	210	90.1	9.2	1.9
155	330	62.4	9.4	12.1
154	460	62.8	13.2	17.2
92	650	59.5	14.4	20.1
93	1220	55.9	18.2	18.6
89	1890	60.3	18.9	19.2
66	2600	53.8	17.2	23.5

[a] 170°, 2.0% nickel, two hours, 70% D-glucitol solution. [b] Analysis by column chromatography.[12] [c] Purged with nitrogen and run in nitrogen at one atmosphere. [d] The D-glucitol charge contained 2% mannitol by analysis.

Hydrogen ion concentration. The isomerization of D-glucitol is significantly influenced by the hydrogen ion concentration of the catalyst:glucitol slurry. Traces of alkali persist in the catalyst due to the method of preparation. Thus, as run 89, Table VII shows, the initial *p*H of the catalyst: glucitol slurry is 8.8. During the isomerization reaction, the *p*H falls to 7.6. When a catalyst:glucitol slurry is neutralized with phosphoric acid to a *p*H of 6.9, the isomerization proceeds to a somewhat lesser extent (run 94, Table VII). However, if the catalyst:glucitol slurry is neutralized to a *p*H of 5.2, the isomerization reaction does not occur to any significant extent (run 95, Table VII).

GENERAL DISCUSSION

The fact that the hexitol isomerization reaction is strongly influenced by the *p*H of the reaction medium is of considerable importance in suggesting a possible mechanism for the reaction. It is probable[20] that hexoses undergo isomerization in mildly alkaline solution *via* enediol intermediates to yield mixtures of aldo- and ketohexoses; however, see Hine[21] for other possible mechanisms. It is not unreasonable, therefore, to suggest that the hexitol isomerization reaction proceeds *via* the formation of a small, but catalytically significant, amount of a related aldohexose. (At 170° and 2000 p.s.i.g. hydrogen pressure, the equilibrium concentration of reducing sugar is approximately 0.02%). Thus, the 1,2-enediol could be formed as shown in the following scheme:

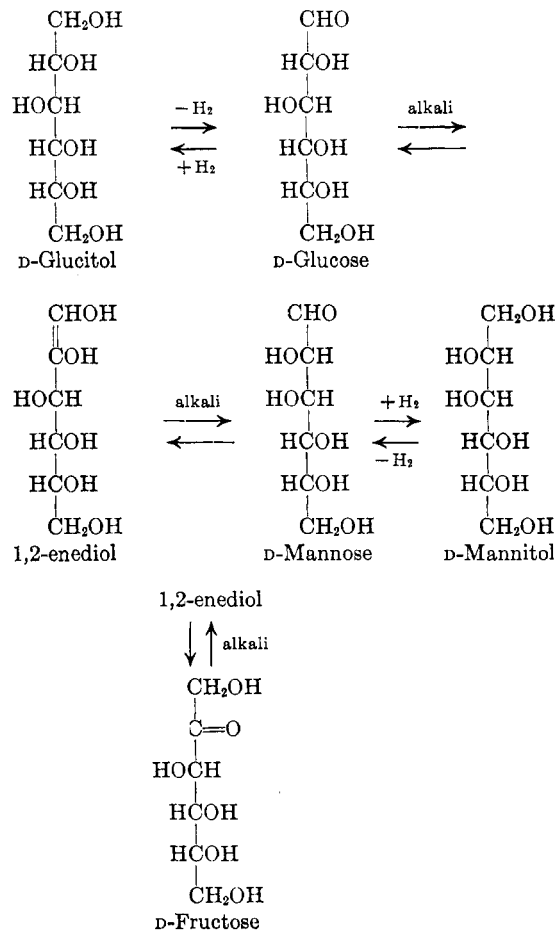

TABLE VII

ISOMERIZATION OF D-GLUCITOL.[a] EFFECT OF HYDROGEN ION CONCENTRATION

Run	Initial pH	Final pH	Product Analysis,[b] Wt. % Glucitol	Mannitol	Iditol
89	8.8	7.6	60.3	18.9	19.2
94	6.9	6.3	68.9	10.9	14.7
95	5.2	6.3	91.0	3.9	0.0

[a] 170°, 2.0% nickel, 1900 p.s.i.g. H_2, 70% D-glucitol solution. [b] Analysis by column chromatography.[12]

Hydrogenation of this equilibrium hexose mixture will yield D-glucitol and D-mannitol.

The dehydrogenation step could theoretically occur with equal probability at C_6 of D-glucitol. Hydrogenation of the expected equilibrium mixture of L-gulose, L-idose, and L-sorbose will yield D-glucitol (L-gulitol) and L-iditol. Thus, this mechanism allows the prediction of the reaction products to be expected from the isomerization of D-glucitol.

One can speculate as to the composition of the equilibrium mixture of glucitol, mannitol, and iditol to be expected from this kind of mechanism. Assuming a random dehydrogenation at the primary hydroxyls of D-glucitol, one might expect that the amounts of D-mannitol and L-iditol ultimately formed should be equal. If one further assumes that the equilibrium concentrations of D-glucitol and D-mannitol ultimately produced by dehydrogenation at C_1 are equal and that similarly, the equilibrium concentrations of D-glucitol and L-iditol produced by dehydrogenation at C_6 are equal, one would expect an equilibrium hexitol composition of 50% D-glucitol, 25% D-mannitol, and 25% L-iditol. Experimentally we obtain 41.4 ± 3% D-glucitol, 31.5 ± 2% D-mannitol, and 26.5 ± 2% L-iditol. These results differ sufficiently from a 50–25–25 mixture to be outside the limits of experimental error. Probably, the initial dehydrogenation at C_1 and C_6 is not completely random, but slightly favors C_1. This suggests that a trans configuration of hydroxyls at C_2 and C_3 or sorbitol may be a more favorable configuration for dehydrogenation than the *cis* configuration of hydroxyls at C_4 and C_5.

The enediol isomerization theory, when applied to D-glucitol, predicts that D-mannitol and L-iditol will be the isomerization products. This assumes that enediol formation is restricted to C_1 and C_2 and C_5 and C_6. If the 2,3-(or 3,4)-enediol is formed, the theory predicts that galactitol and allitol will be found. Galactitol in 1–2% yield has been found as a D-glucitol isomerization product, but allitol has not been isolated.

A somewhat simplified picture of the isomerization reaction can be given by reference to Fig. 3 where Fischer projections are given for the ten isomeric hexitols. Formation of a 1,2 or 5,6-enediol permits inversion of the configuration around C_2 or C_5, respectively, of D-glucitol yielding D-mannitol or L-iditol. Inversion of the configuration at C_3 or C_4 would lead to allitol or dulcitol, respectively.

One would predict from this scheme that D-glucitol would be the only (or major) product of the isomerizations of D-mannitol or L-iditol. This follows since inversion of the configuration around either C_2 or C_5, respectively, of D-mannitol or L-iditol would yield D-glucitol. Experimental data from the isomerizations of D-mannitol and L-iditol confirm this prediction and also show that, eventually, L-iditol is formed (in a D-mannitol isomerization) as a result of secondary isomerization of the primary isomerization product D-glucitol.

To summarize the results obtained from the isomerizations of D-glucitol, D-mannitol, and L-iditol the isomerization products isolated in reasonable purity are tabulated as follows:

D-Mannitol, %		D-Glucitol, %		L-Iditol, %	
D-Glucitol	50.0	D-Glucitol	27.0	D-Glucitol	34.0
D-Mannitol	11.5	D-Mannitol	22.4	L-Iditol	35.0
L-Iditol	11.0	L-Iditol	3.0		
Galactitol	1.0	Galactitol	2.0		
DL-Talitol	2.0	DL-Talitol	4.0		
	75.5		58.4		69.0

The catalytic isomerization of galactitol yields a product containing at least five hexitols. The separation of this complex mixture proved to be difficult. Initially, three crude hexitol fractions were obtained totaling 97% of the galactitol charged. Purification of these fractions by recrystallization and preparation of derivatives resulted in significant material losses due to solubility losses and incomplete derivatization reactions.

The hexitols isolated in reasonable purity from the products of galactitol isomerization experiments consists of: galactitol (25.2%), DL-glucitol (10.3%), DL-talitol (10.2%), DL-mannitol (0.4%), allitol (2.4%), total, 48.5%. These products can be accounted for by assuming that both 1,2- and 2,3-enediols are intermediates in the isomerization reaction. Thus, inversion of the configuration around C_2 and C_5, respectively, of galactitol will yield L- and D-talitol (*cf.* Fig. 3). Inversion of the configuration around C_3 and C_4, respectively, of galactitol will yield D- and L-glucitol. DL-Mannitol can be formed by secondary isomerization of DL-glucitol and allitol by secondary isomerization of DL-talitol.

The severity of the isomerization conditions appears to influence the relative amounts of 1,2- and 2,3-enediol participation in the reaction. Thus,

(20) J. Sowden and R. Thompson, *J. Am. Chem. Soc.*, **80**, 1435 (1958); J. Sowden and R. Schaffer, *J. Am. Chem. Soc.*, **74**, 505 (1952); see also Y. J. Topper and D. Stetten, Jr., *J. Biol. Chem.*, **189**, 191 (1951).

(21) J. Hine, *Physical Organic Chemistry*, McGraw-Hill, N. Y. (1956) pp. 264–5.

milder isomerization of galactitol at 4.0% nickel for three hours (at 170° and 1900 p.s.i.g. hydrogen) resulted in the formation of considerably more DL-talitol (14.1%) than DL-glucitol (2.7%). This indicates that isomerization is initiated at the ends of the molecule (1,2-enediol) and progresses toward the center (2,3-enediol) as isomerization conditions become more severe.

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On the Nitration of D-Fructose. II

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Among the reduction products of a mixture of nitrates formed by nitration of D-fructose with nitronium sulfate, a compound of formula $C_9H_{14}O_7$ could be isolated. This proved to be a new type of sugar derivative: a compound of an anhydride of D-fructose with pyruvaldehyde, probably having an acetal-like linkage between the two components.

In our previous communications on this subject[1,2] we described the large variety of products obtained by the action of different nitrating agents on D-fructose. The nature of these products depends largely upon the acidity of the reaction mixture. Whereas nitration with dinitrogen pentoxide yields a monomeric nitrated derivative of D-fructose,[3] in strongly acid media, the formation of di-D-fructose dianhydrides is predominant. Only one of these dianhydrides could be obtained as a nitrate ester in the form of crystals; the others were isolated after reductive denitration. These anhydrides gave a positive anthrone test, but did not reduce Fehling's solution. When hydrolyzed they yielded D-fructose quantitatively, with one exception.

This exceptional compound (I) exhibits a striking similarity to the compound described as di-D-fructose dianhydride II by Jackson and Goergen,[4] but it proved to be a sugar derivative of quite a new type: When hydrolyzed, the change in its rotatory power indicated the formation of D-fructose in a yield of about 60%,[5] the hydrolyzate reduced an amount of Benedict's solution equivalent to 150% of fructose, and it also reduced sodium hypoiodite equivalent to an aldose content of about 30%. The molecular weight and analytical data for I, (mol. wt. 260, C, 45.7; H, 6.2) correspond to a formula of $C_9H_{14}O_7$, *i.e.*, a C_6—C_3 compound. This compound is easily hydrolyzed. The C_3-moiety could be split off by brief heating with dilute acids and proved to be volatile, so that it could be separated from the hydrolyzate of I by distillation. The distillate reduced Fehling's solution rapidly, was optically inactive, and gave a 2,4-dinitrophenylosazone of melting point 145°.

The paper chromatogram of the hydrolyzate revealed two spots: one identical with that for D-fructose, and another, moving faster than trioses, giving a reaction with resorcinol. This second spot could be detected only if the developed chromatogram were dried without elevation of temperature.

All of these properties of the C_3-component of I indicated its identity with pyruvaldehyde. This component was either present in I or was derived from it during hydrolysis. It is well known that trioses afford pyruvaldehyde when they are treated with acids.[6-8] Compound I could, therefore, be either a compound of (a) D-fructose with a triose or (b) D-fructose with pyruvaldehyde; neither the analytical data nor the molecular weight determined allow a clearcut distinction. In order to decide between them, control experiments were performed on the formation of pyruvaldehyde from 1,3-dihydroxy-2-propanone and glycerose by the action of acids. It was found that far higher concentrations of acid, or much more prolonged heating, was necessary in order to produce traces of pyruvaldehyde from the trioses than from I. We also made sure that no pyruvaldehyde is pro-

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(2) A. Shamgar-Schwager and J. Leibowitz, *Bull. Res. Counc. of Israel*, **7A**, 84 (1958).
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(7) W. Lloyd Evans and Brook, *Am. Chem. J.*, **35**, 115 (1906).
(8) C. Enders, *Biochem. Z.*, 312 (1942).