

neomannide, is described and its structure determined as 1,5,3,6-dianhydromannitol. The observation that the latter is not identical with isomannide eliminates this structure and leaves only

the 1,4,3,6-dianhydromannitol structure for isomannide.

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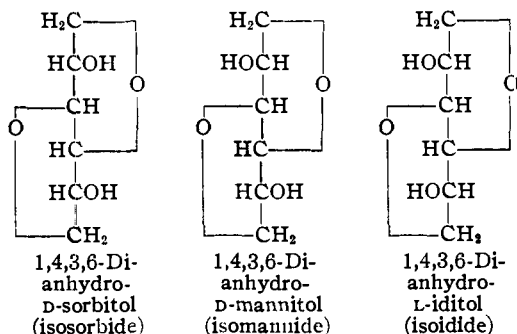
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, AND FROM THE RESEARCH DEPARTMENT, ATLAS POWDER COMPANY]

Hexitol Anhydrides.¹ 1,4,3,6-Dianhydro-L-iditol and the Structures of Isomannide and Isosorbide

BY HEWITT G. FLETCHER, JR.,² AND R. MAX GOEPP, JR.²

The ring structure of isomannide has recently been determined independently by the present authors with their collaborators³ and by Wiggins⁴ as 1,4,3,6. The closely analogous substance, isosorbide, was shown by Hockett, Fletcher, Sheffield and Goepf⁴ to contain the same ring system. The present research provides independent and conclusive proof of the correctness of these structure assignments and has also resulted in the characterization of a new dianhydrohexitol, 1,4,3,6-dianhydro-L-iditol.

Comparison of the structures of isosorbide and isomannide shows that they are identical save for the configuration of the second carbon atom. Partial oxidation of isosorbide would produce 1,4,3,6-dianhydro-D-fructose, 1,4,3,6-dianhydro-L-sorbose or 1,4,3,6-dianhydro-D-threo-2,5-diketohexitol. Isomannide, because of its end-to-end symmetry would yield only the first and the third of these compounds. Subsequent reduction of 1,4,3,6-dianhydro-D-fructose would presumably give rise to a mixture of isomannide and isosorbide; reduction of 1,4,3,6-dianhydro-L-sorbose would lead to isosorbide and 1,4,3,6-dianhydro-L-iditol, while reduction of 1,4,3,6-dianhydro-D-threo-2,5-diketohexitol would result in the formation of a mixture of all three dianhydro-hexitols.

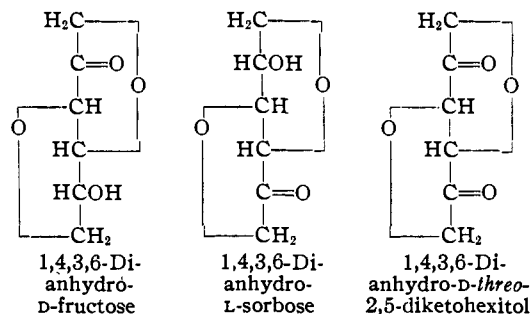


(1) The previous paper of this series, *THIS JOURNAL*, **68**, 937 (1946). See also Fletcher and Goepf, *ibid.*, **67**, 1042 (1945).

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(3) Hockett, Fletcher, Sheffield, Goepf and Soltzberg, *THIS JOURNAL*, **68**, 930 (1946); Hockett and Sheffield, *ibid.*, **68**, 937 (1946); Wiggins, *J. Chem. Soc.*, **4** (1945).

(4) Hockett, Fletcher, Sheffield and Goepf, *THIS JOURNAL*, **68**, 927 (1946).



The dehydrogenating properties of the catalysts usually employed for hydrogenation are well known. With this fact in mind a suspension of Raney nickel in molten isosorbide was heated at 140° *in vacuo* (2 mm.) for a brief period. Subsequent treatment of the mixture of sirup and catalyst at 190 to 200° under a pressure of 3750 pounds per square inch of hydrogen was, indeed, found to produce an amorphous mixture which, unlike isosorbide, could not be induced to crystallize. Complete benzoylation of this sirup and fractional crystallization of the resulting mixture gave a well-defined crystalline substance having the analysis of a dianhydrohexitol dibenzoate. It proved to be unlike the dibenzoate of either isosorbide or isomannide and apparently one or both of two changes had taken place during the treatment of isosorbide. Either isomerization had altered the ring structure of the isosorbide to a form more stable under the rather drastic conditions of the experiment, or inversion of one or more of the hydroxyl groups, as pictured above, had taken place. The latter hypothesis indicated that the crude isomerizate might contain, along with unchanged or reformed isosorbide, isomannide and the new hexide 1,4,3,6-dianhydro-L-iditol. Actually, chromatography of the crude isomerizate in another laboratory demonstrated the presence of three compounds.⁵

It is obvious that if this isomerization involves simply inversion of the hydroxyl groups in isosorbide, a similar isomerizate, containing the same new dianhydrohexitol, should be obtained by a similar treatment of isomannide. A parallel hydrogenation of isomannide was therefore run and yielded a sirupy mixture from which the new

(5) Lew, Wolfrom and Goepf, *ibid.*, **67**, 1865 (1945).

dianhydrohexitol was again isolated as its dibenzoate.

This fact substantiates the hypothesis that the positions of the oxide rings have suffered no change during the reaction. Further, the conversion of isosorbide and isomannide to a common derivative in this manner confirms the epimeric relationship of the two and implies that the new dianhydro-hexitol has the same structure with, however, the L-iditol configuration. To prove this a sample of L-iditol was dehydrated in the presence of sulfuric acid under conditions which result in the conversion of sorbitol to isosorbide and mannitol to isomannide.⁶ On benzylation the product was found to be identical with that isolated subsequent to the isomerization of isosorbide and isomannide by hydrogenation.

The isolation of this dianhydro-L-iditol from isosorbide, isomannide and L-iditol indicates that the remaining hydroxyl groups in the three dianhydrides occupy positions two and five and that these substances all have either the 1,4,3,6 or 1,3,4,6 structure. The structural proofs for isosorbide and isomannide already cited^{3,4} eliminate this latter structure and, therefore, all three compounds are 1,4,3,6-dianhydro-hexitols.

In conformity with the usage established in the sorbitol and mannitol series for 1,4,3,6-dianhydrides⁴ the trivial name *L-isoidide* is proposed for 1,4,3,6-dianhydro-L-iditol.

Acknowledgment.—The authors wish to express their indebtedness to Professor C. S. Hudson and Dr. Nelson K. Richtmyer of the National Institute of Health for the generous donation of a sample of L-iditol, to Dr. B. W. Lew of the Ohio State University for chromatographic examinations and to Mrs. H. I. Fitz for combustion analyses.

Experimental⁷

2,5-Dibenzoyl-1,4,3,6-dianhydro-L-iditol

A. From 1,4,3,6-Dianhydrosorbitol (Isosorbide).—Fifty grams of recrystallized isosorbide, prepared as described in an earlier paper⁴ was treated with 10 g. of Raney nickel suspended in absolute alcohol. The alcohol was removed *in vacuo* and the residue finally heated at 135–140° (bath) for ten minutes at a pressure of 2 mm. After cooling the viscous suspension in an atmosphere of nitrogen, it was subjected to a pressure of 3750 pounds per square inch of hydrogen and a temperature of 190–200° for two hours. On cooling, the mixture, visibly unchanged, was dissolved in 125 ml. of water and freed of catalyst. The rotation of the resulting clear, colorless solution was +28.03° (2-dm. tube, 23.5°) while 37.2° would be expected had no change taken place. Evaporated *in vacuo* the solution afforded a sirup from which no crystalline material could be obtained. A sample of the sirup (46.1 g.) was partially distilled at 140° (bath) and 2 mm. pressure giving 27.2 g. of distillate which eventually crystallized in part. In glacial acetic acid solution samples

of both the residue and the distillate were unattacked by lead tetraacetate. The former showed in water a rotation of +27.4° (25.0°) and the latter a rotation of +44.2° (25.0°). The residue (18.1 g.) was dissolved in 50 ml. of pyridine, the solution cooled to 0°, and treated with 32 ml. of benzoyl chloride. After standing overnight at room temperature the mixture was poured slowly into 726 ml. of rapidly stirred ice water to give a sirup which eventually crystallized. Recrystallized from alcohol, the product (31.0 g.) melted at 81.8 to 90° and was obviously a mixture. It was dissolved in chloroform and the solution shaken with aqueous sodium bicarbonate to remove any traces of benzoic acid. After removal of the chloroform, the material was recrystallized twice from alcohol and then twice from *n*-butyl alcohol to give 16.1 g. of fine white needles whose melting point (111.0–111.3°) was unchanged by further recrystallization. The compound showed a rotation in chloroform of +140.3° (*c*, 2.03, 23.4°), in pyridine of +110.5° (*c*, 2.07, 28.2°) and exhibited solubility characteristics similar to isosorbide dibenzoate. When mixed with this latter compound, prepared as described in an earlier paper² and melting at 101.8–102.0°, its melting point was depressed markedly.

Anal. Calcd. for C₂₀H₁₆O₆: C, 67.79; H, 5.12; sapon. equiv., 177. Found: C, 68.1, 67.6, 67.8; H, 5.10, 5.27, 5.10; sapon. equiv., 187.

B. From 1,4,3,6-Dianhydro-D-mannitol (Isomannide).—Recrystallized 1,4,3,6-dianhydro-D-mannitol (50.0 g.), prepared as described earlier,² was mixed with 20 g. of Raney nickel suspended in absolute alcohol. Removal of the alcohol *in vacuo* was followed by heating at 140° (bath) at a pressure of 2 mm. for twenty-eight minutes. After cooling the sirup in nitrogen it was subjected to a hydrogen pressure of 3300 pounds per square inch at 190 to 203° for one hour. Solution of the resulting product in water and removal of the catalyst gave 218 ml. of clear liquid which rotated +22.95° (2-dm., 24°) while a rotation of +41.8° would have been expected had the dianhydro-mannitol remained unchanged. Evaporated *in vacuo*, the solution gave 46.1 g. of colorless sirup which was dissolved in 100 ml. of pyridine, cooled to 0° and treated with 80.3 g. of benzoyl chloride. After heating at 85° for fifteen minutes, the solution was poured into ice water and the resulting crystalline mass taken up in 310 ml. of chloroform. The solution was washed once with sodium bicarbonate solution, twice with water and the chloroform then removed to give a mixture whose resolution proved somewhat difficult. After five recrystallizations from alcohol, followed by one from *n*-butyl alcohol, 0.92 g. of material melting at 110.0 to 111.9° was obtained. One more recrystallization from *n*-butyl alcohol yielded white crystals melting at 111.1 to 111.9° and showing a rotation in chloroform of +141.9° (*c*, 2.15, 25.2°). A mixed melting point with the material obtained from the hydrogenation of isosorbide was undepressed.

C. From L-Iditol.—L-Iditol (0.97 g., m. p. 75.7–76.7°) was treated with two drops (0.0246 g.) of concentrated sulfuric acid in an apparatus designed for semi-micro high vacuum sublimation⁸ and heated at 140 to 145° (bath) under a vacuum of 4 cm. for one and one-fourth hours. The pressure was then decreased to 2 mm. and a colorless, crystalline material collected on the condenser. This was dissolved in 4 ml. of warm dry pyridine, chilled to 0°, and mixed with 1.25 ml. of benzoyl chloride. After warming at 100° for twenty minutes, the solution was cooled and diluted with a few small fragments of ice and 2 ml. of 0.1 *N* sodium carbonate solution. The crystals which resulted were washed with water, dissolved in chloroform and freed of any remaining benzoic acid by treatment with sodium bicarbonate solution. After removal of the chloroform, the residue was crystallized from 9 ml. of alcohol to give 0.59 g. (31.4%) of material melting at 110.0 to 111.0°. A second recrystallization from hot *n*-butyl alcohol gave crystals melting at 110.7 to 111.4°. Mixed melt-

(6) Müller and Hoffmann (to I. G. Farbenind. A.-G.) German Patent 488,602 (1927); U. S. Patent 1,757,468 (1930); Wiggins, ref. 3.

(7) All melting points reported in this paper have been corrected for stem exposure. Specific rotations are for the *D* line of sodium at the indicated temperature while concentrations are expressed in grams of substance to 100 ml. of solution.

(8) This apparatus represented a minor modification of that described by Weygaard. "Organisch-chemische Experimentierkunst," Johann Ambrosius Barth, Leipzig, 1938, p. 115.

ing points with the compounds obtained in parts A and B showed no depression.

1,4,3,6-Dianhydro-L-Iditol from 2,5-Dibenzoyl-1,4,3,6-dianhydro-L-Iditol.—Ten grams of 2,5-dibenzoyl-1,4,3,6-dianhydro-L-Iditol was dissolved in 40 ml. of chloroform and chilled to 0°. A similarly chilled solution of 0.1 g. of sodium in 40 ml. of absolute methanol was then added and the solution left at 0° for twenty-three hours. Excess base was removed by passing carbon dioxide through the solution until it was acid to phenolphthalein. After filtration, the solvent was removed *in vacuo* and the residual sirup dissolved in 10 ml. of warm ethyl acetate. On cooling, there was obtained 1.46 g. (35.5%⁹) of long, white, asbestos-like needles melting at 63.8 to 64.4° and rotating in water +20.8° (*c*, 2.02, 24.5°) and in pyridine +33.3° (*c*, 2.24, 28.2°). In contrast to isosorbide and isomannide, this substance is sparingly soluble in chloroform. When mixed with these dianhydrides it caused a substantial depression of their melting points.

Anal. Calcd. for $C_{14}H_{10}O_4$: C, 49.31; H, 6.89. Found: C, 49.1, 49.1; H, 6.86, 6.84.

(9) Distillation of the residue from the mother liquors at 140° (bath) and 2 mm. pressure gave an additional 2.26 g. of substantially pure 1,4,3,6-dianhydro-L-Iditol and raised the total yield to 90.4%.

Summary

1,4,3,6-Dianhydro-L-Iditol has been prepared by the hydrogenation isomerization of both 1,4,3,6-dianhydrosorbitol and 1,4,3,6-dianhydro-D-mannitol as well as by the acid catalyzed anhydridization of L-Iditol.

These facts are best explained by the assumption that Raney nickel exerts a dehydrogenating action on these secondary alcohols, converting one or both of the free hydroxyl groups to symmetrical carbonyl groups which are subsequently reduced with the formation of a mixture of diastereoisomers.

The isolation of a dianhydro-L-Iditol in this manner from isosorbide and isomannide proves the structure of the new dianhydride as 1,4,3,6-dianhydro-L-Iditol and confirms those of isosorbide and isomannide.

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[CONTRIBUTION FROM THE THOMPSON LABORATORY OF THE PHILLIPS EXETER ACADEMY AND THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Optically Active Ketonic Beta Lactones

BY CHARLES L. BICKEL

The bromination of racemic α -phenyl- β -benzoylpropionic acid gives two β -bromo derivatives which differ markedly in the speed with which they form β -lactones. The rate of lactone formation is dependent on the configuration of the bromo acid, but Kohler and co-workers^{1,2} were not able to establish the configurations of the bromo acids in relation to those of the lactones since the opening or closing of the lactone ring may involve inversion. By using cyclic ketonic acids of fixed and known configuration, Kohler and Jansen³ later proved that the configuration of the bromo acid and the corresponding lactone was the same and that no inversion occurred.

A study of the optically active forms of α -phenyl- β -benzoylpropionic acid I, their β -bromo derivatives II and IIa, and the optically active β -lactones III and IIIa throws new light on the problem of these configurational relationships and is the subject of the present paper. The discussion is limited to one of the optically active acids and its derivatives, although identical results were obtained with the optical opposites. The racemic derivatives were also prepared in the case of compounds which had not previously been studied.

The bromination of each of the optically active acids yields two bromo acids differing considerably in specific rotation. In dilute sodium bicarbonate solution one of the bromo acids II is

rapidly converted into a β -lactone III, hereafter called the fast lactone; in sodium hydroxide solution the other bromo acid IIa is converted much more slowly into an isomeric β -lactone IIIa, the slow lactone. In both instances, the specific rotations of the bromo acid and the corresponding lactone are of the same order of magnitude. Racemization of the groups attached to the α -carbon atom does not occur since hydrogen iodide converts the fast lactone into the active acid from which it was derived, while hydrogen bromide regenerates the active bromo acid II. The conclusion of Kohler and Jansen that the formation of the lactones does not involve inversion supports, and is supported by, the polarimetric data herein described.

The fast lactone III reacts with methanol⁴ to give an open-chained methoxy acid VII, the specific rotation of the methoxy acid indicating that the configuration is unchanged. Methanol and sulfuric acid react with the fast lactone to give an open-chained hydroxy ester IVa, while aqueous sulfuric acid gives the corresponding hydroxy acid Va. The specific rotations of these compounds point to inversion around the β -carbon atom and place them in the series headed by the slow lactone IIIa and the bromo acid IIa.

Both the hydroxy acid Va and the hydroxy ester IVa obtained from the fast lactone can be converted into a methoxy ester VIa and a methoxy acid VIIa which are isomeric with the meth-

(1) Kohler and Kimball, *THIS JOURNAL*, **56**, 729 (1934).

(2) Kohler, Peterson and Bickel, *ibid.*, **56**, 2000 (1934).

(3) Kohler and Jansen, *ibid.*, **60**, 2142 (1938).

(4) Kohler and Bickel, *ibid.*, **63**, 1531 (1941).