[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, FEDERAL SECURITY AGENCY]

1,4-Anhydro-D-galactitol

BY ROBERT K. NESS,[1] HEWITT G. FLETCHER, JR., AND C. S. HUDSON

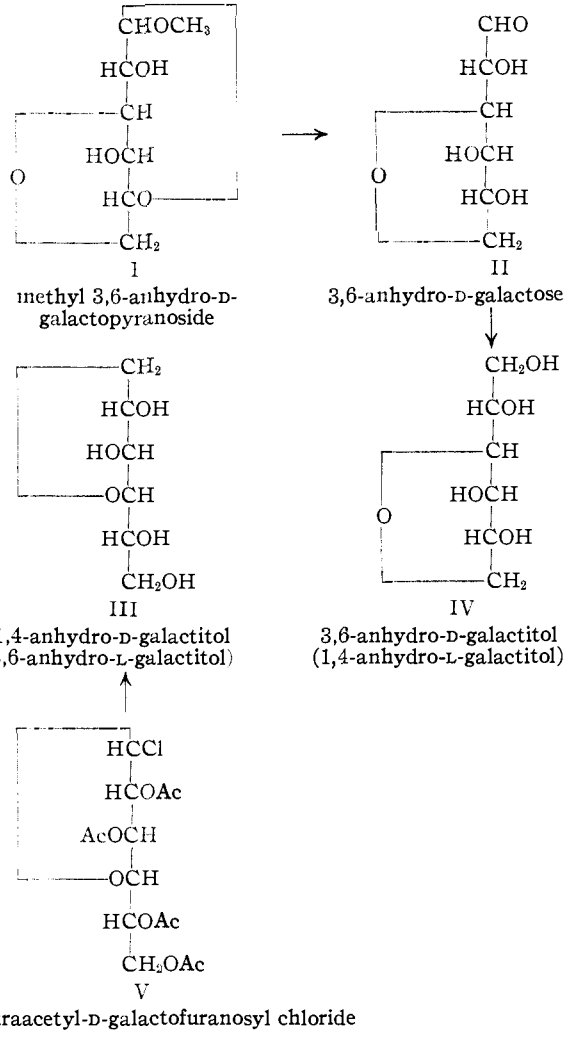
Reduction of tetraacetyl-D-galactofuranosyl chloride with lithium aluminum hydride has been found to give crystalline 1,4-anhydro-D-galactitol (= 3,6-anhydro-L-galactitol) which has been characterized by its behavior with sodium metaperiodate and by the preparation of a crystalline tetrabenzoate. The optical rotation of the new anhydride shows it to be the enantiomorph of the amorphous 3,6-anhydro-D-galactitol (= 1,4-anhydro-L-galactitol) which is recorded in the literature as the reduction product of 3,6-anhydro-D-galactose.

It was recently shown[2] that acetylated glycopyranosyl bromides may be reduced with lithium aluminum hydride to give the corresponding 1,5-anhydroglycitols in high yield. The present paper describes the similar reduction of an acetylated glycofuranosyl chloride to a 1,4-anhydroglycitol.

Several years ago, in the course of an investigation of the structure and configuration of 1,4-anhydro-D-glucitol (arlitan), Hockett, Conley, Yusem and Mason[3] prepared 3,6-anhydro-D-galactitol (IV) for comparison purposes. Methyl 3,6-anhydro-D-galactopyranoside (I), the structure of which had previously been proved by Haworth, Jackson and Smith,[4] was hydrolyzed with dilute sulfuric acid and the 3,6-anhydro-D-galactose (II) thus liberated, reduced with sodium amalgam. The product, IV, was obtained as a sirup which, purified through its amorphous acetate, showed in water $[\alpha]^{22}D$ +17.5° (*c*, 1.43).

Now, of the ten hexitols, only allitol and galactitol show what might be termed "end-to-end enantiomorphism"[5]; thus 3,6-anhydro-D-galacitol (IV) is the enantiomorph of 1,4-anhydro-D-galactitol (III). It is apparent, therefore, that if the long-known and relatively accessible tetraacetyl-D-galactofuranosyl chloride (V)[6] could be reduced in a fashion similar to that found possible for the glycopyranosyl bromides, the expected product, 1,4-anhydro-D-galactitol (III), would be the enantiomorph of that produced by Hockett and his coworkers and it could equally well be named 3,6-anhydro-L-galactitol. Experiment verified this expectation; reduction of crystalline tetraacetyl-D-galactofuranosyl chloride with lithium aluminum hydride in ether solution gave, in 41% yield, a crystalline anhydrohexitol showing a rotation in water of $[\alpha]^{20}D$ −18.0°, *i.e.*, opposite in sign to, but practically equal numerically with the value ($[\alpha]^{22}D$ +17.5°) obtained by the earlier workers. The new substance was further characterized through its crystalline tetrabenzoate; attempts to obtain a crystalline tetraacetate were unsuccessful.

Hockett, Conley, Yusem and Mason[3] observed that 3,6-anhydro-D-galactitol consumes more than the two moles of lead tetraacetate required to cleave the two pairs of vicinal hydroxyl groups which it contains; in this respect it resembles 1,4-anhydro-D-glucitol and ethyl β-D-galactofuranoside.[3,7] Huebner, Ames and Bubl,[8] in a study of the action of periodate on a variety of compounds, subsequently showed that 1,4-anhydro-D-glucitol consumes six moles of oxidant and produces three moles of acid. A scheme similar to the following was proposed. The 1,4-anhydro-D-galactitol (III) obtained in the course of the present research, was found to behave with periodate in a similar manner. After 11 days at 5°, 1,4-anhydro-D-galactitol con-



(1) Senior Research Fellow, National Institutes of Health, 1948-1950.

(2) R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, THIS JOURNAL, **72**, 4547 (1950)

(3) R. C. Hockett, M. Conley, M. Yusem and R. I. Mason, *ibid.*, **68**, 922 (1946).

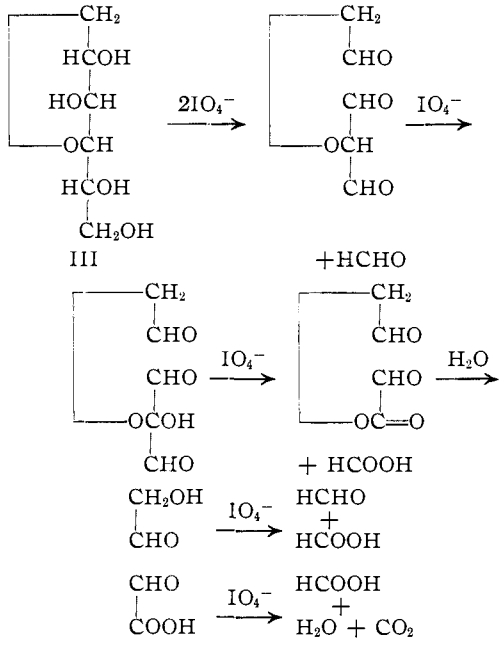
(4) W. N. Haworth, J. Jackson and F. Smith, *J. Chem. Soc.*, 620 (1940).

(5) M. A. Rosanoff [THIS JOURNAL, **28**, 114 (1906)] used the term *amphi* to refer to those sugar derivatives having similar terminal groups (such as the glycitols and glycaric acids) which may be construed as belonging to either the D- or L-series.

(6) C. S. Hudson and J. M. Johnson, *ibid.*, **38**, 1223 (1916).

(7) R. C. Hockett, M. H. Nickerson and W. H. Reeder, III, *ibid.*, **66**, 472 (1944).

(8) C. F. Huebner, S. R. Ames and E. C. Bubl, *ibid.*, **68**, 1621 (1946).



sumed 5.99 moles of periodate while 2.95 moles of acid were produced. The reaction scheme predicts the formation of two moles of formaldehyde; analysis of the reaction mixture showed the presence of 1.86 mole equivalents of formaldehyde.

In the earlier work on the reduction of acetylated glycopyranosyl bromides it was found that actual isolation of the halide was unnecessary; the fully acetylated glycopyranose was treated with hydrogen bromide, washed free of excess acid, dried and reduced in ether solution with lithium aluminum hydride. A similar procedure, involving conversion of crystalline β-D-galactofuranose pentaacetate to a solution of tetraacetyl-D-galactofuranosyl chloride, was tried in the course of the present research. While the yield of 1,4-anhydro-D-galactitol by this procedure was 33% of theory the crude product was contaminated with both D-galactose and galactitol[9] and proved more difficult to purify than the product obtained from the crystalline halide.

Schlubach and Prochownick[10] described a preparation of D-galactofuranose pentaacetate, involving acetylation of D-galactose with a mixture of acetic anhydride and pyridine at an elevated temperature. This procedure was restudied in the course of the present research and an improved description of the method is therefore included in the experimental section.

Experimental[11]

β-D-Galactopyranose and β-D-Galactofuranose Pentaacetates.—A modification of the procedure of Schlubach and Prochownick[10] was used. Forty grams of pure powdered D-galactose was added gradually to a boiling mixture of 600 ml. of pyridine and 185 ml. of acetic anhydride. After the addition, the reaction mixture was heated under reflux until all the solid was dissolved (2–3 min.) and then boiled for five additional minutes. The dark reaction mixture was then concentrated *in vacuo* to a thin sirup, combined with three similar batches and diluted with 500 ml. of chloroform. After washing with cold water, 3 *N* sulfuric acid and aqueous sodium bicarbonate, water was removed with sodium sulfate and the solution filtered through a bed of decolorizing carbon. The solvent was removed *in vacuo* and the resultant straw-colored sirup diluted with 50 ml. of alcohol and reconcentrated *in vacuo*. After another, similar treatment with 50 ml. of alcohol the residue was dissolved in 500 ml. of 95% alcohol, the solution was seeded with β-D-galactopyranose pentaacetate, and was left at +5° for 14 hours. Filtration then removed 107 g. (31%) of crude β-D-galactopyranose pentaacetate, rotating +27.4° in chloroform and melting at 143–144°. Recrystallized from two parts of 95% alcohol this product gave, with little loss, material which rotated +25.2° in chloroform. A specific rotation of +25° is recorded[12] for pure β-D-galactopyranose pentaacetate.

After removal of the crude β-D-galactopyranose pentaacetate the mother liquor was immediately seeded with β-D-galactofuranose pentaacetate and left at +5° for two days to give 59.6 g. (17%) of crude product rotating −40.6° in chloroform. One recrystallization from two parts of 95% alcohol gave, with negligible loss, pure β-D-galactofuranose pentaacetate melting at 99–100° and rotating in chloroform −42.2° (*c*, 0.89). A value of −41.6° has been recorded[13] for the rotation of β-D-galactofuranose pentaacetate in chloroform.

Tetraacetyl-D-galactofuranosyl Chloride (V).—A solution of 10.0 g. of β-D-galactofuranose pentaacetate in 20 ml. of glacial acetic acid was treated with 22 ml. of a glacial acetic acid solution of hydrogen chloride (*ca.* 10% HCl, w/w). After 100 minutes at room temperature the reaction mixture was diluted with ethylene dichloride, washed with cold aqueous sodium bicarbonate solution, dried over sodium sulfate and then filtered through a bed of decolorizing carbon. The solvent was removed *in vacuo* (45° bath) and the residue dissolved in a mixture of 40 ml. of absolute ether and almost sufficient pentane to cause a turbidity. Cooling in a Dry Ice–acetone-bath initiated the crystallization of 5.0 g. (53%) of tetraacetyl-D-galactofuranosyl chloride as clear prisms melting at 71–73° and rotating in chloroform −77.8° (*c*, 3.9). Hudson and Johnson[6] have recorded a melting point of 67° and a rotation in chloroform of −77.1° for tetraacetyl-D-galactofuranosyl chloride.

1,4-Anhydro-D-galactitol (III).—A solution of 4.5 g. of pure, crystalline tetraacetyl-D-galactofuranosyl chloride in 100 ml. of absolute ether was added slowly to 100 ml. of 1.3 *M* lithium aluminum hydride in ether. After one hour, 300 ml. of water was cautiously added, care being taken to prevent the mixture from overheating. The precipitate was removed by filtration and washed thoroughly with water. Filtrate and washings were then deionized by successive passage through columns of Amberlite IR-120[14] and Duolite A-4[15] and concentrated *in vacuo* (50° bath) to a sirup which was dried by solution in 100 ml. of absolute alcohol and reconcentration *in vacuo*. The product was finally dissolved in absolute alcohol and, after several days, 0.83 g. (41%) of 1,4-anhydro-D-galactitol, melting at 91–94°, was obtained. One recrystallization from cold ethyl acetate and another from dioxane gave pure 1,4-anhydro-D-galactitol as clusters of elongated plates melting at 95–96° and rotating in 95% ethanol −35.2° (*c*, 1.60) and in water −18.0° (*c*, 1.66).

1,4-Anhydro-D-galactitol is insoluble in benzene and pentane, sparingly soluble in ethyl acetate and alcohol and readily soluble in water.

Anal. Calcd. for $C_6H_{12}O_5$: C, 43.90; H, 7.37. Found: C, 44.17; H, 7.41.

A sample (97.6 mg.) of 1,4-anhydro-D-galactitol in aqueous solution with 7.62 molar equivalents of sodium metaperiodate was kept at 5°, aliquots being removed periodi-

(9) Reduction of D-galactofuranose pentaacetate with litbium aluminum hydride in a mixture of ether and tetrahydrofuran was found to give galactitol in 72% yield.

(10) H. H. Schlubach and V. Prochownick, *Ber.*, **63**, 2298 (1930).

(11) Melting points were measured with a calibrated Anschütz-type thermometer completely immersed in the bath liquid. Rotations are specific rotations for the D line of sodium at 20°; concentration is expressed in g. of substance per 100 ml. of solution.

(12) C. S. Hudson and H. O. Parker, THIS JOURNAL, **37**, 1589 (1915).

(13) C. S. Hudson, *ibid.*, **37**, 1591 (1915).

(14) A product of the Resinous Products and Chemical Co., Washington Square, Philadelphia 5, Pa.

(15) A product of the Chemical Process Co., 901 Spring St., Redwood City, Calif.

cally and analyzed for acid and residual oxidant. After 4.7 days, 5.85 moles of oxidant had been consumed and 2.76 moles of acid formed; after 11 days, 5.99 moles of oxidant had been consumed while 2.95 moles of acid had been formed. Analysis of the remaining oxidation mixture, using dimedone according to the procedure of Fleury and Lange,[16] showed the presence of 1.86 moles of formaldehyde.

1,4-Anhydro-D-galactitol Tetrabenzoate.—1,4-Anhydro-D-galactitol (0.30 g.) was benzoylated in pyridine (5 ml.) with benzoyl chloride (1.5 ml.) in the usual manner to give from methanol solution 0.92 g. (87%) of crystals melting at 87–92°. After recrystallization from a variety of solvents this material was obtained as a mixture of prisms and needles which still showed a wide melting point range although chromatography on alumina indicated that it was chemically homogeneous. A wholly independent preparation (involving benzoylation of very impure, sirupy 1,4-anhydro-D-galactitol) later furnished seeds of higher melting material and thereafter the product was obtained only as clear tetragonal prisms melting at 99–101° and showing in chloroform +41.7° (*c*, 1.03). In order to ensure that no alteration had taken place in the structure of the substance, a sample was debenzoylated with barium methylate in methanol to give (in 93% yield), 1,4-anhydro-D-galactitol, identified by melting point and mixed melting point.

Anal. Calcd. for $C_{34}H_{28}O_9$: C, 70.33; H, 4.86. Found: C, 70.29; H, 4.99.

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(16) P. Fleury and J. Lange, *J. pharm. chim.*, **17**, 196 (1933).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TORONTO]

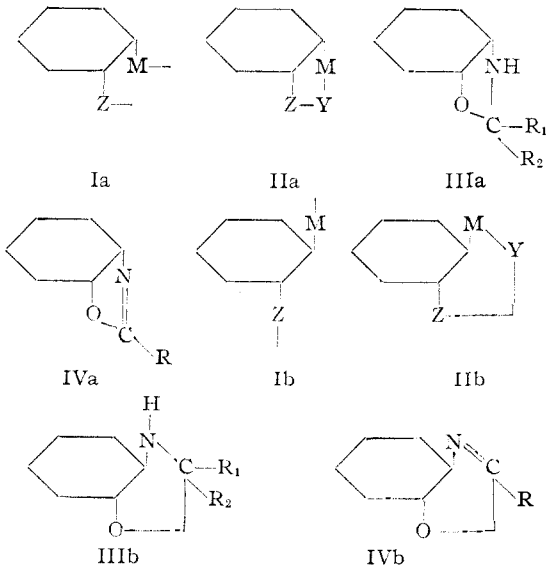
Heterocyclization of Epimeric Aminocyclanols. I. Oxazolines[1,2]

BY G. E. MCCASLAND AND E. CLYDE HORSWILL

The conversion of aminocyclanols to bicyclic (heterocyclic) derivatives has been investigated with regard to its possible utility as an indicator of diastereomeric configuration. The formation of oxazolines by reaction of aminocyclanol free base with ethyl iminobenzoate free base in homogeneous solution in ethylene dichloride was studied. The *trans* epimers of 2-aminocyclohexanol and -pentanol each yielded a large precipitate found to consist of the N-(2-hydroxycycloalkyl)-benzamidine hydrochloride. The *cis* epimers gave negligible amounts of precipitate. Both *cis*- and *trans*-2-aminocyclohexanols readily formed oxazolines. The conversion of *cis*-2-aminocyclopentanol to oxazoline was also easy, but formation of a *trans*-cyclopentanoöxazoline has thus far not been found possible.

Introduction

One of the classical methods for determining the diastereomeric configuration of a disubstituted cycloalkane is to compare the ease of conversion of the two epimers (Ia, Ib) to bicyclic derivatives (IIa, IIb). The new ring is usually heterocyclic and the process may then be called *heterocyclization*. M and Z are the directly attached atoms of functional groups such as –OH, $-NH_2$, –COOH, and Y is a bridge containing zero, one, two or more atoms. The heterocyclization is presumed to occur with retention of configuration at C–M and C–Z.



The validity of the method depends on the sizes of both rings. When the cycloalkane ring contains two to five carbon atoms the expected sharp differences in proximity of M and Z for the two epimers often cause pronounced differences in the ease of ring formation. The more flexibile and non-coplanar cyclohexane ring may or may not show a significant *cis–trans* difference. Cycloheptane and higher rings are unsuitable for the heterocyclization method.

The heterocyclic ring to be formed should contain not more than four (possibly five) atoms for cyclohexanes; not more than five atoms for cyclopentanes,[3,4] and not more than six (possibly seven) atoms for cyclobutane and smaller rings. It should also be noted that three-membered heterocyclic ring formation is not useful due to the possibility of Walden inversion and that methods are rarely available for preparing four-atom rings with two adjacent hetero-atoms.

The above conclusions are based largely on reported work[5,6,7] with alicyclic diols, dicarboxylic

(1) We wish to thank the Research Council of Ontario for a generous grant in support of this work.

(2) For related publications see: (a) G. E. McCasland, THIS JOURNAL, **73**, 2295 (1951); (b) **73**, 2293 (1951); (c) G. E. McCasland and D. A. Smith, *ibid.*, **72**, 2190 (1950); (d) G. E. McCasland, R. K. Clark, Jr., and H. E. Carter, *ibid.*, **71**, 637 (1949); (e) H. E. Carter, R. K. Clark, Jr., Betty Lytle and G. E. McCasland, *J. Biol. Chem.*, **175**, 683 (1948); (f) G. E. McCasland and D. A. Smith (to be submitted for publication).

(3) Bicyclic saturated hydrocarbons of the *trans* "five-five" type have been isolated by R. P. Linstead, *et al.*, *J. Chem. Soc.*, 436 (1935). A double bond should increase the ring-strain.

(4) R. P. Linstead and E. M. Meade, *ibid.*, 935 (1934).

(5) See C. S. Marvel, in Gilman, "Organic Chemistry: An Advanced Treatise," 2nd Edition, Wiley, New York, N. Y., 1943, pp. 447–453, 477–483.

(6) R. C. Fuson, *ibid.*, pp. 108–115.

(7) C. J. Maan, *Rec. trav. chim.*, **48**, 332 (1929); J. Böeseken, *Advances in Carbohydrate Chem.*, **IV**, 189 (1949); A. Windaus, *et al.*, *Ber.*, **56**, 91 (1923).