under suitable acidic conditions to yield D-glucose and 2′-naphthyl 1-thio-β-D-glucopyranoside. In like manner the 2′-naphthyl 1-thio-β-D-lactopyranoside yields the same 1-thioglucoside and D-galactose.

BETHESDA, MARYLAND RECEIVED MARCH 6, 1947

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

1,5-Anhydro-D-arabitol

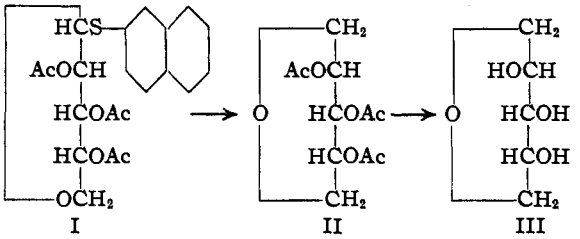
BY HEWITT G. FLETCHER, JR., AND C. S. HUDSON

Until quite recently the chief method of synthesizing the 1,5-anhydrides of the sugar alcohols has been through the catalytic reduction of the acetylated 2-hydroxy-glycals.[1] This synthetic path suffers from two drawbacks: the acetylated 2-hydroxy-glycals are not always readily preparable in substantial yield[2] and their catalytic reduction gives rise to new asymmetry at carbon two, usually necessitating such laborious configurational proofs for the product as was required in the case of 1,5-anhydro-D-mannitol (styracitol), the reduction product of 2,3,4,6-tetraacetyl-2-hydroxy-D-glucal.[1d,3]

In contrast the recently developed process of reductive desulfurization of cyclic 1-thio-sugar derivatives with Raney nickel affords a ready means of synthesizing 1,5-anhydro sugar alcohols of unequivocal structure and configuration. Thus, 1,5-anhydro-D-sorbitol (polygalitol) has been prepared from 2,3,4,6-tetraacetyl-1-thio-β-D-glucopyranose,[1c] octaacetyl-β,β-di-D-glucopyranosyl disulfide[1c] and ethyl tetraacetyl-D-glucopyranosyl xanthate.[4] It has also been prepared in 80% yield from phenyl 1-thio-β-D-glucopyranoside tetraacetate and from *p*-cresyl 1-thio-β-D-glucopyranoside tetraacetate.[5] 1,5-Anhydro-xylitol has likewise been prepared by the reductive desulfurization of phenyl 1-thio-β-D-xylopyranoside triacetate.[1e]

The purpose of the present investigation was to explore this general synthetic method further and, specifically, to apply it to the preparation of one of the pair of unsymmetrical 1,5-anhydropentitols, the 1,5-anhydro-arabitols. The greater availability of pure D-arabinose through the directions of Hockett and Hudson for the Ruff degradation of calcium D-gluconate,[6] led to the choice of the D- rather than of the L-series for this work.

For a 1-thio-D-arabinopyranose derivative we chose the 2′-naphthyl 1-thio-α-D-arabinopyranose triacetate (I), first prepared by Haskins, Hann and Hudson,[7] a readily available and beautifully crystalline compound like the majority of 2′-naphthyl 1-thioglycoside acetates. When treated in absolute alcoholic solutions with Raney nickel this substance gave naphthalene and a sirup, presumably 2,3,4-triacetyl-1,5-anhydro-D-arabitol (II), which could not be induced to crystallize. Catalytic deacetylation of the sirup, however, gave the desired pentitan in crystalline form.



I — 2′-Naphthyl 1-thio-α-D-arabinopyranoside triacetate

II — 2,3,4-Triacetyl-1,5-anhydro-D-arabitol

III — 1,5-Anhydro-D-arabitol

That the original tetrahydropyrane ring of the acetobromo-D-arabinose had remained unchanged in the 2′-naphthyl 1-thio-α-D-arabinoside triacetate and survived in the anhydropentitol was demonstrated by the behavior of the last-named substance toward sodium metaperiodate. On a molar basis the anhydride consumed two atoms of oxygen with the formation of one mole of formic acid. The product is therefore 1,5-anhydro-D-arabitol, III. It was further characterized as its triacetate and tribenzoate.

While a crystalline 1-thio-D-arabinose derivative is most convenient for use in this synthesis it is not indispensable since 1,5-anhydro-D-arabitol triacetate, like 1,5-anhydro-xylitol triacetate,[1e] is somewhat volatile, and can be purified prior to the final deacetylation. Thus both phenyl 1-thio-D-arabinopyranoside triacetate and ethyl triacetyl-D-arabinopyranosyl xanthate, obtained by the condensation of 2,3,4-triacetyl-β-D-arabinopyranosyl bromide with potassium thiophenolate and potassium ethyl xanthate respectively, were obtained only as crude sirups. However, treatment of each of these with Raney nickel gave a sirup which at an elevated temperature and low

(1) *Cf.* (a) L. Zervas, *Ber.*, **63**, 1689 (1930); (b) K. Maurer and K. Plötner, *ibid.*, **64**, 281 (1931); (c) N. K. Richtmyer, C. J. Carr and C. S. Hudson, THIS JOURNAL, **65**, 1477 (1943); (d) R. C. Hockett and Maryalice Conley, *ibid.*, **66**, 464 (1944); (e) H. G. Fletcher and C. S. Hudson, *ibid.*, **69**, 921 (1947).

(2) R. T. Major and E. W. Cook [*ibid.*, **58**, 2333 (1936)], for instance, reported their failure to obtain 2,3,4-triacetyl-2-hydroxy-D-xylal in crystalline form while the present authors have had a similar experience with 2,3,4-triacetyl-2-hydroxy-D-arabinal.

(3) (a) N. K. Richtmyer and C. S. Hudson, *ibid.*, **65**, 64 (1943); (b) L. Zervas and I. Papadimitriou, *Ber.*, **73**, 174 (1940).

(4) H. G. Fletcher, THIS JOURNAL, **69**, 706 (1947).

(5) N. K. Richtmyer and C. S. Hudson, unpublished results from this Laboratory.

(6) R. C. Hockett and C. S. Hudson, THIS JOURNAL, **56**, 1632 (1934).

(7) W. T. Haskins, R. M. Hann and C. S. Hudson, *ibid.*, **69**, 1668 (1947).

pressure could, in part, be distilled. The distillates were then easily deacetylated to give the crystalline 1,5-anhydro-D-arabitol.

It is planned to use this reductive desulfurization procedure to synthesize authentic anhydrosugar alcohols for comparison with three anhydrides of uncertain configuration which have been reported in the literature, namely, the so-called "heptaacetyl-6-β-D-glucopyranosylstyracitol" and "heptaacetyl-4-β-D-glucopyranosylstyracitol" reported by Maurer and Plötner[1b] and the 1,5-anhydride of D-galacitol or D-talitol described by Freudenburg and Rogers.[8]

Acknowledgment.—We are indebted to Mr. C. A. Kinser for combustion analyses.

One of us (H. G. F.) held the Chemical Foundation Research Associateship while carrying out this research.

Experimental

1,5-Anhydro-D-arabitol from 2'-Naphthyl 1-Thio-α-D-arabinopyranoside Triacetate.—Six grams of 2'-naphthyl 1-thio-α-D-arabinopyranoside, prepared by the directions of Haskins, Hann and Hudson,[7] melting at 114–115°[9a] and rotating −8.29°[9b] in chloroform, was suspended in 50 ml. of absolute alcohol and the solution treated with about 50 g. of freshly prepared Raney nickel suspended in absolute alcohol. After boiling under a reflux condenser for two hours the solution was filtered from the nickel, the latter being extracted repeatedly with hot absolute alcohol. Concentration of the combined filtrate and washings *in vacuo* afforded a sirup which could not be induced to crystallize. This crude 2,3,4-triacetyl-1,5-anhydro-D-arabitol was therefore dissolved in 20 ml. of cold anhydrous methanol and treated with 1 ml. of 0.7 *N* barium methylate. After standing at 4° overnight the solution was freed of barium by the addition of the required quantity of 0.1 *N* sulfuric acid and then filtered through a funnel precoated with carbon. The naphthalene and methanol were removed by directing a gentle stream of air into the mixture while it was heated on the steam-bath. The residual sirup, dissolved in 2 ml. of absolute alcohol and treated with ethyl acetate to incipient turbidity, gave button-like aggregates of crystalline material; 0.84 g. (44%). Recrystallized twice from two parts of warm absolute alcohol the 1,5-anhydro-D-arabitol prisms melted at 96–97°; further recrystallization failed to change this value. In water the pure substance showed a rotation of −98.6° (*c*, 0.8928).

1,5-Anhydro-D-arabitol resembles 1,5-anhydro-xylitol[10] in its solubility characteristics, being soluble in water and warm alcohol, sparingly soluble in cold alcohol and relatively insoluble in ethyl acetate, benzene and pentane.

Anal. Calcd. for $C_5H_{10}O_4$: C, 44.78; H, 7.52. Found: C, 44.60; H, 7.65.

Because of the fact that the final yields in the following two preparations were low and that in each case it was necessary to pass through amorphous intermediates, we describe the experimental procedure in full detail.

1,5-Anhydro-D-arabitol from 2,3,4-Triacetyl-β-D-arabinopyranosyl Bromide *via* the Amorphous Phenyl 1-Thio-D-arabinopyranoside Triacetate.—Condensation of 2,3,4-triacetyl-β-D-arabinopyranosyl bromide with potassium thiophenolate was carried out following the general procedure of Purves[10] for the synthesis of acetylated aryl 1-thioglycosides. Ten grams of pure 2,3,4-triacetyl-β-D-arabinopyranosyl bromide, prepared by conventional methods,[11] was dissolved in 25 ml. of ethylene dichloride and the solution poured into a solution of 3.33 ml. of thiophenol in 53.0 ml. of 0.555 *N* absolute ethanolic potassium hydroxide. After refluxing gently for one-half hour the solution was cooled and washed four times with aqueous sodium bicarbonate and then once with water. After desiccation with anhydrous sodium sulfate the solution was passed through a filter precoated with carbon and evaporated *in vacuo* (45° bath). Removal of the last traces of ethylene dichloride was accomplished by successively evaporating *in vacuo* three 25-ml. portions of absolute ethanol from the residual sirup (45° bath). Efforts to crystallize the phenyl 1-thio-D-arabinopyranoside triacetate thus prepared were unsuccessful.

Seventeen grams of amorphous phenyl 1-thio-D-arabinopyranoside triacetate prepared as described above was dissolved in 100 ml. of absolute alcohol and treated with about 75 g. of freshly prepared Raney nickel suspended in absolute alcohol. The mixture became perceptibly warm and within five minutes the odor of benzene was apparent. The suspension was refluxed gently for one-half hour and then filtered to remove the nickel, the latter being washed thoroughly with hot absolute alcohol. The combined filtrate and washings were concentrated *in vacuo* to a sirup which at 160° (bath) and a pressure of 0.25 mm. afforded 7.49 g. of a clear viscous distillate. This sirupy distillate, dissolved in 30 ml. of cold methanol, was treated with 2 ml. of 0.7 *N* barium methylate solution and left overnight at 4°. The barium was then removed quantitatively with 0.1 *N* sulfuric acid and the clear solution evaporated to a sirup under an air jet on the steam-bath. Solution of the sirup in a mixture of 4 ml. of absolute alcohol and 12.5 ml. of ethyl acetate led to the isolation of 1.16 g. of crystalline material melting at 95–96° either alone or in admixture with 1,5-anhydro-D-arabitol obtained as described above. A second crop of almost equally pure material was separated and it raised the total yield of crystalline product to 1.70 g. (27% calculated on the sirupy phenyl 1-thioarabinopyranoside triacetate).

1,5-Anhydro-D-arabitol from 2,3,4-Triacetyl-β-D-arabinopyranosyl Bromide *via* the Amorphous Ethyl Triacetyl-D-arabinopyranosyl Xanthate.—The preparation of ethyl triacetyl-D-arabinopyranosyl xanthate from 2,3,4-triacetyl-β-D-arabinopyranosyl bromide was modeled after the preparation of ethyl tetraacetyl-D-glucopyranosyl xanthate described by Schneider, Gille and Eisfeld.[12] Five grams of pure 2,3,4-triacetyl-β-D-arabinopyranosyl bromide was added directly to a boiling solution of 2.6 g. of potassium ethyl xanthate in 12 ml. of absolute alcohol. After boiling gently for five minutes the suspension was cooled, diluted with 25 ml. of ethylene dichloride and washed thrice with water. After desiccation with anhydrous sodium sulfate the solution was passed through a filter precoated with carbon and then concentrated *in vacuo* (45° bath). The resulting sirup was freed of residual ethylene dichloride by repeated evaporation *in vacuo* (45° bath) of small portions of absolute alcohol. It was then dissolved in 100 ml. of absolute alcohol and treated with a suspension of about 60 g. of freshly prepared Raney nickel in absolute alcohol. After boiling gently under a reflux condenser for six hours the solution was cooled, freed of nickel by filtration and concentrated *in vacuo* (45° bath) to a clear, colorless sirup. At 105° (bath) and 0.2 mm. there was obtained from this sirup 2.27 g. of clear, colorless, viscous distillate which was dissolved in 10 ml. of methanol and treated with 8 drops of 1 *N* sodium methylate solution. After standing for several days at room temperature the solution was evaporated under a jet of filtered air on the steam-bath to a thin sirup. This sirup was dissolved in 2 ml. of *n*-propyl alcohol, passed through a filter precoated with carbon, and then treated with 3 ml. of ethyl acetate. The result-

(8) W. Freudenburg and E. F. Rogers, THIS JOURNAL, **59**, 1602 (1937).

(9) (a) All melting points were taken with a calibrated Anschütz-type thermometer completely immersed in the bath liquid; (b) rotations are specific rotations for sodium light at 20°; concentration is expressed in grams per 100 ml. of solution.

(10) C. B. Purves, THIS JOURNAL, **51**, 3619 (1929).

(11) *Cf.* F. J. Bates, *et al.*, "Polarimetry, Saccharimetry, and the Sugars," U. S. Government Printing Office, Washington, 1942, p. 500.

(12) W. Schneider, R. Gille and K. Eisfeld, *Ber.*, **61**, 1244 (1928).

ing clear prismatic crystals melted at 92–95° and, with a second, slightly less pure crop, amounted to 0.48 g. (24% calculated on the 2,3,4-triacetyl-β-D-arabinopyranosyl bromide).

Sodium Metaperiodate Oxidation of 1,5-Anhydro-D-arabitol.—The technique of Jackson and Hudson[13] was employed. The 1,5-anhydro-D-arabitol (0.1007 g.) was dissolved in a little water, treated with 5.0 ml. of 0.480 *M* sodium metaperiodate solution and the solution diluted to 25.0 ml. with water. After twenty-three hours at room temperature a 5-ml. sample was titrated for formic acid and for residual oxidant. On a basis of one mole of 1,5-anhydro-D-arabitol, the reaction consumed 1.95 moles of sodium metaperiodate and produced 1.03 moles of formic acid, in a manner similar to the behavior of 1,5-anhydro-xylitol (ref. 1e).

2,3,4-Triacetyl-1,5-anhydro-D-arabitol.—One-half gram of 1,5-anhydro-D-arabitol was dissolved in 2 ml. of pyridine and treated with 1.37 ml. of acetic anhydride. After warming the solution in a 110° oven for twenty minutes it was cooled and diluted with 10 ml. of chloroform. The solution was then washed twice with ice-cold 3 *N* sulfuric acid, once with aqueous sodium bicarbonate and finally dried over calcium chloride. It was then freed of desiccant by filtration and concentrated on a steam-bath to a sirup. Dissolved in 1 ml. of ethanol, the material crystallized spontaneously on scratching. The minute clusters of needle-shaped crystals were washed with ethanol; a second crop of equally pure material was obtained from the filtrate by the addition of pentane to make a total of 0.574 g. (59%). Recrystallized once from a mixture of two parts of absolute alcohol and four parts of benzene the triacetate melted at 58°; further recrystallization failed to change this value. In chloroform the 1,5-anhydro-D-arabitol triacetate rotated −74.2° (*c*, 1.018).

Anal. Calcd. for $C_{11}H_{16}O_7$: C, 50.77; H, 6.19. Found: C, 50.47; H, 6.18.

2,3,4-Tribenzoyl-1,5-anhydro-D-arabitol.—1,5-Anhydro-D-arabitol (0.3004 g.) was dissolved in pyridine (2.0 ml.) and treated with benzoyl chloride (1 ml.). After one-half hour at 40° the reaction mixture was diluted with cold aqueous sodium bicarbonate solution and the crystalline precipitate removed by filtration; yield quantitative. Twice recrystallized from six parts of ethanol, the product melted at 120–121° and exhibited in chloroform the high negative rotation of −220°.

Anal. Calcd. for $C_{26}H_{22}O_7$: C, 69.95; H, 4.97. Found: C, 70.17; H, 4.96.

Summary

1,5-Anhydro-D-arabitol has been prepared through the reductive desulfurization with Raney nickel of crystalline 2′-naphthyl 1-thio-α-D-arabinopyranoside triacetate, sirupy phenyl 1-thio-D-arabinopyranoside triacetate and sirupy ethyl triacetyl-D-arabinopyranosyl xanthate. Its analysis and those of its derivatives, as well as its behavior with sodium metaperiodate, serve to confirm its structure. Its configuration is confirmed by the fact that it is optically active.

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(13) E. L. Jackson and C. S. Hudson, THIS JOURNAL, **59**, 994 (1937).

[CONTRIBUTION FROM THE DEPARTMENT OF AGRICULTURAL CHEMISTRY, NORTH DAKOTA AGRICULTURAL COLLEGE AND EXPERIMENT STATION]

A New Synthesis of *dl*-Aspartic Acid[1]

BY HAROLD J. KLOSTERMAN AND EDGAR PAGE PAINTER[2]

Aspartic acid has been synthesized by the addition of ammonia to fumaric acid[3,4] or to diethyl fumarate[5]; by the reduction of diethyl oximino succinate,[6,7] and by the benzamidomalonic ester method.[8] While the first two methods gave fairly good yields in the single steps described, the addition of ammonia required pressure equipment and diethyloximinosuccinate was not prepared in good yield. The yields by the benzamidomalonic ester synthesis were poor when calculated on the original malonic ester.

Since γ-butyrolactone is now readily available and can be converted to α-amino-γ-hydroxybutyric acid in satisfactory yields[9] it seemed that the latter compound might be readily converted to aspartic acid by oxidation of the carbinol.

Oxidation of α-amino-γ-hydroxybutyric acid failed to yield aspartic acid. However, oxidation of the benzamido derivative by the method of Billman and Parker[10] gave satisfactory yields of benzamido-aspartic acid. This compound was hydrolyzed to aspartic acid in good yields. The over-all yields of aspartic acid were approximately 40%.

During the benzoylation of α-amino-γ-hydroxybutyric acid a small amount of the γ-benzoic acid ester of α-benzamido-γ-hydroxybutyric acid was obtained.

Experimental

α-Bromo-γ-butyrolactone.—The method of Livak, *et al.*,[9] was used to prepare 1620 g. of α-bromo-γ-butyrolactone [b. p. 137 to 140° at 20 mm.] from 908 g. of γ-butyrolactone. The yield of crude product was 93%.

α-Amino-γ-hydroxybutyric Acid.—The α-bromo-γ-butyrolactone (1540 g.) was treated with ammonium hydroxide[9] to give 493 g. of α-amino-γ-hydroxybutyric acid, m. p. 180° (uncor.).

Anal. Calcd. for $C_4H_9NO_3$: N, 11.76. Found: N, 11.70.

An additional 401 g. of α-amino-γ-butyrolactone hydrobromide, m. p. 212°, were recovered from the filtrates.[9] The total yield of amino acid was about 68%.

(1) Published by permission of the Director of the North Dakota Agricultural Experimental Station.

(2) Present address: Division of Chemistry, College of Agriculture, University of California, Davis.

(3) Tutiya, Yosio., *J. Agr. Chem. Soc., Japan*, **17**, 706 (1941).

(4) Enkrist and Laasonen, *Ber.*, **72B**, 1927 (1939).

(5) Dunn and Fox, *J. Biol. Chem.*, **101**, 493 (1933).

(6) Hamlin and Hartung, *ibid.*, **145**, 349 (1942).

(7) Cocker, *J. Chem. Soc.*, 1489 (1940).

(8) Redemann and Dunn, *J. Biol. Chem.*, **130**, 341 (1939).

(9) Livak, Britton, VanderWeele and Murray, THIS JOURNAL, **67**, 2218 (1945).

(10) Billman and Parker, *ibid.*, **66**, 538 (1944); **65**, 2455 (1943).