tion from ethanol gave 0.07 g, 24%, with mp 165–167°, not depressed by admixture with **17**. The infrared spectrum of this compound was identical with that of **17**. Since component B is different from **16** and **18**, it must be methyl 3,6-di-*O*-mesyl-α-D-galactopyranoside (**19**).

Dimolar Mesylation of Methyl β-D-Galactopyranoside.—The syrupy product obtained by treatment of methyl β-D-galactopyranoside (25 g) with 2 equiv of mesyl chloride was fractionated on a column of silica gel (700 g) with ethyl acetate as solvent. The main component of the mixture, a methyl di-*O*-mesyl-β-D-galactoside, was obtained crystalline in 26% yield. After recrystallization from ethanol, it had mp 144–145°, $[\alpha]^{25}D$ +22° (*c* 1.3, acetone).

Anal. Calcd for $C_9H_{18}O_{10}S_2$: C, 30.85; H, 5.14; S, 18.28. Found: C, 30.77; H, 5.18; S, 18.19.

To a solution of this compound (0.7 g) in dimethylformamide (10 ml) at 0° was added methyl iodide (2 ml) and silver oxide (2 g), and the mixture was stirred in the dark. After 20 hr, tlc (ether–methyl acetate, 1:2) indicated complete methylation and the formation of a single product. The mixture was filtered and the filtrate was concentrated to a residue which was extracted with chloroform. Concentration of the extracts afforded a crystalline methyl di-*O*-mesyldi-*O*-methyl-β-D-galactoside (0.6 g, 78%). After recrystallization from ethanol, the crystals had mp 95–97°, $[\alpha]^{21}D$ −11.2° (*c* 1.0, chloroform).

Anal. Calcd for $C_{11}H_{22}O_{10}S_2$: C, 34.91; H, 5.86; S, 16.94. Found: C, 34.99; H, 5.88; S, 17.21.

A solution of the methyl di-*O*-mesyldi-*O*-methyl-β-D-galactopyranoside (0.3 g) in 1 *N* sodium hydroxide (30 ml) was boiled under reflux. The reaction was followed by tlc (ethyl acetate) and, after 2 hr, no starting material remained. The solution was cooled, deionized (Amberlite MB 3 resin), and concentrated to a syrup which partially crystallized. The crystalline product was purified by sublimation: yield 0.07 g, 39%, mp 83°, $[\alpha]^{25}D$ −74° (*c* 0.7, water).

Anal. Calcd for $C_9H_{16}O_6$: C, 52.94; H, 7.84. Found: C, 53.16; H, 8.00.

Haworth, *et al.*,[11] report mp 83° and $[\alpha]D$ −77° (water) for methyl 3,6-anhydro-2,4-di-*O*-methyl-β-D-galactopyranoside (**22**). The infrared spectrum recorded for this compound[18] was identical with that obtained for the above product.

(18) R. Stephens and D. H. Whiffen, from a collection of the University of Birmingham, also available in DMS Index No. 4533, Butterworth and Co. (Publisher), Ltd., London.

Derivatives of α-D-Glucothiopyranose[1]

R. M. ROWELL AND ROY L. WHISTLER

Department of Biochemistry, Purdue University, Lafayette, Indiana

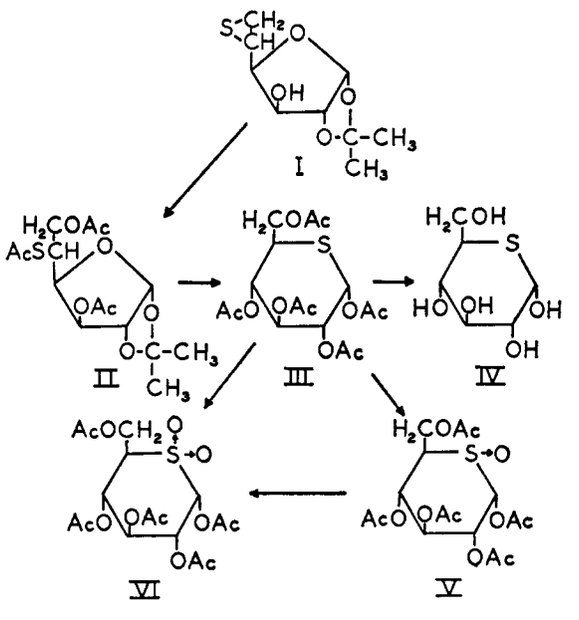
Received December 7, 1965

Treatment of 5-deoxy-3,6-di-*O*-acetyl-1,2-*O*-isopropylidene-5-thioacetyl-α-D-glucofuranose with 50% aqueous acetic acid followed by acetylation gives the penta-*O*-acetate of α-D-glucothiopyranose. Deacetylation of this pentaacetate produces the crystalline α-D-glucothiopyranose. Oxidation of the sugar pentaacetate with sodium metaperiodate in methanol and water gives a sulfoxide. Oxidation of this sulfoxide or direct oxidation of the pentaacetate with peracetic acid gives the sulfone.

Two reports have appeared on the formation of 5-deoxy-5-thiohexoses and their derivatives. One of these[2] dealt with the preparation of penta-*O*-acetyl-L-idothiopyranose and a second[3] with the preparation of methyl D-glucothiopyranoside. The present report describes the preparation of crystalline α-D-glucothiopyranose and the sulfoxide and sulfone oxidation products of its pentaacetate.

The starting material, 5,6-epithio-1,2-*O*-isopropylidene-α-D-glucofuranose[4] (I), is acetolyzed with a solution of acetic anhydride, acetic acid, and potassium acetate to open the 5,6-epithio ring and give 5-deoxy-3,6-di-*O*-acetyl-1,2-*O*-isopropylidene-5-thioacetyl-α-D-glucofuranose[3] (II) (Scheme I). It is assumed that the acetate ion attacks the 5,6-epithio ring in a manner similar to its attack on the 5,6-anhydro derivative with retention of the D-gluco configuration[5] and attachment of the thioacetate at carbon C-5. This material shows a characteristic absorption for a thiol acetate in the ultraviolet[6] spectrum at 230–240 mμ and in the infrared[7] spectrum at 1675 cm.$^{-1}$.

SCHEME I



Acetolysis[8] of II with sulfuric acid, acetic acid, and acetic anhydride produces a syrupy pentaacetate.[3] Usually acetone sugar derivatives, when subjected to sulfuric acid, give rise to condensation products which hinder the crystallization and hence the purification of the reaction product. To overcome this difficulty in the present preparation, the triacetate II is first treated with aqueous acetic acid to initially hydrolyze

(1) This work was supported by the Agricultural Research Service, U. S. Department of Agriculture, Grant No. 12-14 100-7662(71) (Journal Paper No. 2693 of the Purdue Agricultural Experiment Station, Lafayette, Ind.), administered by the Northern Regional Research Laboratory, Peoria, Ill.

(2) T. J. Adley and L. N. Owen, *Proc. Chem. Soc.*, 418 (1961).

(3) M. S. Feather and R. L. Whistler, *Tetrahedron Letters*, **No. 15**, 667 (1962).

(4) L. D. Hall, L. Hough, and R. A. Pritchard, *J. Chem. Soc.*, 1537 (1961).

(5) H. Ohle and W. Mertens, *Ber.*, **63B**, 2176 (1935); S. Peat, *Adv. Carbohydrate Chem.*, **2**, 37 (1946).

(6) H. P. Koch, *J. Chem. Soc.*, 387 (1949).

(7) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958.

(8) A. T. Ness, R. M. Hann, and C. S. Hudson, *J. Am. Chem. Soc.*, **66**, 665 (1944).

the *O*-isopropylidene group. Once this group is removed, a ring shift occurs from the less stable oxyfuranose ring to the more stable thiopyranose ring. Acetylation of this hydrolyzed intermediate gives crystalline 1-4,6-penta-*O*-acetyl-α-D-glucothiopyranose (III). The disappearance of the thiol acetate infrared band at 1675 cm^{-1} along with the analytical analysis of III confirms the presence of sulfur as part of the stable pyranose ring system. When the acetolysis reaction product is seeded with those crystals from the hydrolysis–acetylation reaction, it immediately crystallizes.

Oxidation of III with sodium metaperiodate in methanol–water[9] gives a sulfoxide V. Thin layer chromatography of this reaction mixture shows either that only one diastereoisomeric sulfoxide is formed or that the two isomers are formed but can not be resolved in these solvent systems. The α and β anomers of 1-4-tetra-*O*-acetyl-α-D-xylothiopyranose[10] are not oxidized under these conditions or with other stronger oxidizing agents such as hydrogen peroxide in acetone[11] or chromic acid in pyridine[12] which normally give rise to sulfoxides. 1-4,6-Penta-*O*-acetyl-α-D-glucothiopyranose sulfoxide is the first sugar molecule to be synthesized in which every atom of the ring is asymmetric.

Further oxidation of this sulfoxide V or direct oxidation of III with hydrogen peroxide in glacial acetic acid yields the crystalline sulfone VI. When subjected to deacetylation in methanol with sodium methoxide both sulfoxide and sulfone give a mixture of three components in approximately equal amounts as shown by paper chromatography.

Deacetylation of III with sodium methoxide in methanol gives α-D-glucothiopyranose (IV). One of the effects of the sulfur atom in the molecule is to increase specific optical rotation. This effect is observed in all thio sugars thus far synthesized.

The sulfur atom also affects the taste of the sugar. In water solution, the sugar has a sweet taste although not as sweet as an equivalent amount of D-glucose. When crystals are tasted on the tip of the tongue there is an initial astringent, alum-like, effect followed by a sweetish sensation.

Experimental Section

Analytical Methods.—Purity of crystalline products was determined by tlc on silica gel G[13] coated microscope slides irrigated with (A) chloroform–acetone (9:1 v/v) or (B) ethyl acetate–hexane (1:1 v/v). Components were located by spraying with 5% sulfuric acid in ethanol and heating until permanent char spots were visible. Sugar flow rates are reported relative to that of D-glucose (R_{G1} values) and were determined at 25° on Whatman No. 1 filter paper developed in irrigants (C) 1-butanol–ethanol–water (40:11:19 v/v) or (D) ethyl acetate–acetic acid–formic acid–water (18:3:1:4 v/v). Spray indicators employed were potassium permanganate–periodate[14] and silver nitrate–sodium hydroxide.[15] A spray reagent of hydriodic acid specifically sensitive to sulfoxides[16] was used in the preparation and identification of the sugar sulfoxide. Acetyl groups were qualitatively determined by a spray reagent of ferric hydroxamate.[17] Molecular weights were measured in a Mechrolab vapor phase osmometer with a water solvent.

5-Deoxy-3,6-di-*O*-acetyl-1,2-*O*-isopropylidene-5-thioacetyl-α-D-glucofuranose (II).—5,6-Epithio-1,2-*O*-isopropylidene-α-D-glucofuranose (30 g) was added to 22 g of potassium acetate, 50 ml of acetic acid, and 250 ml of acetic anhydride. The mixture was heated at 140° (oil bath) for 4 hr then poured into 1000 ml of ice and water and stirred. After several minutes, the product crystallized. The crystals were filtered, washed with water, and then dissolved in chloroform. The chloroform solution was washed with a saturated solution of ice-cold sodium bicarbonate followed by a water wash then dried over sodium sulfate. The dried solution was concentrated under reduced pressure to a solid residue which was crystallized from hot ethanol to give 30 g (61%): mp 149°, $[\alpha]^{20}D$ +7.4° (*c* 3.75, chloroform); lit.[3] mp 149°, $[\alpha]^{25}D$ +7.2° (*c* 1.8, chloroform). Compound II showed characteristic absorption for thiol acetate in the infrared at 1675 cm^{-1} and gave an immediate color at 25° with both sodium nitroprusside[18,19] and 2,3,5-triphenyl-2H-tetrazolium chloride.[15]

1,2,3,4,6-Penta-*O*-acetyl-α-D-glucothiopyranose (III).—Compound II (10 g) was dissolved in 200 ml of 50% aqueous acetic acid and heated at 70° (oil bath) for 48 hr. The total reaction mixture was concentrated under reduced pressure to a sirup which was taken up in ethanol and again concentrated. After three such treatments the sirup was dissolved in 60 ml of pyridine and cooled to 0°. To this was added 40 ml of acetic anhydride and the mixture was allowed to stand 16 hr at 25°. The solution was poured into 800 ml of ice and water and the aqueous solution was extracted three times with 100-ml portions of chloroform. The combined chloroform extracts were washed with an ice-cold 5% aqueous solution of sodium bicarbonate, then with an ice-cold 5% aqueous solution of sulfuric acid, and finally with water. The chloroform solution was dried over sodium sulfate and a small amount of activated charcoal. After filtering through a pad of Celite, the solution was concentrated to a thick sirup which was dissolved in a small volume of hot ethanol and allowed to crystallize in the cold. The yield was 5 g (45%); mp 103°; $[\alpha]^{20}D$ +213° (*c* 1.35, chloroform); R_f 0.74 in irrigant A. The compound showed no absorption for thiol acetate in the infrared at 1675 cm^{-1}.

Anal. Calcd for $C_{16}H_{22}O_{10}S$: C, 47.3; H, 5.43; S, 7.9. Found: C, 47.3; H, 5.33; S, 8.1.

α-D-Glucothiopyranose (IV).—Pentaacetate (III) (5 g) were dissolved in 20 ml of absolute methanol and 30 ml of a methanolic sodium methoxide solution (made by adding 500 mg of powdered sodium methoxide to 100 ml of absolute methanol) was added. The mixture was allowed to stand at 4° overnight then passed through a column of Amberlite IR 120 (H) resin. The effluent was concentrated to a thick sirup which crystallized in the cold from dilute ethanol. The compound was recrystallized from hot methanol to give 1.73 g (72%): mp 135–136°; $[\alpha]^{20}D$ +188° (*c* 1.56, water); R_{G1} 1.24 in solvent C and R_{G1} 1.16 in solvent D.

Anal. Calcd for $C_6H_{12}O_5S$: C, 36.8; H, 6.14; S, 16.3; mol wt, 196. Found: C, 36.6; H, 6.09; S, 16.3; mol wt, 194.

1,2,3,4,6-Penta-*O*-acetyl-α-D-glucothiopyranose Sulfoxide (V).—To 30 ml of absolute methanol was added 2 g of the pentaacetate III and to this was added 2 g of sodium metaperiodate dissolved in 15 ml of distilled water. The mixture was allowed to stand at 25° for 1 week then diluted with 100 ml of distilled water. The solution was extracted three times with 50-ml portions of chloroform and the combined extracts were dried over sodium sulfate. The dried solution was concentrated under reduced pressure to a syrup which crystallized. Recrystallization from hot ethyl acetate gave 1.56 g (75%), mp 171°, $[\alpha]^{20}D$ +121 (*c* 1.23, chloroform), R_f in solvent A 0.43.

Anal. Calcd for $C_{16}H_{22}O_{11}S$: C, 45.5; H, 5.22; S, 7.59. Found: C, 45.5; H, 5.29; S, 7.49.

The sulfoxide showed intensification of the peak at 1040 cm^{-1} due to the C–SO–C group.

1,2,3,4,6-Penta-*O*-acetyl-α-D-glucothiopyranose Sulfone (VI).—To a mixture of 10 ml of glacial acetic acid and 4 ml of 30% hydrogen peroxide was added 1 g of the pentaacetate and the solution was allowed to stand at 25° for 48 hr. The mixture was poured into 100 ml of distilled water and the product crystallized

(9) N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, **27**, 282 (1964).
(10) R. L. Whistler, T. van Es, and R. M. Rowell, *ibid.*, **30**, 2719 (1965).
(11) S. Hunig and O. Boes, *Ann.*, **579**, 23 (1953).
(12) D. Edwards and J. B. Stenlake, *J. Chem. Soc.*, 3272 (1954).
(13) Brinkmann Instruments Inc., Westbury, N. Y. 11590.
(14) R. U. Lemieux and H. F. Bauer, *Anal. Chem.*, **26**, 920 (1954).
(15) W. E. Trevelyan, D. P. Procter, and J. S. Harrison, *Nature*, **166**, 444 (1950).
(16) J. F. Thompson, W. N. Arnold, and C. J. Morris, *Nature*, **197**, 380 (1963).
(17) M. E. Tate and C. T. Bishop, *Can. J. Chem.*, **40**, 1043 (1962).
(18) K. A. H. Mörner, *Z. Physiol. Chem.*, **28**, 594 (1899).
(19) W. I. Patterson, W. B. Geiger, C. R. Mizell, and M. Harris, *J. Res. Natl. Bur. Std.*, **27**, 89 (1941).

from solution. The crystals were filtered, washed with water and air dried on the filter pad. Recrystallization from either hot ethanol or hot ethyl acetate gave 0.858 g (80%): mp 205–206; $[\alpha]^{20}D$ +85.9 (*c* 1.92, chloroform); R_f 0.64 in solvent A.

Anal. Calcd for $C_{16}H_{22}O_{12}S$: C, 43.8; H, 5.02; S, 7.32. Found: C, 44.0; H, 4.90; S, 7.10.

The sulfone, dissolved in chloroform, showed peaks in the infrared spectrum at 1330 and 1145 cm^{-1} which are characteristic for asymmetric and symmetric sulfone stretching vibrations in $C-SO_2-C$ type compounds.

The sulfone can also be made from the sulfoxide as follows. To a mixture of 6 ml of glacial acetic acid and 3 ml of 30% hydrogen peroxide was added 1 g of the sulfoxide V. The mixture was allowed to stand at 25° for 48 hr then worked up as described above. Recrystallization from hot ethyl acetate gave 0.856 (83%), mp 205–206°.

Alicyclic Carbohydrates. XXIX.[1,2] The Synthesis of a Pseudo-Hexose (2,3,4,5-Tetrahydroxycyclohexanemethanol)

G. E. McCasland,[3] Stanley Furuta,

Department of Chemistry and Institute of Chemical Biology, University of San Francisco, San Francisco, California 94117

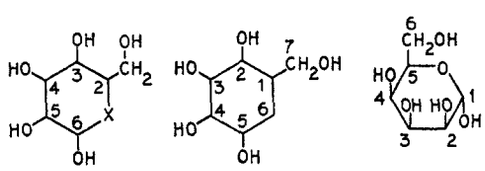
and Lois J. Durham

Department of Chemistry, Stanford University, Stanford, California 94305

Received October 18, 1965

The expression "pseudo-sugar" is proposed to designate any alicyclic analog of a cyclic monosaccharide, in which the usual ring-oxygen atom is replaced by methylene. A compound, 2,3,4,5-tetrahydroxycyclohexanemethanol, has been synthesized and appears to be the first known pseudo-hexose. It has the α-DL-talopyranose configuration. It was obtained by reduction of the corresponding tetraacetoxycyclohexanecarboxylic acid methyl ester which had been prepared by a Diels–Alder synthesis from 2-acetoxyfuran and maleic anhydride. Pentaacetate and trityl ether tetraacetate derivatives were also prepared. With the aid of nmr spectroscopy, it was established that the conformation with side chain equatorial was preferred for the pseudo-hexose and its derivatives. Conformational assignments were based upon spin–spin coupling patterns and comparisons with other spectra in the same series.

Recently several research groups have synthesized sugar analogs (**2** and **3**) in which the ring-oxygen atoms were replaced by other atoms, such as sulfur[4] or nitrogen (NH or NCOR).[5] Continuing our studies on alicyclic carbohydrates,[2] we have now synthesized a monosaccharide analog (**4**) in which the ring oxygen is replaced by *carbon* (CH_2). The term "pseudo-sugar"



1, X = O
2, X = S
3, X = NH or NCOR

4

5

has been coined to designate any such analog. It is hoped that pseudo-sugars may be found acceptable in place of corresponding true sugars to some but not all enzymes or biological systems, and thus might serve to inhibit growth of malignant or pathogenic cells.[6] Only aldohexopyranose analogs are here considered.[7]

Thirty-two stereoisomers (including anomers) are predicted for a true or pseudo-aldohexopyranose (**1** or **4**). The stereoisomer now reported has the α-DL-talopyranose or DL(1234/5) configuration[8a,8c] **5** or **11**. Syntheses of biologically more interesting analogs, *e.g.*, of glucose, mannose, and galactose, are in progress. In order to help increase the application of nmr spectroscopy in carbohydrate chemistry,[9] our numerous intermediates and products were characterized by nmr.

Synthesis of Pseudo-Talose

It appeared that pseudo-talose **11** would be the most readily accessible pseudo-hexose, since it might be

(1) Presented to the American Chemical Society (Division of Carbohydrate Chemistry), at the Winter Meeting, Phoenix, Ariz., Jan 1966, and (in part) at the 148th National Meeting, Chicago, Ill., Sept 1964.

(2) For preceding paper, see G. E. McCasland, S. Furuta, L. F. Johnson, and J. N. Shoolery, *J. Org. Chem.*, **29**, 2354 (1964). The combined series "Alicyclic Carbohydrates" incorporates papers I–XVIII in the series previously entitled "Stereochemistry of the Cyclitols," and also ten publications on hydroxylated cyclohexanes by G. E. McCasland and co-workers from the period 1949–1965 which were not assigned numbers at the time of publication. A complete list is available on request.

(3) To whom any correspondence should be addressed.

(4) Regarding sulfur-in-ring sugars, see (a) *Chem. Eng. News*, **41**, 70 (Sept 16, 1963); (b) R. L. Whistler, W. E. Dick, T. R. Ingle, R. M. Powell, and B. Urbas, *J. Org. Chem.*, **29**, 3723 (1964); (c) earlier work cited in these references.

(5) Regarding nitrogen-in-ring sugars, see A. J. Dick and J. K. N. Jones, *Can. J. Chem.*, **43**, 977 (1965), also earlier work of various authors there cited.

(6) P. A. J. Gorin, K. Horitsu, and J. F. T. Spencer in studies on certain inositols and sugars found that the absence of pyranose ring oxygen had little effect on the activity of certain glycosyl transfer enzymes [*ibid.*, **43**, 2259 (1965)].

(7) Pseudo-analogs of other aldoses or ketoses can similarly be defined. Thus certain (known) cyclohexanetetrols would correspond to pentopyranoses; certain hydroxymethylcyclopentanetriols to pentofuranoses; certain dihydroxyethylcyclopentanetriols to hexofuranoses; and certain cycloheptanepentols to hexoseptanoses. Pseudo-D-fructofuranose would be a certain isomer of trihydroxycyclopentanedimethanol.

(8) (a) For explanation of the fractional notation here used to designate stereoisomers, *e.g.*, DL(1234/5), see G. E. McCasland, *Advan. Carbohydrate Chem.*, **20**, 13 (1965). (b) The fractional notation for the two derivatives of 3-acetoxy-3,6-epoxycyclohexane presents a special problem, since neither "group" at position 3 is a hydrogen atom. According to a priority rule proposed by G. E. McCasland in 1953, the group *O–CH* comes alphabetically before the group *O–CO*, and is therefore the basis for fractional notation. Since in the stereoisomers **19** and **20**, the group *O–CH* at position 3 is *cis* to groups at 1, 2, and 6, or 1, 2, 4, 5, and 6, the fractional notation chosen is DL(1236/0) and DL(123456/0), respectively. (c) The organic compounds in this article are numbered and named as *cyclohexane* derivatives, according to *Chemical Abstracts* rules, *e.g.*, 2,3,4,5-tetrahydroxycyclohexanemethanol. Some chemists may prefer to use *carbohydrate* numbering and nomenclature, according to which the tertiary ring-carbon atom would be numbered 5 and the side-chain carbon atom 6, and the sixth ring-carbon atom would remain unnumbered (see formulas **5** and **11**).

(9) For reviews on the applications of nmr to carbohydrates, see L. D. Hall, *Advan. Carbohydrate Chem.*, **19**, 51 (1964); G. E. McCasland, *ibid.*, **20**, 11 (1965).