

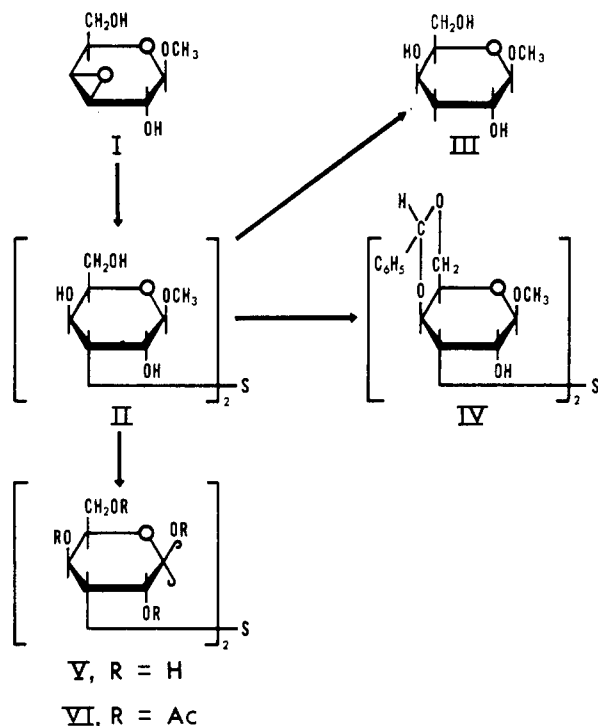
Methyl 3,4-Anhydro- β -D-galactopyranoside.III. Reaction with Hydrogen Sulfide^{1,2}

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Recently much interest has been shown in the synthesis of carbohydrate derivatives in which an oxygen atom of a hydroxyl group has been replaced by a sulfur atom.³ We were interested in the preparation of 3- and 4-thiohexoses for use as possible antimetabolites of the pentose phosphate pathway of carbohydrate metabolism.^{2,4,5} A possible route to such compounds involved the reaction of sugar epoxides with hydrogen sulfide. We wish to report the results of experiments in which methyl 3,4-anhydro- β -D-galactopyranoside (I) was treated with hydrogen sulfide in the presence of aqueous base.



It had been shown earlier that the reaction of 5,6-anhydro-1,2-*O*-isopropylidene- α -D-glucofuranose with hydrogen sulfide in the presence of aqueous barium hydroxide led to the formation of the 6-thio deriva-

tive.⁶ Since it had been reported also that cleavage of methyl 3,4-anhydro- β -D-galactopyranoside in basic solution resulted in either predominant or total attack at C-3,^{2,4} we expected to obtain methyl 3-thio- β -D-gulopyranoside as the main or only product. The results showed that attack did occur at C-3, but the only product isolated was the sulfide, 3,3'-thiobis(methyl 3-deoxy- β -D-gulopyranoside) (II), as a white solid, m.p. 219–220°, along with some unreacted oxide (94% yield based on the oxide consumed).

Proof that the sulfide II actually possessed a 3,3' linkage was obtained by reductive desulfuration of II with Raney nickel to give the known methyl 3-deoxy- β -D-xylo-hexopyranoside (III), m.p. 175–176°, which showed no depression in melting point when mixed with an authentic sample of III.⁴ Additional proof was furnished by hydrolysis of the original reduction mixture, followed by paper chromatography. Only one spot was detected and its R_{xylose} value of 1.30 was very close to the reported value of 1.33 for 3-deoxy-D-xylo-hexose.⁴ No evidence of attack at C-4 was obtained.

From these results it seems probable that the initial attack of the HS⁻ anion occurred at C-3 with formation of methyl 3-thio- β -D-gulopyranoside and that the anion of the latter, being a more effective nucleophile than the HS⁻ anion, reacted immediately with a second molecule of the oxide to give the sulfide. This behavior is reminiscent of that observed with 5,6-episulfides, substances which polymerize in aqueous alkali.⁷ The sulfide II has also been obtained from the reaction of the oxide I with potassium thiolacetate.⁸

Hydrolysis of the sulfide II with either Amberlite IR-120 (H⁺) ion-exchange resin or with 0.2 *N* sulfuric acid yielded 3,3'-thiobis(3-deoxy-D-gulopyranose) (V), a white waxy solid, m.p. 92°. This substance appeared to undergo decomposition on standing; therefore, in subsequent preparations it was fully acetylated immediately with acetic anhydride in pyridine and characterized as the octaacetate VI, m.p. 202–203°.

When the sulfide II was treated with benzaldehyde in the presence of zinc chloride, a benzylidene derivative (IV) was obtained which showed a double melting point of 119–120° and 139–140° when recrystallized from benzene. This substance absorbed at 2.82 μ in the infrared region, indicating the presence of free hydroxyl groups, and had an approximate molecular weight of 598. It could not be separated into more than one component on a column of aluminum oxide. From the elementary analysis the structure of IV appears to be the 4,6,4',6'-dibenzylidene derivative of II, containing 0.5 mole of benzene of recrystallization. This would require a molecular weight of 601 and would show absorption at 2.82 μ . Because the homogeneity of this substance was in doubt, it was converted into the diacetyl derivative, 3,3'-thiobis(methyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-deoxy- β -D-gulopyranoside), obtained as colorless needles from 95% ethanol, m.p. 259–260°.

Results of the biological testing of the compounds described above will be reported elsewhere.

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(2) Part II: M. Dahlgard, B. H. Chastain, and R. L. Han, *J. Org. Chem.*, **27**, 932 (1962).

(3) See, for example, (a) E. J. Reist, D. E. Gueffroy, and L. Goodman, *J. Am. Chem. Soc.*, **85**, 3715 (1953); (b) D. Horton and D. H. Hutson, *Advan. Carbohydrate Chem.*, **18**, 123 (1963).

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(8) M. Dahlgard, unpublished results.

Experimental Section⁹

3,3'-Thiobis(methyl 3-deoxy- β -D-gulopyranoside) (II).—The method was based on that used for the preparation of 1,2-O-isopropylidene-6-thio- α -D-glucopyranose.⁶ A suspension of barium hydroxide hydrate (31.2 g., 0.10 mole) in 120 ml. of water at 0° was saturated with hydrogen sulfide. Methyl 3,4-anhydro- β -D-galactopyranoside⁴ (I) (17.6 g., 0.10 mole) was added, and hydrogen sulfide was passed into the solution for 140 min. at 0°. After standing 30 min. gaseous carbon dioxide was passed into the mixture until it was no longer basic to precipitate the barium ions as insoluble barium carbonate. The solution was filtered, and the filtrate was evaporated to dryness at 45° on the evaporator. The crude yield was 19 g. Unreacted oxide was removed by extraction with hot ethyl acetate, leaving 14 g. of crude II, m.p. 215–217°, 94% yield based on the oxide consumed. Recrystallization from dioxane gave a constant melting point of 219–220°. Ethanol can also be used as a recrystallization solvent: $[\alpha]^{25}_D -76.0^\circ$ (*c* 2.1, water).

Anal. Calcd. for $C_{14}H_{26}O_{10}S$: C, 43.52; H, 6.74; S, 8.29. Found: C, 43.54; H, 6.55; S, 8.37.

Methyl 3-Deoxy- β -D-xylo-hexopyranoside (III) from II by Reductive Desulfuration.—Raney nickel catalyst was prepared from 15.0 g. of nickel-aluminum alloy by the method of Mozingo, *et al.*,¹⁰ final heating being carried out at 50° for 1 hr. To the catalyst, freed from excess alcohol by decantation, was added a solution of 0.45 g. of II in 20 ml. of ethanol, followed by 7 ml. of water. After refluxing on a steam bath for 2 hr., the mixture was cooled and filtered free of catalyst, the catalyst was washed well with ethanol and water, and the combined filtrates were evaporated to dryness. The residue was recrystallized from isopropyl alcohol to give 0.31 g. (73%) of III, m.p. 175–176°, showing no depression in melting point when mixed with an authentic sample of methyl 3-deoxy- β -D-xylo-hexopyranoside, m.p. 174–175°.⁴

The above reductive desulfuration was repeated and the crude reduction product was hydrolyzed by heating in 0.2 *N* sulfuric acid for 5 hr., followed by treatment with Duolite A4 anion-exchange resin (amine form) to remove the acid and evaporation to a small volume. A chromatogram of this material using Whatman 1MM paper (*n*-butyl alcohol-acetic acid-water, 4:1:1; 16 hr.) when sprayed with aniline hydrogen phthalate in *n*-butyl alcohol and heated at 125° for 5 min. showed only one spot with R_{xylose} 1.30, very close to the value of R_{xylose} 1.33 reported⁴ for 3-deoxy-D-xylo-hexose.

Reaction of 3,3'-Thiobis(methyl 3-deoxy- β -D-gulopyranoside) (II) with Benzaldehyde.—A mixture of 5.0 g. of II, 20 ml. of benzaldehyde, and 5.0 g. of fused anhydrous zinc chloride was shaken for 1 hr., then left to stand overnight at room temperature. When the reaction mixture was poured into ice-water a gummy layer separated from the water solution. The water was decanted and the organic layer was washed several times with small portions of pentane to remove benzaldehyde. The residue was treated with hot benzene and upon cooling there was obtained 4.0 g. of crude product. Several recrystallizations from benzene resulted in a white waxy solid with a double melting point: shrank and became wet at 119–120°, melted completely at 139–140°. The infrared spectrum showed some absorption still present at 2.82 μ , indicating the presence of free hydroxyl groups. A molecular weight determination (Rast) gave a value of 598, which is close to the value of 601 calculated for the dibenzylidene derivative containing 0.5 mole of benzene of recrystallization. Attempts were made to purify the benzylidene derivative on an aluminum oxide column. Only one substance was eluted (with chloroform as solvent) and this seemed to be identical with the original product when recrystallized from benzene. The most likely structure for this derivative would appear to be 3,3'-thiobis(methyl 4,6-O-benzylidene-3-deoxy- β -D-gulopyranoside) (IV), containing 0.5 mole of benzene of recrystallization: $[\alpha]^{25}_D -29.1^\circ$ (*c* 1.052, $CHCl_3$).

Anal. Calcd. for $C_{28}H_{34}O_{10}S \cdot 0.5C_6H_6$: C, 61.90; H, 6.16; S, 5.32. Found: C, 62.84; H, 6.21; S, 5.32.

3,3'-Thiobis(methyl 2-O-acetyl-4,6-O-benzylidene-3-deoxy- β -D-gulopyranoside) from IV.—Acetic anhydride (1.0 ml.) was added to 0.3 g. of IV in 3 ml. of pyridine in the cold; after standing overnight the mixture was poured into ice-water, yielding

0.3 g. of a white solid, m.p. 253–256°. Recrystallization to constant melting point (95% ethanol) gave 0.24 g., m.p. 259–260°, $[\alpha]^{25}_D -24.9^\circ$ (*c* 2.084, $CHCl_3$). The infrared spectrum showed no absorption band at 2.82 μ .

Anal. Calcd. for $C_{32}H_{38}O_{12}S$: C, 59.44; H, 5.88; S, 4.95. Found: C, 59.33; H, 6.02; S, 5.26.

3,3'-Thiobis(3-deoxy-D-gulopyranose) (V).—A solution of II (2.5 g.) in 250 ml. of water was refluxed with 25 ml. of Amberlite IR-120 (H^+) ion-exchange resin until constant rotation was obtained (6 hr.). The resin was removed by filtration and washed well with water. The filtrate was evaporated to a small volume and filtered through a thin mat of Norit and Celite No. 535, then taken to dryness (<55°) on the flash evaporator, final removal of water being accomplished by several evaporations with small portions of ethanol and benzene. The residue was repeatedly extracted with acetone, and the combined acetone extracts were evaporated to dryness, leaving a fluffy white waxy solid with a rather sweet odor, m.p. 92°, $[\alpha]^{25}_D -27.6^\circ$ (*c* 1.068, absolute ethanol). Upon standing the free sugar appeared to undergo decomposition.

3,3'-Thiobis(3-deoxy-D-gulopyranose) Octaacetate (VI).—The acid hydrolysis of 4.2 g. of II with 0.2 *N* sulfuric acid for 5 hr. at 95° gave 3.4 g. of crude V which was acetylated immediately by addition of 25 ml. of pyridine and 15 ml. of acetic anhydride in the cold. After standing overnight, the mixture was poured over ice, and the solid which formed was removed by filtration. It amounted to 4.3 g., m.p. 170–173°. It was recrystallized to a constant melting point of 202–203° (95% ethanol), $[\alpha]^{25}_D +1.0^\circ$ (*c* 2.0, $CHCl_3$).

Anal. Calcd. for $C_{28}H_{38}O_{18}S$: C, 48.41; H, 5.48; S, 4.61. Found: C, 48.85; H, 5.35; S, 4.63.

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Nucleosides. II. Reactions of 5'-Trityluridine 2',3'-O-Thionocarbonate

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A recent communication by Fox and Wempen¹ described an attempt to prepare a 2',3'-unsaturated nucleoside by an application of the olefin synthesis of Corey and Winter.² When 5'-O-trityluridine (I) was heated with bis(imidazol-1-yl)thione³ in refluxing toluene,² 2,2'-anhydro-1-(5'-O-trityl- β -D-arabinofuranosyl)uracil (III) was obtained in good yield instead of the expected 5'-O-trityluridine 2',3'-thionocarbonate (II). Our results from the use of these experimental conditions are in precise agreement with those of Fox and Wempen.¹ In addition, we have found that II can be obtained by conducting the reaction of I with bis(imidazol-1-yl)thione in tetrahydrofuran at room temperature. As expected,¹ II is easily converted to III by treatment with base, *e.g.*, imidazole in refluxing toluene or potassium *t*-butoxide in ethanol. The conversion of II to 2',3'-didehydro-2',3'-dideoxy-5'-O-trityluridine (IVa)⁴ was accomplished in low yield by

(9) Microanalyses were performed by Schwarzkopf Microanalytical Laboratory. The descending technique was used in paper chromatography.

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