The product was chromatographically pure and had on paper chromatography $R_{thymine}$ values of 0.79, 1.08, and 1.09 in solvents A, B, and C, respectively.

Anal. Calcd for $C_{10}H_{14}N_2O_5S$: C, 43.79; H, 5.14; N, 10.21; S, 11.69. Found: C, 43.54; H, 5.02; N, 10.44; S, 11.62.

1-(2,3,4-Tri-*O*-acetyl-5-thio-D-xylopyranosyl)-4-ethoxy-2(1H)-pyrimidinone (X).—A mixture of 3.1 g (0.01 mole) of the chloro sugar VIII and 3.1 g of 2,4-diethoxypyrimidine was heated at 100° for 24 hr and then at 120–125° for 24 hr. The cooled reaction mixture was diluted with an equal amount of ether, filtered, and stored overnight at 0°. Compound X crystallized from the solution and was removed by filtraion to yield 0.6 g of material, mp 188°. Additional product was obtained from the concentrated mother liquor to give a total yield of 0.91 g (22%). Three recrystallizations from ethanol gave an analytically pure product, mp 201°, $[\alpha]^{22}D$ +27.9° (*c* 1.04, chloroform).

Anal. Calcd for $C_{17}H_{22}N_2O_8S$: C, 49.27; H, 5.35; N, 6.76; S, 7.74. Found: C, 49.07; H, 5.48; N, 6.40; S, 7.99.

1-(5-Thio-D-xylopyranosyl)uracil (XI).—To a solution of 0.41 g (0.001 mole) of compound X in 5 ml of methanol was added 1 ml of methanol previously saturated at 0° with hydrogen chloride. The solution was kept at 25° for 3 days during which time compound XI crystallized from the solution and was removed by filtration to give 0.24 g, mp 275–278°. Two recrystallization from 90% ethanol gave a pure product: mp 284–285° dec (uncor); $[\alpha]^{25}D$ +40.1° (*c* 1.52, water); $\lambda_{max}^{pH\ 2}$ 265 mμ (ε 11,692), $\lambda_{min}^{pH\ 2}$ 231 mμ (ε 2311); $\lambda_{max}^{pH\ 12}$ 265 mμ (ε 9051), $\lambda_{min}^{pH\ 12}$ 243 mμ (ε 6153). On chromatographic examination this nucleoside had R_{uracil} values of 0.87, 1.06, and 1.05 in solvents A, B, and C, respectively.

Anal. Calcd for $C_9H_{12}N_2O_5S$: C, 41.54; H, 4.64; N, 10.76; S, 12.32. Found: C, 41.33; H, 4.64; N, 10.63; S, 12.12.

1-(5-Thio-D-xylopyranosyl)cytosine (XII).—Compound X (0.3 g) was partially dissolved in 6 ml of methanol; the mixture was saturated at 0° with anhydrous ammonia and heated in a sealed tube at 90° for 3 days. The resultant solution was concentrated under reduced pressure to dryness. Crystallization of the residue from 90% ethanol gave compound XII (0.20 g): mp 287–288° dec (uncor); $[\alpha]^{25}D$ +26.3° (*c* 1.48, water); $\lambda_{max}^{pH\ 2}$ 281, 215 mμ (ε 14,313, 10,490), $\lambda_{min}^{pH\ 2}$ 242 mμ (ε 1981); $\lambda_{max}^{pH\ 12}$ 273, 231 mμ (ε 10,488, 8699), $\lambda_{min}^{pH\ 12}$ 251 mμ (ε 7398). The paper chromatography $R_{cytosine}$ values were 0.89, 1.05, and 1.03 in solvents A, B, and C, respectively.

Anal. Calcd for $C_9H_{13}N_3O_4S$: C, 41.69; H, 5.05; N, 16.21; S, 12.36. Found: C, 41.84; H, 5.23; N, 15.84; S, 12.50.

9-(5-Thio-D-xylopyranosyl)adenine (XIII).—A solution of 6.2 g (0.02 mole) of the sugar chloride VIII in 20 ml of azeotropically dried toluene was added to a mixture of 9.5 g of 6-benzamido-9-chloromercuripurine[19] in 500 ml of toluene previously dried by azeotropic distillation. The mixture was refluxed with stirring for 6 hr. The hot solution was filtered, and the filter cake was washed with toluene. The combined filtrate was concentrated under reduced pressure to a volume of 100 ml and precipitated with 400 ml of hexane. The precipitated blocked nucleoside was filtered and dissolved in 200 ml of chloroform. The chloroform solution was washed with two 100-ml portions of 30% potassium iodide, then with two 100-ml portions of water and dried over sodium sulfate. The solution was evaporated under reduced pressure to give a yellow gum, which was dissolved in 10 ml of ethyl acetate and stored overnight at 0°. The crystalline product (6-benzamidopurine) was removed by filtration and washed with ethyl acetate. The combined mother liquors were evaporated to dryness and the residue was dissolved in 20 ml of methanol, a catalytic amount of metallic sodium was added, and the solution was held at 25° for 10 hr and then refluxed for 15 min and evaporated to dryness. The residue was dissolved in 10 ml of water and neutralized with dilute acetic acid. To the neutralized solution was added 15 ml of a 10% ethanolic picric acid solution, and the mixture was left at 0° for 10 hr. The yellow picrate which formed was removed by filtration: yield 1.1 g, mp 230–231° dec (from water).

Anal. Calcd for $C_{16}H_{16}N_8O_{10}S$: C, 37.50; H, 3.15; N, 21.87; S, 6.26. Found: C, 37.68; H, 3.45; N, 22.09; S, 6.25.

The above picrate was dissolved, with stirring in hot water, and IR-400 (CO_3^{2-}) resin was added until the solution was colorless. The resin was then removed by filtration, and the filtrate was concentrated under reduced pressure to a white solid, which was recrystallized three times from absolute ethanol, giving 0.55 g (10%) of pure material which had mp 266–267° (uncor), $[\alpha]^{27}D$ +63.1° (*c* 1.52, 50% aqueous pyridine), $\lambda_{max}^{pH\ 2}$ 258 mμ (ε 14,752), $\lambda_{max}^{pH\ 7,12}$ 260 mμ (ε 15,104). The product was chromatographically pure and had on paper chromatography $R_{adenine}$ 0.95, 1.12, and 1.16 in solvents A, B, and C, respectively.

Anal. Calcd for $C_{10}H_{13}N_5O_3S \cdot 0.5C_2H_5OH$: C, 43.11; H, 5.26; N, 22.87; S, 10.47. Found: C, 42.95; H, 5.25; N, 23.24; S, 10.28.

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Synthesis of Septanose Derivatives of 6-Deoxy-6-mercapto-D-galactose[1]

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6-*O*-Tosyl-2,3,4,5-tetra-*O*-acetyl-D-galactose diethyl mercaptal was treated with thiolacetate to give the 6-deoxy-6-thioacetyl derivative. This on treatment with mercuric chloride and then hydrogen sulfide produced 6-deoxy-6-mercapto-2,3,4,5-tetra-*O*-acetyl-*aldehydo*-D-galactose, which on acetylation gave the crystalline α and β anomers of the pentaacetylthioseptanose. These, with hydrogen chloride, produced the α and β anomeric chlorides of which the α-D crystallized. These were converted to anomers of the methyl D-galactothioseptanoside tetraacetate of which the β-D anomer crystallized and on deacetylation gave crystalline methyl β-D-galactothioseptanoside, which hydrolyzed in 0.5 *N* acid at 25° with $k = 9.6 \times 10^2$ min^{-1}. The appropriate structure is shown by periodate oxidation.

This laboratory has been interested for some time in the preparation of metabolically important sugars and sugar derivatives wherein the normal ring oxygen is replaced by sulfur. Sulfur as a thiol in the appropriate location of a sugar molecule is found to react readily with the potentially aldehydic carbon to form, depending on the location of the mercapto group, either a thiofuranose or thiopyranose ring. Such thio sugars behave chemically in much the same way as the normal oxygen sugars. In the course of characterization of thio sugar ring systems, it is of interest to determine if a 6-deoxy-6-mercaptohexose can form a seven-membered septanose ring. A thiepane ring has been made by the interaction of sodium sulfide with 1,6-dibromohexane.[2] Thiolevoglucosan[3,4] has been pre-

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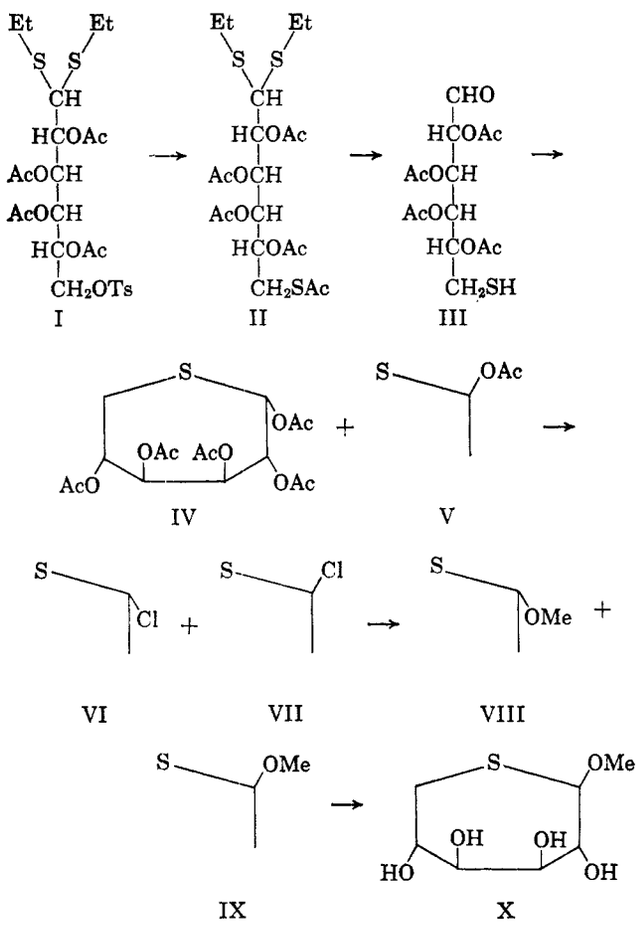
pared by several methods and the mechanism of formation has been fairly well elucidated. Another interesting fused ring sugar, 1,6-anhydro-5,6-dideoxy-6-mercapto-β-D-xylohexofuranose,[5] has been obtained by the hydrolysis of 5,6-dideoxy-6-thioacetyl-1,2-*O*-isopropylidene-α-D-xylohexofuranose.

The preparative route to the thioseptanose was similar to the route used by Micheel and co-workers[6-8] in their synthesis of methyl α-D-galactoseptanoside, which is the only septanose sugar prepared heretofore.

The starting material is the known 6-*O*-tosyl-2,3,4,5-tetra-*O*-acetyl-D-galactose diethyl mercaptal (I).[9] Displacement of the tosyloxy group with thiolacetate anion gives the 6-thioacetyl derivative II (see Chart I). Treatment of this compound with mercuric

CHART I



chloride and mercuric oxide gives the mercuric chloride sugar mercaptide which, on removal of mercury with hydrogen sulfide, yields the 6-deoxy-6-mercapto-2,3,4,5-tetra-*O*-acetyl-*aldehydo*-D-galactose (III), which undoubtedly undergoes some ring formation although a part may be transformed and remain in the open-chain aldehydrol form. Cleavage of thiol esters with mercury salts to yield a mercaptide and a carboxylic acid is well known.[10-12] Compound III undergoes mutarotation in pyridine with ring formation, and acetylation of the mixture yields the crystalline α and β anomers of 1,2,3,4,5-penta-*O*-acetyl-D-galactothioseptanose (IV and V). Treatment of IV and V with ethereal hydrogen chloride gives a mixture of α and β anomers of 2,3,4,5-tetra-*O*-acetyl-D-galactothioseptanosyl chloride (VI and VII). The α-D anomer (VI) is crystalline, while the β-D anomer (VII) is a syrup. The mixture of VI and VII is treated with methanol and silver carbonate to give a mixture of α and β anomers of methyl 2,3,4,5-tetra-*O*-acetyl-D-galactothioseptanoside (VIII and IX).

After separation of VIII and IX by silica gel column chromatography, the α-D anomer (VIII) is obtained as a syrup and the β-D anomer (IX) is obtained crystalline. Deacetylation of IX with methanolic ammonia gives methyl β-D-galactothioseptanoside (X). Compound X is obtained crystalline after purification by paper chromatography.

Proof of the septanose ring is based on infrared spectral data and periodate oxidation studies. Examination of the infrared spectrum of II reveals an absorption band at 1680 cm^{-1} characteristic of a thiol ester. This absorption band is absent in IV and V indicating that sulfur is no longer linked to a carbonyl group. When compound X is subjected to oxidation with sodium metaperiodate at 10°, 3.37 moles of periodate is consumed and 1.80 moles of formic acid is produced. These values agree well with the theoretical consumption of 3.00 moles of periodate and the production of 2.00 moles of formic acid.

Experimental Section

Analytical Methods.—Thin layer chromatography was done on 5 × 12.5 cm plates coated with silica gel G.[13] Components were located by spraying with a 5% solution of sulfuric acid in ethanol and charring until permanent spots were visible. Silica gel[14] with a particle size of 80–200 mesh was used for column chromatography. A calibrated Fisher-Johns apparatus was used for melting point determinations. Evaporations were conducted under reduced pressure.

6-Deoxy-6-thioacetyl-2,3,4,5-tetra-*O*-acetyl-D-galactose Diethyl Mercaptal (II).—Crystalline 2,3,4,5-tetra-*O*-acetyl-6-*O*-tosyl-D-galactose diethyl mercaptal[9] (I, 50 g) was refluxed in 1000 ml of dry acetone containing 11 g of potassium thiolacetate. After 6 hr the reaction mixture was cooled and the potassium tosylate was removed by filtration. The filtrate was concentrated to dryness and the residue was dissolved in chloroform. The chloroform solution was washed three times with water, dried over sodium sulfate, and evaporated to dryness. The solid mass, when crystallized from methanol, gave 37 g (88%) of compound II, mp 119–120°. Recrystallization of II from a boiling mixture of ether and pentane gave pure material: mp 121–122°; $[\alpha]^{25}D$ +17.9° (*c* 1.58, chloroform); λ_{max}^{KBr} 1680 (thiol ester), 1740 cm^{-1} (ester).

Anal. Calcd for $C_{20}H_{32}O_9S_2$ (512.7): C, 46.86; H, 6.29; S, 18.76. Found: C, 46.83; H, 6.14; S, 18.99.

6-Deoxy-6-mercapto-2,3,4,5-tetra-*O*-acetyl-D-galactose (III).—Mercuric chloride (180 g) was dissolved in 1500 ml of acetone. Finely powdered yellow mercuric oxide (180 g) and 60 ml of water were added. Compound II (70 g) was added to this stirred mixture. Stirring was maintained for 36 hr at 25°. The mixture was then filtered into a flask containing 250 ml of pyridine, and the residue was washed with 500 ml of warm acetone. Hydrogen sulfide was passed through the filtrate until all mercury salts were precipitated, and the mercuric sulfide was removed by filtration. The acetone solution was evaporated at 25° to a syrup, which was dissolved in chloroform.

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The chloroform solution was washed three times with water, dried over sodium sulfate, and evaporated at 25–30° to a syrup. Further purification of compound III was not attempted.

1,2,3,4,5-Penta-*O*-acetyl-α- and -β-D-galactothioseptanose (IV and V).—Compound III obtained from 70 g of II was dissolved in 600 ml of dry pyridine. The pyridine solution was evaporated at 25–30° to a volume of 450 ml. After keeping the pyridine solution under nitrogen for 24 hr at 25°, it was cooled to 0° and 125 ml of acetic anhydride was added. The reaction mixture was allowed to return to 25° and stand at this temperature for 24 hr. It was then cooled to 0° and chips of ice were added to destroy excess acetic anhydride. This mixture was dissolved in chloroform, and the solution was washed with copper sulfate solution until free of pyridine, then washed twice with water. The chloroform solution was dried over sodium sulfate and evaporated to a syrup.

This syrup showed one major component of medium mobility and several minor components on silica gel plates in hexane–ethyl acetate (1:1). A 1.5-g portion of this syrup was fractionated on a silica gel column (2.8 × 50 cm) using the same solvent. The major component was obtained as a syrup (435 mg). The syrup showed two very close running components on silica gel plates in hexane–ethyl acetate (2:1) when irrigated three successive times. The syrup was dissolved in a small amount of ether and induced to crystallize by scratching. The faster moving component, IV, crystallized at 25°. The slower moving component, V, crystallized when the supernatant was placed in the refrigerator.

Two recrystallizations of IV from ether gave the pure α-D anomer: mp 154–155°, $[\alpha]^{25}D$ −2.8° (*c* 1.52, chloroform), λ_{max}^{KBr} 1740 cm^{-1} (ester).

Anal. Calcd for $C_{16}H_{22}O_{10}S$ (406.4): C, 47.29; H, 5.46; S, 7.89. Found: C, 47.21; H, 5.30; S, 8.05.

Two recrystallizations of V from ether gave the pure β-D anomer: mp 148–149°, $[\alpha]^{25}D$ −233° (*c* 1.54, chloroform), λ_{max}^{KBr} 1740 cm^{-1} (ester).

Anal. Calcd for $C_{16}H_{22}O_{10}S$ (406.4): C, 47.29; H, 5.46; S, 7.89. Found: C, 47.56; H, 5.35; S, 8.11.

In further preparations, IV and V were obtained by introduction of seed crystals into an ether solution of the crude syrup. A crystal of IV was introduced and the mixture was allowed to stand for 3 days at 25°. The crystals were removed by filtration. A crystal of V was introduced into the filtrate and the mixture was kept for 3 days in the refrigerator. From 70 g of II, 4.7 g of IV (8.5%) and 3.6 g of V (6.5%) were obtained.

2,3,4,5-Tetra-*O*-acetyl-α- and -β-D-galactothioseptanosyl Chloride (VI and VII).—Five grams of the syrupy mixture of IV and V was dissolved in 500 ml of absolute ether which had been saturated with dry hydrogen chloride gas at 0°. The reaction mixture was kept at 5° for 48 hr. Dry benzene (50 ml) was added and evaporated. After evaporation of two more 50-ml portions of benzene, the syrup was dissolved in dry ether and decolorized with charcoal, and the charcoal was removed by filtration. Evaporation of the ether gave 4.3 g (91%) of colorless syrup: $[\alpha]^{25}D$ −149° (*c* 1.11, chloroform).

This syrup showed two components on silica gel plates in hexane–ethyl acetate (2:1). The syrup was dissolved in a small amount of dry ether, and dry pentane was added. Scratching induced the slower moving component, VI, to crystallize. Two recrystallizations of VI from a mixture of ether and pentane gave the pure α-D anomer: mp 143–144°, $[\alpha]^{25}D$ −48.9° (*c* 1.63, chloroform).

Anal. Calcd for $C_{14}H_{19}ClO_8S$ (382.8): Cl, 9.26. Found: Cl, 9.23.

Methyl 2,3,4,5-Tetra-*O*-acetyl-α- and -β-D-galactothioseptanoside (VIII and IX).—To 3.5 g of a mixture of VI and VII was added 3.5 g of "active" silver carbonate and 50 ml of anhydrous methanol. This mixture was stirred for 20 hr at 25°. The mixture was then centrifuged and the supernatant was evaporated to dryness. The residue was extracted with ether and the ether extract was filtered. Evaporation of the ether solution gave 3.18 g (92%) of colorless syrup.

This syrup showed two components on silica gel plates in hexane–ethyl acetate (55:45). A 2.8-g portion of this syrup was fractionated on a silica gel column (4.0 × 50 cm), using the same solvent. This fractionation gave 0.97 g of the slower moving component, VIII, and 1.36 g of the faster moving component, IX.

Compound VIII was obtained as a glass: $[\alpha]^{25}D$ +45° (*c* 1.46, chloroform).

Anal. Calcd for $C_{15}H_{22}O_9S$ (378.4): OCH_3, 8.20; CH_3CO, 45.50. Found: OCH_3, 7.90; CH_3CO, 45.10.

Compound IX crystallized after its syrup was allowed to stand for 3 weeks at 25° with occasional scratching. Recrystallization of IX from a mixture of ether and pentane gave the pure β-D anomer: mp 99–100°, $[\alpha]^{25}D$ −211° (*c* 1.49, chloroform).

Anal. Calcd for $C_{15}H_{22}O_9S$ (378.4): C, 47.61; H, 5.86; S, 8.47. Found: C, 47.83; H, 5.78; S, 8.58.

Methyl β-D-Galactothioseptanoside (X).—One gram of IX was dissolved in 25 ml of dry methanol and cooled to 0° in an ice bath, and the solution was saturated with dry ammonia. The solution was kept for 20 hr at 5° and was then concentrated to a syrup. The syrup (1.0 g) was purified by chromatography on Whatman No. 3M filter paper, using 1-butanol–ethanol–water (40:11:19) as the irrigant. Guide strips were treated with silver nitrate and sodium hydroxide solution[15] to locate the bands. The bands were excised and eluted from the paper with several portions of acetone. The acetone solution was filtered and concentrated to a syrup (400 mg). Compound X crystallized from its syrup after standing several weeks with occasional scratching. Compound X was recrystallized from acetone–ether to give pure material: mp 90–91°, $[\alpha]^{25}D$ −235° (*c* 1.09, methanol).

Anal. Calcd for $C_7H_{14}O_5S$ (210.3): C, 39.99; H, 6.71; S, 15.25. Found: C, 40.26; H, 6.80; S, 15.22.

In further preparations the crude syrup containing X was dissolved in a mixture of acetone and ether. A seed crystal was introduced and the mixture was placed in a refrigerator to crystallize.

Methyl 2,3,4,5-Tetra-*O*-*p*-nitrobenzoyl-β-D-galactothioseptanoside (XI).—A solution of X (200 mg) in 15 ml of pyridine was treated at 0° with 1 g of *p*-nitrobenzoyl chloride, and the resulting suspension was stirred overnight at 25°. Chips of ice were then added to destroy excess *p*-nitrobenzoyl chloride. This mixture was dissolved in chloroform, and the solution was washed with copper sulfate solution until free of pyridine, then twice with water. The chloroform solution was dried over sodium sulfate and evaporated to dryness. Recrystallization of XI from a mixture of acetone and methanol gave pure material: mp 236–237°, $[\alpha]^{25}D$ −120° (*c* 1.08, chloroform).

Anal. Calcd for $C_{35}H_{26}N_4O_{17}S$ (806.7): C, 52.11; H, 3.25; N, 6.95; S, 3.98. Found: C, 52.11; H, 3.66; N, 6.58; S, 4.19.

Periodate Oxidation of X.—A 50-mg sample of X was oxidized with sodium metaperiodate.[16] The oxidation was judged complete when periodate uptake and total acid production became constant. Consumption of oxidant leveled off at 3.37 moles/mole of sugar and the production of 1.80 moles of formic acid/mole of sugar.

Hydrolysis of X.—Rates of hydrolysis were measured as described by Isbell and Frush.[17] A 46.5-mg sample of X was dissolved in 3 ml of 0.5 *N* aqueous hydrochloric acid, and the hydrolysis was conducted at 25°. Optical rotations were taken until constant. The rate constants were calculated from eq 1,

$$k = \frac{1}{t} \log \frac{r_0 - r_\infty}{r_t - r_\infty} \quad (1)$$

where *t* is the time in minutes, r_0 is the initial rotation, r_∞ is the rotation when the hydrolysis is complete, and r_t is the rotation at time *t*. At 25°, $k = 9.6 \times 10^2$ min^{-1} and at 75°, $k = 2.1 \times 10^5$ min^{-1}.

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