scribed for I. The evaporated residue was crystallized from a mixture of ethyl acetate–hexane to give 0.87 g. Thin layer chromatography showed that the crystalline material obtained was composed of three different compounds. The fastest moving component was unreacted starting material, R_f 0.71. The other two components, R_f 0.28 and 0.18, were separated by column chromatographic fractionation as described earlier. The compound V, of R_f 0.28 from the chromatographic column and crystallized from ethyl acetate on addition of hexane, had m.p. 149–150°, $[\alpha]^{24}D$ +27.2° (*c* 1.95, in chloroform).

Anal. Calcd. for $C_{12}H_{18}O_8S$: C, 44.7; H, 5.59; S, 9.94. Found: C, 44.4; H, 5.54; S, 9.68.

The compound VI of R_f 0.18 on similar crystallization had m.p. 203°, $[\alpha]^{24}D$ −133° (*c* 2.1, chloroform).

Anal. Found: C, 44.9; H, 5.55; S, 9.63.

Both sulfoxides showed intensification of the peak at 1040 cm.$^{-1}$ due to the C–SO–C group.[24]

To 250 mg. of each sulfoxide were added 3 ml. of glacial acetic acid and 0.5 ml. of 30% hydrogen peroxide and the oxidation was allowed to continue at 25° for 48 hr. On dilution with 15 ml. of distilled water, each gave crystals of sulfone IV, m.p. 193–194°, R_f 0.46.

Methyl 2,3,4-Tri-*O*-acetyl-α-D-xylothiopyranoside (VII).—To 40 ml. of dry pyridine was added 6 g. of methyl α-D-xylothiopyranoside[3] and to this solution, cooled to 0°, was added slowly 30 ml. of acetic anhydride. After standing at 25° for 24 hr. it was poured into 500 ml. of ice and water. The water solution was extracted four times with 100-ml. portions of chloroform and the combined extracts were washed sequentially with bicarbonate solution, a dilute copper sulfate solution, and finally with water. The chloroform was dried over sodium sulfate and removed under reduced pressure. The sirup obtained (7.8 g.) did not crystallize, $[\alpha]^{20}D$ +228° (*c* 1.0, chloroform), R_f 0.71.

Methyl 2,3,4-Tri-*O*-acetyl-α-D-xylothiopyranoside Sulfone (VIII).—To a mixture of 10 ml. of glacial acetic acid and 4 ml. of 30% hydrogen peroxide was added 1 g. of the triacetate VII. The mixture was allowed to stand at 25° for 48 hr., then diluted with 75 ml. of distilled water, and worked up as described for I. Crystallization of the residue from water gave 0.95 g., m.p. 147–148°, $[\alpha]^{20}D$ +86° (*c* 1.0, chloroform), R_f 0.64.

Anal. Calcd. for $C_{12}H_{18}O_9S$: C, 42.6; H, 5.32; OCH_3, 9.16. Found: C, 42.7; H, 5.00; OCH_3, 9.38.

The sulfone showed infrared bands at 1330 and 1145 cm.$^{-1}$.

Methyl 2,3,4-Tri-*O*-acetyl-α-D-xylothiopyranoside Sulfoxide (IX).—To 7 ml. of methanol was added 0.56 g. of compound VII and the solution was cooled to 0°. To this was added a solution to 0.43 g. of sodium metaperiodate in 3 ml. of distilled water. The mixture was stirred at 5° for 48 hr. followed by dilution with 30 ml. of distilled water and was worked up as described for compound I. The evaporated residue was crystallized from ethyl acetate–hexane to give 0.32 g., m.p. 137–138°, $[\alpha]^{20}D$ +134° (*c* 1.0, chloroform), R_f 0.27.

Anal. Calcd. for $C_{12}H_{18}O_8S$: C, 44.7; H, 5.59; OCH_3, 9.62. Found: C, 44.8; H, 5.42; OCH_3, 9.63.

The sulfoxide showed infrared absorption at 1040 cm.$^{-1}$.

To 3 ml. of glacial acetic acid and 0.5 ml. of3 0% hydrogen peroxide was added 250 mg. of IX. The solution was allowed to stand at 25° for 48 hr., diluted with 15 ml. of distilled water, and worked up as described for compound II. Crystallization from water gave the sulfone VIII, m.p. 147°, R_f 0.64.

Methyl α-D-Xylothiopyranoside Sulfone (X).—To 6 ml. of glacial acetic acid and 2 ml. of 30% hydrogen peroxide was added 0.79 g. of methyl α-D-xylothiopyranoside.[3] The mixture was allowed to stand at 25° for 1 week. Evaporation under reduced pressure gave a sirup which was chromatographically pure and had infrared peaks at 1330 and 1145 cm.$^{-1}$. Acetylation with acetic anhydride in pyridine gave the known acetylated sulfone VIII.

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1,6-Anhydro-5,6-dideoxy-6-mercapto-β-D-*xylo*-hexofuranose[1]

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5,6-Dideoxy-6-thioacetyl-D-*xylo*-hexofuranose is prepared from 5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose by tosylation and displacement of the tosyloxy group with thioacetate. Hydrolysis removes the isopropylidene group. Extended treatment of this compound in acidic methanol or acidic water leads to the title compound, a cyclic system formed by nucleophilic displacement of the conjugate acid group at C-1 with attachment of the sulfur from C-6.

Experience has shown that sulfur, when located as a thiol on either C-4 or C-5 of a sugar, preferentially enters the ring under normal glycoside-forming conditions in acidic methanol.[2] It is interesting that this preference to react with the carbonyl function and to participate as the ring hetero atom persists even when the position of sulfur is on C-4, and leads to selective formation of the furanose over the normally expected pyranose ring.[3]

The high reactivity of acidic alkyl mercaptans with sugar carbonyl functions is well known from the formation of dialkyl dithiols. Under the same acidic conditions alcohols form glycosides. Preferential participation of a thiol group at C-4 of an aldose to give a five-membered ring under normal Fischer glycoside-forming conditions is facilitated by the ease with which sulfur forms smaller bond angles than oxygen.

In examining a further aspect of the introduction of sulfur into sugar rings, an initial exploration has been made of the possibility of introducing sulfur into a seven membered sugar ring. Seven-membered rings are not easily formed with oxygen and do not occur in detectable amounts under normal Fischer glycoside-forming conditions. A seven-membered ring containing sulfur might be more stable than an oxygen-containing seven-membered ring owing to the somewhat greater flexibility of sulfur bond angles.

This laboratory recently found a route to the preparation of 5-deoxy-D-*xylo*-hexose.[4] Hence it was of interest to prepare 5,6-dideoxy-6-thioacetyl-D-*xylo*-hexofuranose to see whether this sugar, with the formation of the normal pyranose ring blocked, would form the unstable furanose ring on oxygen or the normally still less stable seven-membered ring on sulfur.

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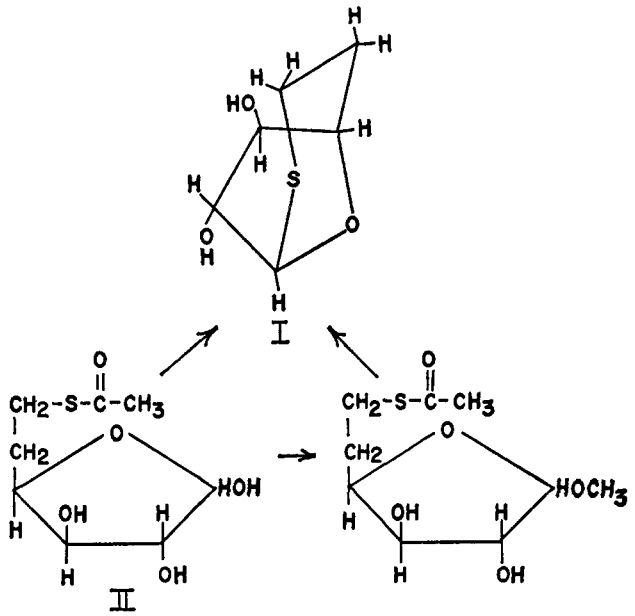
Tosylation or mesylation of 5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose at −12° leads easily to esterification of the primary hydroxyl group only. Warming either of these compounds to 25° results in displacement of the ester group by the hydroxyl oxygen at C-3 to produce the 3,6-anhydro derivative. These ester groups are also very easily displaced at 25° with thioacetate anion, to produce 5,6-dideoxy-1,2-*O*-isopropylidene-6-thioacetyl-α-D-*xylo*-hexofuranose (III). Tosyloxy groups are displaced in greater yield than mesyloxy, as is usually observed. Hydrolysis gives compound II which on methanolysis produces the methyl glycoside. Continued heating of compound II in acidic methanol converts it to 1,6-anhydro-5,6-dideoxy-6-mercapto-β-D-*xylo*-hexofuranose (I). Presumably the protonated methoxy group is displaced by the nearby thiol sulfur at C-6, without opening of the furanose ring to form a stable cyclic ring system containing the five-membered furanose ring, a six-membered 1,3-oxathiane ring, and a seven-membered thioseptanose ring. The five-membered furanose ring is in its normal C-5 envelope conformation, while the six-membered thiooxy ring is most likely in a chair conformation wherein the hydrogens on C-4, C-5, and C-6 are in *gauche* relationship.



The stability of this cyclic system is strikingly illustrated by the observation of its formation in approximately 45% yield when a 1.2% aqueous solution of II is heated at 65° for 20 hr. in the presence of acidic resin. Even under such aqueous conditions, water is eliminated from the conjugate acid of compound II and attachment of sulfur occurs.

Compound I is a very hydroscopic waxy solid which can be converted to a crystalline di-*p*-nitrobenzoyl derivative or an oily diacetate. Compound I, on treatment with periodate, consumes 1 mole of oxidant without production of formic acid or aldehyde groups. It is known[5,6] that *trans*-hydroxyls in a furanose ring are not oxidized by periodate anion. The oxidant probably oxidized the sulfur to a sulfoxide since the products, after thin layer separation, gave a positive test with hydriodic acid.[7]

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Experimental

Analytical Methods.—Purity of products was determined by thin layer chromatography on silica gel G[8] coated plates irrigated with (A) chloroform–acetone (7:3 v./v.) or (B) hexane–ethyl acetate (7:3 v./v.). Components were located by spraying with potassium permanganate.[9] Acetates were detected on the plates by the ferric hydroxamate reaction.[10] Molecular weights were determined in a Mechrolab vapor pressure osmometer with water or chloroform as solvent. Solutions were evaporated under diminished pressure at 35° or less. Melting points were corrected and all optical rotations were equilibrium values.

5-Deoxy-1,2-*O*-isopropylidene-6-*O*-(*p*-tolylsulfonyl)-α-D-*xylo*-hexofuranose.—To a solution containing 2 g. (0.019 mole) of 5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose in 14 ml. of dry pyridine previously cooled to about −12° was added with stirring 1.99 g. (0.019 mole) of *p*-toluenesulfonyl chloride in small portions over a 4-hr. period. The reaction mixture after stirring for an additional 12 hr. at −10° was diluted with 20 ml. of chloroform and poured into a mixture of ice and water. The chloroform layer was washed sequentially with water, 5% copper sulfate, and water and was dried over sodium sulfate. Removal of the solvent under reduced pressure yielded 3.5 g. of a thick sirup.

5-Deoxy-1,2-*O*-isopropylidene-6-*O*-(methylsulfonyl)-α-D-*xylo*-hexofuranose.—This compound was prepared by following the above esterification procedure. The reaction yielded 2.5 g. of a semicrystalline product.

5,6-Dideoxy-1,2-*O*-isopropylidene-6-thioacetyl-α-D-*xylo*-hexofuranose (III).—A solution of 3.5 g. of 5-deoxy-1,2,-*O*-isopropylidene-6-*O*-(*p*-tolylsulfonyl)-α-D-*xylo*-hexofuranose and 4 g. of potassium thioacetate in 80 ml. of dry acetone was allowed to stand at 25° for 3 hr. Deposited salts were removed by filtration and washed three times with acetone. The combined solutions were concentrated to dryness under reduced pressure. The concentrate was dissolved in 10 ml. of water and extracted with 60 ml. of chloroform. The chloroform extract was dried over sodium sulfate and concentrated under reduced pressure to a thick sirup which solidified to a crystalline mass. It was recrystallized three times from hexane, yield 1.4 g. (55.5%), m.p. 90–92°, $[\alpha]^{25}D$ −14.2° (*c* 2.0, chloroform). The mixture melting point of this compound and the compound obtained by the thioacetate addition[11] to 5,6-dideoxy-1,2-isopropylidene-α-D-*xylo*-hexofuran-5-enose remained unchanged.

Compound III was also obtained from crude 5-deoxy-1,2-*O*-isopropylidene-6-*O*-(methylsulfonyl)-α-D-*xylo*-hexofuranose under the above displacement conditions in 31% yields.

Methyl 2,3-Di-*O*-acetyl-5,6-dideoxy-6-thioacetyl-α,β-D-*xylo*-hexofuranoside.—5,6-Dideoxy-1,2-*O*-isopropylidene-6-thioacetyl-α-D-*xylo*-hexofuranose (2 g.) was dissolved in 50 ml. of 20% acetic acid and the solution was heated at 60° for 16 hr. The hydrolyzed solution was concentrated under reduced pressure to yield 1.2 g. of 6-thioacetyl-α,β-D-*xylo*-hexofuranose (II) as a yellow sirup. This was dissolved in 20 ml. of methanol, a catalytic amount of metallic sodium was added and the solution was held at 25° for 2 hr. To this solution which contained free sugar, 100 ml. of methanol and 40 ml. of Amberlite IR-120 (H) resin were added and the mixture was heated for 2 hr. at 65°, at which point the solution did not give a test with *p*-anisidine-hydrochloride.[12] The resin was removed by filtration and washed three times with methanol. The combined filtrates and washings were concentrated at 35° to a sirup. This sirup was mixed with 20 ml. of pyridine and 20 ml. of acetic anhydride and left overnight at 25°. The solution was worked up as usual to give 0.99 g. of sirupy methyl 5,6-dideoxy-2,3-di-*O*-acetyl-6-thioacetyl-D-*xylo*-hexofuranoside. It was purified by fractionation on 80–200-mesh silica gel with benzene as a solvent. The yield was 0.6 g. This was distilled at 80–85° and 0.01 mm., $[\alpha]^{21}D$ +25.5° (*c* 2.98 chloroform).

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Anal. Calcd. for $C_{13}H_{20}O_7S$: C, 48.73; H, 6.29; S, 10.02. Found: C, 48.77; H, 5.97; S, 10.32.

1,6-Anhydro-5,6-dideoxy-6-mercapto-β-D-*xylo*-hexofuranose (I).—5,6-Dideoxy-6-thioacetyl-D-*xylo*-hexofuranose, obtained from III by removal of the isopropylidene group as described above, was dissolved in 150 ml. of absolute methanol. After addition of 40 ml. of Amberlite IR-120 (H) resin, the mixture was heated with stirring at 65° for 20 hr. until the thiol activity of the solution disappeared as indicated by a negative sodium nitroprusside[13] or 2,3,5-triphenyl-2*H*-tetrazolium chloride[14] test. The resin was removed by filtration and was washed three times with methanol. Combined filtrate and washings were concentrated to 0.99 g. (72.5% yield) of sirup. This was purified by thin layer chromatography using irrigant A. Elution of the major component with acetone followed by concentration produced 0.55 g. (44.5% yield) of chromatographically pure sirup. This was further purified by distillation, b.p. 135–140° (0.01 mm.), $[\alpha]^{20}D$ −43.6° (*c* 2.04, water). The product was very hygroscopic. The freshly distilled material solidified to a white, waxy product but took up moisture very quickly on exposure to air and immediately liquefied. Its molecular weight was 145 (calcd., 165). On periodate oxidation it consumed 0.97 moles of periodate[15] in 5 hr. and did not liberate formic acid.[2]

1,6-Anhydro-5,6-dideoxy-2,3-di-*O*-(p-nitrobenzoyl)-6-mercapto-β-D-*xylo*-furanose was prepared by esterifying compound I in pyridine with *p*-nitrobenzoyl chloride. The ester was crystallized from methanol, m.p. 201–202°, $[\alpha]^{21}D$ +109° (*c* 1.0, chloroform).

Anal. Calcd. for $C_{20}H_{16}N_2O_9S$: C, 52.17; H, 3.50; S, 6.97. Found: C, 52.29; H, 3.64; S, 6.73.

1,6-Anhydro-5,6-dideoxy-2,3-di-*O*-acetyl-6-mercapto-β-D-*xylo*-furanose was prepared from compound I by acetylation with acetic anhydride in pyridine. The product was a sirup, b.p. 75–80° (0.01 mm.), $[\alpha]^{20}D$ −46.9° (*c* 1.28, chloroform).

Anal. Calcd. for $C_{10}H_{14}O_5S$: C, 48.77; H, 5.73; S, 13.02; mol. wt., 246. Found: C, 48.98; H, 5.85; S, 12.76; mol. wt., 242.

Formation of Compound I in Aqueous Medium.—5,6-Dideoxy-6-thioacetyl-D-*xylo*-hexofuranose obtained from compound III by the procedure described under the preparation of compound I was treated with IR-120 (H) in water at 65° for 20 hr. and was isolated as described above. It was characterized by preparing its *p*-nitrobenzoyl derivative in the usual manner, m.p. 201°. The mixture melting point with the authentic specimen described above remained unchanged. Treatment of 5-deoxy-1,2-isopropylidene-α-D-*xylo*-hexofuranose with IR-120 (H) in aqueous media under the same conditions, but for 48 hr., produced 5-deoxy-D-*xylo*-hexose which was identified as its osazone,[16] m.p. 153°.

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Pyrimidine Disaccharide Nucleosides. Synthesis of an Amino Sugar Disaccharide Nucleoside

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The 1-halo sugar derivatives of lactose, Ia and c, and cellobiose, Ib and d, were converted to their corresponding pyrimidine nucleoside derivatives, II, III, and IV, by two established procedures. The β-D configuration of the nucleoside bond was established by degradation of IIIa and b to the known nucleoside V. An amino sugar disaccharide nucleoside VIII was prepared from the appropriate chloro sugar VIIb by condensation with 2,4-diethoxypyrimidine. The β-D configuration of the nucleoside bond in VIII was established by its preparation *via* an alternate route involving formation of the disaccharide link between the nucleoside Xb and the halo sugar VI.

The antibiotic amicetin[1] has been shown to have a structure which includes in it a pyrimidine disaccharide nucleoside moiety. Specifically, the structural sequence in question has 4,6-dideoxy-4-dimethylamino-α-D-glucose[2] linked *via* an O-glycosidic bond to the 4-position of 2,3,6-trideoxy-β-D-*erythro*-hexopyranose.[3] The deoxy sugar, in turn, is linked *via* a β-glycosylamine bond to the 1-position of cytosine. The synthetic challenge involved in preparing a disaccharide nucleoside incorporating the unique amino sugar–deoxy sugar–pyrimidine sequence of amicetin has necessitated exploration into the general area of disaccharide nucleoside synthesis. We wish to report, herein, the first syntheses of pyrimidine disaccharide nucleosides and also the first synthesis of an amino sugar containing disaccharide nucleoside. Preparation of this latter compound was accomplished by two routes, the second of which comprises the first synthesis of a disaccharide nucleoside by the coupling of a *mono*saccharide nucleoside with a second monosaccharide.

The first synthetic disaccharide nucleoside, which contained the base purine and the disaccharide lactose, was prepared by Wolfrom[4] and his co-workers. Wolfrom subsequently prepared purine nucleosides of the disaccharides maltose and cellobiose.[5] Of the procedures available for the synthesis of pyrimidine nucleosides[6] the dialkoxypyrimidine method of Hilbert and Johnson[7] and the mercury salt procedure of Fox[8] appeared to be the methods of choice. For the initial

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