perature. To this thin slurry was added in one portion an intimate mixture of 9.04 g. (0.13 mole) of hydroxylamine hydrochloride and 12.1 g. (0.115 mole) of anhydrous sodium carbonate followed by dropwise addition of 8 ml. of water. After stirring for 4 days at room temperature, the ether was decanted and the gummy residue triturated with 200 ml. of ice water, the pH (7.5) being adjusted to 6 with acetic acid. Filtration followed by air drying for 10 hr. and then oven-drying (60°) to constant weight gave 13.2 g. of a light gray solid, m.p. 230, partial decomposition, with no further melting after 300°. This material gave a violet color with aqueous ferric chloride. Recrystallization of 2 g. from 100 ml. of distilled water (not all dissolved) gave 0.8 g. of an off-white solid with an indeterminate melting point, violet color with ferric chloride, and an infrared spectrum different from the peracetic acid oxidation product of acetoguanamine.

Anal. Calcd. for $C_4H_7N_5O$: C, 34.1; H, 4.98; N, 49.7. Found: C, 34.3; H, 5.09; N, 49.6.

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Preparation of Several Methyl D-Pentothiapyranosides[1]

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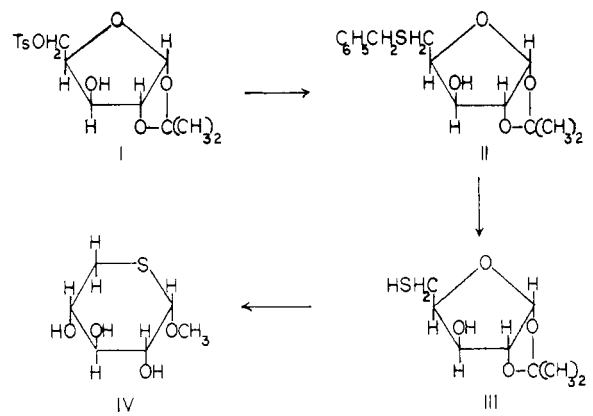
The preparation of D-xylothiapyranose is described. The synthesis and certain properties of methyl-D-xylothiapyranoside, methyl D-ribothiapyranoside, and methyl 2-deoxy-D-ribothiapyranoside are given.

The possibility of producing analogs of sugars in which the ring oxygen is replaced by sulfur or nitrogen is intriguing, not only from the point of view of the chemistry involved but from the possibility that analogs of important metabolic sugars such as D-glucose, D-ribose and 2-deoxy-D-ribose may be of biochemical and medical interest. Consequently, work was initiated here to produce sugars wherein the ring oxygen atoms are suitably replaced, initially with sulfur. To obtain such sugars in which sulfur is positively located in a stable sugar ring, several methyl D-pentothiapyranosides were first prepared.

Previous work involved analogs of methyl D-xylopyranoside in which sufur replaced the ring oxygen.[2] Ring size was determined by periodate oxidation and isolation of the expected amount of formic acid. Shortly before the announcement of the synthesis of methyl α-D-xylothiapyranoside, two other reports[3,4] appeared on the synthesis of D-xylose and L-idose with sulfur as the ring hetero atom as indicated mainly by spectral data. However, production of crystalline methyl α-D-xylothiapyranoside made it easy to obtain definite chemical evidence that sulfur was a part of a stable ring. This initial work is now extended to D-ribose and 2-deoxy-D-ribose.

Synthesis of the two latter pentothiapyranosides is somewhat more difficult than the synthesis of methyl α-D-xylothiapyranoside. This sugar derivative is prepared by displacement of the tosyloxy group in 1,2-O-isopropylidene-5-O-tosyl-α-D-xylofuranose[5] (I) with the thiobenzyl nucleophile, reduction to the mercapto derivative (III), and methanolysis. The methyl α-D-xylothiapyranoside (IV) has the expected molecular weight and liberates one mole of formic acid on treatment with periodate. During oxidation, excess periodate is consumed, probably in the formation of a sulfoxide or sulfone.[6] The alpha configuration at the anomeric carbon is suggested by the high positive specific rotation of the glycoside which mutarotates downward on acid hydrolysis.



Somewhat similar reactions are possible for the introduction of sulfur into D-ribose. Methyl 2,3-O-isopropylidene-D-ribofuranoside is converted to the crystalline 5-O-tosyl derivative[7] (V) and thence by tosyloxy displacement, to the 5-deoxy-5-thiobenzyl derivative (VI) which on reduction results in the

(1) Journal Paper No. 1913 of the Purdue University Agricultural Experiment Station. Presented in part at the 141st National Meeting of the American Chemical Society, Washington, D. C., March, 1962.

(2) R. L. Whistler, M. S. Feather, and D. L. Ingles, *J. Am. Chem. Soc.*, **84**, 122 (1962).

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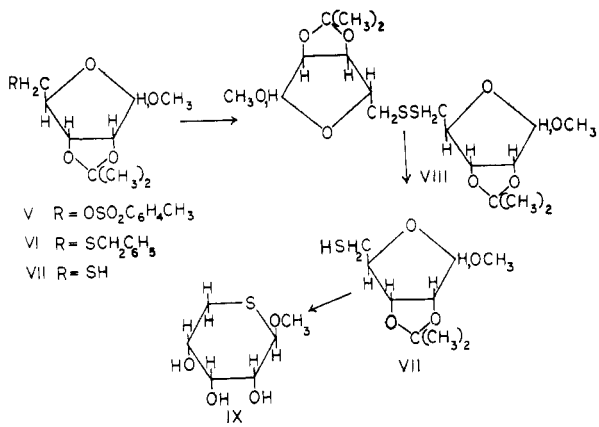
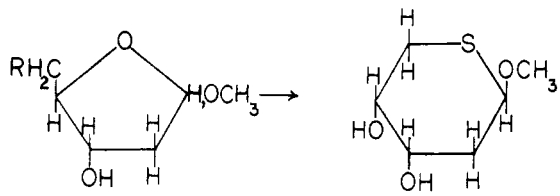


5-deoxy-5-mercapto derivative (VII). Oxidation of this with iodine solution produces a nicely crystalline disulfide (VIII) which offers an excellent method for purification of the reaction intermediate. The disulfide is quantitatively reduced by lithium aluminum hydride to the pure thiol. Methanolysis yields a mixture of substances containing some water insoluble polymer, but methyl β-D-ribothiapyranoside (IX) can be crystallized in small yield from the reaction mixture.

In the preparation of the 2-deoxy-D-ribose analog, methyl 2-deoxy-D-ribofuranoside[8] (X) is subjected to monomolecular tosylation to yield (XI) and thence converted by tosyloxy displacement to the 5-thiobenzyl derivative (XII). Reduction of this gives the 5-deoxy-5-mercapto derivative (XIII) which equilibrates rapidly during methanolysis to form methyl β-D-2-deoxyribothiapyranoside (XIV).



XIV

X R = OH

XI R = $OSO_2C_6H_4CH_3$

XII R = $SCH_2C_6H_5$

XIII R = SH

Experimental

1,2-O-Isopropylidene-5-deoxy-5-thiobenzyl-α-D-xylofuranose (II).—A solution of 12 g. of 1,2,O-isopropylidene-5-O-tosyl-α-D-xylofuranose (I) and 12 g. of the sodium salt of benzyl mercaptan in 300 ml. of ethanol was refluxed for 2.5 hr. Sodium toluenesulfonate deposited in 0.5 hr. and produced an 80% yield in 2.5 hr. The complete reaction mixture was concentrated to dryness under vacuum and the solid residue was extracted with 200 ml. each of chloroform and water. The chloroform extract was washed with 1 *N* sulfuric acid solution and then with water. It was dried with sodium sulfate and was concentrated to a sirup which crystallized on addition of ether and petroleum ether. The yield of crystals was 7.0 g., 71%. The product was twice recrystallized from ethanol, m.p. 103°, $[\alpha]^{25}D$ −64.2° (*c*, 1.24 in methanol).

Anal. Calcd. for $C_{15}H_{20}O_4S$: C, 60.81; H, 6.76; S, 10.81. Found: C, 60.78; H, 6.74; S, 11.03.

1,2-O-Isopropylidene-5-deoxy-5-mercapto-α-D-xylofuranose (III).—To a solution of 5.0 g. of 1,2-O-isopropylidene-5-deoxy-5-thiobenzyl-α-D-xylofuranose (II) in liquid ammonia, small pieces of sodium were added until a blue color persisted for 10 min. Ammonium chloride was added to just discharge the blue color and then a 10-g. excess of ammonium chloride was added. Ammonia was allowed to evaporate and the residue was extracted with 200 ml. of chloroform. After filtration, the chloroform was evaporated. The residual sirup crystallized upon addition of ether–petroleum ether. Recrystallization from hot petroleum ether gave 3.3 g. of pure crystalline 1,2-O-isopropylidene-5-deoxy-5-mercapto-α-D-xylofuranose in 95% yield, m.p. 85°, $[\alpha]^{25}D$ −40.4° (*c*, 1.22 in methanol).

Anal. Calcd. for $C_8H_{14}O_4S$: C, 46.62; H, 6.79; S, 15.53. Found: C, 46.68; H, 6.98; S, 15.61.

Titration with 0.1 *N* iodine solution showed that 98% of the thiol groups were free. The compound was soluble in both water and ether and gave an immedite color in the cold with both sodium nitroprusside and 2,3,5-triphenyl-2H-tetrazolium chloride.[9] When 3.5 g. of III was dissolved in 100 ml. of 1 *N* sulfuric acid solution and kept at 25° for 48 hr., the isopropylidene group hydrolyzed to yield the free sugar. Sulfuric acid was removed with barium carbonate and the solution was filtered. Concentration of the filtrate produced a sirup which crystallized to give 1.48 g. or a 52.2% yield of α-D-xylothiapyranose. The sugar was recrystallized from a mixture of ethanol–water, m.p. 127°, $[\alpha]^{25}D$ + 198 → +173° (*c*, 1.0 in water).

Methyl α-D-Xylothiapyranoside (IV).—A solution of 2.3 g. of 1,2-O-isopropylidene-5-deoxy-5-mercapto-α-D-xylofuranose was refluxed in 100 ml. of 1% methanolic hydrogen chloride for 1 hr. during which time the thiol activity disappeared. The solution was passed through a column of Dowex-1(OH) to remove acids and the effluent was evaporated to a sirup which crystallized. Recrystallization from either ethanol–ether mixture or ethyl acetate gave 1.1 g. or a 54.5% yield of pure methyl α-D-xylothiapyranoside, m.p. 113°, $[\alpha]^{25}D$ +332 (*c*, 1.0 in water).

Anal. Calcd. for $C_6H_{12}O_4S$: C, 40.00, H, 6.66; S, 17.77; OCH_3, 17.22. Found: C, 39.92; H, 6.49; S, 17.86; OCH_3, 17.49. Rast molecular weight: Found, 189; calcd. 180.

Methyl α-D-xylothiapyranoside consumed 3 moles of sodium metaperiodate after 2 hr., increasing slowly to 4.2 moles after 10 hr. at 25°. Acid production of 1 mole/mole was constant from 3–6 hr. but then increased to 1.5 moles after 10 hr. Steam distillation of the acid yielded 1 mole of formic acid per mole of methyl α-D-xylothiapyranoside. Reduction of the distilled formic acid with magnesium gave formaldehyde which was identified as the dimedone derivative, m.p. 189°.

Hydrolysis of methyl α-D-xylothiapyranoside with 1 *N* sulfuric acid solution at 80° caused a decrease from an initial value in specific rotation $[\alpha]^{25}D$ +332° (*c*, 1.1 in water), to $[\alpha]^{25}D$ + 197°. The latter value was the equilibrium value obtained at the end of 45 min.

Methyl 2,3-O-Isopropylidene-5-O-tosyl-D-ribofuranoside (V).—Unimolecular tosylation of methyl 2,3-O-isopropylidene-D-ribofuranoside by the method of Levene and Stiller[7] gave V in 20% yield with the constants previously recorded.[6]

Methyl 2,3-O-isopropylidene-5-deoxy-5-thiobenzyl-D-ribo-

(8) R. E. Deriaz, W. G. Overend, M. Stacey, and L. F. Wiggins, *J. Chem. Soc.*, 2836 (1949).

(9) W. E. Trevelyn, D. P. Proctor, and J. S. Harrison, *Nature*, **166**, 444 (1950).

furanoside (VI).—Reaction of 10 g. of V with 12 g. of the sodium salt of benzyl mercaptan in 300 ml. of ethanol under reflux for 3 hr. caused rapid precipitation of sodium toluenesulfonate and 7.8 g. of the sirupy thiobenzyl derivative VI, 91% yield, was isolated in the usual way.

Methyl 2,3-O-Isopropylidene-5-deoxy-5-mercapto-D-ribofuranoside (VII).—Reduction of 7.8 g. of VI with sodium in liquid ammonia gave 4.7 g. or 85.5% yield of (VII) as a sirup which by iodine titration had 80% of the sulfur in the form of free thiol groups. The sirup was dissolved in a solution consisting of 10 ml. each of methanol, acetic acid, and water. The solution was titrated with iodine solution and a small amount of water was added. Sirup separated but soon crystallized and 1.6 g. or a 35% yield of crystalline (VIII) was removed by filtration. The product was washed with water and recrystallized from ethanol, m.p. 67°, $[\alpha]^{25}D$ −124° (*c*, 1.04 in methanol).

Anal. Calcd. for $C_{18}H_{30}O_8S_2$: C, 49.31; H, 6.84; S, 14.61. Found: C, 50.05; H, 6.67; S, 14.49.

Reduction of 0.5 g. of VIII in 5 ml. of ether with lithium aluminum hydride (50 mg. in 2 ml. ether) and 1 hr. at 25° caused complete reduction. Excess reducing agent was destroyed with water and hydrochloric acid and the ether layer separated. Concentration of the ether solution gave 0.5 g. of VII as a sirup. Iodine titration showed 93% of the expected free thiol groups.

Methyl β-D-Ribothiapyranoside (IX).—A solution of 1 g. of methyl 2,3-O-isopropylidene-5-deoxy-5-mercapto-D-ribofuranoside was refluxed in 50 ml. of 1% methanolic hydrogen chloride for 5 hr., during which the thiol activity was reduced to 10% of the original value. Hydrogen chloride was absorbed on a 20-g. column of Dowex-1(OH). The effluent was concentrated to a sirup, 20 ml. of ether was added, and the mixture was kept at 0° for 3 days. The sirup crystallized and filtration gave 0.1 g. or a 12.2% yield of methyl β-D-ribothiapyranoside. This was recrystallized from ethyl acetate, m.p. 97°, $[\alpha]^{25}D$ + 18.6° (*c*, 0.59 in water).

Anal. Calcd. for $C_6H_{12}O_4S$: C, 40.00; H, 6.66; S, 17.77; OCH_3, 17.22. Found: C, 40.05; H, 6.46; S, 17.70; OCH_3, 17.11.

When hydrolyzed with 0.5 *N* hydrochloric acid solution at 75° the specific rotation of methyl β-D-ribothiapyranoside increased from + 18.6 to + 51.0° where it became constant after 0.5 hr.

When oxidized with sodium metaperiodate under the usual conditions at 25°, methyl β-D-ribothiapyranoside liberated 1 mole of formic acid per mole after 1 hr., with the formic acid increasing to 1.2 mole/mole after 8 hr.

Methyl β-D-2-Deoxyribothiapyranoside.—A solution of 10 g. of 2-deoxy-D-ribose was treated with 192 ml. of 0.1% methanolic hydrogen chloride for 12 min. at 25°. Acid was removed with Dowex-1(OH) and the neutral effluent concentrated to give 9.3 g. of the sirup, methyl 2-deoxy-D-ribofuranoside (X). A solution of this sirup in 100 ml. of pyridine was treated at 0–5° with a solution of 12.0 g. of tosyl chloride in 25 ml. of pyridine for 20 hr. The mixture was worked up in the usual way to give 9.3 g. or a 49% yield, of a sirup (XI). Reaction of XI with 12 g. of the sodium salt of benzyl mercaptan in 300 ml. of ethanol gave 7.7 g. of methyl 5-deoxy-5-thiobenzyl-2-deoxy-D-ribofuranoside (XII). Reduction of XII with sodium in liquid ammonia gave 3.1 g. or a 62.8% yield of the thiol (XIII), containing 95% of the sulfur as free thiol groups. Equilibration of XIII in 50 ml. of 1% methanolic hydrogen chloride under reflux caused the loss of 95% of the thiol activity in 20 min. Acid was removed with Dowex-1(OH) and the effluent concentrated to yield 2.2 g. of sirupy methyl β-D-2-deoxyribothiapyranoside (XIV), $[\alpha]^{25}D$ −26.9° (*c*, 5.29 in methanol).

Anal. Calcd. for $C_6H_{12}O_3S$: C, 43.90; H, 7.33; S, 19.51; OCH_3, 18.9. Found: C, 44.20; H, 6.98; S, 19.10; OCH_3, 18.4.

When hydrolyzed at 75° with 0.25 *N* hydrochloric acid in 50% aqueous methanol, the specific rotation increased to −4.16° after 1.5 hr.

Azo Compounds.[1] Preparation and Decomposition of 3,6-Dimethyl-3-phenyl-2,3,4,5-tetrahydropyridazine

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The addition of phenyllithium to 3,6-dimethyldihydropyridazine led to the formation of the monoaddition product, 3,6-dimethyl-3-phenyl-2,3,4,5-tetrahydropyridazine. Attempts to prepare the analogous cyclic azo compound from the cyclic hydrazine, obtained from the hydrazone by reduction over platinum oxide, led only to the formation of the parent cyclic hydrazone. The cyclic hydrazone could be decomposed at 250° to form nitrogen, propylene, α-methylstyrene, *cis*- and *trans*-1-phenyl-1,2-dimethylcyclobutane, and a small amount of acetophenone. The products are consistent with a mechanism involving the cyclic azo compound and a 1,4-biradical as intermediates.

In a continuation of the study of the preparation and behavior on oxidation of 1,2-disubstituted cyclic hydrazines,[3a] an attempt was made to prepare six-membered ring hydrazones, hydrazines, and azo compounds unsymmetrically substituted in the 3- and 6-positions. Earlier workers[3b] had reported the preparation and decomposition of 3-phenyl-3,4,5,6-tetrahydropyridazine to yield phenylcyclobutane as the only product. During the course of this study, Kuzmin[4] reported the preparation of a number of 3-aryl- and 3-aryl-6-alkyl-1,4,5,6-tetrahydropyridazines which were decomposed to give aryl- and alkylarylcyclobutanes and olefinic cleavage products.

(1) This is the 40th in a series of papers concerned with the preparation and decomposition of azo compounds. For the previous paper in this series, see C. G. Overberger and L. P. Herin, *J. Org. Chem.*, **27**, 2423 (1962).

(2) A portion of a thesis submitted by G. Kesslin in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of the Polytechnic Institute of Brooklyn.

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(4) R. Ya. Levina, Yu. S. Shabarov, M. G. Kuzmin, N. I. Vasilev, and E. G. Treschova, *Dokl. Akad. Nauk SSSR* **121**, 303 (1958).