Nucleophilic Opening of the Oxetane Rings in 3,5-Anhydro-1,2-*O*-isopropylidene-β-L-idofuranose and -α-D-xylofuranose[1,2]

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Nucleophilic attack on the oxetane ring in 3,5-anhydro derivatives of β-L-idofuranose and α-D-xylofuranose by benzylthio and thiosulfate anions results in the formation of derivatives of α-D-glucofuranose and α-D-xylofuranose, respectively. These reactions of the β-L-idofuranose derivatives provide a new route to α-D-glucothiopyranose. Similar reactions in the D-xylose series indicate that nucleophilic opening of the oxetane ring in 3,5-anhydropentoses is, expectedly, less hindered.

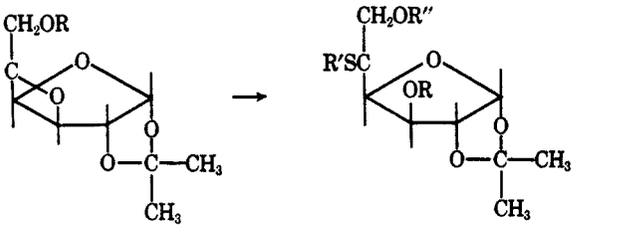
During the past several years this laboratory has been interested in methods for introducing sulfur[3-8] into sugars. Nucleophilic opening of oxetane rings offers a potential route to these derivatives. The work reported here shows the possibility of introducing the desired groups by opening oxetane rings in a 3,5-anhydrohexose and a 3,5-anhydropentose.

Starting material in the hexose series is 3,5-anhydro-1,2-*O*-isopropylidene-β-L-idofuranose (III)[9,10] or its 6-*O*-triphenylmethyl ether (II), so as to yield a final derivative with the D-*gluco* configuration. In the pentose series the anhydro sugar is 3,5-anhydro-1,2-*O*-isopropylidene-α-D-xylofuranose (XIV).[11] The L-idose derivative (III) is prepared in general according to a described procedure[10] but with modifications which increase the yield from 6 to 14%. The D-xylose derivative XIV preparation follows the procedure of Levene and Raymond,[11] but uses a temperature of 100° for 15 min which leads to nearly quantitative yield of the 3,5-anhydro product.

Treatment of the 3,5-anhydro derivative II with benzylthio anion in *N*,*N*-dimethylformamide (DMF) at 150° for 24 hr produces 5-*S*-benzyl-1,2-*O*-isopropylidene-5-thio-6-*O*-triphenylmethyl-α-D-glucofuranose (IV) in only 10% yield (Scheme I). However, detritylation of II gives 3,5-anhydro-1,2-*O*-isopropylidene-β-L-idofuranose (III) which on reaction with benzylthio anion at 150° for 1 hr gives 5-*S*-benzyl-1,2-*O*-isopropylidene-5-thio-α-D-glucofuranose (V) in 70% yield. Reductive debenzylation[12-14] of V followed by acetylation gives the known 5-*S*-acetyl-3,6-di-*O*-acetyl-1,2-*O*-isopropylidene-5-thio-α-D-glucofuranose (IX) which is evidence for the D-*gluco* configuration.

Debenzylation of V by a Birch reduction gives the free thiol compound, 1,2-*O*-isopropylidene-5-thio-α-D-glucofuranose (VIII), which can be oxidized to the disulfide XI under such mild conditions as bubbling air through the solution. If disulfide formation is to be entirely prevented, the Birch reduction is performed under a nitrogen atmosphere. Reduction of the disulfide XI, or the acetylated disulfide XII, with lithium aluminum hydride affords VIII.

SCHEME I



II, R = Tr
III, R = H

IV, R = H; R′ = $CH_2C_6H_5$; R″ = Tr
V, R = H; R′ = $CH_2C_6H_5$; R″ = H
VI, R = Ac; R′ = $CH_2C_6H_5$; R″ = Tr
VII, R = Ac; R′ = $CH_2C_6H_5$; R″ = Ac
VIII, R = H; R′ = H; R″ = H
IX, R = Ac; R′ = Ac; R″ = Ac

Compound VIII is also prepared in lower yields by reaction of III with thiosulfate anion in 80% aqueous DMF. The Bunte salt (XIII) obtained is analogous to that of Schwarz and Yule.[15] It can be reduced with sodium borohydride in water to give VIII.

Hydrolysis of VIII in 50% acetic acid yields α-D-glucothiopyranose (X) in 72% yield.

Analogous reactions in the D-xylose series, in all instances, give higher yields of products as would be expected from attack at an unhindered primary carbon. Better methods, however, are available for producing 5-thio derivatives of D-xylose.[3,5]

Thus, it is not surprising to find that the 3,5-anhydro ring in XIV is quantitatively opened with benzylthio anion at 150° in DMF giving 5-*S*-benzyl-1,2-*O*-isopropylidene-5-thio-α-D-xylofuranose (XV). Compound XIV also reacts with thiosulfate anion to give a Bunte salt, XVI, identical with the one prepared by Schwarz and Yule.[15] Reductive debenzylation of XV or hydrogenation of XVI with sodium borohydride in water yields the free thiol compound, 5-deoxy-1,2-*O*-isopropylidene-5-thio-α-D-xylofuranose (XVII).

Experimental Section

Analytical Methods.—Purity of crystalline products was determined by thin layer chromatography (tlc) on silica gel G[16]

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coated microscope slides irrigated with (A) chloroform–acetone (9:1 v/v), (B) benzene–diethyl ether (9:1 v/v), or (C) isopropyl ether. Components were located by spraying with 5% sulfuric acid in ethanol and heating until permanent char spots were visible. Chromatographic identification of sugar derivatives were made at 25° on Whatman No. 1 filter paper developed in irrigant (D) 1-butanol–ethanol–water (40:11:19 v/v). Spray indicator used was silver nitrate–sodium hydroxide.[17] Acetyl groups were qualitatively determined by a spray reagent of ferric hydroxamate.[18] A calibrated Fisher-Johns apparatus was used for melting point determinations. Molecular weights were measured in a Mechrolab vapor phase osmometer with chloroform as the solvent.

3-*O*-Acetyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-6-*O*-triphenylmethyl-α-D-glucofuranose (I).—3-*O*-Acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose (240 g) was dissolved in 950 ml of dry pyridine and cooled to 0°, then 270 g of chlorotriphenylmethane (trityl chloride) was added slowly. The solution was allowed to stand at 25° for 30 hr, cooled to 0°, and 460 g of *p*-tolylsulfonyl chloride (tosyl chloride) dissolved in 600 ml of alcohol-free chloroform was added slowly. The reaction mixture was stirred at 37° for 48 hr, then poured into 2 l. of ice and water, and extracted three times with 500-ml portions of chloroform. The chloroform extracts were combined, partitioned against solutions of cupric sulfate saturated water until the light blue color of the aqueous phase remained unchanged, dried over sodium sulfate, and concentrated to a syrup. This syrup was immediately dissolved in 2 l. of hot methanol. Crystals resulted upon scratching in the cooled solution. Recrystallization from methanol yielded 430 g of product: mp 113°, $[\alpha]^{25}D$ −23.5° (*c* 2.0, chloroform) (previously reported for syrup, $[\alpha]^{25}D$ −21.4° (*c* 1.8, chloroform)).[19]

Anal. Calcd for $C_{37}H_{38}O_9S$: C, 67.5; H, 5.82; S, 4.87. Found: C, 67.7; H, 5.77; S, 4.90.

3,5-Anhydro-1,2-*O*-isopropylidene-6-*O*-triphenylmethyl-β-L-idofuranose (II).—Compound I (60 g) was dissolved in 200 ml of absolute methanol, 9.4 g of sodium methoxide was added, and the solution refluxed for 20 min. The cooled solution was filtered to remove the salts and concentrated to a solid, which was extracted four times with 100-ml portions of chloroform. The chloroform was concentrated to approximately 150 ml, hexane was added to the hot solution just to the turbid point, and chloroform was added to remove the cloudiness. The cooled solution was filtered to remove the major product of the reaction, 5-deoxy-1,2-*O*-isopropylidene-6-*O*-triphenylmethyl-α-D-*xylo*-hexofuran-5-enose. The procedure was repeated twice and the resulting syrup chromatographed on neutral silica gel[20] with benzene–diethyl ether (49:1 v/v) as irrigant. The proper effluent was concentrated to a syrup which was chromatographically pure.

3,5-Anhydro-1,2-*O*-isopropylidene-β-L-idofuranose (III) was prepared from the crude syrup, II, before chromatography by dissolving it in 35 ml of ethanol, adding 75 ml of acetic acid, and then 18 ml of water. The solution was refluxed for 15 min, cooled to −10°, and the triphenylcarbinol filtered off. The filtrate was concentrated to a syrup which was then chromatographed on silica gel using irrigant A. The obtained compound III crystallized spontaneously on concentrating to dryness: yield from the starting material, 2.5 g (14%); mp 49°; $[\alpha]^{25}D$ +48.2° (*c* 1.0, chloroform) (lit.[10] mp 49–50°; $[\alpha]^{27}D$ +53.2° (*c* 1.2, chloroform)).

5-*S*-Benzyl-1,2-*O*-isopropylidene-5-thio-6-*O*-triphenylmethyl-α-D-glucofuranose (IV).—Compound II (12 g) was dissolved in 350 ml of dry DMF and 36 g of sodium α-toluenethiol added. The solution was heated at 150° for 24 hr, after which time no further reaction was observed by tlc. The reaction solution was diluted with an equal volume of *p*-xylene, cooled to −10°, filtered, and then concentrated to dryness. The residue was dissolved in 100 ml of chloroform and 100 ml of water and extracted three times with 100-ml portions of chloroform. The combined chloroform extracts were washed with water twice, dried over sodium sulfate, and concentrated to a syrup. The syrup was chromatographed on neutral silica gel with irrigant B. The yield was 1.5 g of pure IV in syrup form.

Anal. Calcd for $C_{35}H_{36}O_5S$: S, 5.64. Found: S, 5.40.

5-*S*-Benzyl-1,2-*O*-isopropylidene-5-thio-α-D-glucofuranose (V). Method A.—Compound IV (1.5 g) was dissolved in 10 ml of ethanol and 25 ml of acetic acid, and then 6 ml of water was added. The solution was refluxed for 20 min, cooled, diluted with water, and neutralized with Amberlite IR-45(OH) resin. The effluent was concentrated to a syrup and chromatographed on silica gel with irrigant A. Yield was 0.65 g of pure syrupy V $[\alpha]^{25}D$ −53.6° (*c* 2.07, chloroform).

Anal. Calcd for $C_{16}H_{22}O_5S$: S, 9.82. Found: S, 9.68.

Method B.—Compound III (2.5 g) was dissolved in 50 ml of dry DMF and 10 g of sodium α-toluenethiol was added. The reaction was heated to 150° for 1 hr, then worked up as for IV. Chromatography on silica gel irrigated with chloroform–acetone (9:2 v/v) yielded 2.8 g (70%) of pure V. The product showed the same rotation as V above.

3-*O*-Acetyl-5-*S*-benzyl-1,2-*O*-isopropylidene-5-thio-6-*O*-triphenylmethyl-α-D-glucofuranose (VI).—Compound IV (1 g) was dissolved in 5 ml of dry pyridine and cooled to 0°. Acetic anhydride (3 ml) was added and the solution allowed to stand at 25° for 16 hr. The reaction solution was poured into ice and water and extracted with chloroform. The chloroform extracts were combined, partitioned against cupric sulfate saturated water to remove the pyridine, washed with water, dried over sodium sulfate, and concentrated to a syrup. The syrup was chromatographed on neutral silica gel with irrigant A. Yield was 0.63 g of a colorless syrup which solidified. The solid had a softening point of 55–56°, $[\alpha]^{25}D$ −47.5° (*c* 0.8, chloroform).

Anal. Calcd for $C_{37}H_{38}O_6S$: C, 72.7; H, 6.27; S, 5.25. Found: C, 72.4; H, 6.24; S, 5.25.

5-*S*-Benzyl-3,6-di-*O*-acetyl-1,2-*O*-isopropylidene-5-thio-α-D-glucofuranose (VII).—Compound V (1.5 g) was dissolved in 10 ml of dry pyridine, cooled to 0°, and 8 ml of acetic anhydride added. The solution was allowed to stand at 25° for 16 hr and was worked up in a manner similar to VI. The resulting syrup was taken up in a small amount of warm ethanol and on cooling crystalline material resulted which was recrystallized from ethanol: yield, 1.03 g; mp 94°; $[\alpha]^{25}D$ −51.7° (*c* 1.2, chloroform).

Anal. Calcd for $C_{20}H_{26}O_7S$: C, 58.5; H, 6.38; S, 7.81. Found: C, 58.8; H, 6.49; S, 7.83.

1,2-*O*-Isopropylidene-5-thio-α-D-glucofuranose (VIII).—Compound V (0.65 g) was dissolved in 75 ml of liquid ammonia (in Dry Ice–acetone bath) and small pieces of oxide-free sodium metal were added until the deep blue color remained for 15–20 min. Ammonium chloride was added until the blue color disappeared and a 3-g excess was added. The ammonia was allowed to evaporate to dryness under nitrogen. The residue was extracted with 100 ml of chloroform and filtered, and the chloroform was concentrated to a thick syrup, VIII. The yield was 0.47 g and was pure by tlc. It gave an immediate positive reaction with both 2,3,5-triphenyl-2H-tetrazolium chloride (TTC),[17] and sodium nitroprusside (SNP)[21,22] at 25°. Titration with 0.1 *N* iodine solution[23] showed that 88% of the thiol groups were free. Compounds VIII oxidized slowly to the disulfide XI on standing in the presence of air.

3,6-Di-*O*-acetyl-5-*S*-acetyl-1,2-*O*-isopropylidene-5-thio-α-D-glucofuranose (IX).—The resulting syrup VIII was dissolved in 5 ml of dry pyridine, cooled to 0°, and 3 ml of acetic anhydride added. The solution was allowed to stand at 25° for 16 hr and worked up in the usual manner. A homogeneous syrup resulted which crystallized after dissolving in hot ethanol and concentrating to a small volume. Recrystallization from ethanol gave 0.73 g (81%), mp 147°; $[\alpha]^{25}D$ +7.7° (*c* 1.83, chloroform) (lit.[3,4] mp 149°, $[\alpha]^{25}D$ +7.2° (*c* 1.8, chloroform)).

Compound IX showed characteristic absorption for thiol acetate in the ultraviolet region[24] at 230–240 mμ and in the infrared region[25] at 1675 cm^{-1} and gave an immediate positive reaction with both TTC and SNP at 25° after treatment with

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alcoholic sodium hydroxide. A mixture melting point with an authentic sample remained unchanged.

α-D-Glucothiopyranose (5-Thio-α-D-glucopyranose) (X).—Acetolysis of 0.25 g of VIII was accomplished with 50% aqueous acetic acid for 30 hr at 70°. The reaction solution was concentrated under reduced pressure and water was added and again concentrated. This procedure was repeated four times and the resulting colorless syrup was dissolved in a small amount of absolute methanol and cooled. After 2 days at −10° crystalline material resulted. It was recrystallized from absolute methanol to give 0.15 g (72%), mp 136°.

Compound X showed no absorption for thiol acetate in the infrared region at 1675 cm^{-1}. A mixture melting point with an authentic sample remained unchanged.

Bis(5-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose) 5,5'-Disulfide (XI).—Compound VIII (1 g) was dissolved in 40 ml of hot ethanol, a crystal of iodine added, and oxygen bubbled through the solution for 3 hr. The solution was concentrated to a syrup which was chromatographed on silica gel irrigated with chloroform–acetone (8:3 v/v). The product showed no thiol activity when titrated with 0.1 *N* iodine solution[23] and did not react with TTC or SNP until the disulfide bond was reduced with lithium aluminum hydride[26] in diethyl ether. The syrupy product was obtained in 85% yield, $[\alpha]^{25}D$ +171° (*c* 0.86, chloroform).

Anal. Calcd for $C_{18}H_{30}O_{10}S_2$: S, 13.6. Found: S, 13.5.

Bis(5-deoxy-3,6-di-*O*-acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose) 5,5'-Disulfide (XII).—Compound XI (0.5 g) was dissolved in 10 ml of dry pyridine, cooled to 0°, and 5 ml of acetic anhydride added. The solution was allowed to stand at 25° for 16 hr and was worked up in the usual manner. The resulting syrup was dissolved in a small amount of hot ethanol which crystallized on cooling. Recrystallization from ethanol gave 0.55 g of XII, mp 160°, $[\alpha]^{25}D$ −29.3° (*c* 1.0, chloroform).

Anal. Calcd for $C_{26}H_{38}O_{14}S_2$: S, 10.0; mol wt, 638. Found: S, 10.2; mol wt, 629.

Bunte Salt of 5-Deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (XIII).—Compound III (0.2 g) was dissolved in 40 ml of 80% aqueous DMF and 1.5 g of sodium thiosulfate was added. The reaction mixture was stirred vigorously while refluxing for 72 hr. The mixture was concentrated to dryness and extracted with water. Both excess sodium thiosulfate and the product were in the water phase.

Compound XIII was characterized by sodium borohydride reduction[27] to the free thiol, VIII. The reduction was accomplished by dropwise addition of 0.5 g of sodium borohydride in 25 ml of water at 0°. The reaction was continued for 4 hr, after which time the excess hydride was destroyed with 1 *N* sulfuric acid solution. The resulting solution was passed through an Amberlite IR-120(H^+) resin column and the effluent was concentrated to a syrup. Boric acid was removed by repeatedly dissolving the syrup in methanol and evaporating under reduced pressure. A thick syrup resulted which was identical with VIII on paper and on tlc and displayed the same color reactions. The yield was 15% from compound III.

3,5-Anhydro-1,2-*O*-isopropylidene-α-D-xylofuranose (XIV).—Crystalline 1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-xylopyranose[11] (10 g) was dissolved in 25 ml of absolute methanol and 9 g of sodium methoxide added. The solution was then refluxed for 15 min. Sodium toluenesulfonate started precipitating after 5 min of refluxing. The complete reaction mixture was concentrated to dryness under reduced pressure and the solid residue was extracted with 200 ml each of chloroform and water. The chloroform solution was washed with water, dried over sodium sulfate, and concentrated to a syrup. The yield was 4.6 g (92%), $[\alpha]^{25}D$ +12.7° (*c* 2.1, chloroform).

5-*S*-Benzyl-1,2-*O*-isopropylidene-5-thio-α-D-xylofuranose (XV).—A solution of 5 g of XIV and 5 g of sodium α-toluenethioxide in 40 ml of dry DMF was refluxed for 30 min. The solution was diluted with an equal volume of *p*-xylene and allowed to cool. The mixture was filtered and the filtrate concentrated to a solid mass. This residue was extracted with three sequential 100-ml portions of chloroform and the combined chloroform extracts were washed with water, dried over sodium sulfate, and concentrated to yield 96% of XV. Recrystallization from ethanol to give 82% pure product, mp 103°.

Bunte Salt of 5-Deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (XVI).[15]—Compound XIV (3 g) was dissolved in 40 ml of 80% aqueous DMF and 4 g of sodium thiosulfate added. The mixture was stirred vigorously at reflux for 36 hr. The reaction was worked up the same as for compound XIII.

1,2-*O*-Isopropylidene-5-thio-α-D-xylofuranose (XVII). Method A.—Syrup XVI was reduced by dropwise addition of a solution of 1.0 g of sodium borohydride in 50 ml of water. After 4 hr at 0°, excess hydride was destroyed with 1 *N* sulfuric acid solution. The mixture was passed through an Amberlite IR-120(H^+) resin column and the effluent was concentrated to a syrup. Boric acid was removed by repeatedly dissolving in methanol and evaporating. The resulting syrup crystallized on addition of petroleum ether. It was recrystallized from boiling petroleum ether to give 32% yield of XVII, mp 85°. It was identical with an authentic sample.

Method B.—Compound XVII can be prepared in much higher yield by a Birch reduction of XV as described for VIII. The product was obtained in 95% yield by this method and was pure. It was identical with XVII above.

Registry No.—I, 14795-89-2; III, 4118-61-0; α-D-xylofuranose, 14795-83-6; IV, 14795-84-7; V, 14795-85-8; VI, 15038-89-8; VII, 14795-86-9; XI, 14795-90-5; XII, 14795-91-6; XIV, 4118-63-2; XV, 10579-10-9.

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