Synthesis of 1-Deoxy-D-Glucitol Sulfide and Disulfide

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Summary: Bis(1-deoxy-D-glucitol) 1,1'-disulfide 10 and the corresponding 1,1'-sulfide 11 have been prepared. Nucleophilic displacement reaction of the 1-tosylate 6 with potassium thioacetate afforded the 1-S-acetate 7 which on deesterification gave the 1-thiol-D-glucitol 8. Oxidation of 8 followed by removal of the protecting groups gave the target compound 10. The 1,1'-sulfide 11 has been obtained from 8 by condensation with the 1-tosylate 6 followed by cleavage of the acetal groups.

Introduction

In this communication we describe [1] the synthesis, oxidation and the condensation reactions of the 1-thiol-D-glucitol derivative.

Results and Discussions

Synthesis of Bis(1-deoxy-D-glucitol) 1,1'-disulfide 10.

The synthesis of 3,4:5,6-di-O-isopropylidene-D-glucitol 2 has been achieved by treating D-glucitol 1 with an equimolar proportion of 2,2'-dimethoxy propane and catalytic amount of p-toluenesulfonic acid [2]. The reaction mixture when monitored on a t.l.c. plate gave two prominent spots (benzene-acetone 5:1 v/v). The mixture was then column chromatographed to separate the two component present, to give 40% yield of the required compound 2 melting at 55-56° and 45-50% yield of 1,2:3,4:5,6-tri-O-isopropylidene-D-glucitol 3 which melts at 45-46°. The infrared spectra of compounds were in full agreement with the structure. E.J. Bourne and his co-workers [3] have prepared compound 3 by the condensation of acetone with D-glucitol in presence of catalytic amount of sulfuric acid stirring at room temperature to give quantitative yield of 3 in colourless needles. The foregoing compound 3 was treated with dilute hydrochloric acid which afforded the compound 2 and 3,4-O-isopropylidene-D-glucitol 4 by fractional crystallization [3]. We have employed 70% acetic acid to deblock the group present between C-1 and C-2 position by stirring the mixture for 24 hours. The column chromatography of the concentrated mixture afforded 40% yield of the required compound 2, and 15% yield of compound 4 and approximately 33-35% of the unreacted material of triisopropylidene glucitol derivative was recovered. The infrared spectra and R_f values of these fractions was found matching with the compounds 2,3 and 4. Figure No.1.

The presence of the two primary hydroxyl groups of compound 4 was further characterized by preparing 1,2:5,6-tetra-O-acetyl-3,4-O-isopropylidene-D-glucitol derivative 5 in a clear syrup. Thus, it has been established that 1,2 and 5,6 (α) isopropylidene groups [4] can cleave under very mild acidic condition.

In H^1 n.m.r. spectrum of 3, the Me protons appeared in different

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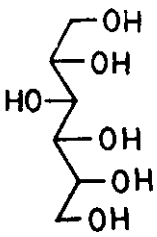

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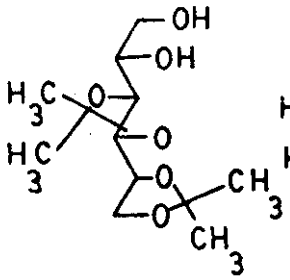

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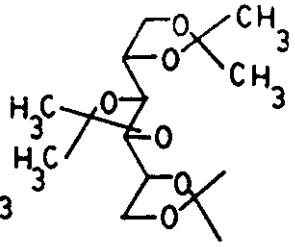

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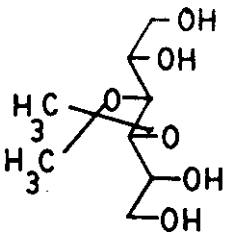

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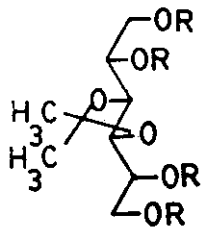

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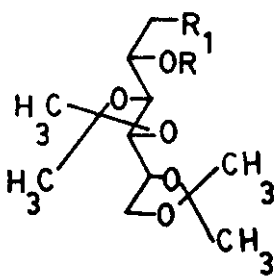


5 R=Ac

6 R=OTs, R^1=H

7 R=SAc, R^1=H

8 R=SH, R^1=H

Fig.1:

environment, the splitting of the other protons appeared in the region H-1 (δ 5.25 d), H-2(δ 4.47 dd),H-3 (δ 4.09 dd) and the coupling constants $J_{1,2}$(3.5 Hz), $J_{4,5}$(2.0 Hz) and $J_{3,4}$ (7.5 Hz). These assignments were verified by decoupling experiments at 220 MHz. The signals for Me (α) proton of isopropylidene groups were unsplited and found in the region δ2.0 to 1.0. The signals of Me (α) and Me (β) protons appearance are cis H/H and H/R (where R=H) in the 1,3-dioxalan type ring conformation of compound 3. Me (β) is more effectively deshielded than Me (α) and this causes the signal for Me (β) to appear at lower field [5]. For example, 1,2-O-isopropylidene glycerol has equal signal at δ 1.16 and δ 1.21 which may be assigned to Me (α) and Me (β) respectively.

The primary hydroxyl group of compound 2 was blocked by tosylation, using p-toluenesulfonyl chloride and pyridine at 0° afforded in 81% yield of compound 6. The infrared spectrum was in full agreement with the structure. The ^1H n.m.r. spectrum of compound 6 indicated Me proton singlet at δ 2.50 and tosyl ring protons appeared at δ 7.69 as multiplet. The coupling constant $J_{6,6'}$=(11.3 Hz) at C-6 position and a broad peak for the free hydroxy group at C-2 position appeared at δ 6.14. The nucleophilic displacement reaction of 1-tosylate sugar 6 with potassium thio-acetate [6,7] afforded 1-S-acetyl-3,4:5,6-di-O-isopropylidene-D-glucitol 7 which was saponified to give 1-deoxy thiol sugar derivative 8 in quantitative yield. The replacement reaction was conducted in dry acetone under reflux using 1:1 to 1:2 equivalent of potassium thioacetate. The solid which was precipitated during refluxing has been filtered off. The filtrate was worked up in the usual manner [1] to afford 72% yield of compound 7 as viscous syrup. The H^1 n.m.r. spectrum of 7 was in accord with the structure.

1-S-acetate 7 was suspended in methanol, the sodium methoxide was

dropped and the mixture was magnetic stirred at room temperature under nitrogen atmosphere. Deacetylated product was monitored on t.l.c. plate and finally deionized by ion-exchange resin IR 120 H^+ through column chromatography. The infrared spectrum was in full agreement with the structure 8. The light absorption at λ 224, λ 226 nm in methanol also supported the presence of the thiol group present in the compound 8. Then, the thiol sugar 8 was oxidized with 30% hydrogen peroxide solution, after stirring for 24 hours the reaction mixture was neutralized with sodium hydroxide. Then extracted with dichloromethane and washed thoroughly with water and dried. The evaporation of solvent gave 48% yield of bis(1-deoxy-3,4:5,6-di-O-isopropylidene)1,1'-disulfide 9. The required compound 10 was achieved after the acidic hydrolysis with 90% aqueous triflouroacetic acid, stirring at 0° for 24 hours under nitrogen atmosphere to yield bis(1-deoxy-D-glucitol)1,1'-disulfide 10 as a thick viscous syrup. The infrared spectrum and light absorption values were in full agreement with the structure of compound 10.

Synthesis of Bis(1-deoxy-D-glucitol) 1,1'-sulfide 12.

The synthesis of bis(1-deoxy-D-glucitol)1,1'-sulfide was achieved by the base catalyzed nucleophilic replacement reaction. The equimolar ratios of 1-tosylate 6 and 1-thiol sugar 8 were dissolved in dry triethylamine. After refluxing for 7 hours the mixtue was washed with dilue hydrochloric acid, and extracted with dichloromethane, finally washed with sodium bicarbonate solution and water. After the evaporation of the solvent resulting product 11 was obtained as a yellow viscous oil. The infrared spectrum supported the structure.

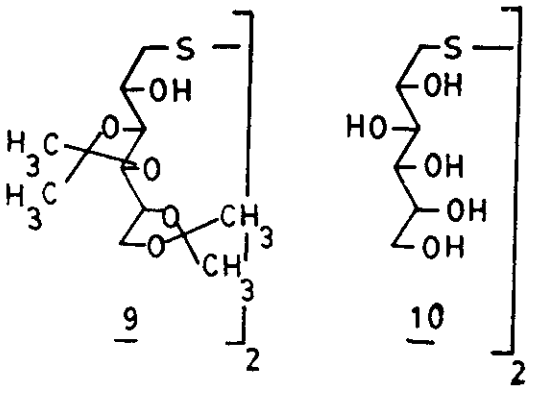
The compound 11 was deblocked by stirring the 1,1'-sulfide sugar 11 with 90% triflouroacetic acid at room temperature. The resulting syrup was column chromatographed, eluted with ethyl alcohol-chloroform (11:8 v/v) mixture. Finally, recovered a pale yellow syrup of compound 12 in 70% yield. The infrared spectrum and light absorption values supported the structure.

Experimental

Purity of the compounds were determined by thin layer chromatography (TLC) on silica gel G 11 coated glass plate 5 x 13 cm irrigated with different solvents. Components were located by spraying with 5% sulfuric acid in ethanol and heating until permanent char spot were visible. Melting points were determined on Fisher-John apparatus. NMR spectra were obtained with a Varian Associates A-60 instrument (otherwise stated). Infrared spectra were recorded with a Perkin-Elmer 1060 spectrophotometer.

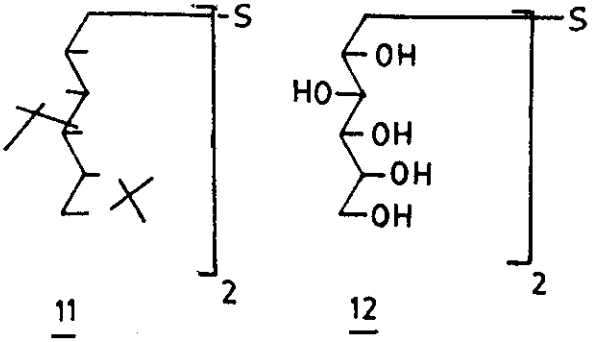
3,4:5,6-Di-O-isopropylidene-D-gluciton 2.

To a solution of 2,2'-dimethoxy propane (30 g, 0.3 mole) and a catalytic amount of p-toluenesulfonic acid was added D-glucitol (18.2 g, 0.1 mole) and the mixture was stirred at 0°. After a short time, the crystalline D-glucitol went into solution. The reaction was monitored on a t.l.c. plate (benzene-acetone 5:1 v/v). After 6-8 hours stirring t.l.c. plate indicated two spots. The solvent was evaporated and the concentrated material was chromatographed on silica gel column to separate the components present, eluted with benzene-acetone (20:1 v/v) mixture. The infrared spectra showed that lower mobile fraction contain primary hydroxyl group, while the other fraction does not show any absorbance in that region. Therefore, it had been considered as tri-



9 10

Fig.2:



11 12

Fig.3:

substituted acetal derivative 3. The yield of compound 2 40%; m.p. 55-56°C and $[\alpha]_D^{20}$ + 23.1 (c, 1.0 ethanol). Lit[3]. $[\alpha]_D^{19}$ + 25.2 (c, 1.4 in ethanol). IR: ν (cm^{-1}) 3590-3510 (OH), 2950 and 2835 ($C-CH_3$) and 1380 ($C(CH_3)_2$.

Hydrolysis of 1,2:3,4:5,6-Tri-O-isopropylidene-D-glucitol 3

Partial hydrolysis of tri-ketal-D-glucitol 3 (10 g) was mixed with 70% aqueous acetic acid (100 mL). The reaction mixture was magnetic stirred for 24 hours at room temperature. The t.l.c. results benzene-acetone (5:1 v/v) indicated three spots which were separated by silica gel column, eluted with benzene-acetone (30:1 v/v) mixture. The 33% yield of the unreacted product 3 melting at 45-46°C.

NMR: ($CDCl_3$) H-1 (δ 5.25 d), H-2 (δ4.47 dd), H-3(δ 4.09 dd), and coupling constants $J_{1,2}$ (3.5 Hz), $J_{2,3}$ (2.0 Hz) and $J_{3,4}$ (7.5 Hz).

3,4:5,6-Di-O-isopropylidene-D-glucitol 2 recovered in 40% yield in a syrup which crystallized in a mixture of acetone-ethanol (2:1 v/v), m.p. 55-56°C; $[\alpha]_D^{20}$ + 26.1 (c, 1.4 in ethanol).

(Found: C, 53.0; H, 8.50% $C_{12}H_{22}O_6$ requires C, 53.1; H, 8.59%). The concentrated syrup of the last fraction crystallized with dry acetone which melts at 91-92°C $[\alpha]_D^{20}$ + 26.1 (c, 1.4 in ethanol). The mixed melting point was found identical with E.J.Bournes Procedure [3].

(Found: C, 48.51; H, 8.34% $C_9H_{18}O_6$ requires C, 48.62; H, 8.25%).

3,4-O-isopropylidene-D-glucitol 4 (0.5 g) was suspended in acetic anhydride (2 ml) and pyridine (5 ml) left at room temperature for 24 hours. Then, the mixture was diluted with saturated sodium bicarbonate, extracted with dichloromethane, washed with water and dried. On evaporation of the solvent gave 45% yield of tetra-O-acetyl-3,4-O-isopropylidene-D-glucitol 5. B.p. 180-188°C at 1 mm, n_D^{20} 1.451 and $[\alpha]_D^{20}$ + 8.2 (c, 2.3 chloroform).

(Found: C, 52.33; H, 6.75 $C_{17}H_{26}O_{10}$ required C, 52.30; H, 6.71%).

1-O-p-Toluenesulfonyl-3,4:5,6-di-O-isopropylidene-D-glucitol 6.

Compound 2(26.2 g, 0.1 mole) was dissolved in minimum amount of dry pyridine, then added p-toluenesulfonyl chloride (20.9 g, 0.11 mole) in dry pyridine (50 ml) at 0° with magnetic stirring for 8 hours. The

mixture was poured into water and extracted with dichloromethane. The organic layer was washed successively with 1N hydrochloric acid and saturated sodium bicarbonate solution than with water. It was dried and evaporated to give 21.3 g(81% yield) as a yellow syrup. $[\alpha]_D^{20}$ + 23.1 (c, 1.2 in methanol).

IR: $\nu(cm^{-1})$ 3450 (OH), 2990 ($ArCH_3$). 2940 ($C-CH_3$), 1600 and 1460 (Aromatic -CH=CH-CH-) 1380 ($C(CH_3)_2$, 1180 (SO_2-sym. stretching).

NMR: ($CDCl_3$) C_6H_4- (tosyl) δ 7.69 (m), Me, δ 2.50(s), C-2 OH δ 3.86 coupling constant $J_{5,6}$(6.2 Hz), $J_{6,6'}$ (11.3 Hz).

(Found: C, 54.85; H, 6.67; S, 7.59% $C_{19}H_{28}O_8S$ requires C, 54.81; H, 6.77; S, 7.68%).

1-S-Acetyl-3,4:5,6-di-O-isopropylidene-D-glucitol 7.

The 1-tosylated sugar 6 (20.75 g, 0.05 mole) was dissolved in 100 ml of dry acetone and potassium thioacetate (6.84 g, 0.06 mole) was gradually added with stirring and the mixture was refluxed for 7 hours. The reaction mixture was monitored on t.l.c. plate benzene-acetone (9:1 v/v) showed R_f 0.5 with one spot. It was cooled at room temperature and the solid material was filtered off, washing of the solid crystals was combined with acetone. Finally, the solvent was evaporated to give 11.5 g of the required material 7 as a pale oil.

$[\alpha]_D^{21}$ - 21.3 (c, 2.3 in methanol).

IR: ν (cm^{-1}) 3450 (OH), 2940-2890 ($C-CH_3$), 1700 (C=O), 1380 ($C(CH_3)_2$.

NMR: ($CDCl_3$) H-1 (δ 4.0 d), H-2 (δ 5.12 d), H-3 (δ 5.35 dd), and invariable broad peaks for H-4, H-5 and H-6 in the area between 5.4 to 6.35. Coupling constants $J_{1,2}$ (3.9 Hz), $J_{2,3}$ (0.5 Hz) and $J_{3,4}$ (1.8 Hz).

(Found: C, 50.02; H, 7.13; S, 9.54% $C_{14}H_{24}O_6S$ requires C, 49.99; H, 7.19; S, 9.51%).

1-Mercepto-3,4:5,6-di-O-isopropylidene-D-glucitol 8.

1-S-acetate sugar 7 (3.1 g, 0.01 mole) was dissolved in dry methanol (5 ml) and cooled to 0°, then added methanolic sodium methoxide (15 ml dry methanol and 0.11 g. of sodium metal) under nitrogen atmosphere. Deacetylation was monitored on a t.l.c. plate benzene-acetone (4:1 v/v) R_f 0.35. The solvent was evaporated resulting to a thick syrup which immediately passed through resin IR 120 H^+ eluting with a mixture of methanol-chloroform.

$[\alpha]_D^{21}$ + 42.3 (c, 1.2 in methanol).

IR: $\nu(cm^{-1})$ 3590 (OH), 2940 ($C-CH_3$), 2660 (C-S), 1380 ($C(CH_3)_2$, and 680, 675 for (C-S). λ_{max} 224 and 226 nm ethanol (ε 12,400).

(FOUND: C, 51.74; H, 7.96; S, 11.43% $C_{12}H_{22}O_5S$ requires C, 51.78; H, 7.96; S, 11.49%).

Bis(1-deoxy-3,4:5,6-di-O-isopropylidene-D-glucitol)1,1'-disulfide 9.

Freshly prepared 1-thiol-D-glucitol 8 (1.38g, 0.005 mole) was dissolved in 5 ml of methanol and to this was added 3 ml of hydrogen peroxide solution. The reaction mixture was stirred at 0° for 24 hours, then neutralized with 3N sodium hydroxide and stirred for 1 hour. It was then transferred to another flask and extracted with dichloromethane and the organic layer was washed several times with water. The organic layer was dried and concentrated to dryness gave 48% yield of the disulfide sugar

9 in syrup. $[\alpha]_D^{21}$ + 1.5 (c, 1.0 in methanol).

IR: ν (cm^{-1}) 3580-3550 (OH), 2960 (C-CH_3), 1450 (S-S), 1380 (C(CH_3)$_2$ and 1250 (CH_2, wagging). λ_{max} 220 nm (ε 12,300).

(Found: C, 52.89; H, 7.81; S, 11.77% $C_{24}H_{42}O_{10}S_2$ requires C, 52.92; H, 7.77; S, 11.75%).

Bis(1-deoxy-D-glucitol)1,1'-disulfide 10.

Freshly prepared disulfide sugar derivative 9 (2.7 g, 0.005 mole) was dissolved in 25 ml of 90% aqueous triflouroacetic acid. The mixture was stirred for 24 hours at room temperature under nitrogen atmosphere. The reaction product was monitored on t.l.c. (n-hexane-acetone-methanol 2:1:2) R_f 0.3. It was then evaporated to dryness and removed the traces of acid, the residue was co-evaporated 5 times with aliquots of deionized water. Finally, concentrated to dryness as a thick viscous syrup. The infrared and light absorptions were in full agreement with the structure.

(Found: C, 36.49; H, 6.68; S, 16.23% $C_{12}H_{26}O_{10}S_2$ requires C, 36.54; H, 6.64; S, 16.23%).

Bis(1-deoxy-3,4:5,6-di-O-isopropylidene-D-glucitol)1,1'-sulfide 11.

1-thiol-D-glucitol 8 (6.9 g, 0.025 mole) was dissolved in 15 ml of dry triethylamine and 1-tosylate sugar 6 (10.38 g, 0.025 mole) was added in 25 ml of triethylamine. The mixture was refluxed for 7 hours. During refluxing two distinct layers were formed, which were separated on cooling to room temperature. The upper layer was washed with 1N hydrochloric acid followed by sodium bicarbonate and water. The organic layer was extracted and dried, solvent was evaporated to dryness. It was co-distilled with toluene-ethanol mixture to yield 65% of compound 11, as a syrup. R_f 0.4 (benzene-acetone 9:1 v/v): $[\alpha]_D^{21}$ + 23.1 (c, 1.2 methanol).

IR: ν(cm^{-1}) 3550 (OH), 2945 and 2895 (C-CH_3), 1460 (C-S), 1390 (C(CH_3)$_2$, and 680 (C-S). UV: λ_{max} 224 nm (ε 12,000).

(Found: C, 54.96; H, 8.34; S, 6.16% $C_{24}H_{43}O_{10}S$ requires C, 55.05; H, 8.27; S, 6.11%).

Bis(1-deoxy-D-glucitol)1,1'-sulfide 12.

To 10 ml of aqueous acetic acid was added bis(1-deoxy-3,4:5,6-di-O-isopropylidene-D-glucitol)1,1'-sulfide 11 (2.64 g, 0.005 mole) and also dropped 15 ml of 90% aqueous triflouroacetic acid at O° under nitrogen atmosphere. The reaction mixture was magnetic stirred overnight at room temperature. T.l.c. showed a single spot chloroform-methanol 3:1 v/v) R_f 0.37. The reaction product was concentrated to syrup under vacuum to afford 70% yield. The infrared spectrum supported the structure. UV: λ_{max}220 nm (ε 12,500). $[\alpha]_D^{21}$ + 11.5 (c, 1.0 in methanol).

(Found: C, 39.67; H, 7.19; S, 8.89% $C_{12}H_{26}O_{10}S$ requires C, 39.77; H, Y.23; S, 8.82%).

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