Synthesis of Bis(6-Deoxy-D-glucitol)6,6'-disulfide and bis(6-deoxy-D-glucitol)6,6'sulfide.

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Summary: D-Glucitol is converted to 1,3:2,4-di-O-ethylidene derivative and then into its 6-O-tosyl ester. Nucleophilic displacement with potassium thioacetate yields the 6-S-acetyl compound which may be saponified to the thiol and oxidized to the blocked disulfide. Acid removal of the ethylidene group produces bis(6-deoxy-D-glucitol) 6,6'-disulfide (11).

Alternatively, reaction of 1,3:2,4-dio-O-ethylidene-6-O-tosyl-D-glucitol, with 1,3:2,4-di-O-ethylidene-6-S-acetyl-6-thio-D-glucitol under basic conditions produces the monosulfide (12) which on deblocking by acid yields bis (6-deoxy-D-glucitol)6,6'-sulfide (13).

Introduction

Synthesis of bis(6-deoxy-D-glucitol)6, 6'-disulfide and bis(6-deoxy -D-glucitol)6, 6'-sulfide has been explored. The preparation of 1, 3:2, 4-di-O-ethylidene-D-glucitol [1,2] was achieved by the hydrolysis of 1,3:2,4:5,6-tri-O-ethylidene-D-glucitol using aqueous acetic acid. Selective tosylation of the primary hydroxyl group at C-6 position [3,4], following by the reaction with potassium thioacetate, or sodium hydrosulfide in acetone or dimethyl formamide, provide a useful method for the preparation of thiolacetate, and then, by hydrolysis to intermediate thiol compound. The blocked thiol glucitol derivative was oxidized with hydrogen peroxide which led to the formation of bis(6-deoxy-1,3:2,4-di-O-ethylidene-D-glucitol)6,6'-disulfide, and then by acidic hydrolysis, converted into deblocked sugar.

Similarly, the preparation of monosulfide sugar was achieved, by base catalyzed replacement reaction of 1, 3:2,4-di-O-ethylidene-6-O-tosyl-D-glucitol with 1,3:2,4-di-O-ethylidene -6-S-acetyl-6-thio-D-glucitol or 1,3:2,4-di-O-ethylidene-6-deoxy-6-thio -D-glucitol in the presence of dry triethylamine. Finally, the resulting compound was deblocked by acid treatment, to yield bis(6-deoxy-D-glucitol)6,6'-sulfide (13).

These compound are diastereomers of the compounds substituted by sulfur at C-6 position, and as such offer the possibility of a completely unique set of AH, B and X glucophore which are responsible for sweetness. Study of these compounds as compared to other D-glucitol derivative, both cyclic and acyclic, may lead to the identification of those factors responsible for sweetness or sweetness enhancement.

Results and Discussion

The original Appel's methods [6] of preparation of 1,3:2,4-di-O-ethylidene-D-glucitol (3), namely, hydroly-

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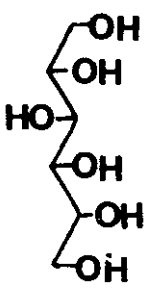
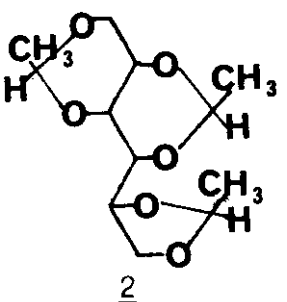
sis of the syrup "1,3:2,4:5,6-tri-O-ethylidene-D-glucitol" (2) with aqueous acetic acid was used. The presence of two free hydroxyl groups in the compound (3), has been demonstrated [7] by the isolation of 5,6-ditosylate (4), diacetate (6) dibenzoate [4] (5) derivatives. These reactions clearly indicate that the C-5 and C-6 are not involved in the acetal linkage after the hydrolysis with aqueous acetic acid.

The conformation of 1,3:2,4:5,6-tri-O-ethylidene-D-glucitol (2) and 1,3:2,4-di-O-ethylidene-D-glucitol (3) shows the possibility of the fused cis-trans ring junction. Therefore, a decision as to the most stable arrangement, however, can be made on the basis of the conformational principle, that an equitorial substituent is preferred over an axial one and also that "O-inside" is preferred over the "H-inside". The 1,3:2,4-di-O-ethylidene-D-glucitol (3a) with a cis-ring junction has the 5,6-side chain equatorial in the preferred "O-inside"conformation, and thus diacetal of the D-glucitol may be expected to have this arrangement. Thus, these arguments are in favour with the ready formation of 1,3:2,4,5,6-tri-O-acetal of D-glucitol [9].

Gatzi and Reichstein [10] have elucidated the configuration of 1,3:2,4-



D-Glucitol



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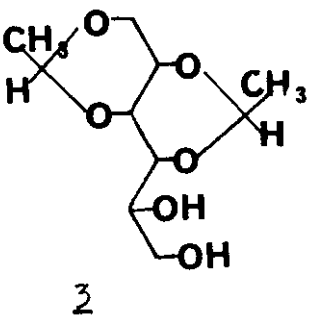

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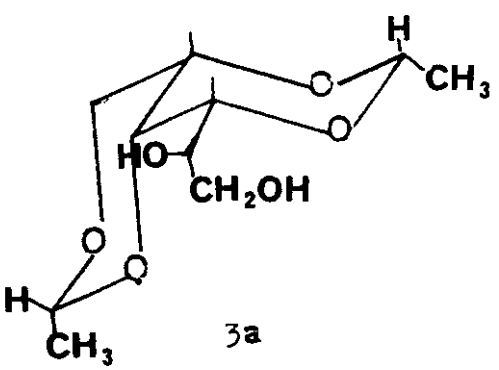
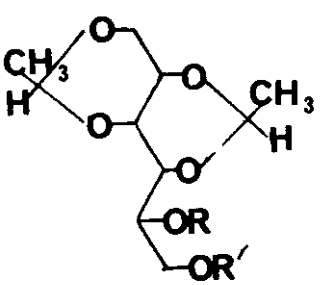


3a



8 L - Di-O-ethylidene xylonic acid

9 L - Monoethylidene threonic acid.

4 R = R' = Ts
5 R = R' = Bz
6 R = R' = Ac
7 R = H; R' = Ts

Fig: 1.

di-O-ethylidene-D-glucitol (3) by oxidation with potassium permanganate in slightly alkaline solution to diethylidene L-xylonic acid and monoethylidene L-threonic acid which would be shown to have their ethylidene residues attached to the 1,3:2,4-positions and the 2,4-position, respectively. These facts clearly proved (3) to be a derivative of D-glucitol in which hydroxyl groups at the C-5 and C-6 position are free.

Reaction of 1,3:2,4-di-O-ethylidene -D-glucitol (3) with a single equivalent of p-toluenesulfonyl chloride in dry pyridine 0°, selectively tosylated the primary hydroxyl group to afford 6-deoxy-1,3:2,4-di-O-ethylidene-6-tosyl-D-glucitol (7) in 48% yield. The infrared spectrum shows absorption of aromatic C-H (stretching) vibration at 3050, $-CH_2-$ at 1250 and 1150 and asymmetric S $(=O)_2$ (stretching) at 1355-1350 cm^{-1} which are in favour of the structure. A small amount of ditosylated product (4) was also obtained via silica gel chromatography.

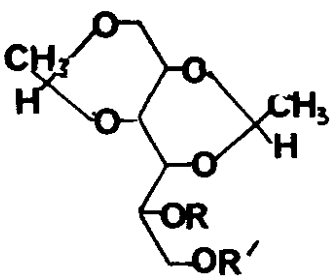
The primary p-toluenesulfonyloxy group (7) was replaced with potassium thioacetate, by refluxing in dry dimethylformamide, to afford 61% yield of 1,3:2,4-di-O-ethylidene-6-S-acetyl-6-deoxy-D-glucitol (8). The infrared spectrum is in conformity with the structure. Similar, reaction procedure has been repeated with, the change in the solvent (acetone instead of dimethylformamide), the resulting product obtained showed that dimethyl formamide is a better solvent for our compound. Unreacted product (7) and other impurities were separated by column chromatography. The potassium thioacetate, however, is sparingly soluble in dry acetone, therefore, it is advisible not to use large amount of the solvent. The solid which remained after completion of reaction in acetone, was a mixture of potassium toluene-p-sulfonate and unchanged potassium thioacetate. Slight discolouration of that reaction mixture was noticed during refluxing. The reaction of strictly hindered p-toluenesulfonyloxy group like in (7) to be due to the solvation abilities of the two solvents for anions. The significant increase in rate of nucleophilic or basic attack in aprotic solvents like tetrahydrofuran, dimethylformamide and dimethylsulfoxide has been subjected to considerable interest in recent year [12,17].

Alkaline hydrolysis of 1,3:2,4-di-O-ethylidene-6-S-acetyl-6-deoxy-D-glucitol (8) with methanolic potassium hydroxide (2.1 mole of KOH per acetyl-thio group) by stirring at room temperature in nitrogen atmosphere, gave quantitative yield of the required compound (9). Another route for obtaining 1,3:2,4-di-O-ethylidene-6-thio-6-deoxy-D-glucitol (9) includes the reaction of sodium hydrosulfide with 1,3:2,4-di-O-ethylidene-6-O-tosyl-6-deoxy-D-glucitol, followed by refluxing in dry dimethyl formamide. Both the reaction paths gave the same product (9), and have same infrared and ultraviolet absorption.

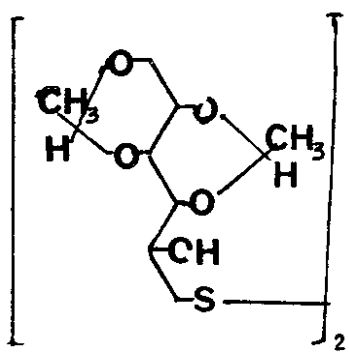
1,3:2,4-di-O-ethylidene-6-thio-6-deoxy-D-glucitol (9) was suspended in 10% hydrogen peroxide solution at 0° with constant stirring. The reaction was monitored on a t.l.c. plate, indicating 60-70% conversion into bis(6-deoxy-1,3:2,4-di-O-ethylidene-D-glucitol)6,6'-disulfide (10) which was isolated in 62% yield. The infrared absorption supported the structure. The stretching vibration of $-CH_2-S-$ at 1440-1425 cm^{-1} indica-

ted the presence of a -S-S- linkage present in the compound. The light absorption of disulfide group at λ_{max} 225, 230 nm in methanol (ε 21, 000), also supported the new linkage in the molecule. Subsequently, it was deblocked by treatment with 2N hydrochloric acid first at room temperature, then under reflux conditions to ensure complete removal of the ethylidene groups. In this way, bis (6-deoxy-D-glucitol)6,6'-disulfide (11) was obtained in 85% yield.

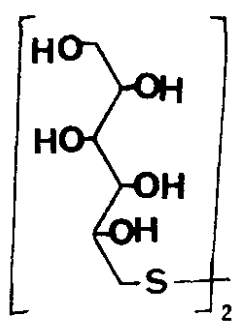
Bis(6-Deoxy-D-glucitol)6,6'sulfide (13) was prepared by the two different routes, involving base-catalyzed condensation reaction in which 1,3: 2,4-di-O-ethylidene-6-tosyl-6-deoxy-D-glucitol (7) has been treated with sodium in presence of dry methanol at 0°, followed dropwise addition of 1,3:2,4-di-O-ethylidene-6-S-acetyl-6-deoxy-D-glucitol (8) under nitrogen atmosphere gave 34% yield of (12); alternatively, compounds (2) and (9) in presence of triethylamine on refluxing gave quantitative con-



10 R = H; R' = SAc
11 R = H; R' = SH

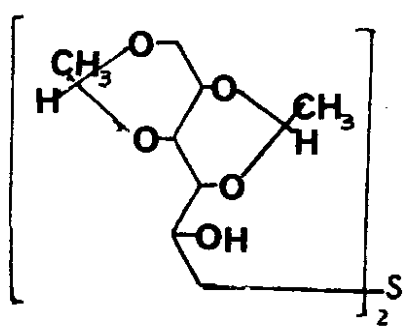


12



13

7 + 10 → (NaOMe)
7 + 11 → ($C_2H_5)_3N$



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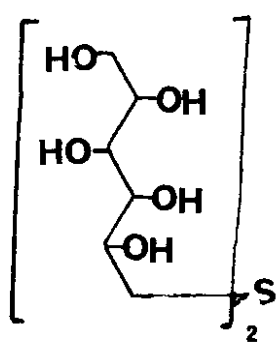

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Fig: 2

version at (12) when examined on tlc plate. In either procedures, the new linkage of $-CH_2-S-CH_2-$ group developed on C-6 position. Further, it was characterized by its infrared and ultra violet absorption data. The separation of tosyl group in compound (7) was collected in a gel, which subsequently was converted into a crystalline compound of p-toluenesulfonic acid and and its sodium salt.

Finally, bis(1,3:2,4-di-O-ethylidene-D-glucitol)6,6'-sulfide (12) was deblocked by a normal procedure, by stirring with 2N hydrochloric acid, followed by refluxing to ensure complete removal of ethylidene groups. The free 6,6'-sulfide (13) was obtained in 80% yield, its infrared and ultraviolet data clearly showing the presence of a $-CH_2-S-CH_2-$ linkage.

Experimental

Purity of the compounds was determined by thin layer chromatography (TLC) on silica gel G coated plass plates 5 x 13 cm irrigated with different solvents. Components were located by spraying with 5% sulfuric acid in ethanol and heating until permanant char spot were visible. Melting points were determined on a Fisher-John appearatus. Infrared spectra were recorded with Perkin-Elmer 1060 spectrophotometer and Ultraviolet absorption recorded from Unicam SP 800 spectrophotomter.

1,3:2,4:5,6-Tri-O-ethylidene-D-glucitol(2)

D-glucitol (18.2 g, 0.1 mole) was shaken overnight with paraldehyde (45 ml) and 48% hydrogen bromide (5 ml). Chloroform (100 ml) and 15 ml of water were added and the mixture was shaken thoroughly. The chloroform extract was separated, washed successively was saturated sodium bicarbonate solution and with water. After being dried (Na_2SO_4), the extract was evaporated to a syrup triethylidene glucitol (12 g). It was then triturated with alcohol and kept at 0° for 24 hours. A semicrystalline product was obtained after standing at room temperature. The crystals were filtered off and the mother liquor was concentrated to a syrup which distilled at 102-108°/0.1-0.5 mm. The distilate when kept at 0° crystallized and was recrystallized from ether-ligrion, m.p. 92-95°[α]$_D^{20}$ -20.2° in water (c, 4.52). Lit [2]. m.p. 96-97° [α]$_D^{22}$ -21.6° in water (c, 5.0).

(Found: C, 55.6; H, 7.6% Calcd for $C_{12}H_{20}O_6$: C, 55.4; H, 7.7%).

Hydrolysis of 1,3:2,4:5,6-Tri-O-ethylidene-D-glucitol to 1,3:2,4-di-O-ethylidene-D-glucitol (3).

Triethylidene glucitol (13 g, 0.05 mole) was hydrolyzed with hot 70% aqueous acetic acid [6]. The solvent was removed under reduced pressure at 70-75°, leaving a syrup material which was then stirred with alcohol (5 ml) and ether (15 ml), resulting to a white solid precipitates which melts at 190-191°. The solid product was rapidly washed with water and with small amount of chloroform to remove any traces of starting material. Recrystallization from the minimum amount of ethanol gave 4.1 g of (30, m.p. 212-214° and [ ]$_D^{19}$ -10.8 in water (c, 5.0). Lit [6]: m.p. 210-214°; [α]$_D^{17}$ -11.1° in water (c, 2.3).

Acetylation of (3) (0.5 g) with pyridine (3 ml) and acetic anhydride (1 ml) at room temperature for 24 hours, followed by pouring into ice-water (25 ml), and recrystallization of the precipitate formed from aqueous ethanol gave 5,6-di-O-acetyl-1, 3:2,4-diethylidene 5,6-dideoxy-D-glucitol (6) of m.p. 152-1525° and $[\alpha]_D^{20}$ + 3.0 (chloroform); Lit [2]: m.p. 153-154°, $[\alpha]_D^{20}$ + 2.8 (chloroform).

1,3:2,4-Di-O-ethylidene-D-glucitol 3.

Appel's method of preparation [6] was slightly modified and applied to D-glucitol (50 g), paraldehyde (50 ml) and concentrated hydrochloric acid (17 ml). After 10 hours of stirring, the mixture was extracted twice with chloroform (30 ml) and the extracts were washed successively with 20 ml portion of water, 10% aqueous sodium hydroxide and water, then dried ($CaCl_2$). The chloroform and most of the excess paraldehyde were removed by distillation under reduced pressure. The residual syrup was heated with acetic acid under reflux and under reduced pressure (20 mm) for 1 hour. The liberated acetaldehyde being removed by a current of air drawn through a capillary leak. The solution was concentrated in vacuo until solid begin to separate, dilution with water then precipitated tri-O-ethylidene-D-glucitol (4.5g) m.p. 166-167°.

Evaporation of the aqueous solution gave a syrup which was taken up in methanol and treated with ether to give 1,3:2,4-di-O-ethylidene-D-glucitol (3) as a fine powder when the solution was kept for few days; yield: 15-16 g (43-45%) and melting at 210-212°. A 5,6-Di-O-benzoyl-1, 3:2,4-di-O-ethylidene-D-glucitol derivative (5) was prepared and recrystallized from light petroleum (40-60°) m.p. 123-124° $[\alpha]_D^{21}$ -36° (chloroform)

6-O-Tosyl-1,3:2,4-di-O-ethylidene-D-glucitol(6)

(7) was prepared by the method of Vargha and Puskas [8] and recrystallized from ethyl acetate-light petroleum (40-60°), yield 48% m.p. 87-90°: $(\alpha)_D^{21}$ = 10.8 (chloroform). Lit [4]: 87-90°; $[\alpha]_D^{20}$ + 11.5 (chloroform). A second fraction was collected on elution from silica gel column with chloroform and ethyl acetate (10:2), on concentration of these fractions gave 12% yield of 5,6-di-O-tosyl-1,3: 2,4-di-O-ethylidene-D-5,6-dideoxy-glucitol (4) m.p. 169-170° $[\alpha]_D^{20}$ - 12.6° (chloroform)

1,3:2,4-Di-O-ethylidene-6-acetyl-thio-6-deoxy-D-glucitol (8)

Freshly crystallized 6-tosylate (7) (4,84 g, 4 mmole) and potassium thioacetate (2.85 g, 25 mmole) in 25 ml of dry acetone were heated under reflux for 6-8 hours. On addition of water to a filtered and concentrated solution, a solid mass was deposited. Recrystallization from ethyl acetate and methanol gave needles of the required product in 61-63% yield which melts at 111-113° $[\alpha]_D^{17}$ -18.5 (chloroform) and λ_{max} 218, 222 nm (ε ,20,550). (Found:C, 49.23; H, 6.89; S, 10.59% Calcd For $C_{12}H_{20}O_6S$: C, 49.30; H, 6.89; S, 10.94%).

1,3:2,4-Di-O-ethylidene-6-mercepto-6-deoxy-D-glucitol (9).

The thiolacetate sugar (8) was hydrolysed under the conventional procedure. The thiol acetate sugar (8) (3.80 g, 1 mmole) was dissolved in 20 ml of 5% methanolic potassium hydroxide solution and left over night under nitrogen at room temperature. The reaction mixture was neutralized with slight excess of 5% hydrochloric acid, keeping in ice. After the removal of methanol under reduced pressure, the thiol sugar (9) was isolated with ether extraction. On evaporation the ether gave (9) as a thick syrup in 56% yield $[\alpha]_D^{18}$ + 12.5° (methanol).

Bis(1,3:2,4-di-O-ethylidene-D-glucitol)6,6'-disulfide (10)

To a solution of 2.66 g of thiol sugar (9) in 20 ml of methanol was added 20 ml of 10% hydrogen peroxide solution, stirred at room temperature for 8 hours. Water was added dropwise until it became turbid, then extracted with dichloromethane several times and washed well with water and dried. On concentration under vacuo gave a syrup of the required disulfide sugar derivative (10) in 62-63% yield. The IR spectra is in conformity with the structure. The light absorption of the $-CH_2-S-S-CH_2-$ group at λ_{max} 230 nm (ϵ ,21, 150). (Found: C, 48.18; H, 6.81; S, 12.72% Calcd for $C_{20}H_{34}O_{10}S_2$: C, 48.18; H, 6.78; S, 12.83%).

Bis(6-deoxy-D-glucitol)6,6'-disulfide (11)

1.0 g of bis (1,3:2,4-di-O-ethylidene-D-glucitol)6,6'-disulfide (10) dissolved in 10 ml of 2N hydrochloric acid and left for 24 hours, the resulting product was monitored on a t.l.c. plate showing the evidence of conversion to required product. It was evaporated under vaccum and the was co-evaporation of the resulting syrup with aqueous ethanol-toluene mixture 2:1 v/v gave a syrup devoid of optical rotation 85% yield. The UV absorption at 226 nm and at 230 nm shoulder bands shows the $-CH_2-S-S-CH_2-$ linkage in the given compound. (Found: C,36.41; H, 6.69; S, 16.18% Calcd for $C_{12}H_{26}O_{10}S_2$: C, 36.54; H, 6.64; S, 16.23%).

Reaction of 1,3:2,4-di-O-ethylidene-6-O-tosyl-6-deoxy-D-glucitol (7) with 1,3:2,4-di-O-ethylidene-6-S-acetyl-6-deoxy-D-glucitol (8) with sodium methoxide

The tosyl compound (7) (700 mg) in 5 ml of chloroform and thioacetate (8) (300 mg) dissolved in 3 ml of chloroform were mixed at O° under nitrogen atomsphere. It was treated with sodium (0.14 g) in 5 ml of dry methanol sodium toluene-p-sulfonate rapidly separated, at first as gel and subsequently in crystalline form. The mixture was kept at room temperature for 7-8 hours then left at O° for overnight. Water (10 ml) was then added, and the chloroform layer separated, the aqueous solution was extracted three times with chloroform. The dried extract was evaporated in vacuo to give (12) as a syrupy product in 34% yield. The IR and UV data are in conformity with the structure.

Bis(1,3:2,4-di-O-ethylidene-D-glucitol 6,6'-sulfide (12)

1,3:2,4-di-O-ethylidene-6-mercepto-6-deoxy-D-glucitol (9) (2.3 g) was dissolved in dry triethylamine

(15 ml) and 1,3:2,4-di-O-ethylidene-6-tosyl-6-deoxy-D-glucitol (7) (4.8 g) was added to the soltuion. The resulting mixture was refluxed for 4-5 hours, during heating two distinct layers were separated. The lower viscous layer was separated and the upper layer was washed with 1N hydrochloric acid then extracted with dichloromethane, finally, the extracts were washed with water. It was dried ($MgSO_4$) and the solvent was evaporated under vacuo gave quantitative yield of the required derivative (12). (Found: C, 51.49; H, 7.25; S, 6.71% Calcd for $C_{20}H_{34}O_{10}S$: C, 51.51: H, 7.34; s 6/85%.

Bis(6-deoxy-D-glucitol)6,6'-sulfide (13)

1.0 g of the above compound (12) was dissolved in 10 ml of 2N hydrochloric acid. The reaction mixture was stirred at room temperature for 16 hours under nitrogen atmosphere and the resulting product was checked on a t.l.c. plate (methanol-chloroform 8:1 v/v) R_f 0.35 showing complete conversion. Evaporation under reduced pressure gave (13) as a thick syrup (500 mg, 80-83% yield) which as yet resisted to crystallize. IR and UV data are in accordonce with the structure; $[\alpha]_D^{20}$ + 0.02° (methanol).

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