Total Syntheses of Carbohydrates. II. DL-Erythrose and DL-Threose

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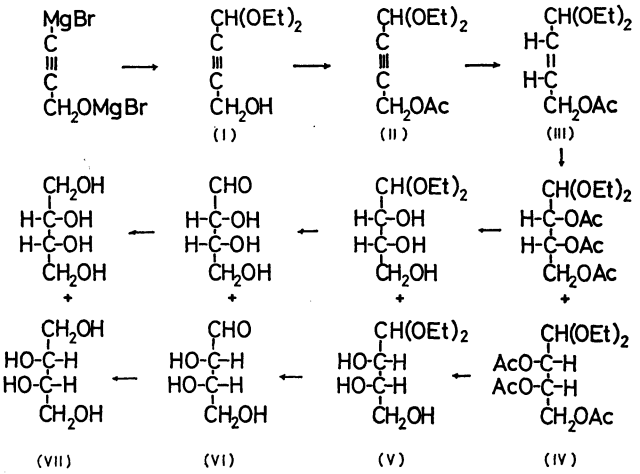
Propargyl alcohol was converted into 4-acetoxy-*cis*-crotonaldehyde diethyl acetal (III) *via* three steps. *cis*-Hydroxylation of III with potassium permanganate followed by acetylation yielded tri-*O*-acetyl-DL-erythrose diethyl acetal (IV). Hydrolysis of IV afforded syrupy DL-erythrose (VI) which could be converted into erythritol (VII) and its dibenzylidene derivative. An acid hydrolysis of III gave 4-acetoxy-crotonaldehyde (VIII) which was converted into triacetyl-DL-threose diethyl acetal (XI) or DL-threose pentaacetate (XII). Hydrolysis of XI and XII gave syrupy DL-threose which could be identified as di-benzylidenethreitol.

The total syntheses of dihydroxyacetone and DL-*glycero*-tetrulose (DL-erythrulose) have been reported.[1] The present paper deals with the total syntheses of DL-etythrose (VII) and DL-threose (XIV). The syntheses were achieved by Glattfeld and Kribben by the Rosenmund reduction of the corresponding aldonic acid chloride derivative which had been derived from allyl alcohol using stereospecific reactions.[2] An excellent total synthesis of DL-threose (XIV) was reported by Schmid and Grob[3] by the *cis*-hydroxylation of *trans*-1,1,4-triacetoxy-2-butene which can be prepared from crotonaldehyde.

cis- and *trans*-Ethylenic compounds have now became readily available from acetylenic precursors by stereoselective half-reduction. Various methods of stereospecific *cis*- and *trans*-hydroxylation of ethylenic bond are also known. A combination of these two seems to offer a new possibility of stereospecific syntheses of carbohydrates.[4] In the present study, propargyl alcohol was used as a starting material.



Scheme 1. Synthesis of DL-erythrose (VII).

The reaction sequence of total synthesis of DL-erythrose (VII) is shown in Scheme 1. *Erythro*-configuration was accomplished by *cis*-hydroxylation of the *cis*-olefinic compound (III) with potassium permanganate. The reaction of ethyl orthoformate with bis-Grignard derivative of propargyl alcohol was carried out according to the reported method[5] with modification to afford C_4-acetal (I). C_4-acetal (I) gave *cis*-olefinic acetoxy-acetal (III) in a high yield by acetylation followed by half-reduction over the Lindlar catalyst.[6] The reduction of C_4-acetal (I) using the same catalyst gave *cis*-olefinic hydroxy-acetal only in a low yield presumably owing to the cleavage of acetal bond.

cis-Hydroxylation of III was carried out in the usual way with aqueous potassium permanganate at temperatures of 0—5°C. Introduction of carbon dioxide into the reaction mixture to neutralize the potassium hydroxide formed during the course of reaction gave no appreciable effect. The crude reaction product was acetylated with acetic anhydride and pyridine. The acetylated product was distilled *in vacuo* to give 2,3,4-tri-*O*-acetyl-DL-erythrose diethyl acetal (IV) in a 28% yeild together with a recovery of III. The results of elemental analysis and IR spectrum were found to be consistent with the assigned structure (IV). Treatment of IV with sodium methoxide in methanol at a low temperature afforded DL-erythrose diethyl acetal (V) as a fairly pure syrup. Syrup V was hydrolyzed with dilute sulfuric acid to yield colorless syrup of DL-erythrose (VI). Paper chromatography of VI thus obtained produced a spot exactly corresponding to

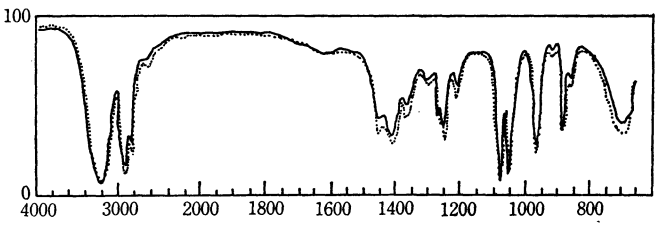


Fig. 1. IR spectra of erythritol. Synthesized material (——); authentic specimen (·····), (KBr-disk).

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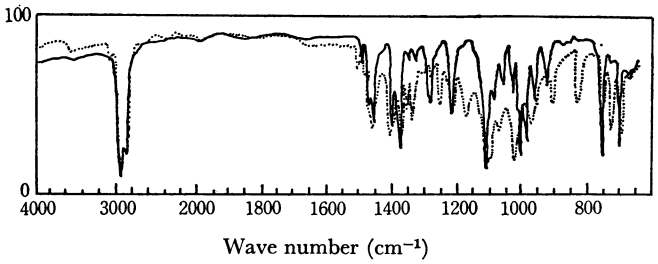
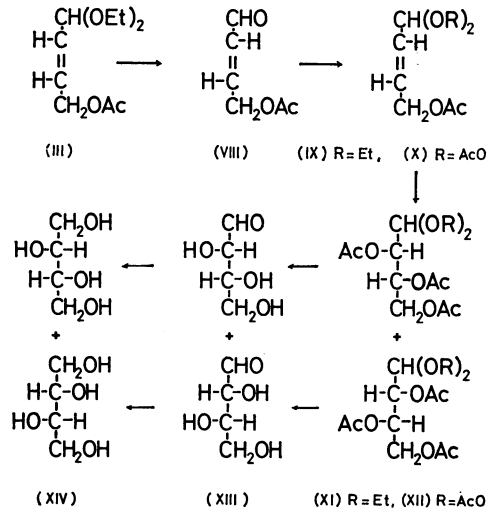


Fig. 2. IR spectra of di-*O*-benzylidene-erythritol (——) and di-*O*-benzylidene-threitol (·····), (KBr-disk).

that of authentic D-erythrose.[7] Hydrogenation of VI over platinum catalyst yielded crystalline erythritol (VII) which gave a superimposable IR spectrum with that of an authentic specimen (Fig. 1). The mixed melting point of VII with an authentic erythritol showed no depression. Di-*O*-benzylidene derivative obtained from VII (mp 201—202°C) showed an identical melting point with the reported value (mp 201—202°C).[8] The IR spectrum of di-*O*-benzylidene erythritol is shown in Fig. 2 toghether with that of threitol derivative.

trans-Hydroxylation of *cis*-ethylenic linkage affords *threo*-configuration. However, all attempts at *trans*-hydroxylation of *cis*-acetoxy acetal (III) with performic, peracetic or perbenzoic acid were unsuccessful. 4-Acetoxy crotonic acid was isolated from the reaction product of performic or peracetic acid oxidation. This indicates that the hydrolysis of acetal bond may occur prior to the epoxidation of the ethylenic linkage. Consequently, an inverse route to *threo*-configuration, *i.e.*, *trans*-hydroxylation of *trans*-olefin, was investigated. Reduction of acetylenic alcohol (I) or its 4-*O*-tetrahydro-2-pyranyl derivative in liquid ammonia with sodium[9,10] and reduction of I with lithium aluminum hydride[11] were found to be infeasible for preparative



Scheme 2. Synthesis of DL-threose (XIV).

purposes owing to the poor yield of *trans*-ethylenic compound. *cis*-Ethylenic acetal (III) was hydrolyzed at room temperature (Scheme 2) with 70% aqueous formic or 50% aqueous acetic acid to give *trans*-ethylenic aldehyde (VIII),[12] which could be converted into *trans*-ethylenic acetal (IX, 64%) by the usual method.[13] *trans*-Ethylenic aldehyde diacetate (X, 71%) was also obtained by the actions of acetic anhydride and sulfuric acid on VIII. *cis*-Hydroxylation of *trans*-ethylenic acetal (IX) was carried out with an aqueous potassium permanganate at a low temperature introducing carbon dioxide into the reaction mixture. The product was acetylated without purification. The resulting acetylated material was distilled *in vacuo* to yield DL-threose derivative (XI, 14%) together with a recovery of IX. DL-Threose derivative (XI) thus prepared was treated successively with sodium methoxide in methanol and sulfuric acid to yeild DL-threose (XIII) as a syrup. The syrupy XIII was reduced over platinum catalyst, and the product was converted into crystalline di-*O*-benzylidene derivative. The benzylidene derivative showed an identical melting point (mp 218—219.5°C) with the reported value of di-*O*-benzylidene-DL-threitol (mp 220.5°C).[3] Di-*O*-benzylidene-erythritol has a much lower melting point than that of threitol derivative, and the IR spectra of these two dibenzylidene derivatives also show the difference seen in Fig. 2. The above results confirm the *threo*-configuration of XIII and XIV.

trans-Ethylenic triacetate (X) prepared by Schmid and Grob[3] from crotonaldehyde diacetate and used as an intermediate of the synthesis of DL-threose could be converted into DL-threose pentaacetate (XII) by their method on treatment with the Milas reagent[14] followed by acetylation. The hydrolysis of XII with sodium methoxide in methanol afforded syrupy DL-threose (XIII) which could be identified as di-*O*-benzylidene derivative of threitol (XIV).

The overall yield of DL-threose (XIII) from propargyl alcohol was found to be *ca.* 3.3% *via* acetal and 2.7% *via* triacetate (X).

Experimental

All the melting points are uncorrected. The IR spectra were obtained on a Hitachi EPI-2 Spectrophotometer.

1,1-Diethoxy-2-butyn-4-ol (I). A solution of propargyl alcohol (39.2 g, 0.7 mol) in tetrahydrofuran (50 m*l*) was added to a solution of ethylmagnesium bromide (prepared from magnesium, 36.5 g, 1.5 g-atom, ethyl bromide, 163.5 g. 1.5 mol and tetrahydrofuran, 400 m*l*) over a period of 1 hr. After the mixture had been refluxed for 3 hr, ethyl orthoformate (104 g, 0.7 mol) was added to the cooled mixture in one portion. The mixture was refluxed for 8 hr under stirring and stood overnight at room temperature. After a part of the solvent (*ca.* 200 m*l*) has been distilled off, the mixture was added to an ice-cooled solution of ammonium

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acetate (200 g) in water (700 ml) and shaken with ether. The emulsion formed was broken by filtering through a layer of celite. The celite layer was washed with ether and the aqueous layer was extracted with the same solvent. The combined extracts and washings were dried (sodium sulfate) and the solvent was removed under reduced pressure. Distillation of the residue *in vacuo* afforded colorless liquid, bp 113—115°C/3 mmHg as main fraction. This material was redistilled to give pure I, 49.5 g (45%), bp 100—102°C/1.5 mmHg, n_D^{25} 1.4491 [lit,[5] bp 118—122°C/9 mmHg, bp 88°C/0.5 mmHg; n_D^{25} 1.4495, IR (neat): 3400 (O–H) cm^{-1}].

Found: C, 60.90; H, 8.97%. Calcd for $C_8H_{14}O_3$: C, 60.73; H, 8.92%.

Diethoxybutynol (I) was found to be unstable and turned pale yellow after several hours at room temperature, but could be kept without decomposition in a tightly stoppered flask in a refrigerator.

4-Acetoxy-1,1-diethoxy-2-butyne (II). A mixture of acetic anhydride (90 ml) and hydroxy acetal (I, 57.9 g, 0.365 mol) was heated to 95—100°C for 2 hr. The residue obtained by evaporation of acetic acid and acetic anhydride under reduced pressure was distilled *in vacuo* to give II as colorless liquid, bp 86—89°C/2.5 mmHg, 62.3 g (85.3%), n_D^{20} 1.4413, IR (neat): 1735, 1235 (CH_3CO_2–) cm^{-1}. An analytical specimen was obtained by redistillation of this material, bp 84°C/2.2 mmHg.

Found: C, 59.98; H, 8.06%. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05%.

II was found to be unstable and turned pale yellow on standing a few hours at room temperature. Acetylation of I with pyridine–acetic anhydride gave II in a low yield (56.2%).

*4-Acetoxy-*cis*-crotonaldehyde Diethyl Acetal (III).* II (20.0 g, 0.1 mol) in benzene (100 ml) was reduced over a Lindlar catalyst[6] (3.5 g) at 16°C. Uptake of 1 mol of hydrogen was observed over a period of 1.5 hr. The catalyst was removed by filtration and the solvent was distilled off under reduced pressure. Distillation of the residue *in vacuo* afforded III as colorless liquid, 19.2 g (96%), bp 91—93°C/4 mmHg, n_D^{20} 1.4318, IR (neat): 1730, 1235 (CH_3CO_2–), 1650 (–CH=CH–) cm^{-1}.

Found: C, 59.42; H, 8.95%. Calcd for $C_{10}H_{18}O_4$: C, 59.38; H, 8.97%.

*2,3,4-Tri-O-acetyl-*DL*-erythrose Diethyl Acetal (IV).* To a vigorously stirred suspension of III (10 g, 0.050 mol) in water (100 ml) was added an aqueous solution (420 ml) of potassium permanganate (7.5 g) over a period of 1.25 hr at 0—5°C. After the addition had been completed, the reaction mixture was warmed to 35°C to coagulate the manganese dioxide formed. The dioxide collected on a sintered glass filter was washed with methanol and water, successively. The washings were combined with the filtrate and concentrated to *ca.* 115 ml under reduced pressure at a temperature below 35°C. The concentrated solution (pH 6.0) was saturated with sodium chloride and repeatedly extracted with ether, and dried (sodium sulfate). The residue obtained by evaporation of the solvent under diminished pressure was mixed with anhydrous methanol and benzene, and the solvent were again removed under reduced pressure. The procedure was repeated twice, giving a syrupy residue (4.6 g, IR (neat): 3450 (O–H) cm^{-1}). The residue was mixed with acetic anhydride (10 ml) and pyridine (10 ml). The mixture was kept at room temperature for 24 hr and then at 40°C for 18 hr. The reaction mixture was concentrated under reduced pressure at a temperature below 30°C. The ice-cooled residue was poured onto ice-water (100 ml) and extracted with ether. The extract was washed successively with 1N hydrochloric acid saturated with sodium chloride, a saturated aqueous solution of sodium hydrogen carbonate and a saturated sodium chloride solution and dried (sodium sulfate). The viscous liquid obtained by evaporation of the solvent under reduced pressure was subjected to high vacuum distillation. Acetoxy-crotonaldehyde diethyl acetal (III) was recovered as a forerun, bp 60°C/10^{-4} mmHg. Triacetyl-erythrose diethyl acetal (IV) was obtained as colorless viscous liquid, bp 94—100°C/10^{-4} mmHg, 4.4 g (28%). The material was redistilled to give pure IV, bp 97—98°C/10^{-4} mmHg, n_D^{20} 1.4327.

Found: C, 52.57; H, 7.53%. Calcd for $C_{14}H_{24}O_8$: C, 52.49; H, 7.55%.

DL*-Erythrose Diethyl Acetal (V).* A solution of IV (2.4 g) in anhydrous methanol (15 ml) was chilled to −13°C and mixed with 0.10N solution of sodium methoxide in methanol (10.0 ml) which had been cooled to the same temperature. After the mixture had been kept at −20°C for 24 hr, it was exactly neutralized with 1N sulfuric acid. The mixture was concentrated under reduced pressure at 20—25°C. The residue containing crystals of sodium sulfate and sodium acetate was extracted with anhydrous ethanol (10 ml). The extract was evaporated again under reduced pressure. The procedure was repeated twice, yielding DL-erythrose diethyl acetal (V) as colorless syrup, IR (neat): 3420 (O–H) cm^{-1}. An analytical specimen was prepared on standing a small portion of the syrup in a highly evacuated desiccator containing phosphorus pentoxide.

Found: C, 49.31; H, 9.22%. Calcd for $C_8H_{18}O_5$: C, 49.47; H, 9.34%.

All attempts to crystallize V failed.

DL*-Erythrose (VI).* The syrupy diethyl acetal (IV) was dissolved in 1N sulfuric acid (20 ml) and the solution was left standing for 5 days at room temperature. After the solution had been neutralized with 1N sodium hydroxide solution, water was removed under reduced pressure at a temperature below 20°C. Anhydrous methanol was added to the residue and the sodium sulfate deposited was removed by filtration. The filtrate was evaporated *in vacuo*, and the residue was extracted with the same solvent. Evaporation of the solvent *in vacuo* gave colorless syrup, 2.5 g (95%). A small portion of the syrup was dried in a highly evacuated desiccator over phosphorus pentoxide and subjected to elemental analysis.

Found: C, 40.91; H, 6.80%. Calcd for $C_4H_8O_4$: C, 40.00; H, 6.71%.

The syrup reduced Fehling's solution at room temperature. Descending paper chromatography (Filter paper: Toyo Roshi No. 51; solvent system: (A) upper layer of *n*-butyl alcohol–benzene–pyridine–water (5:1:3:3) or (B) methyl ethyl ketone saturated with water; detection reagent: anilinium oxalate) of the syrup gave a spot (R_f 0.51 (A); R_f 0.85 (B)). An authentic D-erythrose prepared by the method of Perlin and Brice[7] gave a spot at the same R_f-value (R_f 0.51 (A); R_f 0.85 (B))

Syrupy DL-erythrose (VI, 0.3 g) dissolved in a small amount of water was mixed with a solution of phenylhydrazine (1.5 g) in 50% aqueous acetic acid. The mixture was placed on a water-bath kept at 50°C for 1 hr. The yellow crystalline mass deposited was recrystallized once from water and then twice from benzene to give pure osazone, mp 166—167°C (decomp.) [lit,[2c] mp 166—167°C (decomp.)].

Found: C, 64.50; H, 6.10; N, 18.29%. Cacld for $C_{16}H_{18}O_2N_4$: C, 64.41; H, 6.08; N, 18.78%.

Erythritol and Di-O-benzylidene-erythritol. Syrupy DL-erythrose (VI, 0.41 g) in methanol was reduced over platinum catalyst (prepared from platinum oxide, 25 mg) at 100°C for 2 hr (initial pressure of hydrogen: 44 atm.). The catalyst was removed by filtration and the filtrate was evaporated

under diminished pressure to give colorless crystals, 0.39 g. The crystals were recrystallized twice from a small amount of methanol to yield pure erythritol, mp 116.5—118.5°C, which showed no depression of melting point on admixture with an authentic specimen of erythritol, mp 117—118°C.

Found: C, 39.24; H, 8.22%. Calcd for $C_4H_{10}O_4$: C, 39.34; H, 8.25%.

Erythritol thus obtained was converted into di-*O*-benzylidene-erythritol according to the method of Fischer.[8] The benzylidene derivative showed melting point identical with that of reported value, mp 201—202°C [lit,[8] 201—202°C].

4-Acetoxy-crotonaldehyde (VIII). Acetoxy-*cis*-ethylenic acetal (III, 3.8 g) dissolved in a mixture of formic acid (5 m*l*) and water (2 m*l*) was kept at room temperature for 24 hr. Benzene was added to the residue obtained by evaporation of the mixture and benzene was again removed under reduced pressure. The residue was distilled *in vacuo* to give colorless liquid, bp 54—57°C/1 mmHg. Redistillation of this substance afforded pure 4-acetoxy-crotonaldehyde (VIII) as colorless liquid, 1.4 g (60%), bp 73—76°C/3 mmHg, n_D^{20} 1.4518, IR (neat): 1730, 1225 (CH_3CO_2–), 1680, 2760 (–CHO), 1640, 960 (*trans* –CH=CH–) cm^{-1}.

Found: C, 56.39; H, 6.89%. Calcd for $C_6H_8O_3$: C, 56.24; H, 6.29%.

2,4-Dinitrophenylhydrazone: mp 158—161°C (decomp.) (from ethanol).

Found: C, 46.28; H, 3.98; N, 18.04%. Calcd for $C_{12}H_{12}O_6N_4$: C, 46.76; H, 3.92; N, 18.18%.

4-Acetoxy-crotonaldehyde Diethyl Acetal (IX). Ethyl orthoformate (2.7 g, 0.02 mol) and ammonium nitrate (0.1 g) were added to a solution of *trans*-aldehyde (VIII, 2.65 g, 0.02 mol) in anhydrous ethanol (10 m*l*). The mixture was heated to 100°C and ethyl formate and ethanol were gradually distilled off through a Widmer column. Distillation of the residue *in vacuo* afforded colorless liquid, 1.55 g (37.2%), bp 77—80°C/1.5 mmHg. This material was redistilled to give pure IX, bp 74—75°C/1 mmHg, n_D^{20} 1.4328, IR (neat): 1765, 1230 (CH_3CO_2–), 1650, 950 (*trans* –CH=CH–) cm^{-1}.

Found: C, 59.10; H, 8.93%. Calcd for $C_{10}H_{18}O_4$: C, 59.38; H, 8.97%.

IX could be obtained in a much higher yield without isolation of VIII. After a solution of *cis*-acetal (III, 11.0 g, 0.055 mol) in 50% aqueous acetic acid (20 m*l*) had been kept at 40°C for 48 hr, the solvent was removed under reduced pressure. The residue was mixed with benzene and the solvent was again distilled off *in vacuo*. This procedure was repeated twice. Acetalization of the residue according to the above method yielded IX, 7.0 g (63.6%).

2,3,4-Tri-O-*acetyl*-DL-*threose Diethyl Acetal (XI).* An aqueous solution of potassium permanganate (6.65 g in 220 m*l* of water) was added dropwise to a vigorously stirred suspension of *trans*-acetal (IX, 9.4 g, 0.047 mol) in water (60 m*l*) over a period of 70 min. The mixture was kept at 0°C and carbon dioxide was continuously introduced into the mixture. The reaction mixture was worked up according to the method used for the preparation of tri-*O*-acetyl-erythrose diethyl acetal (IV). The crude acetoxy-dihydroxy-acetal (5.7 g) thus obtained was mixed with pyridine (12 m*l*) and acetic anhydride (12 m*l*). The mixture was allowed to stand at room temperature for 27 hr and then at 35°C for 21 hr. Deep brown liquid obtained by concentration of the mixture under reduced pressure was dissolved in ether. The ice-cooled ether solution was poured onto ice-water (100 m*l*). The mixture was saturated with sodium chloride and repeatedly extracted with ether. The extract was washed twice with 1N hydrochloric acid saturated with sodium chloride, once with a saturated sodium hydrogen carbonate solution and water and then dried (sodium sulfate). The residue obtained by evaporation of the solvent gave on a vacuum distillation a forerun (recovered IX, bp 60—70°C/6×10^{-4} mmHg, 3.2 g) and XI, colorless syrup, 1.4 g (14% based on consumed IX), n_D^{25} 1.4368.

4-Acetoxy-crotonaldehyde Diacetate (X). A solution of *cis*-ethylenic acetal (III, 15.8 g, 0.077 mol) in 50% aqueous acetic acid was kept at 40°C for 48 hr. The residue obtained by evaporation of the solvent under reduced pressure was mixed with acetic anhydride (30 m*l*). A few drops of concentrated sulfuric acid was added to the mixture under cooling with water. After the mixture had been kept at room temperature for 20 hr, powdered sodium acetate (0.6 g) was added and distilled to yield X as colorless viscous liquid, 12.6 g (71%), bp 122—124°C/1.8 mmHg [lit,[3] bp 102—104°C/1×10^{-2} mmHg], n_D^{20} 1.4414.

Found: C, 52.43; H, 6.41%. Calcd for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13%.

DL-*Threose Pentaacetate (XII).* Acetoxy-crotonaldehyde diacetate (X, 4.4 g, 0.02 mol) was treated with Milas' reagent[14] according to the reported method.[3] Acetylation of the reaction product (IR: 3400 (O–H) cm^{-1}) by means of acetic anhydride (12 m*l*) and pyridine (12 m*l*) yielded XII as colorless liquid, 0.7 g (11%), bp 92—100°C/1×10^{-4} mmHg [lit,[3] bp 115—122°C/5×10^{-3} mmHg].

Found: C, 49.05; H, 5.90%. Calcd for $C_{14}H_{20}O_{10}$: C, 48.27; H, 5.79%.

DL-*Threose (XIII).* *a) By Hydrolysis of 2,3,4-Tri*-O-*acetyl*-DL-*threose Diethyl Acetal (XI)*: Hydrolysis of XI (14 g) according to the method used for triacetyl-DL-erythrose diethyl acetal (IV) afforded DL-threose (XIII) as light brown syrup (0.5 g). The syrup reduced cold Fehling's solution. The crude XIII was subjected to the reduction without purification.

b) By Hydrolysis of DL-*Threose Pentaacetate (XII)*: DL-Threose pentaacetate (0.7 g) in anhydrous methanol (30 m*l*) was mixed with 2% solution of sodium methoxide in anhydrous methanol (10 m*l*) at −10°C. The mixture was kept at the same temperature for 24 hr, and then was neutralized with 1N sulfuric acid. Sodium sulfate deposited was removed by filtration. The filtrate was concentrated under reduced pressure. The residue was mixed with anhydrous methanol and the sulfate was again removed. Concentration of the filtrate *in vacuo* afforded DL-threose (XIII) as a light brown syrup (0.2 g). The syrup reduced Fehling's solution at room temperature.

Di-O-*benzylidene-threitol.* *a) From* DL-*Threose Obtained from XI*: Syrupy DL-threose (XIII) obtained from XI in 75% aqueous ethanol was reduced over platinum catalyst (initial pressure: 70 atm; 100°C; 3 hr). The reduction product worked up according to the procedure employed in the preparation of erythritol (VII) gave threitol (XIV, 0.25 g) as a syrup. The syrup was mixed with benzaldehyde (0.75 m*l*) and hydrochloric acid (0.9 m*l*). After the mixture was kept at room temperature for 1 hr, it was extracted with chloroform. The extract was washed successively with a sodium hydrogen carbonate solution and water and dried. The residue obtained by evaporation of the solvent was dissolved in hot ethanol and treated with active charcoal to yield di-benzylidene-threitol as colorless needles, 200 mg, mp 218—219.5°C [lit,[3] 220.5°C], IR: *Cf.*, Fig. 2.

Found: C, 72.78; H, 6.12%. Calcd for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08%.

b) From DL-*Threose Obtained from XII*: Crude DL-threose (XIII) obtained by the hydrolysis of XII was reduced according to the procedure for the preparation of VII. The light brown syrupy threitol (XIV) obtained was converted into

di-benzylidene-threitol, colorless needles, mp 218—219°C. This material showed no depression of melting point on admixture with di-benzylidene-threitol derived from XI. The IR spectrum was found to be superimposable with that of the benzylidene derivative obtained from XI.

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