PREPARATION AND CHARACTERIZATION OF THE 6-ALDEHYDO DERIVATIVES OF AMYLOSE AND WHOLE STARCH*†

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ABSTRACT

The 6-aldehydo derivatives (**5**) of amylose (**1**) and whole starch have been prepared by photolysis of the corresponding 6-azido-6-deoxy derivatives (**4**). The 6-aldehydo derivatives (**5**) were characterized by formation of the (2,4-dinitrophenyl)-hydrazones (**6**) and by reduction with sodium borodeuteride followed by hydrolysis, acetonation, and examination of the resulting 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose-*6-d* (**7**) by mass spectrometry. 6-Aldehydo-amylose (**5**) was further characterized by hydrolysis, and identification of the liberated D-*gluco*-hexodialdose by conversion into the crystalline tetra-*O*-acetyl-D-*gluco*-hexodialdose tetraethyl bis(dithioacetal) (**11**).

INTRODUCTION

The photolysis of primary azides ($R-CH_2N_3$) in sugar systems provides an excellent synthetic route for a wide range of ω-aldehydo derivatives of protected and unprotected glycosides[2-4]. It was considered that an extension of this reaction to the analogous derivatives of such polysaccharides as amylose, starch, and cellulose would provide a good position-specific method for the introduction of aldehyde functionality.

RESULTS AND DISCUSSION

A slightly derivatized amylose (**1**) was *p*-toluenesulfonylated under reaction conditions[5,6] expected to lead to a maximum substitution of primary hydroxyl groups, minimum substitution of secondary ones, and low incorporation of chlorine. The extent of *p*-toluenesulfonylation of primary and secondary hydroxyl groups was determined by the iodination method[7], and the degrees of substitution (d.s.) of the amylose and starch derivatives were computed by the method of Horton and Pardoe[8].

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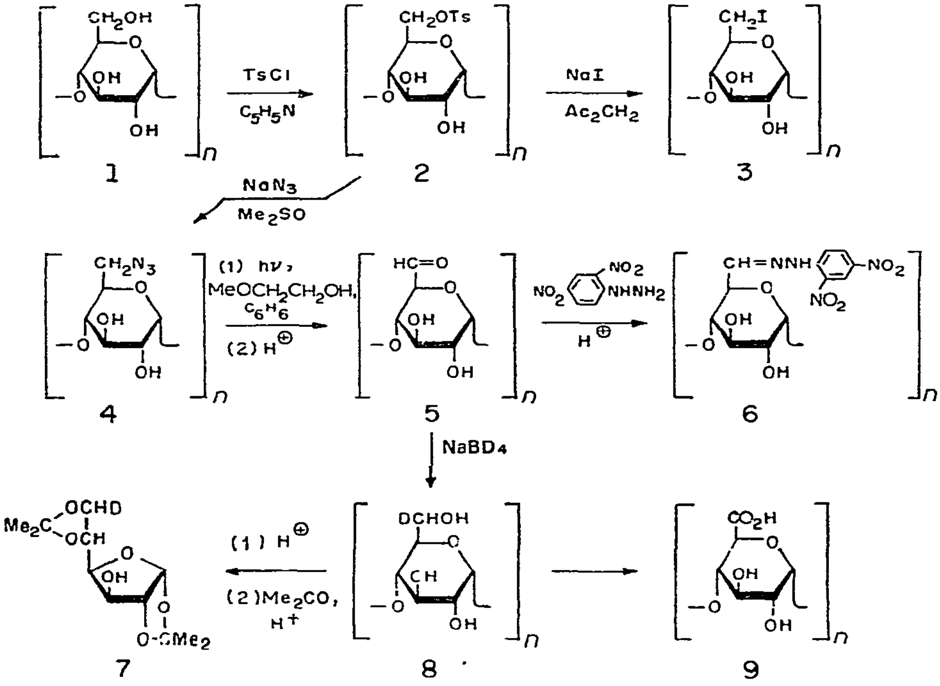
Treatment of the 6-*O*-*p*-tolylsulfonyl derivative (**2**) with sodium azide in methyl sulfoxide led to sulfonate displacement and gave 6-azido-6-deoxyamylose (**4**) of d.s. 0.62.

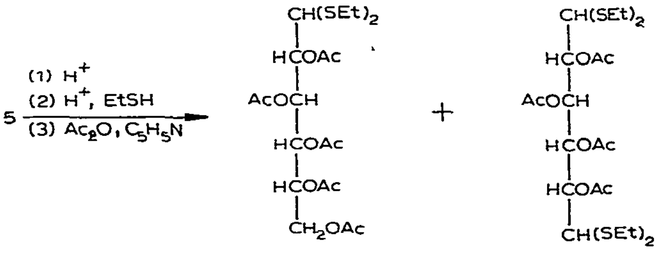
The photolysis of a primary azide to give an aldehyde is presumed to proceed via an intermediate nitrene ($R\text{–}CH_2N\text{:}$) which rearranges by a 1,2-hydrogen migration to give the "imine" isolated from the reaction[9–11]. Very mild, acid hydrolysis of this imine should lead to the expected aldehyde. Photolysis of **4**, followed by mild hydrolysis with acid, gave 6-aldehydo-amylose (**5**), which gave a positive Fehling test and contained no nitrogen. Decomposition of the azide and of the subsequent "imine" intermediate[4] was thus complete.



In order to calculate the extent (d.s.) to which aldehyde groups had been incorporated in the polymer, two methods were employed. A (2,4-dinitrophenyl)hydrazone derivative (**6**) was prepared, and the d.s. (0.5) was calculated from the nitrogen analysis. A more reliable method, however, consisted in reduction of the 6-aldehyde derivative (**5**) with sodium borodeuteride, hydrolysis of the resulting 6-deuterio-amylose (**8**), and preparation therefrom of a derivative suitable for mass spectrometry. The ratio of the peak areas for the deuterated and nondeuterated derivative (after correction for the natural abundance of ^{13}C, ^{2}H, and ^{17}O) was then expected to give the percentage of deuterated material in the mixture, and thence in the parent polymer. 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose was chosen as the derivative, because the fragmentation pattern contains[12] several readily identifiable peaks.

Examination by mass spectrometry of the crystalline 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose-*6-d* (7), obtained by acetonation of the acid-hydrolyzed 6-deuterio-amylose (8), showed ions having *m/e* 245, 187, and 101, known[12] to contain the C-6 moiety in the nondeuterated material, accompanied by peaks of approximately the same intensity but one mass unit higher (*m/e* 246, 188, and 102). From the ratio of the peak areas for the deuterated and nondeuterated fragments just described, the d.s. by isotopic replacement in the polymer **8** was calculated to be 0.48 ±0.01 (see Table I-A). This sequence of reactions starting from the photolysis of azide **4** was repeated, and the crude product of the acetonation, without further purification, was examined by mass spectrometry. The d.s. by isotopic replacement in the polymer **8** was calculated to be 0.48 ±0.01 (see Table I-B), in good agreement with the result for the purified derivative.

Complete hydrolysis of 6-aldehydo-amylose (**5**) with acid gave a product that, by t.l.c., showed two components. The slower-moving component corresponded in mobility to a glucose. Treatment of this mixture with ethanethiol, followed by acetylation, gave a product that again showed two components by t.l.c. Separation of this mixture by column chromatography gave two crystalline compounds. One was indistinguishable from an authentic sample of penta-*O*-acetyl-D-glucose diethyl dithioacetal (**10**), and the other was identified as tetra-*O*-acetyl-D-*gluco*-hexodialdose tetraethyl bis(dithioacetal) (**11**). Hydrolysis of 6-aldehydo-amylose of d.s 0.5 had thus given a mixture of D-glucose and D-*gluco*-hexodialdose. This result provides a classical characterization of the monosaccharide residues in the 6-aldehydo-amylose (**5**).



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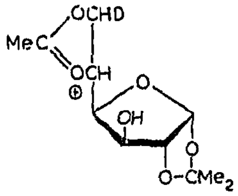
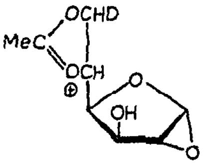
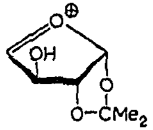
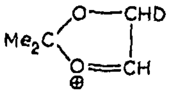
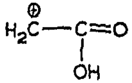
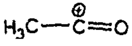
Corn starch was *p*-toluenesulfonylated as described for amylose, and the extent of substitution on primary and secondary hydroxyl groups was again determined by the iodination method. Treatment of the 6-*O*-*p*-tolylsulfonylstarch with sodium azide in methyl sulfoxide gave 6-azido-6-deoxystarch (d.s. 0.92) in good yield. Photolysis of this material, followed by mild hydrolysis, gave 6-aldehydo-starch, which, as for **5**, was characterized by formation of a (2,4-dinitrophenyl)hydrazone derivative (d.s. 0.6) and by reduction with sodium borodeuteride, hydrolysis, acetonation, and examination of the resulting 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose-*6-d* by mass spectrometry (see Table I). The results given by both methods for calculating the d.s. by aldehyde in the starch derivative were in good agreement, the mass-spectral method giving d.s. 0.57.

TABLE I

MASS-SPECTRAL DATA FOR 1,2:5,6-DI-*O*-ISOPROPYLIDENE-α-D-GLUCOFURANOSE-6-*d*

m/e	*Fragment*	*Relative abundances*			*Abundance of natural isotopes* $(^2H+^{13}C+^{17}O)$,%	*Corrected relative abundances*			*Deuterated compound in mixture, %*			*Calc. d.s. by aldehyde in parent polymer*		
		From amylose[a]		*From starch*		*From amylose*[a]		*From starch*	*From amylose*[a]		*From starch*	*From amylose*[a]		*From starch*
		A	*B*			*A*	*B*		*A*	*B*		*A*	*B*	
246		1.3	1.7	1.0	12.69	1.15	1.48	0.911						
245		1.2	1.6	0.7	12.69	1.20	1.60	0.700	48.9	48.1	56.5	0.49	0.48	0.57
188		0.7	0.7	0.55	9.23	0.635	0.635	0.513						
187		0.7	0.7	0.40	9.23	0.700	0.700	0.400	47.6	47.6	56.2	0.48	0.48	0.56
159		0.4	0.5	0.25										
102		3.5	4.2	2.5	5.76	3.29	3.96	2.38						
101		3.6	4.2	2.1	5.76	3.60	4.20	2.10	47.7	48.5	53.1	0.48	0.49	0.53
59	 $H_2\overset{\oplus}{C}-\underset{OH}{\underset{\vert}{C}}=O$	6.8	8.7	5.5										
43	 $H_3C-\overset{\oplus}{C}=O$	10	10	10										

The foregoing reactions, which may be performed at various levels of d.s., provide a convenient route for the preparation of the 6-aldehydo derivatives of natural polymers, including linear ones, such as amylose and cellulose[13], and such branched glycans as amylopectin (and whole starch). They also proffer a simple and convenient route, by mild oxidation, to the glycuronans (9). Moreover these products (5) are of potential value for studies on the substrate specificity of glycan hydrolases, and they also open up the possibility of increased use of starches and cellulosic materials as industrial polymers by application of various crosslinking procedures to the aldehyde groups on the chain in 5 and its relatives. The borodeuteride reduction–mass spectrometry procedure, with the use of 7 and other derivatives whose mass-spectral fragmentations are known, provides a general method for determining on a microscale the position and extent of carbonyl-group incorporation in specifically or nonspecifically oxidized polysaccharides.

EXPERIMENTAL

General. — Melting points were determined with a Thomas–Hoover Unimelt apparatus and are uncorrected. Specific rotations were measured in 1-dm tubes with a Perkin–Elmer Model 141 polarimeter. Infrared spectra were recorded with a Perkin–Elmer Model 137 i.r. spectrometer. Mass spectra were recorded with an A.E.I. MS-9 double-focusing, high-resolution spectrometer with an accelerating potential of 8 KV, an ionizing potential of 70 eV, and a source temperature of 250°. Elemental analyses were performed by W. N. Rond. X-Ray powder diffraction data give interplanar spacings, Å, for CuKα radiation. Relative intensities were estimated visually: m, moderate; s, strong; w, weak. The strongest lines are numbered (1, strongest). The camera diameter was 114.59 mm. T.l.c. was performed on Silica Gel G (E. Merck, Darmstadt, Germany) activated at 110°, and indication was effected with sulfuric acid. Column chromatography was performed with Silica Gel 7734 (70–325 mesh ASTM, E. Merck).

Irradiations were conducted with unfiltered light from a 450-w Hanovia Type L mercury-arc lamp Model 679A (Hanovia Lamp Division, Engelhard Inc., Newark, N. J.) having a 4.5-in. arc. The lamp was placed in a water-cooled, quartz immersion-well (Hanovia Model 19431), and the whole assembly was mounted in a Pyrex reaction-vessel. The most suitable irradiation-time was obtained by periodic sampling and examination by i.r. spectroscopy.

6-O-p-Tolylsulfonylamylose[5,6] (2). — Slightly derivatized amylose (1) [Superlose, HAA-11-HV, Stein, Hall and Co., Inc., New York; a very low-d.s. *O*-(hydroxyethyl)amylose of better solubility properties than pure amylose; 13 g] was dissolved in 90% aqueous pyridine (325 ml) and the water was removed by repeated evaporation of anhydrous pyridine from the amylose until the distillate no longer became turbid when benzoyl chloride was added. To the resulting solution, *p*-toluenesulfonyl chloride (18.2 g, 1.2 equiv.) dissolved in anhydrous pyridine (50 ml) was added, and the mixture was stirred for 30 min at 35°. Water (~2 ml) was then added, and the mixture was poured into 4:1 methanol–water (2.5 liters). The gummy solid formed was dispersed in water in a blender, and the solid product was filtered off, washed with water, and dried, to give a white powder; yield 17.2 g (83%).

Anal. Calc. for $[C_6H_{9.22}O_{4.22}Cl_{0.18}\ (OSO_2C_7H_7)_{0.6}]_n$: C, 47.49; H, 5.24; Cl, 2.48; S, 7.46. Found: C, 47.48; H, 5.41; Cl, 2.81; S, 7.38.

6-Deoxy-6-iodo-amylose[5] (3). — Sodium iodide (0.7 g) was added to a suspension of (2) (0.3 g) in 2,4-pentanedione (25 ml), and the mixture was stirred vigorously under a reflux condenser for 2 h at 120°. The mixture was then poured into an excess of water (500 ml), and the white precipitate formed was filtered off, successively washed well with water, 20mM sodium thiosulfate solution, and water, and dried; yield 0.2 g (67%).

Anal. Calc. for $[C_6H_{9.2}O_{4.2}I_{0.62}(OSO_2C_7H_7)_{0.18}]_n$: C, 33.78; H, 4.09; I, 30.51; S, 2.24. Found: C, 33.97; H, 4.31; I, 30.57; S, 2.42.

6-Azido-6-deoxyamylose (4). — To a solution of **2** (15 g) in methyl sulfoxide (450 ml) was added sodium azide (45 g), and the mixture was stirred for 70 h at 80°, and then poured into water (3 liters). The light-brown solid formed was filtered off, the gummy solid obtained was dissolved in methyl sulfoxide, and the solution was dialyzed against running water for 24 h. The nondialyzable portion was freeze-dried, and the residue was further dried to give a light-brown powder; yield 7.8 g (72%), λ_{max}^{KBr} 4.74 μm (N_3).

Anal. Calc. for $[C_6H_{9.26}O_{4.26}Cl_{0.06}(OSO_2C_7H_7)_{0.05}(N_3)_{0.63}]_n$: C, 40.84; H, 5.19; Cl, 1.14; N, 14.18; S, 0.89. Found: C, 40.39; H, 5.66; Cl, 1.19; N, 13.94; S, 1.07.

*6-*O-p-*Tolylsulfonylstarch.* — Corn starch (10 g) (furnished by the Northern Regional Research Laboratory, U. S. Department of Agriculture, Peoria, Illinois), which had previously been dried for 30 h at 100° under high vacuum, was stirred with 90% aqueous pyridine (250 ml) for 16 h at room temperature. The water was then removed by repeated addition of anhydrous pyridine to, and evaporation from, the starch. *p*-Toluenesulfonyl chloride (35 g, 3 equiv.) was added to the resulting suspension, and the mixture was heated for 2 h at 60°. Water was then added to the mixture and, after 10 min, the clear solution was poured into 4:1 methanol–water (2.5 liters). The liquid was decanted from the syrupy product, water was added, and the solid that formed was filtered off and dried to give a white powder; yield 17 g (92%).

Anal. Calc. for $[C_6H_{8.96}O_{3.96}Cl_{0.18}(OSO_2C_7H_7)_{0.86}]_n$: C, 48.43; H, 5.07; Cl, 2.14; S, 9.25. Found: C, 48.78; H, 5.18; Cl, 2.32; S, 9.05.

6-Deoxy-6-iodostarch was prepared from 6-*O*-*p*-tolylsulfonylstarch by the method previously described for the amylose derivative.

Anal. Calc. for $[C_6H_{8.84}O_{3.84}I_{0.82}(OSO_2C_7H_7)_{0.34}]_n$: C, 33.02; H, 3.71; I, 34.17; S, 3.58. Found: C, 33.99; H, 4.69; I, 35.04; S, 3.28.

6-Azido-6-deoxystarch. — 6-*O*-*p*-Tolylsulfonylstarch (10 g) was treated with sodium azide under the conditions used for the amylose derivative, and 6-azido-6-deoxystarch was isolated as a light-brown powder; yield 5.3 g (79%), λ_{max}^{KBr} 4.73 μm (N_3).

Anal. Calc. for $[C_6H_{8.96}O_{3.96}(OSO_2C_7H_7)_{0.12}(N_3)_{0.92}]_n$: C, 40.34; H, 4.85; N, 18.99; S, 1.89. Found: C, 40.27; H, 5.18; N, 19.00; S, 1.85.

Photolysis of the 6-azido derivatives (**4**). — The 6-azido derivative (**4**, 0.5 g) of amylose or starch was dissolved in 5:1 2-methoxyethanol–benzene (180 ml) and photolyzed under nitrogen for 6 h at 20° with unfiltered light from a mercury arc[14]. The resulting suspension was concentrated under diminished pressure to ~50 ml, and M hydrochloric acid (50 ml) was added. The mixture was stirred for 75 min at room temperature and then dialyzed for 16 h against running water. The nondialyzable portion was freeze-dried to give the aldehydo derivative (**5**) as a light-brown, fluffy solid. Both products showed no azide absorption in their i.r. spectra, and gave positive Fehling tests. 6-Aldehydo-amylose was free from nitrogen, but some nitrogen remained in the 6-aldehydo-starch (Found: N, 2.34).

The (2,4-dinitrophenyl)hydrazone derivatives (**6**) of the foregoing products were prepared by treating the aldehydes (**5**, 50 mg) in 2-methoxyethanol (10 ml) with (2,4-dinitrophenyl)hydrazine (75 mg) in 2-methoxyethanol (10 ml) and M hydrochloric acid (3 ml). The mixture was stirred for 24 h at room temperature, and then dialyzed for 72 h against running water. The nondialyzable portion was freeze-dried to give the (2,4-dinitrophenyl)hydrazones (**6**) as orange solids. T.l.c. (4:1 dichloromethane–ethyl acetate) did not show a component corresponding to (2,4-dinitrophenyl)hydrazine.

Anal. (Amylose derivative) Calc. for $[C_{5.5}H_9O_{4.5}(C{=}NNHC_6H_3(NO_2)_2)_{0.5}]_n$: N, 11.15. Found: N, 11.12.

Anal. (Starch derivative) Calc. for $[C_{5.3}H_{8.6}O_{4.3}(C{=}NNHC_6H_3(NO_2)_2)_{0.6}(CHOSO_2C_7H_7)_{0.1}]_n$: N, 11.82; S, 1.12. Found: N, 11.26; S, 1.00.

Reduction of the 6-aldehydo derivatives (**5**). — A solution of sodium borodeuteride (200 mg) in water (30 ml) was added to a suspension of the 6-aldehydo derivative (**5**, 0.4 g) of amylose or starch in water (30 ml), and the mixture was stirred for 16 h at room temperature. More sodium borodeuteride (200 mg) was added, and the mixture was stirred for a further 7 h at room temperature. The mixture was then dialyzed for 72 h against running water, and the nondialyzable portion was freeze-dried to give the 6-deuterio derivatives (**8**) of amylose and starch, respectively, as light-brown, fluffy solids that gave negative Fehling tests.

*1,2:5,6-Di-*O*-isopropylidene-α-*D*-glucofuranose*-6-d (**7**). — The 6-deuterio derivative (**8**, 200 mg) of either amylose or starch was stirred with 0.5M sulfuric acid (20 ml) for 20 h at 110°, and the resulting suspension was made neutral with barium carbonate. The mixture was filtered through Celite, and the filtrate was evaporated under diminished pressure to a solid. T.l.c. (1:1 ethyl acetate–ethanol) showed one main component, corresponding to a glucose. To the above material was added acetone (20 ml), concentrated sulfuric acid (0.05 ml), and anhydrous cupric sulfate (0.5 g). The mixture was shaken for 20 h at room temperature and then made neutral by the addition of lead carbonate and water. The mixture was filtered, and the filtrate was evaporated under diminished pressure to a syrup. The syrup was partitioned between dichloromethane and water, and the organic layer was separated, dried (magnesium sulfate), and evaporated under diminished pressure to a syrup that crystallized on being kept. T.l.c. (3:2 dichloromethane–ethyl acetate) showed a single component corresponding to a reference sample of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose. The product was then placed on a column of silica gel (5 g) and eluted with 9:1 dichloromethane–ethyl acetate, with collection of 5-ml fractions. The fractions were examined by t.l.c. (3:2 dichloromethane–ethyl acetate) and fractions 12–18, containing the component corresponding to 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, were combined and evaporated under diminished pressure to a syrup that crystallized spontaneously. Mass-spectral data for the crystalline products are shown in Table I.

A second hydrolysis experiment was performed on the 6-deuterio-amylose, and the mass spectrum of the acetonated product was recorded (see Table I) without further purification on silica gel.

Acid hydrolysis of 6-aldehydo-amylose (**5**), *and characterization of component residues as penta-*O*-acetyl-*D*-glucose diethyl dithioacetal* (**10**) *and tetra-*O*-acetyl-*D-gluco*-hexodialdose tetraethyl bis(dithioacetal)* (**11**). — A suspension of 6-aldehydo-amylose (**5**, 1.4 g) in 0.5M sulfuric acid (210 ml) was heated for 17 h on a steam bath. The dark suspension was neutralized with barium carbonate, filtered through Celite, and the filtrate evaporated under diminished pressure to give a solid (0.73 g). T.l.c. (1:1 ethyl acetate–ethanol) showed two main components, having R_F 0.62 and 0.81. The component having R_F 0.62 corresponded to a glucose. The solid was placed on a charcoal column (2×28 cm), which was eluted with 0.3% isopropyl alcohol in water, with collection of 75-ml fractions. Fractions 2–11 were combined, and evaporated under diminished pressure to a solid (0.55 g). T.l.c. (1:1 ethyl acetate–ethanol) showed two components, having R_F 0.62 and 0.81.

Ethanethiol (1 ml) was added to a solution of the product (0.55 g) in concentrated hydrochloric acid (1 ml), and the mixture was shaken for ~5 min, kept for 30 min at 0°, and then made neutral with solid sodium hydrogen carbonate. The mixture was evaporated under diminished pressure to a solid, and the last traces of water were removed by evaporation of benzene from the residue. The resulting solid was treated with anhydrous pyridine (15 ml) and acetic anhydride (15 ml), and the mixture was kept for 16 h at room temperature, poured into ice–water, and the product extracted with dichloromethane. The extract was washed successively with aqueous sodium hydrogen carbonate solution and water, dried (magnesium sulfate), and evaporated under diminished pressure. The pyridine was removed by evaporation of toluene from the residue; yield 1.08 g. T.l.c. (9:1 dichloromethane–ethyl acetate) of the resulting syrup showed two main components, having R_F 0.53 and 0.84, the former migrating with the characteristics of penta-*O*-acetyl-D-glucose diethyl dithioacetal; in this solvent system, penta-*O*-acetyl-α-D-glucopyranose has R_F 0.41. The syrup was placed on a column of silica gel (50 g) and eluted with 19:1 dichloromethane–ethyl acetate, with collection of 25-ml fractions. The fractions were examined by t.l.c. (9:1 dichloromethane–ethyl acetate). Fractions 8–14 contained the component having R_F 0.84; they were combined, and evaporated under diminished pressure to give a syrup (*A*, 0.23 g) that crystallized spontaneously. Fractions 16–23, containing the component having R_F 0.53, were combined and evaporated under diminished pressure to give a syrup (0.49 g) that also crystallized. Recrystallization from aqueous methanol gave pure penta-*O*-acetyl-D-glucose diethyl dithioacetal (**10**); yield 0.34 g, m.p. 45–47°, mixed m.p. 45–47°, $[\alpha]_D^{20}$ $+10.6°$ (*c* 4, chloroform); lit.[15] m.p. 45–47°, $[\alpha]_D^{25}$ $+11°$ (in chloroform).

Component *A* (R_F 0.84) was recrystallized from pentane to give pure tetra-*O*-acetyl-D-*gluco*-hexodialdose tetraethyl bis(dithioacetal) (**11**); yield 0.17 g, m.p. 70.5–71.5°, $[\alpha]_D^{20}$ $-14.6°$ (*c* 2, methanol); lit.[16] m.p. 70–71°, $[\alpha]_D^{24}$ $-13.5°$ (in methanol). (Found: C, 47.26; H, 6.82; S, 23.12. $C_{22}H_{38}O_8S_4$ requires: C, 47.29; H, 6.85; S, 22.95); X-ray powder diffraction data: 10.64 vs (2), 9.02 s (1), 7.95 s (1), 7.42 w, 6.87 w, 6.25 m, 5.53 w, 5.27 m, 4.35 s (3), 3.88 s (4), 3.70 w, 2.81 m, 2.49 w, 2.30 w, 2.24 w, and 2.10 w.

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