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Characterization and interconversions of 2-*S*-ethyl-2-thio-D-mannose diethyl dithioacetal and the facile epimerization of 2-thio-D-mannopyranose derivatives

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Abstract

3,4,5,6-Tetra-*O*-benzoyl-D-glucose diethyl dithioacetal (**2**) reacts with ethanethiol under acidic conditions to afford 3,4,5,6-tetra-*O*-benzoyl-2-*S*-ethyl-2-thio-D-mannose (**3**), the stereochemistry at C-2 of which has been assigned by chemical conversions on its debenzoylated derivative, the crystalline 2-*S*-ethyl-2-thio-D-mannose diethyl dithioacetal (**4**). In the presence of mercuric chloride (1.1 molar equiv), **4** is converted into crystalline ethyl 2-*S*-ethyl-1,2-dithio-α-D-mannofuranoside (**5**). Complete demercaptalation of **4** affords syrupy 2-*S*-ethyl-2-thio-D-mannopyranose (**6**), which was characterized as its phenylhydrazone **7** and the crystalline α-pyranose tetraacetate **9**. Extended treatment of **4** with mercuric chloride and aqueous sodium hydrogencarbonate resulted in isolation of **6**, along with its crystalline 2-epimer, 2-*S*-ethyl-2-thio-β-D-glucopyranose (**10**). Remercaptalation of **6** affords the *manno* diethyl dithioacetal **4** as the major product, whereas similar treatment of **10** yields ethyl 2-*S*-ethyl-1,2-dithio-α-D-glucopyranoside (**13**). The mechanism of conversion of **2** into **3**, as well as the unusually facile interconversion of 2-*S*-ethyl-2-thio-D-mannose (**6**) and its D-*gluco* epimer **10**, has been investigated.

Keywords: 2-Thio sugar; Epimerization; Dithioacetal

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1. Introduction

It has been known for some time that 3,4,5,6-tetra-*O*-benzoyl-D-glucose diethyl dithioacetal (**2**), in the presence of ethanethiol and an acid catalyst such as hydrogen chloride or zinc chloride, is readily converted into a diethyl dithioacetal derivative that bears a third ethylthio group at C-2 [1]. The C-2 stereochemistry of this derivative was not established in the earlier work, and the compound was usually referred to as 3,4,5,6-tetra-*O*-benzoyl-2-*S*-ethyl-2-thio-D-glucose(mannose) diethyl dithioacetal. This compound has been shown to undergo demercaptalation, in the presence of mercuric chloride in methanol, to afford a 3,4,5,6-tetra-*O*-benzoyl-2-*S*-ethyl-2-thio-D-glucose(mannose) dimethyl acetal that was further transformed into 2-deoxy-D-*arabino*-hexose (''2-deoxy-D-glucose'') [2].

We have previously communicated the results of experiments aimed at elucidating the absolute stereochemistry of these 2-*S*-ethyl-2-thioaldohexose derivatives [3] and have published a detailed account of a crystal structure and proton NMR analysis of one of these compounds, 2-*S*-ethyl-2-thio-D-mannose diethyl dithioacetal [4]. We now report the details of a structure elucidation by chemical methods, which independently establishes the absolute stereochemistry of the products of reaction of 3,4,5,6-tetra-*O*-benzoyl-D-glucose diethyl dithioacetal (**2**) with thiols as being D-*manno*.

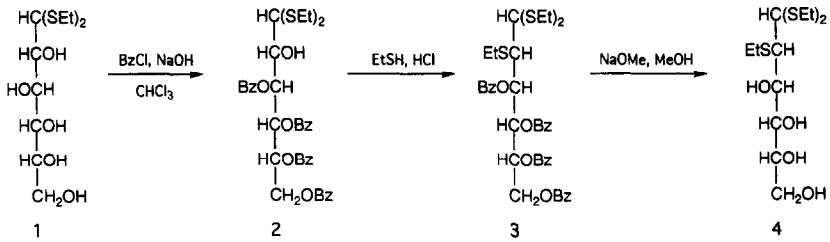
One of the compounds produced during this work, 2-*S*-ethyl-2-thio-D-mannose (**6**), undergoes remarkably facile interconversion with its C-2 epimer, 2-*S*-ethyl-2-thio-D-glucose. A detailed study of this process, as well as a possible mechanism for the conversion of D-*gluco* tetrabenzoate **2** into D-*manno* product **3**, is described here.

2. Results and discussion

Repeating the procedure described by Bolliger and Schmid [2], D-glucose diethyl dithioacetal (**1**) was treated briefly with sodium hydroxide and benzoyl chloride, which converted **1** into 3,4,5,6-tetra-*O*-benzoyl-D-glucose diethyl dithioacetal (**2**). This product had physical constants (mp 165–167 °C, $[\alpha]_D$ +21.5° in $CHCl_3$) in good agreement with those reported previously by Bolliger and Schmid [2] and originally by Brigl and Mühlschlegel [5]. This tetrabenzoate had been firmly identified as the 3,4,5,6-substituted derivative by Bolliger and Schmid [2], an attribution here substantiated by means of high-field NMR measurements.

Using the conditions detailed by Brigl et al. [1], reaction of **2** with ethanethiol in the presence of either hydrogen chloride or zinc chloride afforded 82% of a crystalline product, mp 82 °C, $[\alpha]_D$ +52° (*c* 1, $CHCl_3$) here identified as 3,4,5,6-tetra-*O*-benzoyl-2-*S*-ethyl-2-thio-D-mannose diethyl dithioacetal (**3**). Catalytic deesterification of this compound [1], using sodium methoxide in methanol, yielded 2-*S*-ethyl-2-thio-D-mannose diethyl dithioacetal (**4**); mp 100–101 °C, $[\alpha]_D$ +2.5° (*c* 1, acetone). Compounds **3** and **4** (see Scheme 1) had physical constants in good agreement with those reported previously.

To provide a chemical proof of the stereochemistry at C-2 of compounds **3** and **4**, we set out to convert the acyclic tetrol **4** into cyclic structures that would permit unambigu-



Scheme 1.

ous assignment by NMR of the orientation of the C-2 substituent. Thus, kinetic unimolecular demercaptalation of 2-*S*-ethyl-2-thio-D-mannose diethyl dithioacetal (**4**) by treatment with mercuric chloride (1.1 molar equiv) in the presence of barium carbonate afforded a major crystalline product identified as ethyl 2-*S*-ethyl-1,2-dithio-α-D-mannofuranoside (**5**); yield 63%; mp 90–92 °C; $[\alpha]_D$ +107.5° (*c* 1, $CHCl_3$). This compound was identical in all respects to a sample prepared (but not stereochemically characterized) by an earlier described route [6], and whose structure has been established by X-ray crystallography [7]. The 300 MHz ^{1}H NMR spectrum of **5** exhibited a well-defined doublet at 5.10 ppm for the anomeric proton (H-1) with a $J_{1,2}$ value of 7.9 Hz, concordant with the α anomeric configuration indicated by the high dextrorotation. The ^{1}H NMR shifts and couplings for compound **5** were in good agreement with those previously reported [4,8].

Treatment of **4** with 2.0 molar equiv of mercuric chloride, in the presence of sodium hydrogencarbonate (2.0 molar equiv) for 30 min at room temperature, with rapid work-up of the reaction mixture and immediate chromatography on alumina, gave a syrupy product, homogenous by TLC, whose ^{1}H NMR (300 MHz) spectrum in D_2O revealed the presence of one ethylthio group and signals for two anomeric protons at 5.36 and 5.01 ppm, both having coupling constants of 1.6 Hz. The former signal was ascribed to the α anomer, and the latter to the β anomer of 2-*S*-ethyl-2-thio-D-mannopyranose (**6**) [9]. Equilibration of the mixture for 4 h (in D_2O at room temperature) revealed a 3:2 α:β mixture of the anomers, with integration of the combined anomeric signals corresponding to one proton.

The identity of this syrupy 2-*S*-ethyl-2-thio-D-mannopyranose (**6**) was further confirmed through its conversion into crystalline 2-*S*-ethyl-2-thio-D-mannose phenylhydrazone (**7**) [mp 159–160 °C, $[\alpha]_D$ +102°, (*c* 1, pyridine)], which proved to have physical constants different from values reported previously [10]. As detailed in the Experimental section, the compound described in ref. [10] as being 2-*S*-ethyl-2-thio-D-mannose phenylhydrazone (**7**) is most probably the phenylhydrazone derivative of 2-*S*-ethyl-2-thio-D-glucose, which has been shown to have mp 180–181 °C, $[\alpha]_D$ −157° (*c* 1, pyridine) [11]. Treatment of **6** with an excess of phenylhydrazine under more forcing conditions yielded the well-known [11] D-*arabino*-hexulose phenylosazone (**8**).

Unambiguous confirmation of the stereochemistry at C-2 in **6** was achieved by acetylation of the equilibrated mixture of the α and β anomers of **6** with acetic anhydride in pyridine, which afforded a major crystalline product [mp 116 °C, $[\alpha]_D$

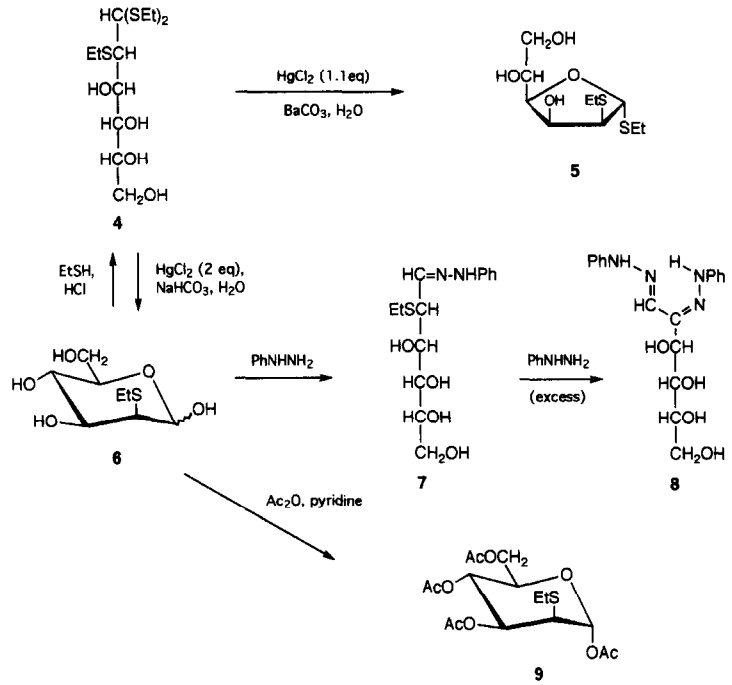
+40° (*c* 1, $CHCl_3$)] that exhibited a doublet at 6.26 ppm ($J_{1,2}$ 1.95 Hz) in its ^1H NMR spectrum, as well as signals corresponding to the methyl groups of four acetate substituents (2.07–2.17 ppm). A coupling of 1.95 Hz between H-1 and H-2 indicated a gauche (diequatorial) relationship between these protons, and therefore the crystalline tetraacetate was identified as 1,3,4,6-tetra-*O*-acetyl-2-*S*-ethyl-2-thio-α-D-mannopyranose (**9**). Although the syrupy β-anomer could not be isolated in pure form, NMR analysis of the crude reaction mixture, after aqueous work-up, revealed a doublet at 5.9 ppm with $J_{1,2} \sim 2$ Hz. Remercaptalation of syrupy **6**, in the presence of ethanethiol and hydrochloric acid, resulted in the reformation of 2-*S*-ethyl-2-thio-D-mannose diethyl dithioacetal (**4**), isolated in 54% yield and identical in all respects to a known sample.

It was found that prolonged exposure of compound **4** to the demercaptalation conditions with $HgCl_2$–$NaHCO_3$ leads not only to the D-*manno* derivative **6**, but also varying amounts of the previously described [12,13] C-2 epimer of **6**, 2-*S*-ethyl-2-thio-D-glucopyranose, isolated as the crystalline β anomer **10**, mp 161–162 °C, $[\alpha]_D$ +30° (initial) → +63° (equil., water). The proportion of **10** formed is dependent upon the time of exposure to the reaction conditions, and varying amounts of this epimeric product also result if silica gel is used in the attempted purification of 2-*S*-ethyl-2-thio-D-mannose (**6**). Compound **10** afforded a crystalline phenylhydrazone (**11**), mp 181–182 °C, $[\alpha]_D$ −157° (*c* 1, pyridine), identical with a sample produced in an earlier study [13]. This compound has been shown to undergo conversion by excess phenylhydrazine into D-*arabino*-hexulose phenylosazone (**8**), affirming that the essential difference between **6** and **10** is their C-2 stereochemistry.

Equilibration of crystalline 2-*S*-ethyl-2-thio-D-glucose (**10**) in D_2O at room temperature for 4 h afforded a 1:1 mixture of anomers with signals in the ^1H NMR spectrum at 5.31 ppm ($J_{1,2}$ 3.14 Hz) and 4.73 ppm ($J_{1,2}$ 8.8 Hz) corresponding to the α and β pyranose anomers, respectively. Acetylation of **10** afforded a crystalline tetraacetate identified as 1,3,4,6-tetra-*O*-acetyl-2-*S*-ethyl-2-thio-β-D-glucopyranose (**12**). The ^1H NMR spectrum of **12** revealed a doublet at 5.66 ppm ($J_{1,2}$ 9.55 Hz). This large coupling constant establishes the diaxial relationship between H-1 and H-2, thus confirming the assignment of compound **12** as the β-*gluco* anomer. Comparison of the two 2-*S*-ethyl-2-thioaldohexoses **6** and **10** at anomeric equilibrium with their parent sugars, D-mannose and D-glucose, shows a small chemical-shift difference (~ 0.2 ppm) in the *manno* series (axial 2-substituent) and a larger one (~ 0.6 ppm) in the *gluco* series. The equatorial 2-ethylthio group in **10** enhances the equilibrium proportion of α anomer relative to the 2-hydroxyl analogue, whereas the axial ethylthio group in **6** enhances the proportion of β anomer relative to the 2-hydroxyl analogue.

Remercaptalation of **10**, under conditions similar to the experiment performed on the D-*manno* epimer **6**, afforded a distinctly different compound. The major product (33%) of this reaction proved to be ethyl 2-*S*-ethyl-1,2-dithio-α-D-glucopyranoside [**13**, mp 138–139 °C, $[\alpha]_D$ +238° (*c* 1, $CHCl_3$)], derivatized as the tribenzoate **14**; mp 115 °C, $[\alpha]_D$ +103° (*c* 1, $CHCl_3$). Literature precedent [14] suggests it is possible that an acyclic diethyl dithioacetal derivative could be formed in this reaction, which subsequently reacts to afford pyranoside **13**.

The observation that the demercaptalation experiments performed on 2-*S*-ethyl-2-thio-D-mannose diethyl dithioacetal (**4**), in which the compound was treated with



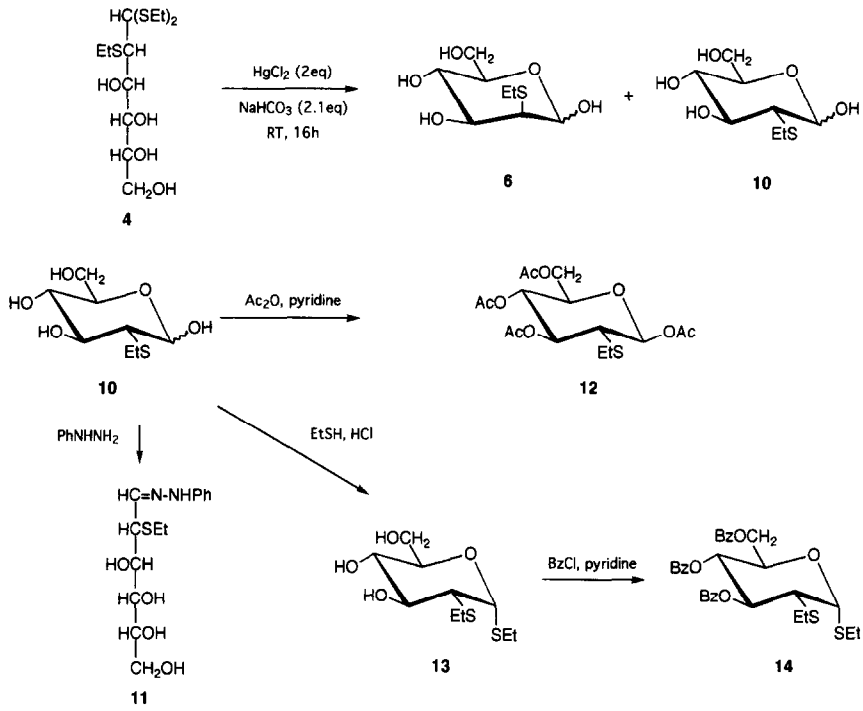
Scheme 2.

varying amounts of mercuric chloride, affords derivatives **5** and **6** having the D-*manno* configuration, combined with the fact that remercaptalation of syrupy **6** regenerates **4**, clearly establishes that the configuration at C-2 of compounds **3** and **4** are in fact D-*manno* (see Schemes 2 and 3).

The formation of 2-*S*-ethyl-2-thio-β-D-glucose (**10**) during the demercaptalation of 2-*S*-ethyl-2-thio-D-mannose diethyl dithioacetal (**4**) led us to question whether compound **10** is formed directly during the demercaptalation step or is a consequence of epimerization at C-2 of the first-produced 2-*S*-ethyl-2-thio-D-mannopyranose (**6**). To address this question, a series of preliminary experiments was performed employing different bases in the demercaptalation of **4**.

Demercaptalation of 2-*S*-ethyl-2-thio-D-mannose diethyl dithioacetal (**4**) with aqueous mercuric chloride (2.1 molar equiv), in the presence of an excess of barium carbonate as acid acceptor, resulted in formation of mostly the syrupy 2-*S*-ethyl-2-thio-D-mannose (**6**, 77%) and only a little of the crystalline 2-*S*-ethyl-2-thio-β-D-glucose (**10**, 18%). Similar reaction using sodium hydrogencarbonate as base, for 12 h at room temperature, again led to a mixture of **6** and **10**, but the product composition was dramatically different. In this case crystalline **10** was isolated in 83% yield and the D-*manno* epimer **6** proved to be the minor component of the mixture, being isolated as the phenylhydrazone **17** in only 8% yield.

These results indicated that the nature of the acid acceptor employed in the demercaptalation of **4** plays an important role in the outcome of the reaction, and that sodium



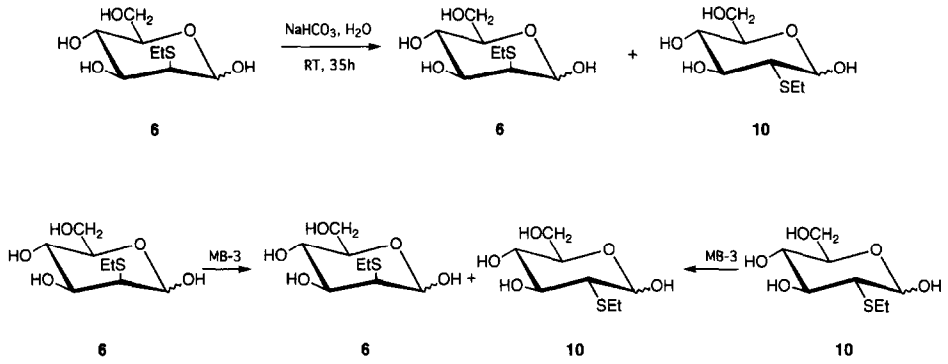
Scheme 3.

hydrogencarbonate, which is water soluble, has a profound effect on the ratio of products formed. Experiments were therefore performed in which aqueous solutions of D-*manno* epimer **6** and D-*gluco* epimer **10** were treated with sodium hydrogencarbonate in order to ascertain whether these compounds might be interconverting under the conditions employed for the demercaptalation of **4**.

Thus, treatment of an aqueous solution of 2-*S*-ethyl-2-thio-D-mannose (**6**) with sodium hydrogencarbonate (25% by weight) for 35 h at room temperature afforded a mixture of products, the major component of which proved to be 2-*S*-ethyl-2-thio-D-glucose (**10**), isolated crystalline in 88% yield. This experiment proves that compounds **6** and **10** are indeed capable of interconversion under the conditions employed for the demercaptalation of 2-*S*-ethyl-2-thio-D-mannose diethyl dithioacetal (**4**).

A second series of experiments were performed employing Amberlite MB-3 resin as base. Starting with the D-*manno* compound **6**, treatment with Amberlite MB-3 in water for 4 h at room temperature, again resulted in a mixture of **6** and **10**; however, the ratio of **6** to **10** in this case proved to be ~ 1:3. A similar experiment beginning with the D-*gluco* epimer **10** resulted in essentially the same outcome, with the ratio of **6** to **10** being ~ 1:3. These results strongly suggest that this ratio corresponds to the equilibrium mixture of the D-*manno* and D-*gluco* epimers **6** and **10** and that the free-energy of interconversion, ΔG°, is 0.65 kcal/mol.

The interconversion of **6** and **10** (see Scheme 4) in aqueous sodium hydrogencarbon-



Scheme 4.

ate solution (pH < 9) represents a C-2 epimerization process occurring under extremely mildly basic conditions. In contrast, the classical Lobry de Bruyn–Alberda van Eckenstein interconversion of epimeric aldoses (along with the corresponding ketose) [15] occurs under much more strongly basic conditions such as aqueous sodium or calcium hydroxide (pH > 11). Such reactions have been studied in detail by Isbell and co-workers [16] and are believed to occur via enediol intermediates as invoked here in Fig. 1

To investigate the mechanism of this extremely facile epimerization, we monitored the interconverison by ^{1}H NMR spectroscopy. Thus, a solution of crystalline D-*gluco* epimer **10** in D_2O at room temperature was allowed to equilibrate for 4 h, which resulted in an approximately 1:1 mixture of the α and β pyranose anomers (5.31 ppm, $J_{1,2}$ 3.14 Hz and 4.73 ppm, $J_{1,2}$ 8.8 Hz, respectively). A catalytic amount of sodium hydrogencarbonate was added to the mixture, and the changes in the ^{1}H NMR spectrum were monitored over time. Initially little change in the spectrum was noticeable, but after ~ 30 min the signal for H-2 at 2.49 ppm began to decrease in intensity, and after 1 h integration of the double doublet at 2.49 ppm indicated ~ 50% deuterium incorporation at C-2. After 90 min the doublets at 5.31 and 4.73 ppm visibly began to collapse to singlets; however, it was several hours before singlets (5.36 and 5.02 ppm) corresponding to the α and β anomers of the D-*manno* epimer **6** were observed. Keeping the mixture at room temperature for 24 h resulted in a spectrum exhibiting singlets for the α and β anomers of both **6** and **10**, with the D-*gluco* epimer **10** predominating by a ratio of ~ 6:1. Analysis of spectra collected after several days reveal the proportions of **6** and **10** to be moving towards the equilibrium values (vide infra).

Experiments were then performed to discern whether the interconversion of **6** and **10** occurs via a mechanism similar to that proposed [16] for other epimerizations at C-2, namely ring-opening to the acyclic *aldehydo* form of the sugar and deprotonation at C-2 to form a planar enolate (or enediol), which can then be reprotonated to form the D-*gluco* and D-*manno* epimers. To this end, samples of D-*manno* epimer **6** and D-*gluco* epimer **10** were separately dissolved in 99% $H_2^{18}O$ and treated with sodium hydrogencarbonate for 48 h at room temperature. Distillation of the solvent and conventional acetylation of the residues in both cases afforded mixtures which, by TLC analysis, contained compounds with identical mobilities to the previously described (vide infra)

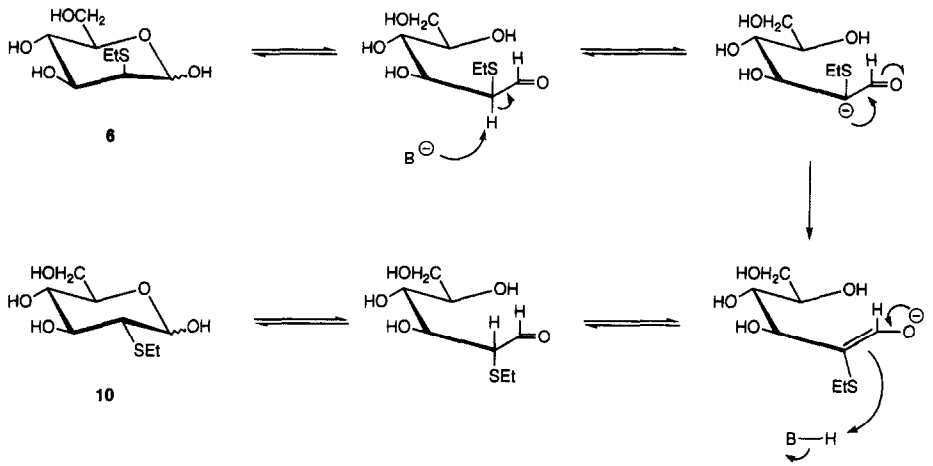


Fig. 1. Proposed mechanism for the base-catalyzed interconversion of 2-*S*-ethyl-2-thio-D-mannopyranose (**6**) and 2-*S*-ethyl-2-thio-D-glucopyranose (**10**).

1,3,4,6-tetra-*O*-acetyl-2-*S*-ethyl-D-glucose and mannose derivatives. Analysis of these mixtures by mass spectrometry (chemical ionization employing ammonia) revealed base signals with m/z 412, namely $[M + NH_4^+]$, corresponding to a molecular mass of 394. Similar analysis of the acetates formed in experiments in which the starting sugars had been equilibrated in $H_2^{16}O$ revealed a base signal with m/z 410 $[M + NH_4^+]$ corresponding to a molecular mass of 392. In the mass spectra of both the labeled and unlabelled tetraacetates, a signal with m/z 350 corresponding to the loss of acetic acid from the molecular ion was observed. This strongly suggested that ^{18}O had been incorporated at C-1 of the labelled tetraacetates, since loss of an acetate group at C-1 is commonly the first fragmentation that occurs in the mass spectra of sugar peracetates [17].

The incorporation of labeled oxygen at C-1 of both D-*manno* epimer **6** and D-*gluco* epimer **10** indicates that ring opening occurs during the epimerization process, since the aldehydrol form must be formed for exchange to occur. Allied with the fact that deuterium is incorporated at C-2 of these sugars under basic conditions in D_2O, as evidenced by the ^1H NMR study, we conclude that the interconversion of **6** and **10** occurs via a mechanism in linc with the classical Lobry de Bruyn–Alberda van Eckenstein interconversion [15], that is, ring opening to the *aldehydo* sugar and deprotonation at C-2 to generate an enolate, which can be reprotonated either above or below the plane to afford the D-*manno* or D-*gluco* derivative (see Fig. 1). The remarkable ease of this interconversion between 2-*S*-ethyl-2-thio-D-mannose (**6**) and 2-*S*-ethyl-2-thio-D-glucose (**10**), at pH < 9, is presumably attributable to the well-known stabilization of carbanions by adjacent sulfur substituents [18].

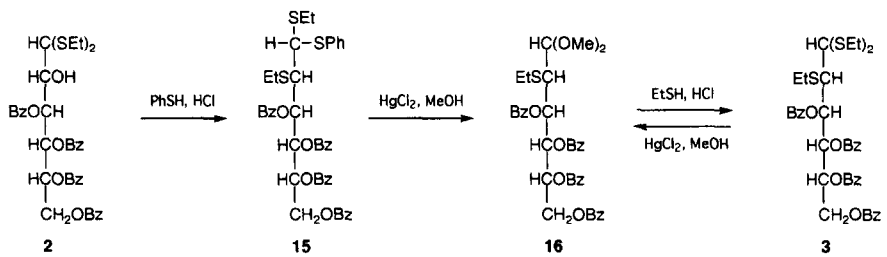
With the configurations of compounds **3** and **4** clearly established, it was of interest to investigate the mechanism operating in the conversion of 3,4,5,6-tetra-*O*-benzoyl-D-glucose diethyl dithioacetal (**2**) into 3,4,5,6-tetra-*O*-benzoyl-2-*S*-ethyl-2-thio-D-mannose diethyl dithioacetal (**3**). In previous studies on the acid-catalyzed deamination of the

hydrochloride salt of 2-amino-2-deoxy-D-glucose diethyl dithioacetal, we reported that the stereochemistry at C-2 of the product was markedly dependent upon the pH of the reaction medium, and that the reaction appeared to occur via an episulfonium ion intermediate [9,13]. At pH 5.6 the major reaction product proved to be ethyl 2-*S*-ethyl-1,2-dithio-α-D-mannofuranoside (**5**) [9], whereas at pH < 1, the major isolated product was shown to be crystalline 2-*S*-ethyl-2-thio-β-D-glucopyranose (**10**) [13]. It was considered that the conversion of **2** into **3** might occur by a similar process.

To test this hypothesis, compound **2** was treated with benzenethiol and hydrogen chloride in chloroform to yield a product identified as 1*R* (or 1*S*)-3,4,5,6-tetra-*O*-benzoyl-2-*S*-ethyl-2-thio-D-mannose ethyl phenyl dithioacetal (**15**) in 71% yield, mp 99–101 °C, $[\alpha]_D$ +37°, (*c* 1 $CHCl_3$). The identity of this product, and proof that the phenylthio group was actually bonded to C-1 of this sugar, was gained by demercaptalation with mercuric chloride (2.0 molar equiv) in methanol, which afforded a crystalline compound whose analysis was consistent with its being 3,4,5,6-tetra-*O*-benzoyl-2-*S*-ethyl-2-thio-D-mannose dimethyl acetal (**16**), mp 94–95 °C, $[\alpha]_D$ +58° (*c* 1 $CHCl_3$), and identical in all respects to a sample prepared by demercaptalation of compound **3** with mercuric chloride (2.0 molar equiv) in methanol. The melting point and specific rotation of **16** differ from those reported [2]; however, the assignment of this compound as the dimethyl acetal derivative is supported by ^{1}H NMR (see Table 1) and mass-spectral data (see Experimental section). Treatment of a sample of **16** with ethanethiol in the presence of zinc chloride regenerated **3**, further supporting the structural assignment of compound **16** (see Scheme 5).

These results indicate that the ethylthio group introduced at C-2 of compound **3** originated at C-1 of 3,4,5,6-tetra-*O*-benzoyl-D-glucose diethyl dithioacetal (**2**). A plausible mechanism would involve acid-catalyzed loss of a hydroxyl group from **2**, possibly from the orthoacid form of **2** (Fig. 2) as has been suggested by Hughes and co-workers [19]. Stabilization of a developing cation at C-2 by an adjacent ethylthio group would produce episulfonium intermediate **17**, and subsequent attack of either ethanethiol or benzenethiol would then occur at the sterically less hindered C-1 to afford D-*manno* product **3** (R = Et) or **15** (R = Ph). The stereochemistry of the newly formed asymmetric center at C-1 of compound **15** was not assigned.

In conclusion, we have shown by chemical means that the product of acid-catalyzed mercaptolysis of 3,4,5,6-tetra-*O*-benzoyl-D-glucose diethyl dithioacetal (**2**) does indeed have the D-*manno* configuration and can be assigned as 3,4,5,6-tetra-*O*-benzoyl-D-man-



Scheme 5.

Table 1
^{1}H NMR data for perbenzoates of D-mannose and D-glucose diethyl dithioacetals

Compd	Chemical shift (δ) and coupling constants										
	H-1	H-2	H-3	H-4	H-5	H-6	H-6′	SCH_2CH_3	SCH_2CH_3	OCH_3	COPh
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{6,6'}$	$J_{5,6'}$	J	J		
2	4.39d	5.49dd	4.70dd	5.86dd	5.91m	4.93dd	4.51dd	2.69m, 2.78m	1.12t, 1.26t	–	7.30–8.07m
	4.9	5.4	6.8	8.4	2.6	12.5	5.1	– –	7.5 7.5		
3	4.17d	3.48dd	5.92d	6.41d	5.86m	4.85dd	4.56dd	2.52m, 2.81m	1.02t, 1.15t	–	7.31–8.06m
	3.3	9.5	0.0	7.5	2.9	12.0	5.6	– –	7.6 7.1		
15	4.50d	3.57dd	5.88d	6.42d	5.82m	4.87dd	4.55dd	2.55m, 2.80m	1.09t, 1.18t	–	7.28–8.04m
	2.7	10.0	0.0	7.2	3.3	12.2	5.4	– –	7.1 7.1		
16	4.58d	3.38dd	4.58m	6.35dd	5.85m	4.81dd	4.51dd	2.60q	1.09t	3.38s, 3.40s	7.30–8.10m
	6.8	5.3	2.8	6.6	3.3	12.2	5.5	7.1	7.1		

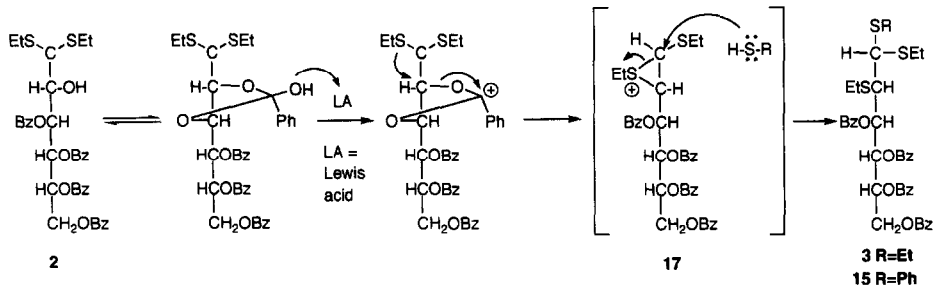


Fig. 2. Possible intermediacy of an episultonium ion (**17**) in the migration of an alkylthio group from C-1 to C-2 during the acid-catalyzed reaction of 3,4,5,6-tetra-*O*-benzoyl-D-glucose diethyl dithioacetal (**2**) with benzenethiol.

nose diethyl dithioacetal (**3**). The mechanism of formation of this compound appears to involve acid-catalyzed loss of the hydroxyl group at C-2, with stabilization of the forming carbocation by an adjacent sulfur atom at C-1, followed by attack of external thiol nucleophile at C-1 and concomitant migration of an ethylthio group to afford the D-*manno* derivative.

In related studies, Wolfrom and von Bebenburg [20] reacted 3,4,5-tri-*O*-benzoyl-D-xylose diethyl dithioacetal with ethanethiol under acidic conditions and isolated a 2-*S*-ethyl dithioacetal of undefined stereochemistry at C-2. It is highly likely, considering the stereochemical similarity between xylose and glucose between C-1 and C-4, that the product isolated in Wolfrom's study actually had the D-*lyxo* configuration in line with the present findings. The interconversion of epimeric 2-thio sugars, in this case sophorose derivatives, has recently been reported by Petrus et al. [21], and these workers concur on the extremely facile nature of the epimerization process. The proposed conversion of D-*gluco* diethyl dithioacetal **2** into D-*manno* compound **3** is in accordance

Table 2
^{13}C NMR data for perbenzoates of D-mannose and D-glucose dithioacetals

Compd	Chemical shift (δ)										
	C-1	C-2	C-3 [a]	C-4 [a]	C-5 [a]	C-6 [a]	SCH_2CH_3	SCH_2CH_3	$C(OCH_3)$	COPh	Aromatic
2	51.5	62.6	70.0	70.5	71.3	75.6	25.4, 25.9	14.4, 14.5	–	165.5, 165.6 166.0, 166.2	128.1–133.7
3	55.5	54.8	63.2	70.8	71.0	72.1	26.5, 26.8 30.6	14.7, 14.9 15.0	–	165.6, 166.0 [b] 166.5	128.7–134.1
15	54.4	61.0	63.2	70.8	71.1	71.9	27.3, 30.2	14.7, 15.1	–	165.5, 166.0 165.4, 165.9 [b] 166.5	128.1–134.1
16	105.8	55.3	56.2	62.5	62.8	70.2	27.4	14.5	70.8, 70.6	165.3 [b], 165.5 166.1	128.2–133.6

[a] Interchangeable.
[b] Double intensity.

with reports by Berthell and Ferrier [22] who have suggested that replacement of OH groups on sugar chains occurs via episulfonium ion intermediates and, in cases where an additional free OH group is present at C-3, have shown that further introduction of thio groups is possible to form 2,3-dithio diethyl dithioacetal products.

3. Experimental

General methods.—Melting points were determined using a Thomas–Hoover Unimelt apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer model 141 polarimeter unless otherwise stated. Reaction solvents were purified and dried by distillation as recommended [23]. Thin-layer chromatography (TLC) was performed on precoated aluminum-backed plates of Silica Gel 60F-254 (E. Merck, Darmstadt) using the eluents noted, and compounds were detected by treatment with 5% aq H_2SO_4 and subsequent heating to 110 °C. Column chromatography was performed on Silica Gel 60 (E. Merck) or neutral alumina as noted. ^1H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively, using a Varian Gemini system. For solutions in $CDCl_3$ and dimethyl sulfoxide-d_6 chemical shifts (ppm) are reported relative to Me_4Si as the internal standard. Splitting patterns are designated: *s*, singlet; *d*, doublet; *dd*, double doublet; *t*, triplet; *q*, quartet; *m*, multiplet. Mass spectra were recorded on a Finnegan 4600 instrument by Wesley White and Noel Whittaker of the Laboratory of Analytical Chemistry, NIDDK, NIH, Bethesda, MD, using chemical ionization with NH_3 as reagent gas. Infrared spectra were recorded on a Bio Rad SPC 3200 instrument. Microanalyses were performed at Atlantic Microlabs, Inc., Norcross, GA.

*Preparation of 3,4,5,6-tetra-*O*-benzoyl-*D*-glucose diethyl dithioacetal* (**2**) .—Following the method of Brigl et al. [1], D-glucose diethyl dithioacetal (**1**) was treated briefly with benzoyl chloride in a mixture of $CHCl_3$ and aq NaOH to afford a crystalline product having physical constants consistent with those reported: mp 165–167 °C, $[\alpha]_D$ 21.5° (*c* 0.1, $CHCl_3$), R_f 0.43 (3:1 hexane–EtOAc). IR ($CHCl_3$) 3450, 1718, 1601, 1450, 1267, 1215 cm^{-1}; for ^1H NMR and ^{13}C NMR ($CDCl_3$) data, see Tables 1 and 2, respectively; MS: *m/z* 720 $[M + NH_4^+]$.

*Preparation of 3,4,5,6-tetra-*O*-benzoyl-2-*S*-ethyl-2-thio-*D*-mannose diethyl dithioacetal* (**3**) [1].—3,4,5,6-Tetra-*O*-benzoyl-D-glucose diethyl dithioacetal (**2**, 8.0 g, 11.11 mmol) was dissolved in $CHCl_3$ (120 mL) which had been saturated with HCl gas at 20 °C. This solution was treated with EtSH (5.0 g) for 15–20 h at room temperature. (Longer reaction times decreased the yield of **3** and resulted in the formation of significant amounts of side products.) The solution was washed succesively with water (3 × 25 mL) and diluted $NaHCO_3$ solution (2 × 25 mL), and then dried (Na_2SO_4). Evaporation of the solvent afforded a syrup that was crystallized from MeOH; yield 7.0 g (9.16 mmol, 82%), mp 82 °C, $[\alpha]_D$ +52° (*c* 1, $CHCl_3$), R_f 0.29 (6:1 hexane–EtOAc). Lit. [1] mp 82–83 °C, $[\alpha]_D$ +57.6° (acetone). IR ($CHCl_3$) 3050, 1610, 1720, 1450, 1280 cm^{-1}; for ^1H and ^{13}C NMR data ($CDCl_3$), see Tables 1 and 2, respectively; MS: *m/z* 764 $[M + NH_4^+]$.

Preparation of 2-S-ethyl-2-thio-D-mannose diethyl dithioacetal (**4**).—The tetrabenzoate **3** was deesterified with NaOMe in MeOH as described by Brigl and co-workers [1] to afford **4**, which was recrystallized from benzene; mp 100–101 °C, $[\alpha]_D$ +2.5° (*c* 1, acetone), R_f 0.32 (1:3 MeOH–PhMe). IR ($CHCl_3$) 3400, 2968, 1413, 1080, 1035 cm^{-1}; MS: *m/z* 348 $[M + NH_4^+]$. The product described by Brigl et al., whose stereochemistry was not established, had mp 101–102 °C, $[\alpha]_D$ +2.7° (acetone).

Preparation of ethyl 2-S-ethyl-1,2-dithio-α-D-mannofuranoside (**5**).—To a solution of 2-*S*-ethyl-2-thio-D-mannose diethyl dithioacetal (**4**, 0.70 g, 2.12 mmol) in water (35 mL) at 40 °C was added $BaCO_3$ (1.0 g) and a warm solution of $HgCl_2$ (0.62 g, 1.08 molar equiv) in water (30 mL). The mixture was stirred vigorously and allowed to cool to room temperature. After 2 h, when all of the starting material had been consumed (TLC), the mixture was filtered and the filtrate evaporated (at 40 °C) to a thin syrup that was extracted with 3:1 benzene–$CHCl_3$. The dried (Na_2SO_4) extract was evaporated to afford crude **8** (0.47 g, 1.75 mmol, 78%), mp 83–86 °C, which was purified by preparative TLC (silica gel, 2 plates, 20 × 20 cm) using 1:1:3 MeOH–$CHCl_3$–benzene as developer. The zone having R_f 0.57 was extracted with 1:3 MeOH–$CHCl_3$, and the solution was clarified by passing through a short (2 cm) column of silica gel. Evaporation of solvent afforded pure **5** as white leaflets; yield 0.36 g (63%), mp 90–92 °C, $[\alpha]_D$ +107.5° (*c* 1, $CHCl_3$). IR ($CHCl_3$) 3300, 2995, 1210, 1090, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.10 (d, 1 H, $J_{1,2}$ 5.92 Hz, H-1), 4.30 (m, 1 H, H-3), 4.10 (m, 2 H, H-6,6′), 3.84 (m, 1 H, H-4), 3.74 (m, 1 H, H-5), 3.25 (m, 1 H, H-2), 2.70 (m, 2 H, SCH_2), 2.60 (m, 2 H, SCH_2), 1.29 (t, 6 H, *J* 7.4 Hz, SCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 88.6, 80.8, 71.2, 70.3, 64.4, 56.5, 26.6, 26.1, 15.2, 14.9; MS: *m/z* 286 $[M + NH_4^+]$. Anal. Calcd for $C_{10}H_{20}O_4S_2$: C, 44.77; H, 7.52; S, 23.88. Found: C, 45.10; H, 7.76; S, 23.75. For this product, then of undefined configuration at C-2, Wolfrom et al. [6] reported mp 88–90 °C $[\alpha]_D$ +139° (*c* 2.5, $CHCl_3$), and a yield of 61%. The cause of the discrepancy between the values of $[\alpha]_D$ for compound **5** found in the present work and that reported by Wolfrom and co-workers [6] is uncertain; however, the compound described here was identical by mixed mp, $[\alpha]_D$, and ^1H NMR spectrum with a sample of **5** produced by a third route [9].

2-S-Ethyl-2-thio-D-mannopyranose (**6**).—Sodium hydrogencarbonate (0.51 g, 2.0 molar equiv) was dissolved in water (50 mL) and the solution was warmed to 50 °C. Compound **4** (1.1 g) was added and the mixture stirred at 50 °C until **4** had completely dissolved. The solution was allowed to cool to room temperature, and $HgCl_2$ (1.8 g, 2 molar equiv) in water (30 mL) added dropwise with stirring during 7 min. Stirring was continued for 15 min and then the solution, clarified by filtration, was evaporated under diminished pressure as rapidly as possible at 35 °C. The residue was immediately chromatographed on a 20 cm column of neutral alumina (Woelm, activity grade 1), using 1:6 MeOH–benzene as eluent. The evaporated eluate afforded a colorless syrup (0.69 g, 92%), R_f 0.25 (1:4 MeOH–benzene). The ^1H NMR spectrum of the syrup (D_2O) revealed that it was practically pure 2-*S*-ethyl-2-thio-D-mannose (**6**). Allowing the reaction to run for 16 h, or using silica gel as the adsorbent in the purification, resulted in formation of varying amounts of the C-2 epimer of compound **6**, namely 2-*S*-ethyl-2-thio-D-glucose (**10**) [12,13], isolated as the crystalline β-pyranose form, mp 161–162 °C (from EtOH). The phenylhydrazone and acetate derivatives of **6** are detailed next.

Table 3
^{1}H NMR data for derivatives of 2-*S*-ethyl-2-thio-D-mannose (**6**) and -D-glucose (**10**)

Compd	Chemical shift (δ) and coupling constants (Hz)										
	H-1 $J_{1,2}$	H-2 $J_{2,3}$	H-3 $J_{3,4}$	H-4 $J_{4,5}$	H-5 $J_{5,6}$	H-6 $J_{6,6'}$	H-6′ $J_{5,6'}$	SCH_2CH_3 J	SCH_2CH_3 J	$COCH_3$	Aromatic
7				3.40–4.63m				2.44m	1.17t 7.0	–	6.67–7.19
9	6.26d 1.95	3.41dd 4.2	5.38dd 9.7	5.31dd 9.9	4.15m 4.6	4.19dd 12.4	4.15dd 2.5	2.63q 6.8	1.24t 6.8	2.06, 2.10 [a] 2.17	–
11				3.30–4.60m				2.39q 7.1	1.14t 7.1	–	6.66–7.17
12	5.66d 9.55	2.82dd 9.0	5.05m [b]	5.07m [b]	3.68m 3.9	4.31dd 9.5	4.06dd 2.3	2.59q 7.6	1.19t 7.6	2.04, 2.09 [a] 2.18	–

[a] Double intensity.
[b] Signals overlap.

*2-S-Ethyl-2-thio-*D*-mannose phenylhydrazone* (**7**) *and* D-arabino-*hexulose phenylosazone* (**8**).—2-*S*-Ethyl-2-thio-D-mannose (0.10 g) was dissolved in 30% 2-propanol–water (2 mL) and $PhNHNH_2$ (0.06 g) and one drop of AcOH were added. The mixture was stirred at room temperature for 1 h, during which time the phenylhydrazone crystallized out as white needles. Filtration afforded **7** (0.105 g, 75%), mp 159–160 °C, $[\alpha]_D$ +102° (*c* 1, pyridine), R_f 0.23 (1:3 MeOH–PhMe); IR (KBr) 3450, 1710, 1540, 1460, 1275, 1045 cm^{-1}. ^{1}H and ^{13}C NMR are reported in Tables 3 and 4, respectively; MS: *m/z* 315 $[M + NH_4^+]$; Anal. Calcd for $C_{14}H_{22}N_2O_4S_2$: C, 53.50; H, 7.01; N, 8.91; S, 10.19. Found: C, 53.43; H, 6.93; N, 9.13; S, 10.11.

Compound **6** was treated with an excess (5 molar equiv) of $PhNHNH_2$ in aq AcOH

Table 4
^{13}C NMR data for derivatives of 2-*S*-ethyl-2-thio-D-mannose (**6**) and -D-glucose (**10**)

Compd	Chemical shift (δ)										
	C-1	C-2	C-3 [a]	C-4 [a]	C-5 [a]	C-6 [a]	SCH_2CH_3	SCH_2CH_3	$COCH_3$	$COCH_3$	Aromatic
7	146.0	48.9	63.6	69.8	70.5	71.1	23.7	14.8	–	–	111.5, 117.9 129.0, 139
9	94.3	47.6	62.0	66.0	70.4	71.0	27.3	14.7	168.7, 169.3 170.2, 170.7	20.6, 20.7 [b] 20.8	–
11	145.7	50.7	63.5	69.5	71.2	71.3	23.4	14.8			
12	94.2	49.4	61.7	68.8	71.9	72.2	25.9	14.9	168.6, 169.6 169.9, 170.6	20.6 [b], 20.7 20.9	–

[a] Interchangeable.
[b] Double intensity.

at 100 °C by the conventional procedure. This afforded the phenylosazone **8**, identical in all respects to an authentic sample [11].

1,3,4,6-Tetra-O-*acetyl-2*-S-*ethyl-2-thio-α*-D-*mannopyranose* (**9**).—Syrupy 2-*S*-ethyl-2-thio-D-mannose (**6**, 0.10 g) was treated with a mixture of pyridine (1 mL) and Ac_2O (1 mL) for 12 h at room temperature. The solution was diluted with $CHCl_3$ (10 mL) and successively extracted with water (5 mL), 3% HCl (5 mL), and water (5 mL), and then dried (Na_2SO_4). The solution was concentrated to a syrup, which was purified by preparative TLC (one plate, 20 × 20 cm) using 1:15 MeOH–benzene as eluent. The zone having R_f 0.79 was excised and extracted with ether. Evaporation afforded the α-tetraacetate **9** as a solid which was recrystallized from CCl_4–petroleum ether to give pure **9** as white crystals (0.105 g, 60%), mp 116 °C, $[\alpha]_D$ +40° (*c* 1, $CHCl_3$). ^1H and ^{13}C NMR data are reported in Tables 3 and 4, respectively. MS: *m/z* 410 $[M + NH_4^+]$. Anal. Calcd for $C_{16}H_{24}O_9S$: C, 48.98; H, 6.16; S, 8.16. Found: C, 48.80; H, 5.96; S, 8.03.

The physical and spectroscopic data for the phenylhydrazone **7** and the α-tetraacetate **9** are in good agreement with the constants reported in the literature [3,7] for these compounds and therefore justify the assignment of the *manno* configuration to compound **6**.

Remercaptalation of 2-S-*ethyl-2-thio*-D-*mannose* (**6**) *with ethanethiol and hydrochloric acid.*—Syrupy 2-*S*-ethyl-2-thio-D-mannose (**6**, 0.40 g) was treated with EtSH (1 mL) and concd HCl (12 mL) at 0 °C. After 5 min the reaction was interrupted by neutralizing with solid $NaHCO_3$. A $CHCl_3$ extract of the resulting slurry was dried (Na_2SO_4) and evaporated. The resultant yellow syrup was dissolved in a small amount of benzene and refrigerated, whereupon colorless crystals separated. A second recrystallization from benzene afforded 2-*S*-ethyl-2-thio-D-mannose diethyl dithioacetal (**4**, 0.32 g, 54%), mp 99–100 °C, mixed mp with an authentic sample 99–101 °C, $[\alpha]_D$ +4.5° (*c* 1, $CHCl_3$), R_f 0.32 (1:3 MeOH–PhMe).

Preparation of 2-S-*ethyl-2-thio*-D-*glucose phenylhydrazone* (**11**).—Following the procedure described in ref. [12], 2-*S*-ethyl-2-thio-D-glucose (**10**, 0.10 g, 0.45 mmol) afforded the pale-yellow phenylhydrazone **11** (0.112 g, 0.38 mmol, 84%), mp 181–182 °C (dec.), $[\alpha]_D$ −157° (*c* 1, pyridine). Lit. [11] mp 180–181 °C, $[\alpha]_D$ −157° (pyridine). ^1H and ^{13}C NMR are detailed in Tables 3 and 4, respectively. MS: *m/z* 315 $[M + NH_4^+]$.

Preparation of 1,3,4,6-tetra-O-*acetyl-2*-S-*ethyl-2-thio-β*-D-*glucopyranose* (**12**).—Following the procedure detailed in ref. [12], a sample of **10** (0.10 g, 0.45 mmol) was equilibrated in water at room temperature for 4 h, and then the solvent was evaporated, and the residue was acetylated in the usual manner to afford crystalline **12**. The ^1H and ^{13}C NMR data for which are detailed in Tables 3 and 4, respectively. The ^1H and ^{13}C NMR spectra of the major crystalline isomer **12** were in agreement with those reported previously [12] for this compound; mp 78–79 °C $[\alpha]_D$ +43° (*c* 1, $CHCl_3$); MS: *m/z* 410 $[M + NH_4^+]$.

Remercaptalation of 2-S-*ethyl-2-thio*-D-*glucose* (**10**) *with ethanethiol and hydrochloric acid to give ethyl 2*-S-*ethyl-1,2-dithio-α*-D-*glucopyranoside* (**13**).—2-*S*-Ethyl-2-thio-D-glucose (0.60 g, 2.68 mmol) was treated with concd HCl (12 mL) and EtSH (1 mL) at 0 °C. After 4 min the mixture was neutralized with $NaHCO_3$ and extracted with $CHCl_3$.

The organic layer was dried (Na_2SO_4) and evaporated to leave a syrupy residue which crystallized in part after being kept for 2 days. Crystalline **13** was obtained by extracting the product with cold benzene; yield 0.24 g (0.895 mmol, 33%), mp 138–139 °C, $[\alpha]_D$ +238° (*c* 1, $CHCl_3$). MS: *m/z* 286 $[M + NH_4^+]$. Anal. Calcd for $C_{10}H_{20}O_4S_2$: C, 44.77; H, 7.52; S, 23.88. Found: C, 44.67; H, 7.35; S, 23.87.

No other compound could be obtained crystalline from the reaction mixture. Benzoylation of the syrupy material remaining after removal of the above described product did not yield a crystalline benzoate. Another remercaptalation experiment, in which 2-*S*-ethyl-2-thio-D-glucose (**10**) was treated with HCl and EtSH for 13 h at room temperature, afforded the crystalline dithio glycoside **13** in 57% yield.

*Ethyl 3,4,6-tri-*O*-benzoyl-2-*S*-ethyl-1,2-dithio-α-*D*-glucopyranoside* (**14**).—Ethyl-2-*S*-ethyl-1,2-dithio-α-D-glucopyranoside (**13**, 0.20 g, 0.75 mmol) was treated with pyridine (0.45 g), BzCl (0.70 g), and $CHCl_3$ (1 mL) for 30 h at room temperature. The mixture was diluted with $CHCl_3$ (30 mL) and extracted with water (10 mL), 5% HCl (10 mL), and water (10 mL). After drying (Na_2SO_4) and evaporating, the residue was applied to a column of silica gel and eluted with benzene to afford **14** as pure white crystals (0.15 g, 0.26 mmol, 35%), mp 115 °C, $[\alpha]_D$ +103° (*c* 1, $CHCl_3$), R_f 0.84 (1:19 MeOH–benzene). IR (KBr) 2950, 1755, 1635, 1480, 1280, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (t, 3 H, *J* 7.3 Hz, SCH_2CH_3), 1.25 (t, 3 H, *J* 7.3 Hz, SCH_2CH_3), 2.52 (m, 2 H, SCH_2CH_3), 2.63 (m, 2 H, SCH_2CH_3), 3.44 (dd, 1 H, $J_{2,3}$ 11.3 Hz, H-2), 4.46 (m, 2 H, H-6,6′), 4.81 (m, 1 H, H-5), 5.48 (m, 2 H, $J_{1,2}$ 5.2 Hz, H-1, H-4), 5.78 (dd, 1 H, $J_{3,4}$ 4.6 Hz, H-3), 7.32–8.04 (m, 15 H, aromatic); MS: *m/z* 616 $[M + NH_4^+]$. Anal. Calcd for $C_{31}H_{32}O_7S_2$: C, 64.11; H, 5.55; S, 11.04. Found: C, 64.43; H, 5.86; S, 11.05.

*Demercaptalation of 2-*S*-ethyl-2-thio-D-mannose diethyl dithioacetal* (**4**) *with partial epimerization of the product.—(a) In the presence of barium carbonate.* Barium carbonate (5.0 g) was suspended in a solution of **4** (2.20 g, 6.67 mmol) in water (70 mL) kept at 50 °C. The mixture was stirred vigorously while a solution of $HgCl_2$ (3.8 g, 2.06 molar equiv) was added dropwise over 2 h, during which time the mixture was allowed to cool to 35 °C. The solids were filtered off and the filtrate evaporated at 40 °C. The residue was extracted with 1-propanol, inorganic salts were filtered off, and the filtrate concentrated to 5 mL. An aliquot of 3 mL was kept at 4 °C for 10 days to afford clear prisms of 2-*S*-ethyl-2-thio-β-D-glucose (**10**, 0.18 g, 18%), mp 161–162 °C identical by mixed mp with an authentic sample [13]. A phenylhydrazone derivative had mp 181–182 °C, and the ^1H and ^{13}C NMR spectra were identical with those detailed for 2-*S*-ethyl-2-thio-D-glucose phenylhydrazone (**11**) in Tables 3 and 4. The mother liquors remaining after removal of crystalline **10** gave a syrup (0.77 g, 77%) that was identical by its ^1H NMR spectrum with 2-*S*-ethyl-2-thio-D-mannose (**6**); little, if any, of the C-2 epimer **10** remained in this product.

(b) In the presence of excess sodium hydrogencarbonate. A solution of compound **4** (2.4 g, 7.27 mmol) was dissolved in water (100 mL) containing $NaHCO_3$ (1.35 g, 2.11 molar equiv). The solution was stirred vigorously while $HgCl_2$ (3.98 g, 2.0 molar equiv) dissolved in water (70 mL) was added dropwise. The mixture was stirred for 12 h at room temperature, and the solids were then filtered off. Evaporation of the filtrate gave a yellow syrup that crystallized partially at room temperature. Crystalline **10** (1.30 g, 5.80

mmol, 83%) was isolated by extraction of the syrup with cold 1-propanol, and recrystallization from EtOH afforded colorless crystals, mp 160–161 °C. The mixed melting point of this compound with an authentic sample of **10** was not depressed, and treatment with phenylhydrazine afforded phenylhydrazone **11**, mp 181–182 °C, $[\alpha]_D$ −157° (pyridine). The 1-propanol mother liquors were treated with phenylhydrazine to give 2-*S*-ethyl-2-thio-D-mannose phenylhydrazone (**7**, 0.11 g, 0.37 mmol, ~8%), mp 157–159 °C, $[\alpha]_D$ +100° (*c* 1.1, pyridine), indistinguishable from an authentic sample by mixed mp.

Epimerization of 2-S-*ethyl-2-thio*-xd-*mannose* (**6**).—*(a) With sodium hydrogencarbonate.* A solution of syrupy **6** (0.10 g, 0.45 mmol) in water (2 mL) containing $NaHCO_3$ (0.025 g, 25% by weight) was evaporated at 35 °C and the residue was kept for 35 h at ~25 °C. The organic product was extracted with EtOH at 30 °C, and concentration of the extract gave, after slow cooling, crystalline 2-*S*-ethyl-2-thio-D-glucose (**10**, 88 mg, 88%), mp 159–160 °C, phenylhydrazone mp 181–182 °C (dec.), $[\alpha]_D$ −157° (pyridine).

(b) With Amberlite MB-3 ion-exchange resin. A solution of syrupy **6** (200 mg, 0.89 mmol) was stirred with Amberlite MB-3 resin (~3 g) for 4 h at room temperature. Filtration of the resin and evaporation of the filtrate gave a colorless syrup (170 mg) that crystallized partially during 2 days at 20 °C. Extraction with cold PrOH gave the D-*gluco* epimer **10** (109 mg, 0.49 mmol, 64%), mp 160 °C, phenylhydrazone mp 181–182 °C (dec.), $[\alpha]_D$ −157° (pyridine). Evaporation of the propanol extracts afforded the syrupy D-*manno* epimer **6** (60 mg, 0.20 mmol), which was characterized as the crystalline phenylhydrazone **7** (50 mg, 0.17 mmol, 19%), mp 159–161 °C, $[\alpha]_D$ +100° (pyridine). The results indicate that the reaction product contained **6** and **10** in about 1:3 ratio.

Epimerization of 2-S-*ethyl-2-thio*-D-*glucose* (**10**) with Amberlite MB-3 ion-exchange resin.—A solution of **10** (100 mg, 0.45 mmol) in water (7 mL) was stirred with Amberlite MB-3 resin (2 g) for 3 h at room temperature. Removal of the resin and the solvent gave a syrup (85 mg) that yielded, after storage under cold PrOH, crystalline starting material **10** (58 mg, 0.26 mmol, 67%), mp 160–161 °C, and the syrupy D-*manno* epimer **6** (28 mg) that afforded phenylhydrazone **7** (26 mg, 0.09 mmol, 20%). The reaction product thus contained **6** and **10** in about 1:3 ratio.

^{1}H NMR study of the epimerization process.—Crystalline **10** (10 mg) was dissolved in 99% D_2O (Aldrich Chemical Company) and $NaHCO_3$ (2 mg) was added. Changes in the NMR spectrum were monitored at 30 min periods at 300 MHz and are detailed in the Results and discussion section.

^{18}O Labelling study of the epimerization process.—Syrupy **6** (20 mg) was dissolved in 99% $H_2^{18}O$ (0.5 mL, Aldrich Chemical Company), and $NaHCO_3$ (5 mg) was added. The mixture was stirred at room temperature for 48 h, then the solvent was removed by distillation on a Kugelrohr apparatus. The residue was dissolved in pyridine (1 mL) and Ac_2O (1 mL), and the solution was stirred at room temperature for 16 h. After conventional work-up, the syrupy residue was analyzed by mass spectrometry. An experiment using D-*gluco* epimer **10** was performed in exactly the same manner using $H_2^{18}O$, as was a blank experiment in $H_2^{16}O$ using **10**. Details of the mass spectral analysis are given in the Results and discussion section.

*1*R *(or 1*S*)-3,4,5,6-Tetra*-O-*benzoyl-2*-S-*ethyl-2-thio*-D-*mannose ethyl phenyl dithioacetal* (**15**).—3,4,5,6-Tetra-*O*-benzoyl-D-glucose diethyl dithioacetal (**2**, 1.5 g)

dissolved in HCl–saturated $CHCl_3$ (20 mL) was treated with benzenethiol (0.7 mL) for 20 h at room temperature. The mixture was washed with water (20 mL), aq sodium hydrogencarbonate (20 mL), and water (20 mL), then dried ($CaCl_2$) and concentrated to a syrup. Crystallization was effected by treating the syrup with PrOH to yield white prisms of **15** (1.2 g, 71%), mp 99–101 °C, $[\alpha]_D$ +37° (*c* 1.6, $CHCl_3$), R_f 0.38 (6:1 hexane–EtOAc). IR (KBr) 3140, 3030, 1735, 1615, 1600, 1442, 1335 cm^{-1}; ^1H and ^{13}C NMR data are detailed in Tables 1 and 2, respectively. MS: *m/z* 812 $[M + NH_4^+]$. Anal. Calcd for $C_{44}H_{42}O_8S_3$: C, 66.47; H, 5.34; S, 12.01. Found: C, 66.33; H, 5.33; S, 12.05.

*3,4,5,6-Tetra-*O*-benzoyl-2-*S*-ethyl-2-thio-*D*-mannose dimethyl acetal* (**16**).—*(a) By demercaptalation of compound* **15**. A mixture of the ethyl phenyl dithioacetal (**15**, 0.5 g), $CdCO_3$ (0.4 g), $HgCl_2$ (1.0 g), and absolute MeOH (30 mL) was refluxed with stirring for 4 h. The cooled mixture was filtered, and the filtrate was concentrated to a syrup, which was leached with $CHCl_3$. The organic extract was washed with water (3 × 5 mL), dried (Na_2SO_4), and evaporated to a colorless syrup which crystallized from a small amount of MeOH; yield 0.4 g (92%), mp 92–94 °C, $[\alpha]_D$ +57° (*c* 1, $CHCl_3$), R_f 0.30 (6:1 hexane–EtOAc). IR ($CHCl_3$) 3025, 1750, 1440, 1260, 1210, 1105 cm^{-1}; see Tables 1 and 2, respectively, for ^1H and ^{13}C NMR data. MS: *m/z* 704 $[M + NH_4^+]$. Anal. Calcd for $C_{38}H_{38}O_{10}S$: C, 66.45; H, 5.57; S, 4.67. Found: C, 66.89; H, 5.30; 4.66.

(b) By demercaptalation of compound **3**. According to the method given in ref. [2], 3,4,5,6-tetra-*O*-benzoyl-2-*S*-ethyl-2-thio-D-mannose diethyl dithioacetal (**3**, 3.0 g) was treated with $HgCl_2$ (6.5 g) and $CdCO_3$ (2.7 g) in absolute MeOH (23 mL) to afford 3,4,5,6-tetra-*O*-benzoyl-2-*S*-ethyl-2-thio-D-mannose dimethyl acetal (**16**, 2.4 g, 87%), mp 94–95 °C, $[\alpha]_D$ +58° (*c* 1, $CHCl_3$), R_f 0.30 (6:1 hexane–EtOAc). For ^1H and ^{13}C NMR, see Tables 1 and 2, respectively. The mixed melting point with a sample prepared in the previous experiment was not depressed.

*3,4,5,6-Tetra-*O*-benzoyl-2-*S*-ethyl-2-thio-D-mannose diethyl dithioacetal* (**3**) *by resulfurization of* **16**.—A mixture of 3,4,5,6-tetra-*O*-benzoyl-2-*S*-ethyl-2-thio-D-mannose dimethyl acetal (**16**, 0.30 g), EtSH (1.5 g), anhydrous $ZnCl_2$ (2.0 g), and $CHCl_3$ (10 mL) was stirred for 16 h at room temperature. The $CHCl_3$ solution was succesively extracted with water (30 mL), 5% H_2SO_4 (30 mL), and saturated $NaHCO_3$ (30 mL). After drying ($CaCl_2$), the solution was evaporated to a syrup that crystallized upon treatment with EtOH to afford **3** (0.21 g, 65%), mp 80–83 °C, mixed melting point with an authentic sample [2] 82–83 °C, $[\alpha]_D$ +52° (*c* 1, $CHCl_3$). The ^1H and ^{13}C NMR spectra of this compound were identical with those reported for **3** in Tables 1 and 2.

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