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SILICA GEL-CATALYZED MIGRATION OF ACETYL GROUPS FROM A SULFUR TO AN OXYGEN ATOM*

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ABSTRACT

During the chromatographic separation of 3-*S*-acetyl-1,2-*O*-isopropylidene-3-thio-α-D-allofuranose on silica gel, a migration of the acetyl group from S to O was observed to give 6-*O*-acetyl-1,2-*O*-isopropylidene-3-thio-α-D-allofuranose, whereas 3-*S*-acetyl-6-*O*-benzoyl-1,2-*O*-isopropylidene-3-thio-α-D-allofuranose gave 5-*O*-acetyl-6-*O*-benzoyl-1,2-*O*-isopropylidene-3-thio-α-D-allofuranose. No acetyl migration was observed, however, in the case of 3-*O*-acetyl-1,2-*O*-isopropylidene-α- D-allofuranose.

INTRODUCTION

In an earlier report[1], this laboratory described the synthesis of methyl 2-deoxy-4-thio-D-*erythro*-pentoside from 3-*S*-acetyl-1,2-*O*-isopropylidene-3-thio-α-D-allofuranose (**1**). The usual procedure for the purification of **1** is by crystallization, but when purification was attempted by chromatography on silica gel, **1** was completely converted into a new compound, on t.l.c. having a mobility higher than that of **1**. We found that the new compound results from acetyl-group migration from the sulfur to an oxygen atom, and describe the conditions under which silica gel effects the migration in this and another compound. We also show that migration from an oxygen atom does not occur under similar conditions on silica gel.

RESULTS AND DISCUSSION

When crude 3-*S*-acetyl-1,2-*O*-isopropylidene-3-thio-α-D-allofuranose (**1**), obtained by the selective hydrolysis of 3-*S*-acetyl-1,2:5,6-di-*O*-isopropylidene-3-thio-α-D-allofuranose[1], was placed on a silica gel column for purification, elution gave in 92% yield a crystalline product having on t.l.c. mobility higher than that of the expected dihydroxy compound **1**. Repetition of this chromatographic operation with pure crystalline **1** also gave the same new product.

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The i.r. spectrum of the product eluted from the silica gel column indicated the presence of a thiol group (2575 cm^{-1}) but the absence of an acetylthio group (1685 cm^{-1}). A new peak at 1735 cm^{-1} was attributed to the carbonyl stretching absorption of an acetoxy carbonyl group[2]. The n.m.r. spectrum showed the significant upfield shift (δ 2.17) of *O*-acetyl protons as compared to the chemical shift of *S*-acetyl protons (δ 2.41) in **1**. The spectrum also showed a downfield shift of the resonance signal for H-6 from δ 3.87 in **1** to δ 4.38. From consideration of the elemental analysis, and i.r. and n.m.r. spectra, it is obvious that the acetyl group had migrated from S-3 to O-6, and the new compound was 6-*O*-acetyl-2-*O*-isopropylidene-3-thio-α-D-allofuranose (**2**).

Occurrence of acyl migrations in the carbohydrate series is well documented[3–6]. It seems that the intramolecular[5] acetyl migration always occurs from a secondary to a primary hydroxyl group[7], if one is sterically available. Acyl migration[8] usually takes place in a direction away from C-1, although some exceptions exist[3,9,10]. In the D-glucopyranose series, a very common acyl migration proceeds from C-4 to C-6, presumably through a six-membered cyclic ortho ester[6]. For the C-3 to C-6 acyl migrations, also common in the D-glucofuranose series[11,12], a seven-membered cyclic ortho ester intermediate was postulated[6]. A similar seven-membered intermediate seems probable for the conversion of **1** into **2**, although migration from S-3 to O-5, followed by migration from O-5 to O-6 has not been eliminated as a possibility.

To examine whether an acetyl group migration from S to O would take place if the C-6 hydroxyl position is blocked, we synthesized 3-*S*-acetyl-6-*O*-benzoyl-1,2-*O*-isopropylidene-3-thio-α-D-allofuranose (**3**) by selective benzoylation of **1**. The i.r. spectrum of **3** showed absorption peaks at 3590 (OH), 1685 (*S*-acetyl), and 1745 cm^{-1} (broad, *O*-acetyl and -benzoyl). The n.m.r. spectrum showed the expected signals at δ 1.48 and 1.30 (due to six isopropylidene protons), 2.42 (*S*-acetyl), 2.83 (OH), 4.55 (H-6), 6.07 (doublet, H-1) and 7.63–8.47 (5-aromatic-proton multiplet). When **3** was passed through a silica gel column, it also underwent transformation to a product, the i.r. spectrum of which showed the absence of a hydroxyl peak at 3590 cm^{-1} but the presence of a thiol absorption at 2575 cm^{-1}. In addition, the compound showed no thioacetate (*S* acid) peak at 1685 cm^{-1} but a broad acetyl peak at 1745 cm^{-1}.

The n.m.r. spectrum of the rearranged product showed an upfield shift of acetyl protons to δ 2.17 (*O*-acetyl), while the H-6 proton signal was moved downfield to δ 4.73. On the basis of the elemental analysis, and i.r. and n.m.r. spectra, the rearranged product was identified as 5-*O*-acetyl-6-*O*-benzoyl-1,2-*O*-isopropylidene-3-thio-α-D-allofuranose (**4**). The formation of **4** from **3** probably involves a six-membered cyclic ortho ester.

Silica gel can bind with the nonbonding electrons of the oxygen atom[13], and this may enhance the polarizability of the carbonyl carbon–oxygen double bond favoring nucleophilic attack of the oxygen atom of the hydroxyl group in **1** and **3** to form ortho ester intermediates. It is interesting to note that when the activity of the

silica gel was progressively reduced by increasing hydration (Table I), the tendency for acetyl migration also fell sharply and no migration was observed with silica gel of activity grade V. As silica gel becomes more hydrated, its acidic centers tend to acquire protonic character, thereby decreasing electron acceptor sites. This concept can explain the decreased acetyl migration found with the less active grades of silica gel.

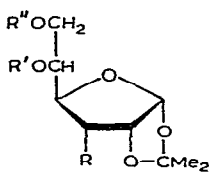
TABLE I

EFFECT OF SILICA GEL HYDRATION ON ACETYL MIGRATION[a]

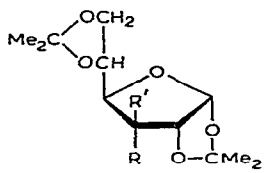
Activity grade	*Acetyl migration* (%)
I	100
II	100
III	25
IV	6
V	0

[a]Silica gel of grades II–V were prepared by adding 5, 15, 25, and 38% water to the grade I adsorbent (Baker Analytical reagents, 60–200 mesh).

The observed catalysis by silica gel of the acetyl group migration from S to O represents, to the best of our knowledge, the first demonstration of this action, although a number of secondary reactions caused by silica gel during chromatography have been noted. These include an oxirane rearrangement[13], shifting of ethylenic linkages[14,15], cleavage of the cyclopropaneting[16,18], detritylation of carbohydrates[17], elimination–rearrangement[18], and isomerization of the enolacetate epoxide[19] and anhydrosugars[20].



1 R = SAc, R′ = R″ = H
2 R = SH, R′ = H, R″ = OAc
3 R = SAc, R′ = H, R″ = OBz
4 R = SH, R′ = OAc, R″ = OBz
5 R = OAc, R′ = R″ = H



6 R = OH, R′ = H
7 R = H, R′ = OCH_2SMe
8 R = OAc, R′ = H

In order to examine whether the substitution of a sulfur by an oxygen atom at C-3 has any effect on the acetyl migration catalyzed by silica gel, we synthesized 3-*O*-acetyl-1,2-*O*-isopropylidene-α-D-allofuranose (**5**). To prepare this compound 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose was oxidized by dimethyl sulfoxide–acetic anhydride and the resulting product reduced by sodium borohydride to give 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose[21] (**6**). During the preparation of **6**, a crystalline by-product was isolated and characterized as 1,2:5,6-di-*O*-isopropylidene-3-*O*-(methylthio)methyl-α-D-glucofuranose (**7**) by consideration of a satisfactory elemental

analysis and of the n.m.r. spectrum that showed singlets[22,23] at δ 2.21 (*S*-methyl) and 4.87 (O–CH_2–S) and the C-2 proton resonating as a doublet at δ 4.68, which confirms the D-glucofuranose configuration[24]. The formations of (methylthio)methyl ethers have been previously reported during the dimethyl sulfoxide–acetic anhydride oxidation of the hydroxyl group, and the probable mechanism[22] suggests that the (methylthio)methyl ether group has the same configuration as the starting hydroxyl group.

The n.m.r. spectrum of **6** showed the H-2 proton as a triplet at δ 4.76, which is consistent with the *allo* configuration[25], and acetylation of **6** gave 3-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**8**). The n.m.r. spectrum of this compound showed a triplet corresponding to the H-2 proton shifted downfield to δ 5.10 because of the presence of the acetyl group at C-3[26]. Selective hydrolysis of **8** with 33% acetic acid gave 3-*O*-acetyl-1,2-*O*-isopropylidene-α-D-allofuranose (**5**), the n.m.r. spectrum of which showed the H-2 resonance as a triplet at δ 5.10. Compound **5** consumed one mole of sodium metaperiodate, which indicates the presence of vicinal hydroxyl groups.

Compound **5** was recovered unchanged after adsorption on a silica gel column and elution with irrigant D. The material recovered from the column had the same i.r. and n.m.r. spectra, and mobility on t.l.c., as the starting compound **5** and consumed one mole of sodium metaperiodate.

The acetyl group migration from S to O of **1** and **3**, catalyzed by silica gel, in contrast to **5** which remained unchanged, may be explained by the observation that the oxygen atom of the carbonyl group of the thioester **1** and **3** is more polarizable[27] than that of the ester group of **5** because of the lower electronegativity of the sulfur atom. This results in a more rapid formation of a cyclic ortho ester intermediate from **1** and **3** than from **5**. It is also important to mention that the π overlap of the C(2P) and S(3P) orbitals in the carbon–sulfur bond in **1** and **3** is much smaller than the C(2P) and O(2P) overlap in the carbon–oxygen bond in **5**, which causes the carbon–sulfur bond to be less stable than the carbon–oxygen bond[28].

EXPERIMENTAL

General. — The purity of products was determined by t.l.c. on silica gel-coated plates irrigated with (A) 6:1 (v/v) benzene–ethyl acetate or (B) 9:2 (v/v) chloroform–acetone. Components were located by spraying with 10% sulfuric acid in ethanol, and heating. Column chromatography was performed on columns (2.5 × 45 cm) of silica gel (Baker Analytical Reagents, 60–200 mesh, pH 6.45), eluted with (C) 10:1 (v/v) benzene–ethyl acetate and (D) 10:1 (v/v) chloroform–acetone at a flow rate of 1 ml/min. All melting points are corrected. The n.m.r. spectra were recorded on solutions in chloroform-*d* with a Varian T-60A spectrometer and the optical rotations were measured with a Perkin–Elmer Model 141 polarimeter. Unless otherwise stated, the i.r. spectra were determined on KBr discs.

6-O-Acetyl-1,2-O-isopropylidene-3-thio-α-D-allofuranose (**2**). — A solution of

1 (1.0 g) in chloroform (5 ml) was applied to a column packed with silica gel, and the column was eluted with solvent D. The fractions containing the component having R_F 0.6 on t.l.c. with solvent B were evaporated, whereupon the residue crystallized. Recrystallization from ether–hexane gave pure **2** as needles, (0.92 g, 92%); m.p. 80–81°, $[\alpha]_D^{25}$ +73.5° (*c* 0.9, chloroform); i.r. data: ν_{max} 3540 (OH), 2575 (SH), and 1735 cm^{-1} (OAc); n.m.r. data: δ 2.72 (singlet, OH), 4.38 (H-6), 4.77 (triplet, H-2), 6.00 (doublets, $J_{1,2}$ 3.0 Hz, H-1).

Anal. Calc. for $C_{11}H_{18}O_6S$: C, 47.48; H, 6.52; S, 11.50. Found: C, 47.53; H, 6.55; S, 11.57.

Another run starting from crude **1** (1.0 g) obtained by the hydrolysis of 3-*S*-acetyl-1,2:5,6-di-*O*-isopropylidene-3-thio-α-D-allofuranose gave **2** (0.8 g) after passage through a silica gel column.

3-S-Acetyl-6-O-benzoyl-1,2-O-isopropylidene-3-thio-α-D-allofuranose (**3**). — To a cold (−15°) solution of **1** (2.78 g) in dry pyridine (30 ml) was added dropwise a solution of benzoyl chloride (1.45 g) in alcohol-free chloroform (10 ml) with exclusion of moisture. The reaction mixture was stirred for 5 h below 0° and for 16 h at 25°, and then concentrated. The residue was dissolved in chloroform and successively washed with saturated sodium hydrogen carbonate solution and water, and dried (sodium sulfate). Evaporation gave **3** as a syrup which was crystallized from benzene–hexane (2.5 g), m.p. 98–100°, $[\alpha]_D^{25}$ +142.5° (*c* 0.9, chloroform); i.r. data: ν_{max} 3590 (OH), 1685 (SAc), and 1745 cm^{-1} (broad, OAc and OBz); n.m.r. data: δ 1.30 and 1.48 (6-proton triplet, CMe_2), 2.42 (3-proton singlet, SAc), 2.83 (broad, OH), 4.55 (H-6), 6.07 (doublet, H-1), and 7.63–8.47 (5-aromatic-proton multiplet); t.l.c.: (in solvent A) R_F 0.45.

Anal. Calc. for $C_{18}H_{22}O_7S$: C, 56.54; H, 5.80; S, 8.37. Found: C, 56.62; H, 5.76; S, 8.37.

5-O-Acetyl-6-O-benzoyl-2-O-isopropylidene-3-thio-α-D-allofuranose (**4**). — The benzoyl derivative **3** (1.0 g) was adsorbed on a column of silica gel, which was eluted with solvent C. The fractions containing the mercapto compound **4** were combined and evaporated to a crystalline residue. Recrystallization from ether–hexane gave **4**, (0.92 g) m.p. 106–107°, $[\alpha]_D^{25}$ +165.3° (*c* 0.9, chloroform); i.r. data: ν_{max} 2575 (SH) and 1745 cm^{-1} (OAc and OBz); n.m.r. data: δ 1.40 and 1.75 (6-proton doublets, CMe), 2.17 (3-proton singlet, OAc), 4.73 (H-6) and 6.0 (doublet, H-2); t.l.c. (solvent A) R_F 0.60.

Anal. Calc. for $C_{18}H_{22}O_7S$: C, 56.53; H, 5.80; S, 8.38. Found: C, 56.58; H, 5.92; S, 8.30.

1,2:5,6-Di-O-isopropylidene-3-O-(methylthio)methyl-α-D-glucofuranose (**7**). — 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (2.0 g) was oxidized with dimethyl sulfoxide–acetic anhydride and then directly reduced with sodium borohydride following the method of Sowa and Thomas[21]. The reaction product was applied to a column packed with silica gel and the column was eluted with 20:1 (v/v) hexane–ethyl acetate. The fractions containing **7** were collected first and concentrated to a syrup which was crystallized from hexane (0.3 g), m.p. 47–48°, $[\alpha]_D^{25}$ −33.6° (*c* 0.9,

chloroform); n.m.r. data: δ 1.33, 1.43 and 1.52 (12-proton, 2-CMe_2) 2.21 (3-proton singlet, SMe), 4.68 (doublet, H-2), 4.87 (2-proton singlet, OCH_2S), and 6.05 (doublet, H-1).

Anal. Calc. for $C_{14}H_{24}O_6S$: C, 52.48; H, 7.54; S, 9.99: Found: C, 52.71; H, 7.60; S, 9.80.

Further elution gave **8** as a major product (1.27 g, 63%), m.p. 78° (lit.[22]: m.p. 77–78°).

3-O-Acetyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (**8**). — Compound **6** (1.0 g) was dissolved in pyridine (20 ml) containing acetic anhydride (8 ml) and the mixture was allowed to stand for 24 h at 25°. The solvent was evaporated *in vacuo* to give **8** which was crystallized from ether–hexane (1.10 g), m.p. 76°, $[\alpha]_D^{25}$ +64.2° (*c* 0.9, chloroform); i.r. datum: ν_{max} 1735 cm^{-1} (OAc); n.m.r. data: δ 1.37, 1.45 and 1.58 (12-proton, 2-CMe_2), 2.12 (3-proton singlet, OAc), and 5.10 (triplet, H-2).

Anal. Calc. for $C_{14}H_{22}O_7$: C, 55.62; H, 7.33. Found: C, 55.50; H, 7.48.

3-O-Acetyl-1,2-O-isopropylidene-α-D-allofuranose (**5**). — Compound **8** (0.5 g) was dissolved in 30% aqueous acetic acid (60 ml) and the solution was stirred for 16 h at 25° under a current of nitrogen. The reaction mixture was concentrated to a syrup which was extracted with ether (3 × 150 ml) and dried (sodium sulfate). Concentration *in vacuo* gave **5** as a colorless syrup (0.3 g) that was homogeneous by t.l.c. (solvent D) and consumed one mole of sodium metaperiodate; $[\alpha]_D^{25}$ +294.3° (*c* 0.9, chloroform); i.r. data: ν_{max} 3435 (H-bonded OH) and 1735 cm^{-1} (OAc); n.m.r. data: δ 1.38 and 1.66 (6 protons, CMe_2), 2.13 (3-proton singlet, OAc), 2.82 (2-proton singlet, 2 OH), 3.82 (2 proton, H-6), and 5.10 (1-proton triplet, H-2).

Anal. Calc. for $C_{11}H_{18}O_7$: C, 50.44; H, 6.91. Found: C, 50.27; H, 7.12.

Compound **5** (1.0 g) was deposited on a silica gel column and, after elution of the column with solvent D, was recovered unchanged (identical i.r., n.m.r., and R_F) in almost quantitative yield (0.96 g). As expected, **5** recovered from the column consumed one mole of sodium metaperiodate.

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