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ACID-CATALYZED TRANSFORMATIONS OF 5-THIO-D-GALACTOSE DERIVATIVES

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ABSTRACT

Alkyl furanoside and pyranoside derivatives of 5-thio-D-galactose undergo a variety of transformations during methanolysis and other acid-catalyzed solvolysis reactions. Among several novel products obtained are 1,5-anhydro-6-*O*-methyl-5-thio-α-D-galactofuranose, methyl 6-chloro-6-deoxy-5-thio-α-D-galactopyranoside, 1,6-anhydro-5-*O*-methyl-6-thio-β-L-altrofuranose, and 2-formyl-5-(methoxymethyl)thiophene. Facile, neighboring-group participation by the sulfur atom in reactions at a β-carbon atom is regarded as the origin of these transformations, which strikingly distinguish the thioaldose from its oxygen analog.

INTRODUCTION

In reporting a synthesis of 5-thio-D-galactose and various derivatives of this sugar, reference was made to several unknown by-products encountered at different stages of the study[1]. The characterization of some of these by-products is described here, and their modes of formation are considered.

RESULTS AND DISCUSSION

Formation of by-products during the methanolysis of ethyl 5-thio-β-D-galactofuranoside. — Methanolysis, catalyzed by hydrogen chloride, was employed[1] to convert ethyl 2,3,6-tri-*O*-acetyl-5-*S*-acetyl-5-thio-β-D-galactofuranoside (**1**) into methyl 5-thio-α- and -β-D-galactopyranoside (**2** and **3**, respectively). However, these pyranosides accounted for barely half of the total product, *i.e.*, **2** constituted 40%, and **3**, ~5%. The rest, as shown by gas-chromatographic analysis of the acetylated methanolysis product, consisted of at least eight, possibly unknown, compounds. When the acetylated material was chromatographed on a column of silica gel, *O*-acetyl derivatives of the three main by-products were isolated. According to the data to be presented, these three compounds are designated 2,3,6-tri-*O*-acetyl-1,5-anhydro-

5-thio-α-D-galactofuranose (**4**)*, 2,3-di-*O*-acetyl-1,5-anhydro-6-*O*-methyl-5-thio-α-D-galactofuranose (**5**)*, and methyl 2,3,4-tri-*O*-acetyl-6-chloro-6-deoxy-5-thio-α-D-galactopyranoside (**6**).

Compound **5**, the first of these to be eluted from the chromatogram, constituted ~5% of the total methanolysis–acetylation product given by **1**. Its mass spectrum showed a parent-ion peak at *m/e* 276, and the presence of a sulfur atom in the molecule was confirmed by the ratio of the intensity of this peak to that of M + 2 (*i.e.*, 17.2:0.7). According to its ^{13}C- and ^{1}H-n.m.r. spectra (see Table I), **5** is a six-carbon compound bearing seven protons and containing one methoxyl and two acetoxyl substituents. These characteristics are consistent with a bicyclic anhydride structure, such as that depicted for **5**. As the resonance of the anomeric carbon atom (at δ 84.6) is ~20 p.p.m. upfield of that of **1** (δ 105.1), but close to that of C-1 of **2** and **3** (δ ~82, ref. 1), C-1 must be bonded to the sulfur atom. The latter must also be bonded to the strongly shielded nucleus (δ 48.6) ascribed to C-5. By contrast, the signal of C-6 is far downfield of the C-6 signals of **1**, **2**, or **3**, *i.e.*, at δ 74.5 as compared with δ 61–64 (ref. 1), indicating[2] that the methoxyl group is on C-6. Support for this conclusion was found

TABLE I

^{1}H- AND ^{13}C-N.M.R. PARAMETERS OF DERIVATIVES OF 1,5-ANHYDRO-5-THIO-α-D-GALACTOFURANOSE (**4** AND **5**)

Atom	*^{1}H (δ)*[a]			*Atom or group*	*^{13}C (δ)*[b]	
	4	5	7[c]		4	5
H-1	5.72	5.73	5.69	C-1	84.7	84.6
H-2	4.96	4.95	4.73	C-2	82.5	82.8
H-3	~4.6	4.76	4.66	C-3	79.4	79.5
H-4	~4.6	4.74	4.38	C-4	85.4	85.4
H-5	3.36	3.4–2.8	3.70	C-5	48.6	49.1
H-6	3.98		4.00	C-6	65.2[d]	74.5[d]
H-6′	3.86		3.82	OCH_3	—	59.2
				CO	170.8	170.8–170.0
				CH_3	21.1	21.1–20.8

Compound	*J (Hz)*							*J (Hz)*	
	1,2	*2,3*	*3,4*	*4,5*	*5,6*	*5,6′*	*6,6′*	*C-1*,H-*1*	*C-4,H-4*[e]
4	4.1	2.5	~0	~0	6.6	8.2	11.0	176	160
5	4.2	2.5	~0	~0	—	—	—		
7[c]	2.4	1.4	~0	~0	5.6	5.6	10.3		

[a]Solvent, C_6D_6. [b]Solvent, $CDCl_3$. [c]2,3,6-Tri-*O*-acetyl-1,5-anhydro-α-D-galactofuranose (data from ref. 3). [d]Triplet (^{1}J). [e]Other ^{1}J values are 155-147 Hz.

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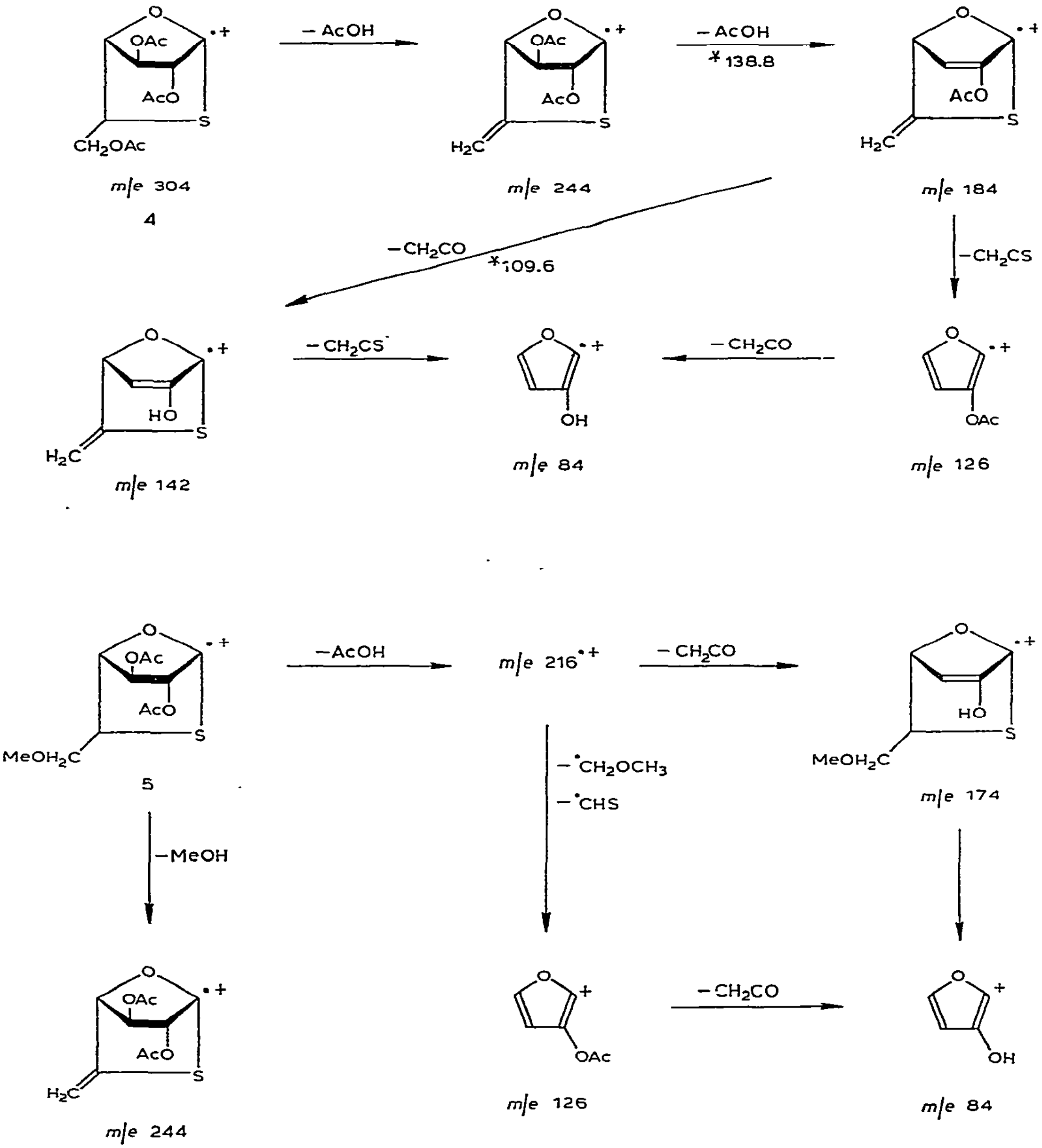
*Alternatively, the compound may be regarded as a derivative of 1,4-anhydro-5-thio-β-D-galactopyranose.

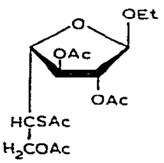
in the mass spectrum, which contains an intense peak (40%) at *m/e* 45, ascribable to $CH_2{=}O\text{-}CH_3^+$ formed by cleavage of the C-5–C-6 bond. Therefore, as product 5 cannot be a 1,6-anhydride, so often encountered with aldohexoses under acidic reaction-conditions, its bicyclic structure most probably consists of a 1,4 and a 1,5 ring, as shown.



Scheme 1. Mass-spectral fragmentation of 2,3,6-tri-*O*-acetyl-1,5-anhydro-5-thio-α-D-galactofuranose (**4**).

The major by-product was **4**, a low-melting solid obtained in 16% yield. From a comparison of the ^{13}C- and ^{1}H-n.m.r. spectra and mass spectra of **4** with those of **5**, it was evident that these two compounds differ only in that **4** contains an *O*-acetyl group instead of the *O*-methyl group of **5**. Thus, the two sets of n.m.r. signals for C-1 to C-5 are almost coincident (see Table I), whereas, as would be expected[2], the C-6 signal of **4** is far upfield of that of **5**, because it bears an ester, not an ether, substituent. Similarly, their ^{1}H-n.m.r. spectra, although only partially resolved, exhibit several characteristics in common (see Table I). Also noteworthy is the fact that the ^{1}H-n.m.r. spectrum of **4** is closely similar to that (see Table I) of its 5-oxa analog, *viz.*, 2,3,6-tri-*O*-acetyl-1,5-anhydro-α-D-galactofuranose (**7**); only the chemical shift of H-5 is strongly affected (upfield shift) by the presence of the ring-sulfur atom, characteristics already noted[1] on comparing **2** and **3** with their oxygen analogs. Hence, these data not only support the structure postulated for **4**, but that of **5** as well.

Other information consistent with formulas **4** and **5** is available from the mass spectra of the compounds. As generally observed[4,5] with peracetates, the parent ion of **4** is extremely weak, and the first prominent fragment encountered (*m/e* 244) represents the loss of a molecule of acetic acid (see Scheme 1). Presumably, this originates from the primary ester group of **4**, because the 6-*O*-methyl derivative (**5**) produces a relatively intense, parent ion. Subsequent, neutral losses of acetic acid, ketene, and thioketene account for other prominent fragments indicated in Scheme 1. Many of the same fragments appear to be formed from **5**, through initial loss of methanol to give an ion of *m/e* 244, and by an alternative pathway involving elimination of acetic acid to form a fragment of mass 216 (see Scheme 1).



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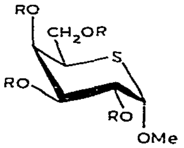

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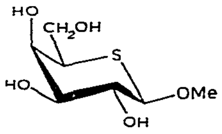
9 R = Ac



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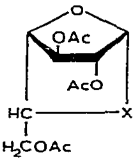
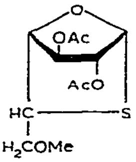


4 X = S
7 X = O



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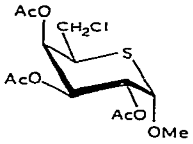

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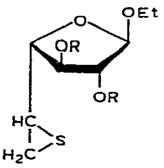


8 R = $Me_3C(Me)_2Si$

Product **6**, the third compound isolated, accounted for 5% of the total methanolyzate. Its identification was facilitated by the fact that more of the same compound

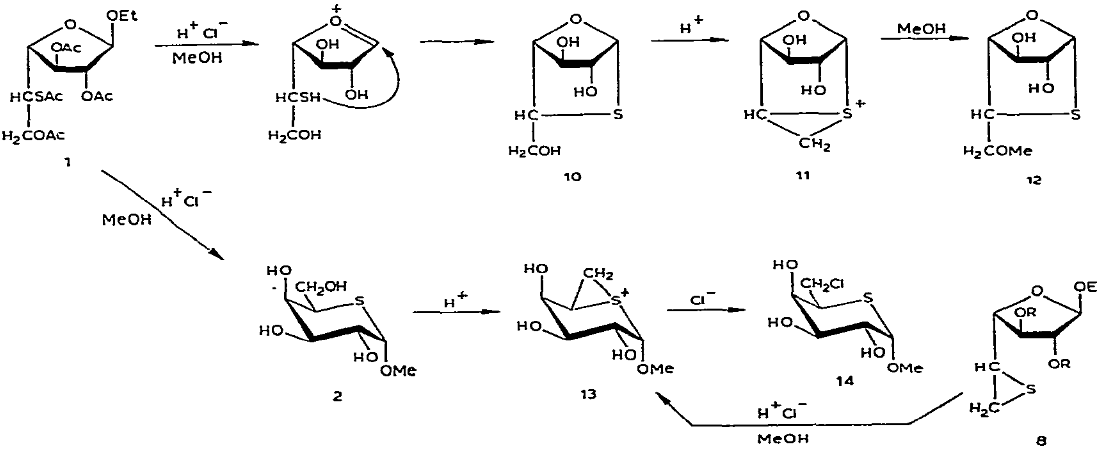
TABLE II

A COMPARISON OF ^{1}H- AND ^{13}C-N.M.R. PARAMETERS[a] OF METHYL 2,3,4-TRI-*O*-ACETYL-6-CHLORO-6-DEOXY-5-THIO-α-D-GALACTOPYRANOSIDE (**6**) WITH THOSE OF METHYL 2,3,4,6-TETRA-*O*-ACETYL-5-THIO-α-D-GALACTOPYRANOSIDE (**9**)

Atom or group	^{1}H (δ)		*Atom or group*	^{13}C (δ)	
	6	**9**		**6**	**9**
H-1	4.67[b]	4.70[b]	C-1	81.9	81.6
H-2	5.44	5.35	C-2	71.2	71.2
H-3	5.35	5.35	C-3	68.8	68.3
H-4	5.80	5.64	C-4	68.6	68.3
H-5	3.5–3.3	3.64	C-5	41.4	38.1
H-6		4.14	C-6	41.7[c]	60.9
H-6′		3.94	OCH_3	56.7	56.5
OCH_3	3.44	3.42			

[a]Solvent, $CDCl_3$. [b]$J_{1,2}$ 2.5 Hz. [c]Triplet ($^{1}J_{C,H}$).

was readily acquired (in 48% yield) by methanolysis of **8***, a precursor of **1**. The relative abundances of the M peak (at *m/e* 354) and the M + 2 peak in the mass spectrum of **6** showed that a molecule of **6** contains an atom of chlorine. From ^{13}C- and ^{1}H-n.m.r. data, it was evident that this product is a glycoside closely related in structure to the peracetate of **2**, *i.e.*, **9**. Thus, for **6** and **9**, the chemical shifts of C-1, C-2, C-3, C-4, and the methoxyl carbon atom are virtually coincident (see Table II); also, the C-6 signal of the former is 19 p.p.m. upfield, which is consistent with replacement of the 6-acetoxyl group of **9** by a chlorine atom. In their ^{1}H-n.m.r. spectra (see



Scheme 2. Formation of by-products **10**, **12**, and **14** during the methanolysis of ethyl 2,3,6-tri-*O*-acetyl-5-*S*-acetyl-5-thio-β-D-galactofuranoside (**1**).

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*This reaction was, in fact, examined, in considering the possibility (see later) that a cyclic sulfonium ion located at C-5 and C-6 is involved in the formation of **4**, **5**, and **6**.

Table II), the only appreciable differences are the relative, upfield locations of the signals for H-5, H-6, and H-6′, as expected, and the evidence for the presence of only three *O*-acetyl groups in **6**, compared to the four in **9**.

The yield of anhydride **4** from **1** is 50 times that[3] of the corresponding oxygen derivative, *viz.*, 1,5-anhydro-α-D-galactofuranose, from D-galactose in acid solution. In fact, the latter sugar produces[6] more of both 1,6-anhydro-β-D-galactopyranose and -α-D-galactofuranose than of the 1,5-anhydride. These differences probably reflect the stronger nucleophilicity of a thiol than of a hydroxyl group, a further indication of which is found[7,8] in the facile, acid-catalyzed formation of 1,6-thioanhydrides from 6-thioaldohexose derivatives. Nevertheless, it appears that 1,5-anhydro-5-thio-aldohexofuranoses or -aldopentofuranoses corresponding to **4** have not been detected as side-products in the synthesis of other 5-thioaldoses. Hence, **4** and **5** are unique examples of this class of bicyclic compound.

Some ways in which these by-products may have been formed from **1** are illustrated in Scheme 2. Nucleophilic attack on the anomeric center by the 5-thiol group*, with retention of the furanose ring, would lead to anhydride **10**, and this, on acetylation, to **4**. In view of the activating effect of a sulfur atom on a β-carbon atom[10], it is possible that **10** is dehydrated to form an episulfonium ion intermediate (**11**) that, in methanol, affords the 6-*O*-methyl anhydride **12**, isolated as its diacetate** (**5**). If the formation of an analogous, cyclic sulfonium ion (**13**) from methyl 5-thio-α-D-galactopyranoside (**2**), the major methanolysis product, is envisaged, the isolation of a 6-chloro-6-deoxy glycoside (**14**), and, subsequently, its triacetate (**6**), may be attributed to opening of the episulfonium ring by chloride in the solvolysis medium. The fact that thiirane **8** also gave **14** on methanolysis may be accounted for by opening of the furanoside ring, followed by cyclization to yield pyranoside **13** (see Scheme 2). As the formation of **11** and **13** implies that the reaction products should also include a chloro derivative analogous to **11**, and a methyl ether analogous to **13**, it should be noted that reference has already been made to several other, as yet unidentified, compounds detected in the mixture.

*Acetolysis of ethyl 2,3,6-tri-*O*-acetyl-5-*S*-acetyl-5-thio-β-D-galactofuranoside.* — Anhydride formation is also an important side-reaction in the acid-catalyzed acetolysis of ethyl 2,3,6-tri-*O*-acetyl-5-*S*-acetyl-5-thio-β-D-galactofuranoside (**1**). As reported earlier[1], when **1** was treated with a mixture of acetic acid, acetic anhydride, and sulfuric acid for three days at room temperature, it afforded the pentaacetates of 5-thio-α-D-galactofuranose, -β-D-galactofuranose, and -β-D-galactopyranose, together with an unidentified compound, in the ratios of 5:8:11:9. The last compound has now been identified as 2,3,6-tri-*O*-acetyl-1,5-anhydro-5-thio-α-D-galactofuranose (**4**). Hence, this is analogous to the formation of **10** as the main side-product obtained

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*It is not yet clear whether protonation favors an oxygen or a sulfur atom[9]. ^{13}C-N.m.r., i.r., and acid–base-equilibrium studies on dimethyl sulfoxide suggest that protonation occurs on oxygen, whereas ^{1}H-n.m.r. data have been interpreted in terms of protonation of the sulfur atom.

Rearrangements observed[11–13] with other thio sugar derivatives may be cited as evidence that cyclic sulfonium ions could be involved in these reactions on methanolysis of **1. Because of the relatively low proportion of pyranose products furnished by acetolysis, this procedure is regarded[1] as unsatisfactory for the preparation of derivatives of 5-thio-D-galactopyranose, in contrast to its successful use[14] in the *gluco* and *rhamno* series.

Hydrobrominolysis of methyl 5-thio-α-D-galactopyranoside. — As already mentioned, methyl 5-thio-α-D-galactopyranoside (**2**) was isolated in 40% yield by methanolysis of **1**, whereas little of the β anomer (**3**) was detected. A larger quantity of the latter was prepared[1] by the Koenigs–Knorr reaction; that is, glycosyl bromide **15**, obtained by the reaction of methyl 2,3,4,6-tetra-*O*-acetyl-5-thio-α-D-galactopyranoside (**9**) with hydrogen bromide, was treated with methanol and silver carbonate, affording a 1:4 mixture of the α- and β-anomeric glycosides (**9** and **16**). However, several by-products were present in this reaction mixture as well.

One of these by-products was a minor component isolated during the chromatographic separation of **9** from **16** on silica gel. It is designated 2,3-di-*O*-acetyl-1,6-anhydro-5-*O*-methyl-6-thio-β-L-altrofuranose (**17**), on the basis of the following evidence. According to its mass spectrum, the molecular weight of **17** is 276 and, as shown by the $M/(M + 2)$ ratio, it contains an atom of sulfur. The ^{1}H- and ^{13}C-n.m.r. spectra of the compound indicated that six carbon atoms and seven protons are associated with the sugar (see Table III), and that there are two *O*-acetyl groups and

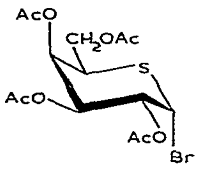
TABLE III

A COMPARISON OF ^{1}H- AND ^{13}C-N.M.R. PARAMETERS OF 2,3-DI-*O*-ACETYL-1,6-ANHYDRO-5-*O*-METHYL-6-THIO-β-L-ALTROFURANOSE (**17**) WITH THOSE OF RELATED ANHYDRIDES (**18**[a] AND **19**[b])[c]

Atom or group	*^{1}H (δ)*			*Atom or group*	*^{13}C (δ)*	
	17	**18**	**19**		**17**	**18**
H-1	5.58	5.50	5.54	C-1	83.2	96.9
H-2	5.30	5.10	5.08	C-2 ⎫	79.4	78.7
H-3	5.07	5.30	5.15	C-3 ⎭	78.7	75.8
H-4	4.25	4.40	4.30	C-4	80.8	79.4
H-5	3.40	4.97	4.72	C-5	70.3	63.9
H-6	3.15	4.10	4.14	C-6	26.2[d]	62.6[d]
H-6′	2.69	3.70	3.87	OCH_3	57.1	—
OCH_3	3.40	—		CO	171.3–170.3	170.8–170.0
				CH_3	21.1	21.2– 21.0

Compound	J *(Hz)*						
	1,2	*2,3*	*3,4*	*4,5*	*5,6*	*5,6′*	*6,6′*
17	6.2	2.5	<1	<1	3.5	2.3	14.2
18	4.5	2.7	~0	4.4	6.7	11.4	11.4
19	3.5	1.5	~0	2.0	3.0	1.1	14.1

[a] 2,3,5-Tri-*O*-acetyl-1,6-anhydro-α-D-galactofuranose. [b] 2,3,5-Tri-*O*-acetyl-1,6-anhydro-β-L-altrofuranose. [c] Solvent, $CDCl_3$. [d] Triplet ($^{1}J_{C,H}$).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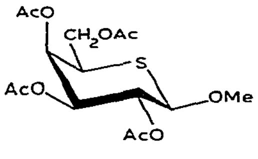
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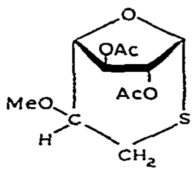
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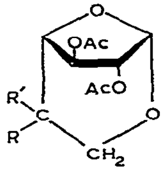
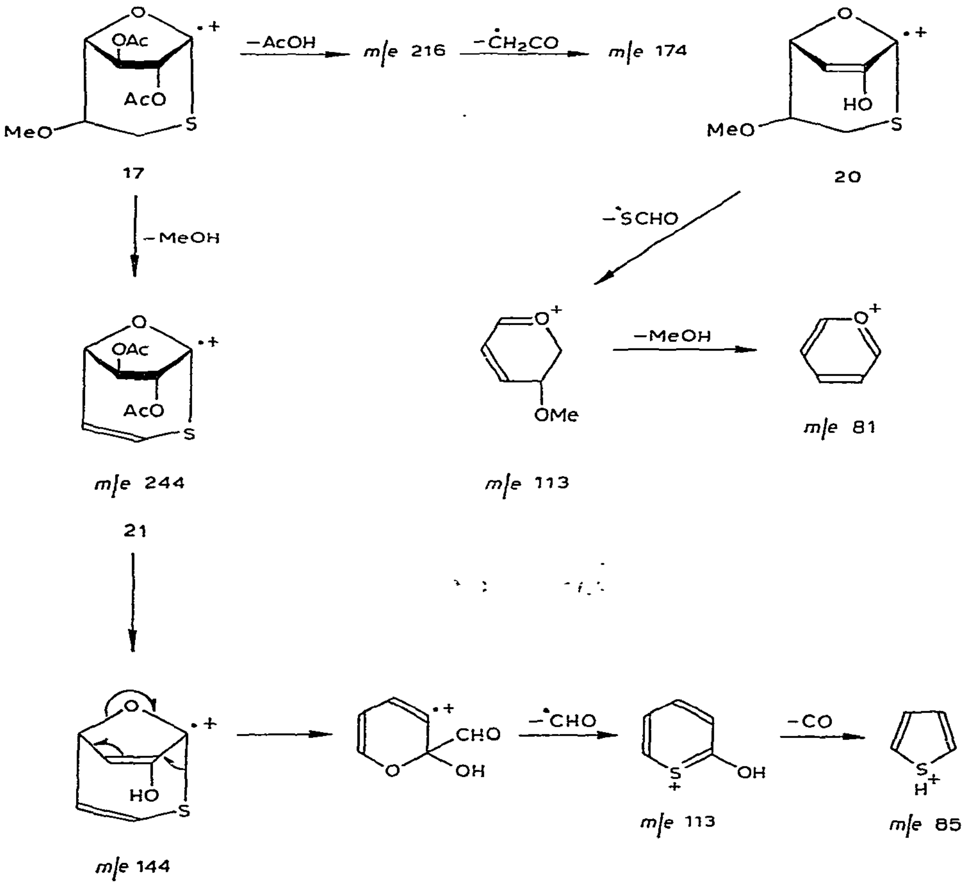

18 R = OAc, R′ = H
19 R = H, R′ = OAc.

one *O*-methyl group. Evidence that the sulfur atom bridges C-1 and C-6 is furnished by the fact that the C-1 and C-6 signals are far upfield (by 14 and 36 p.p.m., respectively) of the corresponding signals of 2,3,5-tri-*O*-acetyl-1,6-anhydro-*β*-D-galactofuranose (**18**), which served as a reference compound. By contrast, the C-5 signal of **17** is relatively downfield (by ~6 p.p.m.), consistent with the presence of a methoxyl



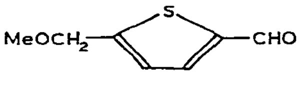
Scheme 3. Mass-spectral fragmentation of 2,3-di-*O*-acetyl-1,6-anhydro-5-*O*-methyl-6-thio-*β*-L-altrofuranose (**17**).

group on C-5. The assignment of the *altro* configuration is based on a comparison of the ^{1}H-n.m.r. spectrum of **17** with those[15] of **18** and its C-5 epimer, namely, 2,3,5-tri-*O*-acetyl-1,6-anhydro-β-L-altrofuranose (**19**) (see Table III). In particular, the coupling-constant patterns for H-5 and H-6,6′ of **17** and **19** are closely similar, and distinct from the pattern for **18**.

The mass spectrum of **17** helped to confirm the structure proposed. A number of the prominent ions detected in this spectrum are analogous to ion fragments already depicted for anhydride **5**. Thus, as illustrated in Scheme 3, an intense ion (**20**) of *m/e* 174 may be accounted for by consecutive losses of acetic acid (giving an ion of *m/e* 216) and ketene. A loss of ·SCHO, and then of methanol, accounts for ions of *m/e* 113 and 81. Alternatively, there is an initial loss of methanol to form ion **21** of mass 244, followed by the loss of acetic acid (giving an ion of *m/e* 184) and ketene, with the production of ion **22** (*m/e* 144). Ions of *m/e* 113 and *m/e* 85 could result from rearrangement of **22** and subsequent loss of ·CHO and carbon monoxide.

Another side-product accompanying the conversion of the α-glycoside **9** into its β anomer (**16**) is 2-formyl-5-(methoxymethyl)thiophene (**23**). The formation of a 2-formylthiophene moiety during hydrobrominolysis of **14** was suggested by the appearance, in the ^{1}H-n.m.r. spectrum of the reaction mixture, of prominent signals at δ 9.84 (singlet), 7.60 and 7.17 (doublets, *J* 3.8 Hz), and 4.67 (singlet). Following the solvolysis step with methanol and silver carbonate, there were analogous signals at δ 9.84 (s), 7.60 (d), 7.04 (d), and 4.64 (s), respectively [*i.e.*, the last two were now slightly upfield, and an additional singlet (OCH_3) appeared at δ 3.88].

The isolation and identification of **23** was facilitated by the finding that this compound is also obtained from the D-*gluco* isomer[16], which is much more readily available than **14**. Commercial 5-thio-D-glucose was converted into methyl 2,3,4,6-tetra-*O*-acetyl-5-thio-α-D-glucopyranoside (**24**), which was then treated with hydrogen bromide, followed by methanolysis of the product in the presence of silver carbonate. When the mixture of products obtained was chromatographed on a column of silica gel, the material first eluted was a syrupy compound having a ^{1}H-n.m.r. spectrum superposable on the group of five signals described at the end of the preceding paragraph. The mass spectrum of this product showed an intense, parent-ion peak of mass 156, and the base peak (at *m/e* 127) corresponded to the loss of ·CHO from the molecular ion. In the i.r. region, the compound absorbed strongly at 1690 cm^{-1}, close to the C=O frequency[17] of 2-formylthiophene. From a comparison of the ^{13}C chemical-shifts with those[18] of 2-formylthiophene, the aldehyde group was assigned to C-2. Furthermore, the observed coupling (*J* 3.8 Hz) between the AB



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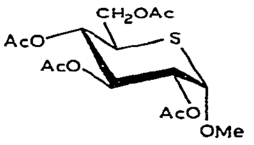

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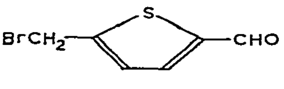

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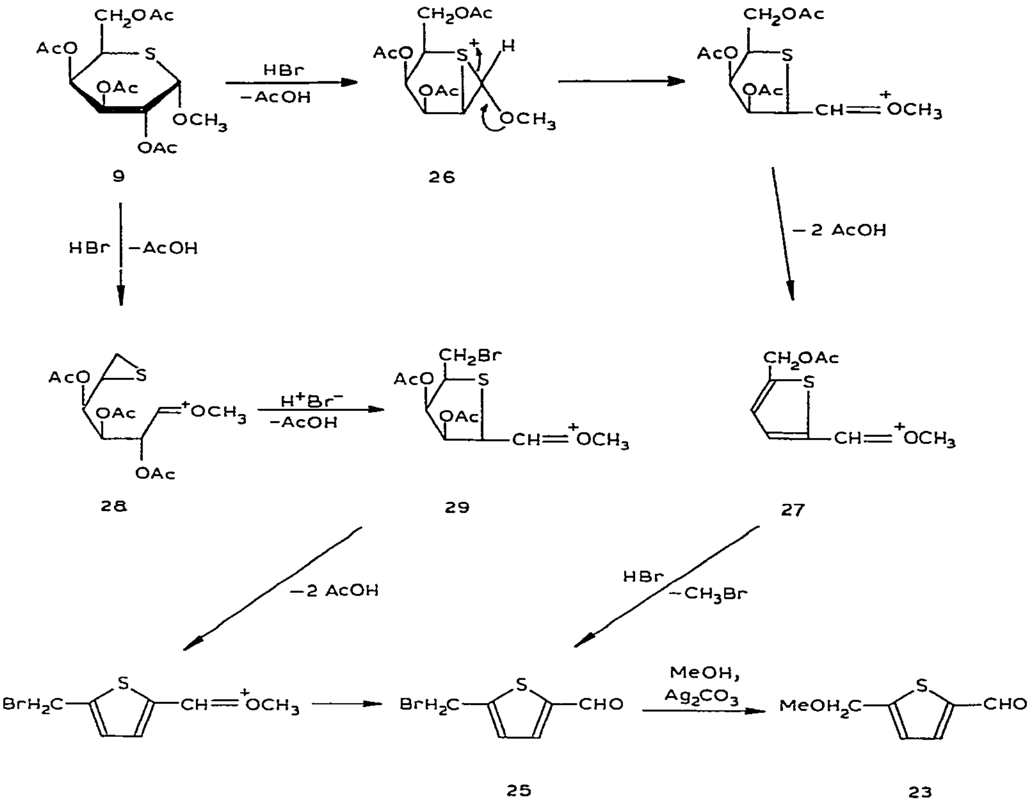
pair of protons resonating at δ 7.60 and 7.04 is also consistent[19] with the 2,5-disubstituted thiophene structure proposed (**23**).

Probably, therefore, the hydrobrominolysis of glycoside **9** or **24** leads, *via* the corresponding glycosyl bromide, to 2-formyl-5-(bromoethyl)thiophene (**25**), which yields **23** on methanolysis. Although the formation of these thiophene derivatives from 5-thioaldoses bears some analogy to the acid-catalyzed formation of 2-furaldehyde and derivatives from aldoses, its formation is much more facile in the thio sugar series. Thus, the hydrobrominolysis of methyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside, and similar glycosides, leads[20] to the formation both of pyranosyl and furanosyl bromides, and also to some bromination at C-6, but 5-(bromoethyl)-2-furaldehyde (analogous to **25**) is apparently not produced. This difference is attributed to the greater nucleophilicity of the ring-sulfur atom which, through enhanced participation in intramolecular displacements, favors the formation of such cyclic, sulfonium-ion intermediates as have already been considered. Possible sequences (see Scheme 4) include displacement of the 2-acetoxyl group in **9**, to give intermediates **26** and then **27**, or of the 6-acetoxyl group, to yield **28** and then **29**. Generation of the resonance-stabilized, thiophene ring should then follow readily.



Scheme 4. Formation of 2-formyl-5-(methoxymethyl)thiophene (**23**) from methyl 2,3,4,6-tetra-*O*-acetyl-5-thio-α-D-galactopyranoside (**9**).

EXPERIMENTAL

General methods. — Solutions were usually evaporated below 40° under diminished pressure. Optical rotations were determined at room temperature, for solutions in 1-dm tubes, with a Carl Zeiss polarimeter (Model 367732). I.r. spectra were recorded for films on AgCl or NaCl discs, or for KBr pellets, with a Unicam SP-200G grating spectrophotometer. Plates of Silica Gel G were used for t.l.c., and the developing solvents were as specified. Silica gel for column chromatography (0.08-mm particle size) was obtained from Macherey, Nagel and Co. Gas–liquid chromatography was performed with a Hewlett–Packard F and M 402 gas chromatograph, using an OV-101 or an OV-225 column. Proton magnetic resonance spectra were recorded with a Varian HA-100 or a Bruker WH-90 spectrometer. ^{13}C-N.m.r. spectra were recorded at 22.6 MHz with a Bruker WH-90 spectrometer. Chemical shifts (δ) are reported with reference to tetramethylsilane.

*Methanolysis of ethyl 2,3,6-tri-*O*-acetyl-5-*S*-acetyl-5-thio-β-*D*-galactofuranoside* (**1**): *isolation of* **4**, **5**, *and* **6**. — A solution of **1** (4.0 g) in dry methanol (50 mL) and acetyl chloride (2.5 mL) was boiled under reflux in a nitrogen atmosphere for 10 h, cooled, made neutral with silver carbonate, and the suspension filtered. The filtrate was clarified with charcoal (Darco G-60), and evaporated to a syrup which was acetylated with 2:1 acetic anhydride–pyridine. Chromatography of the acetylation product (2.7 g) on a column (1.8 × 30 cm) of silica gel with 50:1 dichloromethane–acetone afforded a syrup (0.43 g) which, according to t.l.c. in 2:1 hexane–ethyl acetate, consisted of at least three products [R_F 0.59 (**5**), 0.55 (**6**), and 0.50 (**4**)]. This syrup (0.4 g) was re-chromatographed on a column (1.3 × 30 cm) of silica gel with 5:1 hexane–ethyl acetate. Based on t.l.c. and g.l.c. examination of the eluate, pure samples of **4**, **5**, and **6** were collected. The last two products were syrups, whereas **4** crystallized from ether–petroleum ether; m.p. 56–58°, $[\alpha]_D$ +218° (*c* 1.0, chloroform); for the ^{1}H- and ^{13}C-n.m.r. data for **4**, **5**, and **6**, see Table I.

Anal. Calc. for $C_{12}H_{16}O_7S$ (**4**): mol. wt., 304. Found: *m/e* 262 (M — CH_2CO), *m/e* 244 (M — CH_3COOH).

Anal. Calc. for $C_{11}H_{16}O_6S$ (**5**): mol. wt., 276. Found: *m/e* 276 (M), *m/e* 244 (M — CH_3OH), *m/e* 216 (M — CH_3COOH).

*Methyl 2,3-di-*O*-acetyl-6-chloro-6-deoxy-5-thio-α-*D*-galactopyranoside* (**6**) *from the methanolysis of* **8**. — A solution of ethyl 2,3-di-*O*-(*tert*-butyldimethylsilyl)-5,6-dideoxy-5,6-epithio-β-D-galactofuranoside (**8**; 70 mg) in methanolic hydrogen chloride (5%; 5 mL) was boiled under reflux in a nitrogen atmosphere for 6 h, made neutral with Amberlite IR-45 (OH^-) resin, the suspension filtered, and the filtrate evaporated. The syrupy residue was acetylated with 2:1 acetic anhydride–pyridine, and t.l.c. examination (10:1 dichloromethane–acetone) then showed the presence of a major component and at least 8 minor components. Chromatography of the acetylation product on a column (1.5 × 30 cm) of silica gel with 30:1 dichloromethane–acetone gave **6** (27 mg, 48%) as the first compound eluted; $[\alpha]_D$ +201° (*c* 1.1, chloroform); ^{1}H-n.m.r. data ($CDCl_3$): δ 5.80 (t, 1 H, H-4), 5.44–5.35 (2 H, H-2,3), 4.67 (1 H, H-1), 3.5–3.3 (3 H, H-5,6,6′), 3.44 (s, 3 H, OCH_3), and 2.14–1.96 (9 H, 3 $OCOCH_3$); $J_{1,2}$ ~2 Hz; spectrum indistinguishable from that of **6** (see preceding section).

Anal. Calc. for $C_{15}H_{19}ClO_7S$: mol. wt., 354. Found: *m/e* 354 (M), *m/e* 294 (M — CH_3COOH).

2,3-Di-O-acetyl-1,6-anhydro-5-O-methyl-6-thio-β-L-altrofuranose (**17**). — As reported previously[1], the synthesis of methyl 2,3,4,6-tetra-*O*-acetyl-5-thio-*β*-D-galactopyranoside (**16**) was accompanied by the formation of three minor products, as indicated by g.l.c. examination. During the isolation of glycoside **16** by column chromatography on silica gel with 25:1 benzene–ethyl ether, a sample (30 mg) of syrupy **19** was obtained (pure, according to t.l.c. and g.l.c. evidence); for the ^{1}H- and ^{13}C-n.m.r. data, see Table III.

Anal. Calc. for $C_{11}H_{16}O_6S$: mol. wt., 276. Found: *m/e* 276 (M), *m/e* 216 (M — CH_3COOH), *m/e* 174 (M — CH_3COOH — CH_2CO).

2-Formyl-5-(methoxymethyl)thiophene (**23**). — A solution of 5-thio-D-glucose (Aldrich; 0.14 g) in methanolic hydrogen chloride (2%; 20 mL) was stirred in a nitrogen atmosphere for 36 h, made neutral with Amberlite IR-45 (OH^-) resin, and the suspension filtered. The filtrate was evaporated to a syrup which was acetylated with 2:1 acetic anhydride–pyridine. According to its ^{1}H- and ^{13}C-n.m.r. spectra, the acetylation product (syrup, 0.26 g) consisted almost exclusively of methyl 2,3,4,6-tetra-*O*-acetyl-5-thio-α-D-glucopyranoside (**24**). This material (0.25 g) was dissolved in a solution of hydrogen bromide in acetic acid (30%; 5 mL). After 2.5 h, chloroform and ice–water were added, and the chloroform layer was washed successively with saturated sodium hydrogencarbonate and water, dried (anhydrous sodium sulfate), and evaporated, affording a dark residue. The latter was dissolved in methanol (35 mL), silver carbonate (0.4 g) was introduced, the suspension was stirred for 2 days, and filtered, and the filtrate was evaporated. According to t.l.c. (25:1 dichloromethane–acetone), the product consisted of at least four compounds. Chromatography of the mixture on a column (1.4 × 2.5 cm) of silica gel with 50:1 dichloromethane–acetone gave syrupy **23** (20 mg), followed (n.m.r. evidence) by a mixture of **24** and its *β* anomer. ^{1}H-N.m.r. data for **23** ($CDCl_3$): δ 9.84 (s, 1 H, CHO), 7.60 (d, 1 H, H-4), 7.04 (d, 1 H, H-3), 4.64 (s, 2 H, CH_2), and 3.88 (s, 3 H, OCH_3); $J_{3,4}$ 3.8 Hz; ^{13}C-n.m.r. data for **23** ($CDCl_3$): δ 182.7 (CO), 152.0 (C-2), 143.3 (C-5), 131.6 (C-3), and 126.4 (C-4).

Anal. Calc. for $C_7H_8O_2S$ (**23**): mol. wt., 156. Found: *m/e* 156 (M), *m/e* 127 (M — CHO).

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