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SULFUR PARTICIPATION IN METHANOLYSIS AND ACETOLYSIS OF 5-DEOXY-5-THIO-D-GLUCOSE DERIVATIVES

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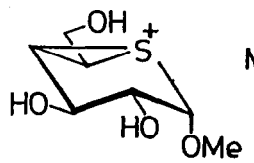
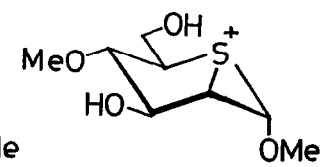
Abstract : Acid methanolysis of 5-deoxy-5-thio-D-glucose derivatives gave the 4-O-methyl glycoside 4 and the 4,6-di-O-methylated dimethyl acetal 7, indicating transannular participation of the sulfur atom. Similarly, acetolysis of the corresponding per-O-alkylated glucosides gave the 1,4-diacetates, 13 and 17.

Nucleophilic substitutions of 2- and 4-O-sulfonates of 5-thiopyranoside derivatives were found to proceed via transannular sulfur participation, giving substituted products with retention of configuration or ring-contracted products[1]. A similar ring contraction was suggested for the formation of 5-bromomethyl-2-formylthiophene on the hydrobrominolysis[2] of methyl 2,3,4,6-tetra-O-acetyl-5-deoxy-5-thio-α-D-glucopyranoside. On the other hand, 5-deoxy-5-thio-D-glucopyranose was shown to inhibit D-glucose transport across the membrane and to interfere with the enzymes involved in carbohydrate metabolism[3]. In the course of synthesis of 5-deoxy-5-thio-D-gluconolactone derivatives[4], acid methanolysis and acetolysis were examined, and a few unexpected products derived via episulfonium ions I∿III were ascertained. In this communication we should like to describe the results indicating participation of the ring sulfur atom in these reactions.



I



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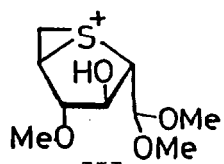


III

Methanolysis of 3,6-di-O-acetyl-5-S-acetyl-1,2-O-isopropylidene-α-D-glucofuranose[5] (1) was carried out under anhydrous and hydrous conditions, i.e., with 3% HCl in methanol and 2.8% HCl in methanol (containing 4.4% H_2O). It was found that the expected methyl 5-deoxy-5-thio-α-D-glucopyranoside (3) was obtained in satisfactory yields (60∿62%) by methanolysis of 1 under the hydrous conditions at room temperature for a long time (Table 1, entry 3) or at refluxing temperature for 1∿1.5 h (entries 5 and 6). In the latter case,

Table 1. Methanolysis of 5-Deoxy-5-thio-D-glucose Derivatives.

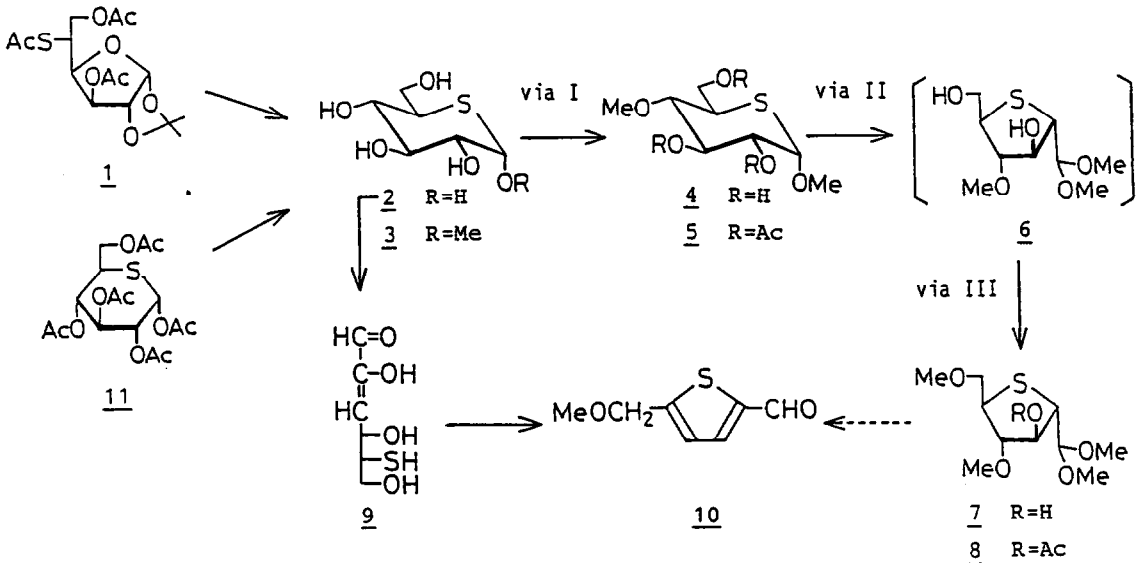
Entry	Starting Material	Method[a]	Conditions		Products (%)			
			Temp.	Time (h)	3	4	7	10
1	1	A	r.t.	24	34	--[b]	--	--
2	1	A	r.t.	50	33	7	--	--
3	1	B	r.t.	168	60	--	--	--
4	1	B	reflux[c]	1/2	42	--	--	--
5	1	B	reflux	1	62	5	--	--
6	1	B	reflux	3/2	62	10	--	--
7	1	B	reflux	5	31	27	--	--
8	1	B	reflux	9	16	23	--	trace
9	1	B	reflux	13	13	26	--	9
10	1	B	reflux	27	trace	18	--	24
11	11	B	reflux	2/3	49	1	--	--
12	11	B	reflux	7	27	23	--	--
13	11	B	reflux	34	3	16	--	27
14	2	A	reflux	12	--	27	14	--
15	3	A	reflux	2	--	14	18	--
16	2	B	reflux	12	11	24	--	16
17	2	B	reflux	36	--	23	--	15
18	3	B	reflux	20	trace	40	--	--

a A: 3% HCl/MeOH, B: 2.8% HCl/MeOH(4.4%H_2O). b Not detected.
c The bath temperature was 70°C.

the second and unexpected product, i.e., the 4-O-methyl derivative[6] 4 was isolated in 5% yield after 1 h. On the other hand, under anhydrous condition the formation of 4 seems to be accelerated, considering its formation even at room temperature (entry 2). In order to clarify the mechanism of the formation of 4, time-dependence of product distribution in this reaction was examined. (Table 1, entries 4∿10). The yield of 3 reached to the maximum value of 62% after 1∿1.5h as described above, and then decreased gradually to trace amount during 27h. After 5h the amount of 4 reached a maximum yield (∿30%), which was maintained for further 10h. The third product was first formed after ca.10h and confirmed to be 2-formyl-5-methoxymethylthiophene 10. Similar time-dependence of the product distribution was observed (entries 11∿13) on the methanolysis of 1,2,3,4,6-penta-O-acetyl-5-deoxy-5-thio-D-glucopyranose (11)[7], which may produce immediately the common intermediate, 5-deoxy-5-thio-D-glucopyranose (2). Thus, in order to prevent the further conversion of 3 into 4 and its decomposition, a short reaction time (entries 5 and 6) or a lower temperature (entry 3) was of choice.

The formation of 4 can be explained by displacement of hydroxyl group at C-4 with methoxyl one via the bicyclic episulfonium intermediate I. As described above the sulfur participation seems to be promoted much more under the anhydrous condition. This was further confirmed in the following experiments.

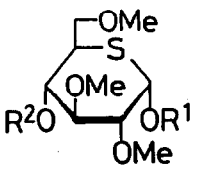
Sulfur participation was also observed on methanolysis of 2 and 3 under the anhydrous condition, giving 4,6-di-O-methyl dimethyl acetal 7 instead of 10 (entries 14 and 15). This indicates that a ring contraction may occur via episulfonium ion II. 6-Methoxylation of a dimethyl acetal 6 suggests the formation of episulfonium ion III, rapid formation of which can be easily deduced by the fast solvolysis rate of 2-(p-nitrobenzoyloxymethyl)-tetrahydrothiophene[8]. Thus, compound 7 may be formed from 1 and 11 as shown in the following scheme.



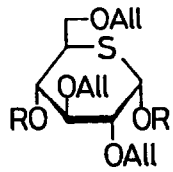
On the other hand, 10 may be formed by another pathway. Hydrolytic conversion of the acetal 7 into the corresponding aldehyde followed by elimination of water and methanol is one of the most plausible pathways to 10, and the pathway seems to be supported by the fact that 10 was obtained in 27% yield by methanolysis of 7 at reflux for 15h under the hydrous condition. However, methanolysis of 2 under the hydrous condition did not give 7 at all (entries 16, 17), although 10 was obtained instead. Further, neither 7 nor 10 could be obtained by methanolysis of 3 as well as 4 under the hydrous condition. This may indicate that the participation of ring sulfur in the reaction at C-2 does not occur under the hydrous condition. For the formation of 10, the importance of free aldose as an intermediate was suggested and also supposed by the fact that 5-benzyloxymethyl analog of 10 was obtained in 59% yield by hydrolysis of methyl 2,3,4,6-tetra-O-benzyl-5-deoxy-5-thio-α-D-glucopyranoside in acidic medium of low water content (0.05M H_2SO_4 in 95% aqueous acetic acid at 90°C). Therefore, an alternative pathway which bears some analogy to the acid catalyzed formation[9] of 2-furaldehyde via the corresponding 3-deoxyhexosulose 9 may be plausible.

Furthermore, similar sulfur participation under acidic conditions was observed in acetolysis of per-O-alkylated glycosides. Acetolysis of methyl per-O-methyl-5-deoxy-5-thio-α-D-glucopyranoside (12) in the presence of

sulfuric acid at room temperature gave the corresponding 1,4-diacetate 13 in 93% yield. 2,3,6-Tri-O-allyl analog (16) of 12 was acetolyzed to give a 1,4-diacetate 17 in 72% yield. These results indicate the formation of an episulfonium ion like I. On the contrary, acetolysis of 12 in the presence of trifluoroacetic acid at 75°C gave the normal acetolysis product 14 and 4-acetate 15 in 48% and 8% yield, respectively.



12 $R^1=R^2=Me$
13 $R^1=R^2=Ac$
14 $R^1=Ac, R^2=Me$
15 $R^1=Me, R^2=Ac$



16 R=Me
17 R=Ac

Methanolysis and acetolysis described in this paper provide further example of transannular participation of sulfur atom under acidic conditions and the participation of the sulfur atom was proved as a general feature in displacement reactions of 5-thiopyranosides.

References and notes.

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6. All new compounds were characterized by elemental analysis and spectroscopic data. ^{1}H-NMR data: 4 (D_2O, 100MHz): δ 4.28(H-2), 4.29(H-3), 4.22(H-4), 5 ($CDCl_3$, 100MHz): δ 5.07(H-2), 5.42(H-3), 3.54(H-4), 7 ($CDCl_3$, 500MHz): δ 4.42(d, $J_{1,2}$ 8.2Hz, H-1), 3.39(dd, $J_{2,3}$ 6.3Hz, H-2), 4.12(dt, $J_{3,4}$ 6.3, $J_{3,OH}$ 4.0Hz, H-3), 3.62(dd, $J_{4,5}$ 6.3Hz, H-4), 3.40(H-5), 8 ($CDCl_3$, 500MHz): δ 5.46 (t, $J_{2,3}=J_{3,4}$=4.2Hz, H-3), 13 ($CDCl_3$, 100MHz): δ 6.16 (d, H-1), 5.12(dd, H-4), 17 ($CDCl_3$, 100MHz): δ 6.08(d, H-1), 4.34(dd, H-4).
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