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14 (11) 1303～1306 (1966)]

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Kazuhiko Araki and Setsuzo Tejima: Thiosugars. IX.[*1] Further Studies on the Anomalous Substitution of the Secondary Mesyl in Thiosugars.

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In the previous papers of this series[1] one of us reported on the anomalous substitution of the secondary mesyl in thiosugars, *viz.*, the mesyl at C2 of D-glucopyranose was easily substituted by thioacetyl to afford 1,2-di-S-acetyl-1,2-dithio-3,4,6-tri-O-acetyl-β-D-mannopyranose (IV) when a mixture of potassium thiolacetate and 1-S-(ethoxythiocarbonyl)-1-thio-2-O-mesyl-3,4,6-tri-O-acetyl-β-D-glucopyranose (I) in acetone-ethanol was refluxed for ten minutes.

Generally, as the secondary mesyl in carbohydrates resists nucleophilic substitution, our finding might be one of a characteristic reactions in thiosugars. We have been speculating the reaction mechanisms as follows.

In the initial stage of the reaction, thiolacetate attacks from the top of C2 and a cyclic carbonium cation as a sulfonium or an oxonium (II) may be formed. In the next step, bond cleavage carries out, from which removal of the ethoxythiocarbonyl and migration of the mesyl from C2 to C1 occur simultaneously (III). Finally, another molecule of thiolacetate attacks from the top of the anomeric carbon to form IV involving the replacement of the mesyl with thioacetyl at C1.

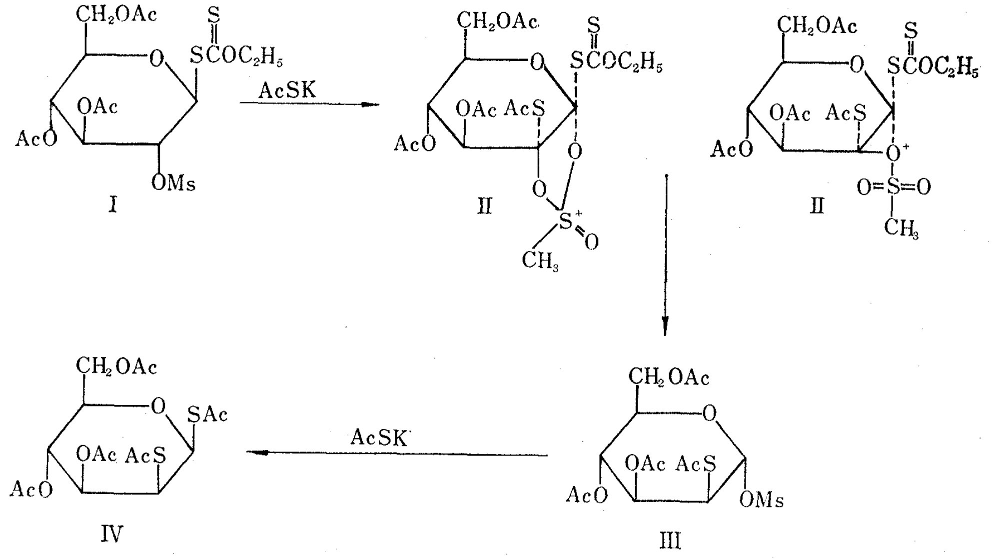

Chart 1.

In the course of the progressive program of this interesting reaction, we projected an epimerization of sugar derivatives assuming that if this reaction were carried out in other nucleophiles as acylates we shoud be obtainable D-mannose derivatives starting from D-glucose.

Contrary to the expectation, the substitution did not occur, while recovered the starting material (I) when one mole of I and two moles of potassium acetate were reacted under the similar condition as mentioned in the case of before.

[*1] Part VIII. H. Nakamura, S. Tejima, M. Akagi: This Bulletin, **14**, 648 (1966).

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1) H. Nakamura, S. Tejima, M. Akagi: This Bulletin, **13**, 1478 (1965); **14**, 648 (1966).

In the next step, we had to select more vigorous condition. Helferich and Gnüchtel[2] reported that the primary mesyl in methyl 2,3,4,6-tetra-O-mesyl-α-D-glucopyranoside was replaced quantitatively by acetyl to give methyl 6-O-acetyl-2,3,4-tri-O-mesyl-α-D-glucopyranoside when refluxed with potassium acetate in acetic anhydride for one hour. The authors applied their condition for the replacement of the active mesyl in I.

A mixture of one mole of I and three moles of potassium acetate in actic anhydride was refluxed for two hours at 140° in an oil-bath, then poured the mixture into an ice-water. Crystals (V), m.p. 144.5°, $[\alpha]_D^{20}$ $-34.5°$ (c=1.05, $CHCl_3$) were separated in 68% yield after extraction from the mixture with chloroform. The structure was assigned to be 1,2-dithio-3,4,6-tri-O-acetyl-D-mannopyranose 1,2-S-carbonate (V), a new type of derivatives which has not yet been reported in carbohydrates.[3] The present paper describes full details of this work.

The ultraviolet absorption spectrum of V did not show any peak near 270 mμ corresponding to the thiocarbonyl in ethoxythiocarbonyl. The infrared absorption spectrum showed a strong band at 1650 cm^{-1} which could not be identified in I, and it was assigned to be the carbonyl in cyclic dithiocarbonate. Mecke *et al.*[4] reported an infrared absorption on 1,3-dithiolan-2-one, who found that the carbonyl occurred at the region of lower wave numbers (1638 cm^{-1}) owing to the mesomeric effect provided with the two sulfur atoms, which is consistent with our assignment on carbonyl in cyclic dithiocarbonate. Neither at 1170 nor at 1360 cm^{-1} bands, corresponding sulfonic acid ester, could be identified in V.

The product (V) was desulfurized with Raney nickel to give a colorless oil, $[\alpha]_D^{20}$ $+50.3°$ (c=1.49, EtOH), its rate of flow was completely identical with that of the authentic 3,4,6-tri-O-acetyl-D-hydroglucal[1] on thin-layer chromatography using silica gel.

The nuclear magnetic resonance spectrum of V was measured at 60 Mc. The anomeric proton showed a doublet at τ 4.36 with the coupling constant ($J_{1,2}$=2.5 c.p.s.). This small value was in agreement with an axial-equatorial orientation at C1 and C2, which clearly confirmed the configuration of the D-mannose type. Nine protons, corresponding three acetyls, appeared at τ 7.92 and 7.95 along with seven protons in the region of τ 4.52~6.20, which were ascribed to sugar molecule.

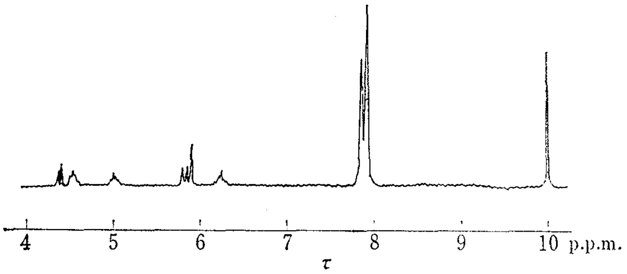

Fig. 1. Nuclear Magnetic Resonance Spectrum of 1,2-Dithio-3,4,6-tri-O-acetyl-D-mannopyranose 1,2-S-Carbonate (V)

The product (V) was also obtained by reflux of a mixture of I and anhydrous sodium acetate in acetic anhydride or glacial acetic acid. The product was stable and prolonged heating did not alter the structure.

On the other hand, when a mixture of 1-S-(ethoxythiocarbonyl)-1-thio-2,3,4,6-tetra-O-acetyl-β-D-glucopyranose,[5] anhydrous sodium acetate and potassium acetate was refluxed in acetic anhydride led to the formation of 1-S-acetyl-1-thio-2,3,4,6-tetra-O-acetyl-β-D-glucopyranose[5] in 80% yield.

In the case of the reaction, thermal decomposition of the ethoxythiocarbonyl might

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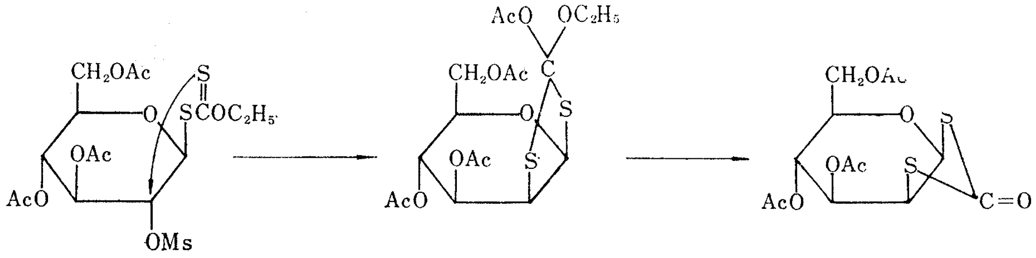
2) B. Helferich, A. Gnüchtel: Ber., **71**, 712 (1938).

3) L. Hough, J. E. Priddle, R. S. Theobald: "Advances in Carbohydrate Chemistry," Vol. 15, 91 (1960), Academic Press Inc., New York and London; D. Horton, D. H. Hutson: *Ibid.*, Vol. 18, 123 (1963); E. E. Reid: "Organic Chemistry of Bivalent Sulfur," Vol. I~V (1963), Chemical Publishing Co., Inc., New York.

4) R. Mecke, R. Mecke, A. Luttringhaus: Chem. Ber., **90**, 975 (1957).

5) W. Schneider, R. Gille, K. Eisfeld: Ber., **61**, 1244 (1928).

have occurred under the evolution of carbonyl sulfide to form thiol, which has been converted to thioacetyl in acetic anhydride. From this datum the presence of an easily replaceable group at C2 must be indispensable to the formation of the cyclic 1,2-S-carbonate (V). The authors assumed the mechanisms on the formation of V as showed in Chart 2.



I V

Chart 2.

The only other example of sugar derivatives having cyclic thiocarbonate group, which has been known in literature, was 4,6-[6] or 5,6-S-thiocarbonate[7] of hexoses. Compound having cyclic S-carbonate in pyranose ring might be the first reported examples in this field. Further, it is remarkable to notice that the formation of the product may be formed through other course of reaction than that of 1,2-di-S-acetyl-1,2-dithio-3,4,6-tri-O-acetyl-β-D-mannopyranose (Ⅳ).

Experimental

Unless stated otherwise, solvents were evaporated *in vacuo* at a bath temperature of 40° in a rotatory evaporator. Thin-layer chromatography was carried out by Wakogel B-5 using benzene-MeOH (19:1) or AcOEt-iso-PrOH-H_2O (18:1:1) as solvent and 50% H_2SO_4 as spray reagent. The NMR spectrum was measured by Varian A60 at 60 Mc. with $(CH_3)_4Si$ as internal standard. Chemical shifs were given in τ values and coupling constants (J) in c.p.s.

1,2-Dithio-3,4,6-tri-O-acetyl-D-mannopyranose 1,2-S-Carbonate (V)——A mixture of 1-S-(ethoxythiocarbonyl)-1-thio-2-O-mesyl-3,4,6-tri-O-acetyl-β-D-glucopyranose (I)[1] (2 g.) and anhyd. AcONa (1 g.) in Ac_2O (15 ml.) was refluxed at 140° in an oil-bath. After 2 hr., stopped the heating, added AcOK (1 g.) and continued the reflux for further 1 hr. The cooled reaction mixture was poured into ice-H_2O (300 ml.), neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$-layer was dried over $CaCl_2$, filtered and the solvent was evaporated from the filtrate to afford pale yellow oils. The residue was triturated with little amounts of EtOH to give white crystals (1 g., 68%). Recrystallization from EtOH gave pure materials, m.p. 144.5°, $[\alpha]_D^{20}$ $-34.8°$ (c=1.05, $CHCl_3$). *Anal.* Calcd. for $C_{13}H_{16}O_8S_2$: C, 42.85; H, 4.43; S, 17.60. Found : C, 43.08; H, 4.48; S, 17.22. IR λ_{max}^{Nujol} cm^{-1} 1750 (-OAc), 1650 (C=O). Ethanolic solution of V did not show UV absorption near 270 mμ. A mixture of V (0.2 g.), AcONa (0.1 g.) and AcOK (0.1 g.) in Ac_2O (5 ml.) was refluxed for 1 hr. at 140° in an oil-bath, while, the starting material (0.15 g.) was recovered from the reaction mixture after treatment as described above.

The product (V) was also obtained when either a mixture of I (2 g.) and AcONa (2 g.), or I (2 g.) and AcOK (2 g.) was refluxed for 2 hr. in either Ac_2O (15 ml.) or AcOH (15 ml.).

3,4,6-Tri-O-acetyl-D-hydroglucal——A solution of V (1 g.) in abs. EtOH (30 ml.) was treated with freshly prepared Raney Ni (20 g. of alloy was activated) and the resulting suspension refluxed for 6 hr. Ni was removed by filtration through Celite and charcoal, then washed throughly with abs. EtOH. The combined filtrate and washings were concentrated to afford a colorless sirup (0.7 g.), $[\alpha]_D^{20}$ $+50.3°$ (c=1.49, EtOH). Fischer[8] reported $[\alpha]_D$ $+35.5°$ for 3,4,6-tri-O-acetyl-D-hydroglucal. Rf value of the sirup was completely identical with that of the authentic 3,4,6-tri-O-acetyl-D-hydroglucal on thin-layer chromatography.

1-S-Acetyl-1-thio-2,3,4,6-tetra-O-acetyl-β-D-glucopyranose——A mixture of 1-S-(ethoxythiocarbonyl)-1-thio-2,3,4,6-tetra-O-acetyl-β-D-glucopyranose (2 g.), anhyd. AcONa (1 g.) and AcOK (1 g.) in Ac_2O (15 ml.) was refluxed for 2 hr. at 140° in an oil-bath. The cooled mixture was poured into ice-H_2O (300 ml.), then

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6) M. Kojima, T. Taguchi : Abstract of Papers presented at the 21st Pharmaceutical Assembly of the Pharmaceutical Society of Japan, 310 (1965).

7) B.R. Baker, L. Goodman : J. Am. Chem. Soc., **80**, 6577 (1958).

8) E. Fischer : Ber., **47**, 196 (1914).

left to stand under stirring. White crystalline powders appeared during several hr., which were filtered and recrystallized from EtOH to give pure material (1.5 g., 80%), m.p. 121°, $[\alpha]_D^{20}$ +15°(c=1.50, $CHCl_3$). IR λ_{max}^{Nujol} cm^{-1}: 1760 (-OAc), 1690 (-SAc). The product did not show mixed m.p. depression with the authentic sample of 1-S-acetyl-1-thio-2,3,4,6-tetra-O-acetyl-β-D-glucopyranose.

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