175. Takao Maki and Setsuzu Tejima: Thiosugars. XI.\textsuperscript{a,3} Further Studies on Thiolevoglycosans.

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2-Deoxy-1,6-anhydro-1,6-sulfide-\(\beta\)-d-glucofuranose (2-Deoxy-thiolevoglycosan) (X), m.p. 189–192\(^{\circ}\), \(\{\alpha\}^D_{	ext{c}} -71.7^\circ\), and 2-deoxy-1,6-anhydro-1,6-sulfide-3,4-anhydro-\(\beta\)-n-altrose (2-Deoxy-3,4-anhydro-thiolevoglycosan) (XIV), m.p. 69–72\(^{\circ}\), \(\{\alpha\}^D_{	ext{c}} -108^\circ\), were synthesized by starting with \(\beta\)-glucal (II), followed by treatment of the intermediate 2-deoxy-6-0-tosyl-3,4-di-O-acetyl-\(\beta\)-d-glucofuranosyl ethylxanthate (VI) and 3-bromo-4-O-acetyl-6-O-tosyl-2,3-dideoxy-\(\beta\)-d-glucopyranosyl ethylxanthate (XII), respectively, with sodium methoxide.

The preparation of 6-O-tosyl-3,4-di-O-acetyl-\(\beta\)-d-glucal (III), m.p. 106–107\(^{\circ}\), \(\{\alpha\}^D_{	ext{c}} +14^\circ\), which is a key intermediate in this paper, and the addition of hydrogen bromide upon III were also described.

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In 1963 our laboratory reported the synthesis of 1,6-anhydropyranose with sulfur in the 1,6-anhydro ring, and designated the product as thiolevoglucosan.\textsuperscript{9} The product has presumably been the first thio analogue of 1,6-anhydroglycosans hitherto been described.\textsuperscript{9} Recently, the preparation of 6-thio-1,6-anhydro-\(\beta\)-d-galactopyranose has also been reported by Whistler and Seib\textsuperscript{9} which must be the second example of the series.

Incidentally, several papers on levoglycosans, parent compounds of thiolevoglycosans, have been reported in literature in this year.\textsuperscript{9} Since levoglucoesan is an easily accessible \(\beta\)-glucose derivative preserving the 1C conformation, it can conceivably be useful as a potential intermediate in synthetic works.

As part of a program in this laboratory on the synthesis of thiosugars, the thiolevoglucosan formation has now been extended to 2-deoxy-\(\beta\)-glucose in which a neighboring group participation at the anomeric position by the oxy anion at C2 is eliminated. The present work describes the preparation of 2-deoxy-thiolevoglycosan and 2-deoxy-3,4-anhydro-thiolevoglactosan both of which have been prepared by starting with 3,4,6-tri-O-acetyl-\(\beta\)-d-glucal (I).\textsuperscript{3}

Tosylation of \(\beta\)-glucal (II) with an equimolecular amount of tosyl chloride in pyridine, followed by acetylation, yielded 3,4-di-O-acetyl-6-O-tosyl-\(\beta\)-d-glucal (III), m.p. 106–107\(^{\circ}\), \(\{\alpha\}^D_{	ext{c}} +14^\circ\), in 74\% yield. The structure was characterized by infrared spectrum in nujol which showed the presence of tosyl (1175 cm\(^{-1}\)) and carbon–carbon double bond (1650 cm\(^{-1}\)), and by the satisfactory elemental analysis. In addition, the tosyl was easily replaced with potassium acetate in boiling acetic anhydride to regenerate the starting material (I). The fact shows that III has a primary tosyl group. The replacement con-

\textsuperscript{a1} Part X. S. Ishiguro, S. Tejima: This Bulletin, \textbf{15}, 255 (1967).
\textsuperscript{a2} Kitu-15-jo, Nishi-7-chome, Sapporo (巻 季雄, 手島第三).
\textsuperscript{a3} Regarding the addition products of I, following papers have been reported from our laboratory. M. Akagi, S. Tejima, H. Nakamura: Yakugaku Zasshi, \textbf{82}, 1337 (1962); H. Nakamura, S. Tejima, M. Akagi: This Bulletin, \textbf{12}, 1302 (1964); \textbf{12}, 448 (1964); T. Maki, H. Nakamura, S. Tejima, M. Akagi: \textit{Ibid.}, \textbf{13}, 764 (1965).
dition was the similar to that reported by Helferich and Gnüchtel who replaced the primary mesyl in methyl 2,3,4,6-tetra-O-mesyl-α-D-glucopyranoside.

Although few papers have been reported on sulfonated D-galactals and pseudoglycals, regarding partly sulfonated D-glucals, so far as we know, not yet have been referred in literature. Accordingly, the product (III) must be an useful intermediate for studies on unsaturated sugars which have now been exciting remarkable interests.

Therefore, with the aim of establishing a simpler preparative method of III, a modification involving the reduction of 6-O-tosyl-2,3,4-tri-O-acetyl-α-D-glucopyranosyl bromide with zinc in acetic acid was designed, while it was unsuccessful.

Attempts were next made to synthesize 2-deoxy-6-O-tosyl-3,4-di-O-acetyl-β-D-glucopyranosyl ethylxanthate (IV). Product (II) was treated with a saturated solution of hydrogen bromide in benzene for thirty minutes at 0°, and then the excess bromide removed completely to give a sirup (V), $[\alpha]_D^{25} + 111.3^\circ$. The procedure was in the similar fashion to that used by Novák and Šorm in the addition of hydrogen bromide upon I. A mixture of V and potassium ethylxanthate in dry acetone was refluxed for fifteen minutes. Crystals (VI), m.p. 110–112°C, $[\alpha]_D^{25} - 35.5^\circ$, were obtained from the reaction mixture. The identical product was also formed by starting with 2-deoxy-D-glucopyranosyl ethylxanthate (VII) via one mole tosylation and sequential acetylation. An ethanolic solution of VI showed the absorption maximum at 274 mp, characteristic of the thiocarbonyl, and the infrared spectrum in nujol showed the presence of tosyl (1180 cm$^{-1}$), which were in consistent with the postulated structure.

Recently, Lundt and Pedersen have reported on the addition of hydrogen fluoride upon acylated D-glucals in benzene with the aim of separating stable acylated 2-deoxy-D-glucopyranosyl fluorides. However, in contrast to their expectation, stable fluorides could not be isolated, while unstable sirups which were believed to be 2,3-didehydro-2,3-dideoxy-4,6-di-O-acetyl-α-D-erythroseosyl fluorides were obtained. The finding would be of interest as compared with that of hydrogen bromide.

Treatment of VII with sodium methoxide with a similar procedure for the preparation of thiolevoglucosan gave 2-deoxy-thiolevoglucosan in 84% yield, which was isolated as a crystalline diacetate (VIII), m.p. 79–81°C, $[\alpha]_D^{25} - 128^\circ$. The product showed neither tosyl (1180 cm$^{-1}$) by infrared nor thiolelecarbonyl (274 mp) by ultraviolet. Reductive desulfurization with Raney nickel gave 1,5-anhydro-2,6-dideoxy-3,4-di-O-acetyl-D-glucitol (VIII), m.p. 39–40°C, $[\alpha]_D^{25} + 45.5^\circ$ in 85% yield.

Deacetylation of VIII with cold methanolic ammonia afforded 2-deoxy-thiolevoglucosan (K) in 80% yield. The product, m.p. 189–192°C, $[\alpha]_D^{25} - 71.7^\circ$, was easily recrystallizable from ethyl acetate and showed a satisfactory elemental analysis.

Thus, the facile formation of 2-deoxy-thiolevoglucosan from VII not only indicates that 1,6-anhydro-1,6-sulfide ring formation involves direct participation of the sulfur atom on C1 as has been mentioned in the previous papers from our laboratory, but also the β-configuration of the xanthate group in VII.

5) B. Helferich, A. Gnüchtel : Ber., 71, 712 (1938).
In 1920 Fischer, et al. recorded that when I and hydrogen bromide were treated in acetic acid gave a crystalline “diacetyl d-glucal hydrobromide”, which on reacetylation yielded a “triacetyl d-glucal hydrobromide”. Later, Davoll and Lythgoe re-investigated Fisher’s work, however, they were unable to isolate the compound Fischer described.

Accordingly, it is noteworthy to describe that when a solution of III in glacial acetic acid containing hydrogen bromide was left to stand for three hours at room temperature, crystals (X), m.p. 113.5~114°C, [α]°D +126°, were obtained in 75% yield. The product was not identical with the sirupy bromide (V), obtained from III by treatment with hydrogen bromide in benzene.

The product (X) showed a violet coloration with the Dische reagent for 2-deoxysugars, and involved an active bromine which was easily replaceable with methoxy by the Koenigs-Knorr glycosidation to give a crystalline glycoside (XII), m.p. 132°C, [α]°D +10°. It is of interest to notice the resulted glycoside still involved a bromine atom. The nuclear magnetic resonance spectrum of X exhibited a triplet at δ 3.65 (anomeric proton), a multiplet at δ 7.21 (methylene at C2), a singlet at δ 7.55 (methyl in tosyl), and a singlet at δ 7.88 corresponding to one acetyl. The elemental analyses of X and XII were in good agreement with that of C15H19BrO3S and C16H17BrO3S, respectively. From the data mentioned above, the authors postulated the structure of X to be 2-deoxy-3-bromo-3-deoxy-α-D-hexopyranosyl bromide. The comparatively large dextrorotatory value would suggest the α-configuration of the anomeric bromide. According to nuclear magnetic resonance studies of the bromination of I by Davoll, the authors have shown that tri-O-acetyl-2-bromo-2-deoxy-α-D-glucopyranosyl bromide (60%) and tri-O-acetyl-2-bromo-2-deoxy-α-D-mannopyranosyl bromide (30%) are the main products. Thus, it is remarkable that the 2-deoxy glycosyl halides having an axial halogen atom are, presumably, formed preferentially, which would support our α-configuration.

Treatment of X with potassium thiocyanate or ethylxanthate in dry acetone afforded crystals (XII) or (XIII), respectively. The product (XII), m.p. 143~145°C, [α]°D +5°, showed the presence of tosyl (1182 cm⁻¹) and thioacetyl (1710 cm⁻¹) by infrared. The product (XIII), m.p.127~128°C, [α]°D -27.1°, showed the presence of tosyl (1175 cm⁻¹) and thioacetone (274 mp) by infrared and ultraviolet, respectively.

Treatment of XIII with sodium methoxide by the similar procedure in the formation of 2-deoxy-thiolevoglucosan, afforded a solid which was recrystallized from cyclohexane to give pure crystals (XIV), m.p. 69~72°C, [α]°D -108° in 70% yield. The product showed neither Beilstein’s bromine test, absorptions at 3200~3500 (hydroxyl), 1745 (acetyl), 1175 cm⁻¹ (tosyl) by infrared, nor thioacetone (274 m) by ultraviolet. However, it showed absorptions at 865, 1165 and 1205 cm⁻² corresponding to epoxide by infrared. The elemen-

14) E. Fischer, M. Bergmann, H. Schotte: Ber., 53, 517 (1920).
be the same configuration with d-glucose.

The product (XIV) would be of interest as a thio analogue of 3,4; 1,6-dianhydro-β-d-altropyranose, m.p. 104~106°, [α]_5^25° -76°, which has been reported by Černý, et al.

Further studies on the addition of hydrogen bromide upon I and III in glacial acetic acid has now been in progress in our laboratory and the details will be reported in future.

Experimental

Unless stated otherwise, solvents were evaporated in vacuo at a bath temperature of 40° in a rotary evaporator. Thin-layer chromatography (TLC) was performed by ascending method on silica gel G (E. Merck, Darmstadt, Germany) or Wakogel B–5. Spots were located on silica gel plates by spraying with 50% H_2SO_4. The NMR spectra were measured by JNM-3H-60-spectrometer (Japan Optics Laboratory Co., Ltd.) or Model H-6013 (Hitachi Ltd., Tokyo, Japan) at 60 Mc. in CDCl_3 with Me_4Si as an internal standard. Chemical shifts were given in τ values and coupling constants (J) in c.p.s.

6-O-Tosyl-3,4-di-O-acetyl-β-D-glucal (III)—To a solution of d-glucal (3 g.) in dry pyridine (30 ml) was added gradually, under ice-cooling and stirring, a solution of tosyl chloride (4 g.) in dry pyridine (12 ml), and the mixture was stirred for further 1 hr. at 0°. After standing for 48 hr. at room temperature protected from moisture, the mixture was treated with AcO (30 ml) with stirring, then allowed to stand an additional 20 hr. The mixture was poured into ice-H_2O (500 ml) and the resulted sirupy product solidified by scratching the side of the flask and successive standing for several hours. The solid was separated by filtration and recrystallized from EtOH to give pure material (4 g., 74%), m.p. 106~107°, [α]_5^25° +14° (c=1, CHCl_3). IR β: $\nu_{\text{max}}$ cm$^{-1}$: 1175 (SO$_2$-O), 1650 (C=O). Anal. Calcd. for C$_{17}$H$_{13}$O$_6$: C, 53.12; H, 5.22. Found: C, 53.07; H, 5.31. The product was not so stable and decomposed in the air for two weeks.

3,4,6-Tri-O-acetyl-β-D-glucal (I) from III—A mixture of III (2 g.) and AcOK (2 g.) in AcO (30 ml) was refluxed for 1 hr. in an oil bath. The mixture was poured into ice-H$_2$O (200 ml), allowed to stand for 5 hr. at room temperature, then the solution was extracted with CHCl$_3$ (20 ml x 3). The organic layer was washed successively with aq. NaHCO$_3$ and H$_2$O. A sirup which was obtained on solvent removal from the dried extract, crystallized by trituration with a small amount of EtOH and sequential standing in a refrigerator. Recrystallization from EtOH gave pure material (0.8 g., 57%), m.p. 54°, [α]_5^25° -20° (c=1, CHCl$_3$). The product was indistinguishable with an authentic 3,4,6-tri-O-acetyl-β-D-glucal (I) by IR.

2-Deoxy-6-O-tosyl-3,4-di-O-acetyl-β-D-glucopyranosyl ethylxanthate (V) — a) From 2-deoxy-β-D-glucopyranosyl ethylxanthate (N) (4 g.) in pyridine (30 ml) with a solution of tosyl chloride (3.1 g., 1.1 mole) in pyridine (10 ml) and subsequent acetylation with AcO (30 ml) according to the preparation of III afforded a solid which recrystallized from EtOH to give pure material (7 g., 93%), m.p. 110~112°, [α]_5^25° -33° (c=0.5, CHCl$_3$). UV $\lambda_{\text{max}}$ nm: 274 (C=S). IR $\nu_{\text{max}}$ cm$^{-1}$: 1180 (SO$_2$-O). Anal. Calcd. for C$_{29}$H$_{28}$O$_{12}$: C, 47.41; H, 5.17; S, 18.99. Found: C, 47.52; H, 5.42; S, 18.94.

b) From 6-O-tosyl-3,4-di-O-acetyl-β-D-glucal (III) : A solution of III (3 g.) in dry benzene (20 ml) was saturated with HBr under ice-cooling. After standing at 0° for 30 min. the solvent was evaporated to give a sirup which was dissolved in dry benzene (10 ml) and evaporated again. The procedure was further repeated twice. The resulted sirupy 2-deoxy-6-O-tosyl-3,4-di-O-acetyl-β-D-glucopyranosyl bromide (V) had [α]_5^25° +111.3°.

A mixture of V (3.6 g) and potassium ethylxanthate (2.7 g) in dry acetone (25 ml) was refluxed for 15 min. After cooling, the mixture was poured into ice-H₂O (600 ml). The resultant precipitate was collected by filtration and recrystallized from EtOH to give pure material (3.2 g, 56%), m.p. 110~113°, (α)²⁰D -35.3° (c=1, CHCl₃). The product was indistinguishable with a sample prepared by method a) by IR.

2-Deoxy-6-thio-3,4-di-O-acetyl-1,6-anhydro-β-D-gluco.pyranoside (2-Deoxy-3,4-di-O-acetyl-thiolevo-glucosan) (VII) — A solution of VI (10 g) in MeOH (125 ml) containing Na (2 g) was allowed to stand overnight at room temperature. The mixture was neutralized with 50% AcOH until a drop of the solution was neutral to phenolphthalein. The solvent was removed to dryness. Acetylation was effected overnight at room temperature with Ac₂O (50 ml) in pyridine (60 ml) and the solution was poured into ice-H₂O. It was extracted with CHCl₃ (40 ml x 3) and the organic layer was washed successively with ice-cold 3N-H₂SO₄,aq. NaHCO₃ and H₂O. Moisture was removed with NaSO₃ and the solution concentrated to give a sirup which was dissolved in EtOH. The product was isolated from the solution of thiolevo-glucosan (74 mg) by UV.

1,5-Anhydro-2,6-dideoxy-3,4-di-O-acetyl-D-glucitol (VIII) — A solution of VII (3 g) in EtOH (50 ml) was treated with freshly prepared Raney Ni (40 g of alloy was activated) and the resultant suspension was refluxed gently for 6 hr. Nickel was removed by filtration and washed thoroughly with EtOH. The combined filtrate and washings were concentrated to give a colorless oil which was dissolved in dry ether. The insoluble precipitate was removed by filtration and the solvent was evaporated from the filtrate to give an oil (2.3 g, 85%), (α)⁰ D +43° (c=1, EtOH). The product was dissolved in benzene (10 ml) and chromatographed on silica gel (25 g). From the eluate of benzene (150 ml), crystals, m.p. 39~40°, (α)⁰ D +45.5° (c=1, EtOH) were obtained after evaporation of the solvent and successive standing in a vacum desiccator. Anal. Calcd. for C₅H₁₀O₃: C, 55.4; H, 7.46. Found: C, 55.3; H, 7.55.

2-Deoxy-6-thio-1,6-anhydro-β-D-gluco.pyranosan (2-Deoxy-thiolevo-glucosan) (IX) — To a chilled MeOH (6 ml) containing dry NH₄ saturated at 0° was added VII (0.5 g). The mixture was left to stand overnight at room temperature. The solvent was removed to give a sirup which was triturated with a small amount of AcOEt to crystallize. The crystals were collected by filtration and recrystallized from AcOEt to give pure material (0.2 g, 69%), m.p. 189~192°, (α)⁰ D -71.7° (c=0.53, MeOH). Anal. Calcd. for C₅H₁₀O₃: C, 44.4; H, 6.21; S, 19.77. Found: C, 44.55; H, 6.08; S, 19.85.

5-Bromo-4-O-acetyl-6-O-tosyl-2,3-dideoxy-α-D-glucopyranosyl Bromide (X) — A solution of VIII (10 g) in glacial AcOH (35 ml) containing 32% HBr was left to stand for 3 hr. at room temperature. The mixture was diluted with CHCl₃ (200 ml), and the solution was washed with ice-H₂O, aq. NaHCO₃, and H₂O, respectively. Moisture was removed over CaCl₂, filtered, and the solvent was removed from the filtrate to afford a sirup. Crystallization was induced by addition of a small amount of dry ether and scratching the side of the sirup. The crystals were separated by filtration and recrystallized from dry benzene-petr. ether to give pure material (9.5 g, 75%), m.p. 113.5~114° (decomp.), (α)⁰ D +129° (c=0.5, CHCl₃). The AcO—solution showed a violet color with the Dische test for 2-deoxysugars.¹⁰ Anal. Calcd. for C₅H₁₀O₂Br: C, 37.05; H, 3.73; S, 6.60; Br, 32.87. Found: C, 37.15; H, 3.79; S, 6.76; Br, 32.92. The NMR spectrum showed a triplet at 3.65 (anomeric proton), a multiplet at 7.21 (methylene protons at C2), a singlet at 7.53 (methyl proton in tosyl) and a singlet at 7.88 (methyl proton in acetylenic). Methyl 3-Bromo-4-O-acetyl-6-O-tosyl-2,3-dideoxy-β-D-glucopyranoside (XI) — A mixture of X (1 g), and Ag₂CO₃ (1.5 g) in MeOH (8 ml) was stirred for 30 min. at room temperature. Chloroform (5 ml) was added to the solution and stirring was continued for further 10 min. After filtration, the solvent was removed to give a sirup which was recrystallized from MeOH to give pure material (0.8 g, 90%), m.p. 132°, (α)⁰ D -10° (c=0.5, CHCl₃). Anal. Calcd. for C₅H₁₀O₂Br: C, 43.94; H, 4.84; S, 7.33; Br, 18.27. Found: C, 44.11; H, 4.95; S, 7.45; Br, 18.15.

1-S-Acetyl-1-thio-3-bromo-4-O-acetyl-6-O-tosyl-2,3-dideoxy-β-D-glucopyranosyl (XII) — A mixture of X (2 g), and AcSK (0.5 g) in dry acetone (15 ml) was refluxed for 10 min. After cooling, the precipitate was removed by filtration. The filtrate was concentrated to give a sirup which crystallized by addition of EtOH and scratching the side of the flask. Crystals (1.4 g, 73%) were collected by filtration and recrystallized from EtOH to give pure material, m.p. 143~145°, (α)⁰ D -5° (c=0.5, CHCl₃). IR (methanol cm⁻¹): 1182 (O-SO₂), 1710 (SAC). Anal. Calcd. for C₁₀H₁₂O₄S: C, 42.41; H, 4.38; S, 13.32; Br, 16.60. Found: C, 42.40; H, 4.51; S, 13.08; Br, 16.94.

3-Bromo-4-O-acetyl-6-O-tosyl-2,3-dideoxy-β-D-glucopyranosyl Ethylxanthate (XIII) — A mixture of X (1 g), and potassium ethylxanthate (0.4 g) in dry acetone (5 ml) was refluxed for 15 min. After cooling, the mixture was poured into ice-H₂O and the resultant solid was separated by filtration (1 g., 92%). Twice recrystallizations from EtOH and finally from dry ether gave pure material, m.p. 127~128°, (α)⁰ D -27.1° (c=0.6, CHCl₃). IR (methanol cm⁻¹): 1175 (O-SO₂). UV (methanolnm): 274. Anal. Calcd. for C₁₀H₁₂O₄SBr: C, 40.98; H, 4.41; S, 18.24; Br, 15.15. Found: C, 40.95; H, 4.32; S, 18.10; Br, 15.41.

2-Deoxy-6-thio-1,6-anhydro-3,4-anhydro-β-D-altrose (2-Deoxy-3,4-anhydro-thiolevoaltrosan) (XIV) — A mixture of XII (1 g) in MeOH (20 ml) containing Na (0.25 g) was allowed to stand overnight at room temperature. The mixture was neutralized with 50% AcOH until a drop of the solution was neutral to
phenolphthaleine. The solvent was removed to give a solid which was extracted with CHCl₃ and filtered. The filtrate was washed with ice–H₂O, the CHCl₃-layer dried over CaCl₂ and filtered. The solvent was removed to afford crystals which crystallized after standing in a vacuum desiccator. Recrystallization from dry cyclohexane gave pure material (0.34 g., 70%), m.p. 69~72°C, [α]₁₀⁰ᵦ = -108° (c=1, CHCl₃). IR λ₂₅₄ (cm⁻¹): 865, 1165, 1205 (epoxide). Anal. Calcd. for C₅H₆O₂S: C, 49.98; H, 5.59; S, 22.24. Found : C, 49.97; H, 5.79; S, 22.39. The product showed neither Beilstein's bromine test, absorptions at 3200~3500 (OH), 1745 (OAc), 1175 cm⁻¹ (O–SO₂) by IR nor thiolketone (274 μ) by UV.

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