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74. Setsuzo Tejima, Takao Maki, and Masuo Akagi : Thiosugars.

V.*¹ Synthesis of 1-Thio- β -D-ribofuranose and 1-Thio- β -D-mannofuranose Derivatives.*²

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Sugar xanthate, in which one hydroxyl of the sugar is replaced by ethoxydithio-
S
carbonic group ($-\text{S}-\overset{\text{||}}{\text{C}}-\text{OEt}$), is one of a good intermediate for the preparation of thio-
sugars.¹⁾

Recently, the preparation of several kinds of sugar xanthate was reported in our laboratory along with that of thiosugars.²⁾ As a part of a program of synthesis of thio-sugars, the preparation of 1-thio- β -D-ribofuranose and 1-thio- β -D-mannofuranose derivatives was undertaken *via* corresponding acetylated sugar xanthate. As far as we are aware of, this appears to be the first reported example of the preparation of acetylated sugar xanthate obtained from C1-C2-*trans* glycosyl halide. This work will now be described.

Reaction of potassium ethylxanthate upon sirupy 2,3,4-tri-O-acetyl-D-ribofuranosyl bromide in anhydrous acetone afforded 2,3,4-tri-O-acetyl- β -D-ribofuranosyl ethylxanthate (I), m.p. 72~74°, which was first rather difficult to induce crystals, in 48% yield. An ethanolic solution of I had a strong ultraviolet absorption at 274 m μ , which is a characteristic of acetylated sugar xanthate.

The starting bromide was prepared in a fashion similar to that originally used by Baxter, *et al.*³⁾ As it was pointed out in the original paper, the bromide was unstable. The authors found the value of specific rotation in anhydrous chloroform changed rather rapidly from -163.5° to -143.8° during 1.5 hours at room temperature. According to Levene and Tipson,⁴⁾ crystalline 2,3,4-tri-O-acetyl- β -D-ribofuranosyl bromide has a specific rotation of -209.5° in chloroform. From this datum we are assuming the bromide obtained by us consists of ca. 80% of β -anomer.

In the formation of ribosyl xanthate (I), it would be reasonable to consider that I must be in the β -series. This consideration may be consistent with the rule of neighboring group participation.⁵⁾

An amorphous hygroscopic D-ribofuranosyl ethylxanthate (II), which could not be induced to crystals, was obtained when I had been deacetylated with cold methanolic hydrogen chloride. Acetylation of II with acetic anhydride and pyridine gave I in theoretical yield. Treatment of I with cold sodium methoxide led to the formation of 1-thio- β -D-ribofuranose sodium salt (III), m.p. 165° and showing in water a specific rotation of -78.9° . An aqueous solution of III did not show obvious mutarotation during

*¹ Part IV. M. Akagi, S. Tejima, M. Haga : This Bulletin, **11**, 58 (1963).

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1) R. L. Whistler, M. L. Wolfrom : "Methods in Carbohydrate Chemistry" Vol II, 433 (1963), Academic Press Inc., New York and London.

2) M. Akagi, S. Tejima, M. Haga : This Bulletin, **8**, 1114 (1960); **9**, 360 (1961); **10**, 562 (1962); **11**, 58 (1963).

3) R. A. Baxter, A. C. McLean, F. S. Spring : J. Chem. Soc., **1948**, 523.

4) P. A. Levene, R. S. Tipson : J. Biol. Chem., **92**, 109 (1931).

5) A. M. Michelson : "The Chemistry of Nucleosides and Nucleotides" 55 (1963), Academic Press Inc., New York and London.

24 hours at room temperature, while that of free 1-thio- β -D-ribofuranose, which had been prepared by addition of excess hydrochloric acid to the former, mutarotated from -61.9° to 0° during 48 hours. This finding is in agreement with our assumption that the configurations of I, II, and III at C1 must be in β -series.

Crystalline 2,3,4-tri-O-acetyl-1-S-acetyl-1-thio- β -D-ribofuranose (IV) was obtained in 55% yield when III was acetylated with acetic anhydride and pyridine.

Ribosyl xanthate (I) was reductively desulfurized by Raney nickel to 2,3,4-tri-O-acetyl-1,5-anhydribose (V), m.p. 133° and showing no rotation in chloroform solution. 2,3,4-Tri-O-acetyl-1,5-anhydribose has been reported by Hudson, *et al.*⁶⁾ as a crystal, m.p. $132\sim 133^\circ$.

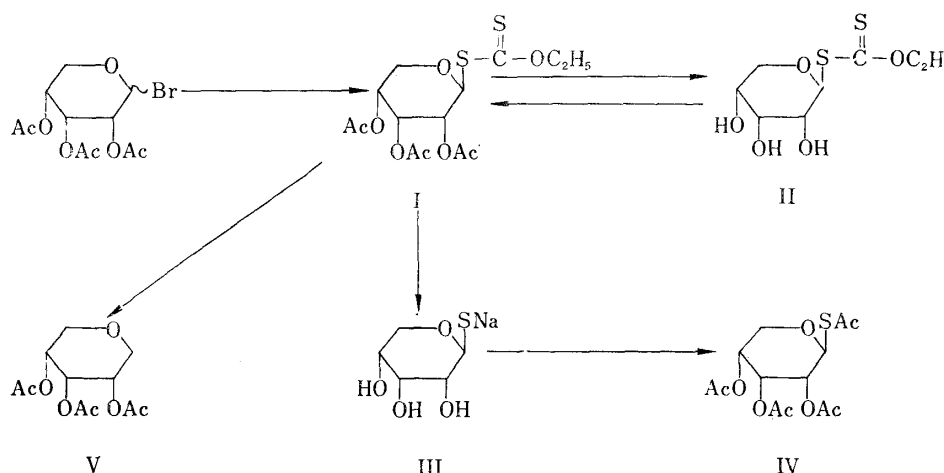


Chart 1.

In the case of D-mannose series, the starting 2,3,4,6-tetra-O-acetyl-D-mannopyranosyl bromide (VI) was prepared in a fashion similar to that originally used by Körösy⁷⁾ for the preparation of acetobromoglucose. Sirupy bromide (VI) obtained by us showed in chloroform a specific rotation of $+114.7^\circ$. According to Levene and Tipson,⁸⁾ crystalline 2,3,4,6-tetra-O-acetyl- α -D-mannopyranosyl bromide has a specific rotation of $+123.2^\circ$ in chloroform. From this datum we are assuming the bromide obtained by us consists of ca. 90% of α -anomer.*⁴

Reaction of bromide (VI) with potassium ethylxanthate in anhydrous acetone afforded a pale yellow sirup showing in chloroform a specific rotation of $+33.9^\circ$. We found the sirup consists of, at least, two substances. Treatment with absolute ethanol gave a levorotatory white powder, which was easily recrystallizable from boiling ethanol; crystal (VII), thus obtained, showed in chloroform a specific rotation of -15.3° . From the filtrate a dextrorotatory orange red sirup (VIII) was obtained after evaporation of the solvent under vacuum. The ratio of VII to VIII was ca. 1:4, so the amount of the sirupy material was far more predominant than that of the crystalline material, while a small amount of VII was also separated from benzene eluate of silica gel chromatography of VIII followed by evaporation of the solvent under vacuum.

The structure of crystal (VII) was demonstrated to be one anomer of 2,3,4,6-tetra-O-acetyl-D-mannopyranosyl ethylxanthates by the following experimental data; first,

*⁴ W. A. Bonner also reported the preparation of sirupy tetra-O-acetyl- α -D-mannopyranosyl bromide, $[\alpha]_D^{25} +111.8^\circ$ (c=4.80, CHCl_3) (J. Am. Chem. Soc., **80**, 3372 (1958)).

6) R. Jeanloz, H. G. Fletcher, Jr., C. S. Hudson: J. Am. Chem. Soc., **70**, 4052 (1948).

7) E. Körösy: Nature, **165**, 369 (1950).

8) P. A. Levene, R. S. Tipson: J. Biol. Chem., **90**, 89 (1931).

ethanolic solution of VII had a strong ultraviolet absorption at 274 m μ ; second, 2,3,4,6-tetra-O-acetyl-1,5-anhydro-D-mannitol (X)⁹ was obtained by reductive desulfurization of VII with Raney nickel, and third, treatment of VII with cold sodium methoxide led to the formation of 1-thio- β -D-mannopyranose sodium salt (X).

Concerning the configuration at C1, we are assuming to be β . In the case of D-mannose, as the starting bromide has C1-C2-*trans* structure, the formation of C1-C2-*trans*, α -anomer should predominate than that of C1-C2-*cis*, β -anomer in halogen displacement. This consideration may be consistent with the rule of neighboring group participation.

However, the yield of crystal (VII) was extremely low, that is only ca. 10~15% calculated from the starting bromide. This fact is presumed to indicate the crystalline xanthate (VII) may be only a minor product of the substitution reaction, while the dextrorotatory sirup (VIII), which was formed simultaneously in far more good yield, may be a main product. Unfortunately, sirup (VIII) has not, as yet, been obtained in pure form, so its structure remains uncertain.

The rotatory powers of derivatives, prepared from mannosyl xanthate (VII) by the methods which do not involve Walden inversion, are levorotatory. Among them, di(β -D-mannopyranosyl) disulfide (XI), prepared by oxidation of X with iodine, has a big minus value. This fact presents a positive proof for our assurance concerning the anomerity of compounds prepared by us.

It is to be noted that another example of the formation of C1-C2-*cis* substitution product from C1-C2-*trans* glycosyl halide has been shown in literature. Thus, Hudson, *et al.*¹⁰ reported the formation of a small amount of methyl β -L-rhamnopyranoside triacetate together with a much larger quantity of methyl α -L-rhamnopyranoside triacetate when crystalline triacetyl α -L-rhamnopyranosyl bromide had been allowed to react with methanol, followed by acetylation.

Crystalline 2,3,4,6-tetra-O-acetyl-1-S-acetyl-1-thio- β -D-mannopyranose (XII) was obtained in 70% yield when X was acetylated with acetic anhydride and pyridine. The product melted at 130~131° and showed in chloroform a specific rotation of -29.1°.

Experimental

2,3,4-Tri-O-acetyl- β -D-ribosepyranosyl Ethylxanthate (I)—Sirupy 2,3,4-tri-O-acetyl-D-ribosepyranosyl bromide was prepared in a fashion similar to that used by Baxter, *et al.*³ $[\alpha]_D^{15} -163.5^\circ$ (15 min.), -143.8° (1.5 hr.) (c=2.03, CHCl₃). Fifteen grams of bromide was dissolved in warm, dry Me₂CO (75 ml.) containing potassium ethylxanthate (7.5 g.), and the mixture was refluxed for 3 min. After cooling, the mixture was poured into 1000 ml. of ice-cold 1% AcOH solution. After standing at 5° for 18 hr., followed by seeding,^{*5} the resulting solid material was filtered, then recrystallized from 20 ml. of warm EtOH to afford short needles, m.p. 72~74°, $[\alpha]_D^{14} +47.1^\circ$ (c=3.84, CHCl₃). Yield, 8 g. (48%). *Anal.* Calcd. for C₁₄H₂₀O₈S₂: C, 44.20; H, 5.30; S, 16.86. Found: C, 44.15; H, 5.33; S, 16.98.

β -D-Ribopyranosyl Ethylxanthate (II)—Four grams of I was dissolved in 25 ml. of MeOH and cooled at 0°. To this solution, 15 ml. of MeOH containing dry HCl, previously had been saturated at 0°, was added drop by drop, then left in a refrigerator. After 18 hr., the solvent was removed under 40° to afford a yellow sirup. Complete drying in a vacuum desiccator gave a pale yellow, hygroscopic, amorphous powder (2.5 g.), $[\alpha]_D^{13} -34.2^\circ$ (c=2.63, H₂O). The product (2 g.) was added to ice-cold mixture of Ac₂O (10 ml.) and pyridine (10 ml.). After 48 hr., the reaction mixture was poured into ice H₂O, and the resulting solid material was collected by filtration. Recrystallization from warm EtOH afforded short needles (3 g.), m.p. 72~74°, $[\alpha]_D^{14} +47.5^\circ$ (c=2.71, CHCl₃). The product showed no depression of the melting point on admixture with I.

*⁵ Seeds of I were first obtained by leaving a sample of the material in EtOH for 6 months in a refrigerator.

9) H. G. Fletcher, Jr., H. W. Diehl: J. Am. Chem. Soc., **74**, 3175 (1952).

10) R. K. Ness, H. G. Fletcher, Jr., C. S. Hudson: *Ibid.*, **73**, 296 (1951).

1-Thio- β -D-ribofuranose Sodium Salt (III) and 2,3,4-Tri-O-acetyl-1-S-acetyl-1-thio- β -D-ribofuranose (IV)—A suspension of 8 g. of I in 25 ml. of dry MeOH was cooled to -15° and treated, under stirring and cooling, with 25 ml. of an equally cold MeOH-solution of MeONa containing 0.9 g. of Na. Starting material went into solution as the reaction took place. Stirring was continued for 30 min. longer. Dil. AcOH (1:1 v/v) was then added dropwise until a drop of the solution was neutral to phenolphthalein. Crystallization was induced by scratching with a glass rod, then 50 ml. of EtOH was added to complete the crystallization. After 1 hr., 1-thio- β -D-ribofuranose Na salt (III) was filtered and dried (3 g.), m.p. 165° (decomp.), $[\alpha]_D^{17} -78.9^{\circ}$ ($c=2.37$, H_2O). Solution of III*⁶ (0.2615 g.) in 25 ml. of H_2O containing 2 ml. of 3N HCl, mutarotated at 15° as follows: -61.9° (15 min.), -52.2° (3.5 hr.), 0° (48 hr.).

Na salt (III) (2.5 g.) was added to an ice-cold mixture of pyridine (10 ml.) and Ac_2O (10 ml.). After 48 hr., the reaction mixture was poured into ice H_2O , and the resulting solid material was collected by filtration. Recrystallization from two parts of warm EtOH gave 2,3,4-tri-O-acetyl-1-S-acetyl-1-thio- β -D-ribofuranose (IV) (2.5 g.), m.p. $85\sim 87^{\circ}$, $[\alpha]_D^{17} +10.7^{\circ}$ ($c=1.97$, $CHCl_3$). Anal. Calcd. for $C_{13}H_{18}O_8S$: C, 46.69; H, 5.43. Found: C, 47.05; H, 5.44.

2,3,4-Tri-O-acetyl-1,5-anhydrosorbitol (V)—A solution of I (4 g.) in 200 ml. of 80% aq. EtOH (v/v) was treated with freshly prepared Raney Ni (60 g. of alloy was activated.) and the resulting suspension refluxed for 6 hr. Ni was removed by filtration, then washed thoroughly with abs. EtOH. The combined filtrate and washings were concentrated under vacuum to afford crystalline residue. It was washed with a small amount of ice-cold EtOH, then filtered. Recrystallization of EtOH-insoluble material (1 g.) from boiling EtOH gave short needles, m.p. 133° and showing no rotation in $CHCl_3$. Anal. Calcd. for $C_{11}H_{16}O_7$: C, 50.77; H, 6.20. Found: C, 50.81; H, 6.14.

2,3,4,6-Tetra-O-acetyl- β -D-mannopyranosyl Ethylxanthate (VII)—Sirupy 2,3,4,6-tetra-O-acetyl-D-mannopyranosyl bromide (VI) was prepared in a fashion similar to that used by Körösy⁶ for the preparation of 2,3,4,6-tetra-O-acetyl-D-glucopyranosyl bromide. Fifty seven grams of VI, $[\alpha]_D^{25} +114.7^{\circ}$ ($c=2.44$, $CHCl_3$) was obtained from 28 g. of D-mannose. In contrast with sirupy 2,3,4-tri-O-acetyl-D-ribofuranosyl bromide, mentioned in the earlier part of this paper, the bromide (VI) was stable and did not show mutarotation in dry $CHCl_3$ during 6 hr. at 25° . Fifty six grams of VI was dissolved in hot, dry Me_2CO (230 ml.) solution of potassium ethylxanthate (23 g.), and the mixture was refluxed for 3 min. After cooling, the mixture was poured into 2300 ml. of ice-cold, 1% AcOH and kept in a refrigerator. Next day, the resulting pale yellow, thick sirup was separated by decantation. A small amount of contaminated aqueous layer was squeezed out by kneading the wet sirup with a glass rod, then air-dried (42 g.), $[\alpha]_D^{12} +33.9^{\circ}$ ($c=1.88$, $CHCl_3$). Abs. EtOH (52 ml.) was added at 0° , and insoluble white powder (9 g.) was collected by filtration. Twice recrystallizations from 4 parts of boiling abs. EtOH afforded pure material (8 g.), m.p. 127° , $[\alpha]_D^{12} -15.3^{\circ}$ ($c=3.99$, $CHCl_3$). Anal. Calcd. for $C_{17}H_{24}O_{10}S_2$: C, 45.09; H, 5.35; S, 14.17. Found: C, 44.95; H, 5.45; S, 14.27.

Filtrate of VII was evaporated under vacuum and residual orange red sirup was taken up in $CHCl_3$ (50 ml.). Solution was washed twice with H_2O , and $CHCl_3$ layer was dried over anhyd. Na_2SO_4 . Evaporation of $CHCl_3$ under vacuum gave orange red sirup (VIII) (32 g.), $[\alpha]_D^{12} +42.1^{\circ}$ ($c=3.22$, $CHCl_3$).

β -Mannopyranosyl Ethylxanthate—Four grams of VII was deacetylated by using a similar method described in the preparation of II. β -Mannopyranosyl ethylxanthate (2.5 g.) was obtained as a hygroscopic, amorphous powder, $[\alpha]_D^{14} -68.6^{\circ}$ ($c=2.96$, H_2O). The product (2 g.) was acetylated by a similar method described in that of D-ribose series. The acetate (3.5 g.), m.p. 127° showed no depression of the melting point on admixture with VII.

Silica Gel Chromatography of Sirup (VIII)—Thirty grams of VIII was dissolved in 60 ml. of benzene and adsorbed on a column (3×25 cm.) prepared from ca. 150 g. of silica gel. Elution was carried out by using benzene as the solvent. Rotatory powers and yields of each fractions were measured after removal of the solvent in vacuum. The results obtained are shown in Table I.

TABLE I. Specific Rotations and Yields in Each Fractions

Fraction No.	Eluate (ml.)	Yield (g.)	$[\alpha]_D^{12}$ ($CHCl_3$)
1	0~100	0	—
2	101~150	5.0	+42.7 ($c=1.87$)
3	151~200	11.5	+49.2 ($c=2.58$)
4	201~250	3.5	+48.7 ($c=2.30$)
5	251~400	0.5	+47.6 ($c=2.13$)

*⁶ White powder turned to pale yellow after the period of three weeks in a closed container.

Fraction No. 2 was solidified after standing overnight at 0°, while others were still sirup. Cold MeOH (5 ml.) was added to fraction No. 2 and insoluble white powder was recrystallized from boiling EtOH. The crystal (0.5 g), m.p. 127°, $[\alpha]_D^{12} -15.0^\circ$ ($c=3.19$, CHCl_3) had same melting point $[\alpha]_D^{12}$, and IR spectrum with VII.

2,3,4,6-Tetra-O-acetyl-1,5-anhydro-D-mannitol (IX)—A solution of VII (4 g.) in 200 ml. of 80% aq. EtOH (v/v) was treated with freshly prepared Raney Ni (60 g. of alloy was activated.) and the resulting suspension refluxed for 6 hr. 2,3,4,6-Tetra-O-acetyl-1,5-anhydro-D-mannitol (IX) (1.5 g.), m.p. 66°, $[\alpha]_D^{15} -43.2^\circ$ ($c=2.06$, CHCl_3) was obtained by using a similar procedure described in the preparation of V. *Anal.* Calcd. for $\text{C}_{14}\text{H}_{20}\text{O}_9$: C, 50.58; H, 6.06. Found: C, 50.50; H, 6.19.

Fletcher and Diehl¹⁹ reported m.p. 66~67° and $[\alpha]_D^{20} -42.4^\circ$ ($c=0.826$, CHCl_3) for 2,3,4,6-tetra-O-acetyl-1,5-anhydro-D-mannitol.

1-Thio-β-D-mannopyranose Sodium Salt (X) and 2,3,4,6-Tetra-O-acetyl-1-S-acetyl-1-thio-β-D-mannopyranose (XII)—A suspension of VII (10 g.) in 30 ml. of dry MeOH was cooled -15° and treated, under stirring and cooling, with 30 ml. of an equally cold methanolic solution of MeONa containing 0.9 g. of Na. The starting material went into solution as the reaction took place. Stirring was continued for an additional 1 hr. 1-Thio-β-D-mannopyranose Na salt (X) (4 g.), m.p. 189° (decomp.), $[\alpha]_D^{14} -15.3^\circ$ ($c=2.49$, H_2O) was obtained by using the procedure described in the preparation of III. Acetylation of Na salt (X) (2 g.) was performed by a similar method described in that of D-ribose series. 2,3,4,6-Tetra-O-acetyl-1-S-acetyl-1-thio-β-D-mannopyranose (XII) (3.5 g.), m.p. 130~131°, $[\alpha]_D^{19} -29.1^\circ$ ($c=1.75$, CHCl_3) was obtained as needles. *Anal.* Calcd. for $\text{C}_{16}\text{H}_{22}\text{O}_{10}\text{S}$: C, 47.27; H, 5.46; S, 7.89. Found: C, 47.41; H, 5.60; S, 7.72.

Di(β-D-mannopyranosyl)disulfide (XI)—An EtOH solution of I_2 was added dropwise, under stirring, to an aqueous solution of X (1 g.) in 5 ml. of H_2O until the contents persist a slight yellow. White needles began to appear at the end point. After standing for several hr. at 0°, disulfide (XI) was filtered. Twice recrystallizations from two parts of warm H_2O gave pure material, $[\alpha]_D^{12} -165.6^\circ$ ($c=1.51$, H_2O). Though it melted completely at 212° under decomp., its color turned to brown at 190°. *Anal.* Calcd. for $\text{C}_{12}\text{H}_{22}\text{O}_{10}\text{S}_2$: C, 36.92; H, 5.68. Found: C, 36.80; H, 5.87.

A part of elementary analyses was carried out by the Shimotakaido Laboratory, Kowa Co., Ltd. to all of whom the authors' thanks are due.

Summary

Crystalline product obtained by the reaction of potassium ethylxanthate upon an anomeric mixture of 2,3,4-tri-O-acetyl-D-ribopyranosyl bromides or that of 2,3,4,6-tetra-O-acetyl-D-mannopyranosyl bromides in anhydrous acetone was confirmed to be one anomer of 2,3,4-tri-O-acetyl-D-ribopyranosyl ethylxanthates or that of 2,3,4,6-tetra-O-acetyl-D-mannopyranosyl ethylxanthates, respectively. Their anomeric configurations at carbon 1 were assumed to be β.

Three derivatives of 1-thio-β-D-ribopyranose and four derivatives of 1-thio-β-D-mannopyranose were synthesized in crystalline forms from acetylated glycosyl ethylxanthates mentioned above.

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