74. Setsuzo Tejima, Takao Maki, and Masuo Akagi: Thiosugars. V.\textsuperscript{81} Synthesis of 1-Thio-\(\beta\)-d-ribopyranose and 1-Thio-\(\beta\)-d-mannopyranose Derivatives.\textsuperscript{82}

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Sugar xanthate, in which one hydroxyl of the sugar is replaced by ethoxydithio-S-carboxylic group (\(-\text{S-C}^\text{\textsuperscript{\textbullet}}\text{-OEt}\)), is one of a good intermediate for the preparation of thiosugars.\textsuperscript{1)}

Recently, the preparation of several kinds of sugar xanthate was reported in our laboratory along with that of thiosugars.\textsuperscript{2)} As a part of a program of synthesis of thiosugars, the preparation of 1-thio-\(\beta\)-d-ribopyranose and 1-thio-\(\beta\)-d-mannopyranose 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 sirup 2,3,4-tri-O-acetyl-\(\beta\)-d-ribopyranosyl bromide in anhydrous acetone afforded 2,3,4-tri-O-acetyl-\(\beta\)-d-ribopyranosyl ethylxanthate (I), m.p. 72\textdegree~74\textdegree, which was first rather difficult to induce crystals, in 48\% yield. An ethanolic solution of I had a strong ultraviolet absorption at 274 m\(\mu\), which is a characteristic of acetylated sugar xanthate.

The starting bromide was prepared in a fashion similar to that originally used by Baxter, \textit{et al.}\textsuperscript{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 \(-163.5\textdegree\) to \(-143.8\textdegree\) during 1.5 hours at room temperature. According to Levene and Tipson,\textsuperscript{4)} crystalline 2,3,4-tri-O-acetyl-\(\beta\)-d-ribopyranosyl bromide has a specific rotation of \(-209.5\textdegree\) in chloroform. From this datum we are assuming the bromide obtained by us consists of ca. 80\% of \(\beta\)-anomer.

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

An amorphous hygroscopic \(\beta\)-d-ribopyranosyl 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-\(\beta\)-d-ribopyranosyl sodium salt (III), m.p. 165\textdegree and showing in water a specific rotation of \(-78.9\textdegree\). An aqueous solution of III did not show obvious mutarotation during

\textsuperscript{81} Part V. M. Akagi, S. Tejima, M. Haga: This Bulletin, 11, 58 (1963).
\textsuperscript{82} This work was presented at the 145th national meeting of the American Chemical Society, Sept. 10, 1963.
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\textsuperscript{2)} M. Akagi, S. Tejima, M. Haga: This Bulletin, 8, 1114 (1960); 9, 350 (1961); 10, 562 (1962); 11, 58 (1963).
24 hours at room temperature, while that of free 1-thio-β-ν-ribopyranose, 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-ν-ribopyranose (V) 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-anhydroxribitol (V), m.p. 133° and showing no rotation in chloroform solution.
2,3,4-Tri-O-acetyl-1,5-anhydroxribitol has been reported by Hudson, et al.,9 as a crystal,
m.p. 132~133°.

![Chart 1](image)

Chart 1.

In the case of ν-mannose series, the starting 2,3,4,6-tetra-O-acetyl-ν-mannopy-
ranosyl bromide (VII) was prepared in a fashion similar to that originally used by
Körösy7) for the preparation of acetobromoglucose. Sirupy bromide (VIII) obtained by us
showed in chloroform a specific rotation of +114.7°. According to Levene and Tipson,9)
crystalline 2,3,4,6-tetra-O-acetyl-α-ν-mannopyranosyl bromide has a specific rotation of
+123.2° in chloroform. From this datum we are assuming the bromide obtained by us
consists of ca. 90% of α-anomer.8,4)

Reaction of bromide (VII) with potassium ethylxanthate in anhydrous acetone afforded
a pale yellow sirup showing in chloroform a specific rotation of +33.9°. 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 (VIII), thus obtained, showed in chloroform a specific rotation of -15.3°. From
the filtrate a dextrorotatory orange red sirup (IX) was obtained after evaporation of
the solvent under vacuum. The ratio of VII to XII was ca. 1:4, so the amount of the
sirup 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 chromato-
graphy 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-ν-mannopyranosyl ethylxanthates by the following experimental data; first.

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84 W. A. Bonner also reported the preparation of sirupy tetra-O-acetyl-α-ν-mannopyranosyl bromide,
[α]D 25 +111.8°(c=4.80, CHCl3) (J. Am. Chem. Soc., 80, 3372 (1958)).
ethanolic solution of VII had a strong ultraviolet absorption at 274 mμ; second, 2,3,4,6-tetra-O-acetyl-1,5-anhydro-β-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-β-mannopyranose sodium salt (X).

Concerning the configuration at C1, we are assuming to be β. In the case of β-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 (VII), which was formed simultaneously in far more good yield, may be a main product. Unfortunately, sirup (VII) 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-β-mannopyranosyl) disulfide (X), prepared by oxidation of X with iodine, has a big minus value. This fact presents a positive proof for our assurance concerning the anomery 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-β-rhamnopyranoside triacetate together with a much larger quantity of methyl α-β-rhamnopyranoside triacetate when crystalline triacetyl α-β-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-β-mannopyranose (VII) 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-β-ribopyranosyl Ethylxanthate (I)—Sirupy 2,3,4-tri-O-acetyl-β-β-ribopyranosyl bromide was prepared in a fashion similar to that used by Baxter, et al.\(^b\) \([\alpha]_D^0 = −163.5°(15\text{ min.}), −143.8°(1.5\text{ hr.})(c=2.03, \text{ CHCl}_3)\). Fifteen grams of bromide was dissolved in warm, dry Me\(_2\)CO (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,\(^a\) the resulting solid material was filtered, then recrystallized from 20 mL of warm EtOH to afford short needles, m.p. 72~74°, \([\alpha]_D^0 = +47.1°(c=3.84, \text{ CHCl}_3)\). Yield, 8 g. (48%). *Anal. Calcd. for C\(_{34}\)H\(_{32}\)O\(_{20}\): C, 44.20; H, 5.30; S, 16.86. Found: C, 44.15; H, 5.33; S, 16.98.*

β-β-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 ICl, 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.), \([\alpha]_D^0 = −34.2°(c=2.63, \text{ H}_2\text{O})\). The product (2 g.) was added to ice-cold mixture of Ac\(_2\)O (10 mL) and pyridine (10 mL). After 48 hr., the reaction mixture was poured into ice H\(_2\)O, and the resulting solid material was collected by filtration. Recrystallization from warm EtOH afforded short needles (3 g.), m.p. 72~74°, \([\alpha]_D^0 = +47.5°(c=2.71, \text{ CHCl}_3)\). The product showed no depression of the melting point on admixture with I.

\(^a\) Seeds of I were first obtained by leaving a sample of the material in EtOH for 6 months in a refrigerator.

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°C 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 phe- noPhthalain. 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 (II) was filtered and dried (3 g.), m.p. 165°C (decomp.), \( [\alpha]_D^2 = -78.9^\circ (c=2.37, H_2O) \). Solution of II \# (0.2015 g.) in 25 ml. of H_2O containing 2 ml. of 3N HCl, mutarotated at 15°C as follows: -61.8^\circ (15 min.), -52.2^\circ (3.5 hr.), 0° (48 hr.).

Na salt (II) (2.5 g.) was added to an ice-cold mixture of pyridine (10 ml.) and AcOEt (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 (V) (2.5 g.), m.p. 85°-87°, \( [\alpha]_B^2 = +10.7^\circ (c=1.97, CHCl_3) \). Anal. Calcd. for C_13H_8O_5S: C, 46.69; H, 4.53. Found: C, 47.05; H, 5.44.

2,3,4-Tri-O-acetyl-1,5-anhydrohexitol (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 throughly 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. 138° and showing no rotation in CHCl_3. Anal. Calcd. for C_7H_12O_3: 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-β-D-mannopyranosyl bromide (VII) was prepared in a fashion similar to that used by Körösy\(^4\) for the preparation of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide. Fifty seven grams of VII, \( [\alpha]_B^2 = +114.7^\circ (c=2.44, CHCl_3) \) was obtained from 28 g. of α-mannose. In contrast with sirupy 2,3,4-tri-O-acetyl-β-D-ribo- pyranosyl bromide, mentioned in the earlier part of this paper, the bromide (VII) was stable and did not show mutarotation in dry CHCl_3 during 6 hr. at 25°C. Fifty six grams of VII was dissolved in hot, dry MeCO_(200 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.), \( [\alpha]_B^2 = +33.9^\circ (c=1.88, CHCl_3) \). Abs. EtOH (52 ml.) was added at 0°C, 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°C, \( [\alpha]_B^2 = -15.3^\circ (c=3.99, CHCl_3) \). Anal. Calcd. for C_6H_12O_3S: 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 (III) (32 g.), \( [\alpha]_B^2 = +42.1^\circ (c=3.22, CHCl_3) \).

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

Silica Gel Chromatography of Sirup (VIII) — Thirty grams of VII was dissolved in 60 ml. of benzene and adsorbed on a column (3 x 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**

<table>
<thead>
<tr>
<th>Fraction No.</th>
<th>Eluate (mL)</th>
<th>Yield (g)</th>
<th>( [\alpha]_B^2 ) (CHCl_3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0~100</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>101~150</td>
<td>5.0</td>
<td>+42.7° (c=1.87)</td>
</tr>
<tr>
<td>3</td>
<td>151~200</td>
<td>11.5</td>
<td>+49.2° (c=2.58)</td>
</tr>
<tr>
<td>4</td>
<td>201~250</td>
<td>3.5</td>
<td>+48.7° (c=2.30)</td>
</tr>
<tr>
<td>5</td>
<td>251~400</td>
<td>0.5</td>
<td>+47.6° (c=2.13)</td>
</tr>
</tbody>
</table>

\(^\#\) 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°, $[\alpha]_D^20 = -15.0^\circ$ (c = 1.9, CHCl$_3$) had same melting point ($[\alpha]_D^20$ and IR spectrum with III.

2,3,4,6-Teta-O-acetyl-1,5-anhydro-d-mannitol (IX) — A solution of III (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-Teta-O-acetyl-1,5-anhydro-d-mannitol (X) (1.5 g.), m.p. 66°, $[\alpha]_D^20 = -43.2^\circ$ (c = 2.06, CHCl$_3$) was obtained by using a similar procedure described in the preparation of V.  

Anal. Caled. for C$_{14}$H$_{22}$O$_5$: C, 50.58; H, 6.06. Found: C, 50.50; H, 6.19.

Fletcher and Diehl(9) reported m.p. 66~67° and $[\alpha]_D^20 = -42.4^\circ$ (c = 0.826, CHCl$_3$) for 2,3,4,6-teta-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 Ill (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.), $[\alpha]_D^20 = -15.3^\circ$ (c = 2.49, H$_2$O) was obtained by using the procedure described in the preparation of Ill. Acetylation of Na salt (X) (2 g.) was performed by a similar method described in that of ν-ribose series. 2,3,4,6-Tetra-O-acetyl-1-S-acetyl-1-thio-β-D-mannopyranose (III) (3.5 g.), m.p. 130~131°, $[\alpha]_D^20 = -29.1^\circ$ (c = 1.75, CHCl$_3$) was obtained as needles.  

Anal. Caled. for C$_{14}$H$_{22}$O$_5$S: C, 47.27; H, 5.46; S, 7.89. Found: C, 47.41; H, 5.60; S, 7.72.

Dl(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$_2$O until the contents persist a slight yellow. White needles began to appear at the end point. After standing for several hr. at 0°, disulfide (X) was filtered. Twice recrystallizations from two parts of warm H$_2$O gave pure material, $[\alpha]_D^20 = -165.5^\circ$ (c = 1.51, H$_2$O). Though it melted completely at 212° under decom., its color turned to brown at 190°.  

Anal. Caled. for C$_{18}$H$_{22}$O$_8$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-β-ribofuranosyl bromides or that of 2,3,4,6-tetra-O-acetyl-β-mannopyranosyl bromides in anhydrous acetone was confirmed to be one anomer of 2,3,4-tri-O-acetyl-β-ribofuranosyl ethylxanthates or that of 2,3,4,6-tetra-O-acetyl-β-mannopyranosyl ethylxanthates, respectively. Their anomeric configurations at carbon 1 were assumed to be β.

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

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