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12. Masuo Akagi, Setsuzo Tejima, and Masanobu Haga : Biochemical Studies on Thiosugars. IV.*1 Synthesis of 1,6-Anhydro-1,6-sulfide-β-D-glucopyranose(Thiolevoglucosan) and 6-Deoxy-6-mercapto-1-thio-D-glucose.

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In this laboratory, several thiosugars have been synthesized and some of them are shown to be effective on tumor.[1] A preceding paper described the synthesis of 6-deoxy-6-mercapto-D-glucose.*1 The present paper, as an extension of this investigation, aimed at the synthesis of 1,6-dideoxy-1,6-dithiol-D-glucose (XII). On dithiols, numerous extensive works have been carried out by Owen *et al.*,[2] however, at present there is no report on XII.

Previously general methods for the preparation of thiosugars were discussed in antecedent paper of this series.[3] By treatment of 6-O-tosyl-2,3,4-tri-O-acetyl-α-D-glucopyranosyl bromide (I)[4] with potassium ethylxanthate in boiling acetone, 6-O-tosyl-2,3,4-tri-O-acetyl-β-D-glucopyranosyl ethylxanthate (IIa) was obtained in 90% yield. Similarly 6-O-tosyl-1-deoxy-1-thioacetyl-2,3,4-tri-O-acetyl-β-D-glucopyranose (IIb) was obtained in 75% yield by reaction of I with potassium thiolacetate. Attempts to replace tosyloxy group of IIa and IIb with potassium thiolacetate[5] were unsuccessful, and merely sirupy products were obtained.

By alkali degradation of IIa with sodium methoxide in anhydrous methanol and successive acetylation was obtained 1,6-anhydro-1,6-sulfide-2,3,4-tri-O-acetyl-β-D-glucopyranose(thiolevoglucosan) (III) in 60% yield.

By similar treatment, III was also obtained from IIb. As discussed by Akagi *et al.*,[6] the formation of intramolecular sulfide ring indicated that the anomeric configurations of IIa and IIb were *beta* form respectively. The preferred formation of 1,6-linkage rather than that of 3,6-anhydro linkage was attributable to the higher nucleophilicity of thiol group as substituting agent[7] than that of hydroxyl group.

By deacetylation with methanolic ammonia, III yielded 1,6-anhydro-1,6-sulfide-β-D-glucopyranose (IV), which did not reduce hot Benedict's solution and did not show appreciable mutarotation. IV, as an intramolecular thioglycoside, was hydrolyzed by dilute mineral acid to 6-deoxy-6-thiol-D-glucose (V), which was characterized through its phenylosazone VI.

Reductive desulfurization of III with Raney nickel gave 6-deoxy-1,5-anhydro-2,3,4-tri-O-acetyl-D-sorbitol(6-deoxy-polygalitol triacetate) (VII), which was also obtained by reduction of I with lithium aluminium hydride in ether and successive acetylation in 35% yield.

The reduction of glycosyl halides to anhydro alditols with lithium aluminium

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*1 Part III. M. Akagi, S. Tejima, M. Haga : This Bulletin, **10**, 562 (1962).

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3) M. Akagi, S. Tejima, M. Haga : This Bulletin, **8**, 1114 (1960).
4) J. Compton : J. Am. Chem. Soc., **60**, 395 (1938).
5) J.H. Chapman, L.N. Owen : J. Chem. Soc., 579 (1950).
6) M. Akagi, S. Tejima, M. Haga : This Bulletin, **10**, 905 (1962).
7) For a summary see E.L. Eliel in M.S. Newman's "Steric Effects in Organic Chemistry," p. 156 John Wiley and Sons, Inc., New York (1956).

hydride were reported by Hudson, *et al.*,[8] and reductive desulfonylation of primary tosyloxy group of carbohydrate derivatives were also reported by Baker, *et al.*[9] Deacetylation of VII with methanolic ammonia yielded 6-deoxy-1,5-anhydro-D-sorbitol (VIII), which consumed two moles of periodate and produced one molar equivalent of formic acid under the usual condition.[10] These facts described above indicated that the structure of III was correct.

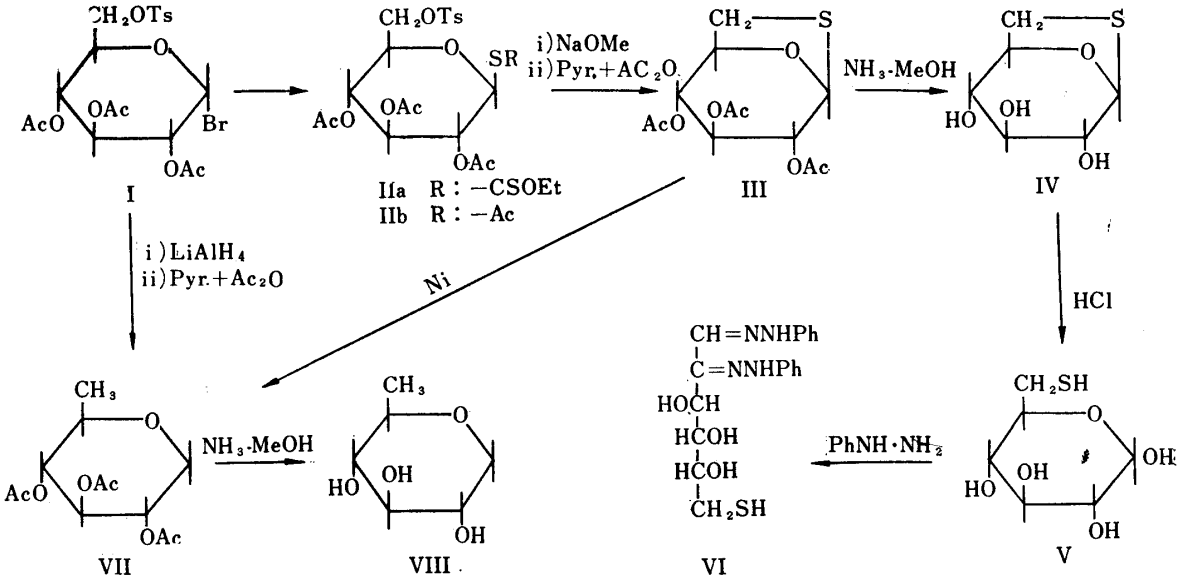

Chart 1.

Owing to failure to replace the tosyloxy group of IIa and IIb with acetylthio group, 6-deoxy-6-acetylthio-2,3,4-tri-O-acetyl-α-D-glucopyranosyl bromide (X) was prepared from 6-deoxy-6-acetylthio-1,2,3,4-tetra-O-acetyl-β-D-glucopyranose (IX)*[1] by treating with hydrogen bromide in acetic acid as usual. On (X), Ohle, *et al.*[11] reported the failure to prepare from IX, however, we obtained X as fine crystals in good yield. By condensation of X with potassium thiolacetate in acetone, 1,6-dideoxy-1,6-diacetylthio-2,3,4-tri-O-acetyl-β-D-glucopyranose (XI) was obtained. On reductive desulfurization with Raney nickel, XI also gave VII.

Deacetylation of XI with methanolic ammonia gave 6-deoxy-6-mercapto-1-thio-D-glucose (XII) as colorless sirup which blackened Benedict's solution and give color reaction of thiol with sodium nitroferricyanide.

XII reacted with phenylhydrazine, to give 6-deoxy-6-thiol-D-glucose phenylosazone (VI) under the evolution of hydrogen sulfide.

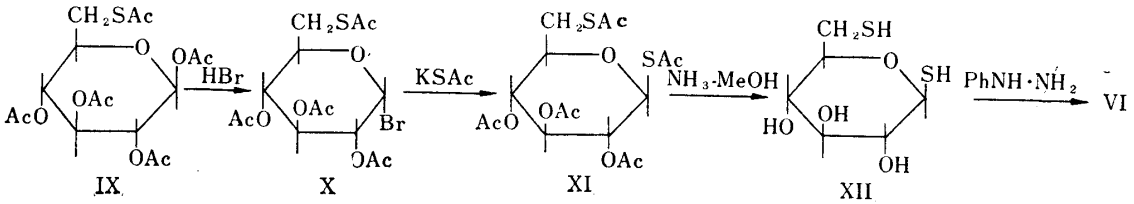

Chart 2.

8) R.K. Ness, H.G. Fletcher, Jr., C.S. Hudson : J. Am. Chem. Soc., **72**, 4547 (1950).
9) E.J. Reist, R.R. Spencer, B.R. Baker : J. Org. Chem., **23**, 1753 (1958).
10) J.M. Bobitt : "Advances in Carbohydrate Chemistry," **11**, 1 (Academic Press Inc., New York (1956).
11) H. Ohle, W. Mertens : Ber., **68**, 2176 (1935).

Experimental

6-O-Tosyl-2,3,4-tri-O-acetyl-β-D-glucopyranosyl Ethylxanthate (IIa)——A solution of 27.5 g. of 6-O-tosyl-2,3,4-tri-O-acetyl-α-D-glucopyranosyl bromide (I), prepared from 6-O-tosyl-1,2,3,4-tetra-O-acetyl-β-D-glucopyranose[12] by the procedure adapted from Compton,[4] m.p. 88~89°, in 200 cc. of dry acetone was treated with a solution of 8.5 g. of potassium ethylxanthate in 50 cc. of dry acetone and then boiled gently for 20 min. After cooling, the mixture was poured into 500 cc. of water. The precipitates were filtered off, washed with water, and air-dried; yield, 25 g. The crude product was recrystallized from acetone and EtOH (1:4) to colorless needles, m.p. 166~167°, $[\alpha]_D^{23}$ +22.1 (c=1.8, $CHCl_3$). *Anal.* Calcd. for $C_{22}H_{28}O_{11}S_3$: C, 46.81; H, 5.00; S, 17.01. Found : C, 47.01; H, 5.21; S, 17.02.

6-O-Tosyl-1-deoxy-1-acetylthio-2,3,4-tri-O-acetyl-β-D-glucopyranose (IIb)——To a solution of 10 g. of I in 100 cc. of acetone, a hot solution of 1.7 g. of potassium thiolacetate in 20 cc. of dehyd. EtOH was added and refluxed for 20 min. After cooling, the reaction mixture was diluted with 200 cc. of water. The separated crystalline substance was filtered off and washed with cold water; yield, 7.5 g. Dried crude product was recrystallized from acetone and EtOH (1:5) to IIb as colorless prisms, m.p. 192~193°(decomp.), $[\alpha]_D^{23}$ +23.8 (c=1.7, $CHCl_3$). In the infrared absorption spectrum of IIb, the absorption attributable to acetylthio(-SAc) group was observed at 1725 cm^{-1} in Nujol. However, in other carbohydrate derivatives such as 1-deoxy-1-acetylthio-2,3,4,6-tetra-O-acetyl-β-D-glucopyranose[13] and 6-deoxy-6-acetylthio-1,2,3,4-tetra-O-acetyl-β-D-glucopyranose,*1 the absorption attributable to -SAc group was observed at 1700 cm^{-1}.[14] *Anal.* Calcd. for $C_{21}H_{26}O_{11}S_2$: C, 48.63; H, 5.05; S, 12.36. Found: C, 48.77; H, 5.04; S, 12.19.

1,6-Anhydro-1,6-sulfide-2,3,4-tri-O-acetyl-β-D-glucopyranose (III)——A solution of 12 g. of IIa in 150 cc. of dehyd. MeOH containing 2.4 g. of sodium was allowed to stand overnight at room temperature (23°). The reaction mixture, neutralized with AcOH, was evaporated under reduced pressure to dryness. The residues were acetylated with 50 cc. of pyridine and 50 cc. of acetic anhydride.

After standing at room temperature overnight, the mixture was concentrated under reduced pressure to 30 cc., diluted with 200 cc. of ice-water, and extracted with 100 cc. of $CHCl_3$. The extract was washed with dilute HCl, sodium bicarbonate solution and water successively, dried over sodium sulfate, and concentrated under reduced pressure to sirup. The brown residue was dissolved in small amount of hot EtOH, decolorized with charcoal and filtered; on cooling, the solution deposited 3.7 g. of colorless crystals. Several recrystallizations from aqueous EtOH gave pure substance, m.p. 93~94°, $[\alpha]_D^{23}$ −25.2 (c=1.1, $CHCl_3$). *Anal.* Calcd. for $C_{12}H_{16}O_7S$: C, 47.36; H, 5.29; S, 10.54. Found: C, 47.41; H, 5.32; S, 10.43.

1,6-Anhydro-1,6-sulfide-β-D-glucopyranose (IV)——Two g. of III was dissolved in 20 cc. of MeOH saturated with ammonia at 0° and the solution was left to stand at room temperature overnight. The solvent was evaporated under reduced pressure to nearly colorless sirup which was dissolved in 5 cc. of dehyd. EtOH and left in refrigerator; yield, 0.8 g.

Recrystallization from EtOH gave crystalline powder, m.p. 180°(decomp.), $[\alpha]_D^{16}$ −5.1 (c=0.8, water). *Anal.* Calcd. for $C_6H_{10}O_4S$: C, 40.44; H, 5.66; S, 17.99. Found : C, 40.52; H, 5.58; S, 18.08.

6-Deoxy-1,5-anhydro-2,3,4-tri-O-acetyl-D-sorbitol (VII)——a) Desulfurization of III : A solution of 3 g. of III in 50 cc. of EtOH, was treated with freshly prepared about 30 g. of Raney nickel suspended in EtOH and refluxed for 3 hr. Then the nickel was removed by filtration and the filtrate was concentrated under reduced pressure to a sirupy residue, which by trituration in ether gave crystals. Recrystallization from EtOH and ether gave needles, m.p. 119~121°, $[\alpha]_D^{16}$ +7.7 (c=1.8, $CHCl_3$). Yield was 1.6 g.(60%). *Anal.* Calcd. for $C_{12}H_{18}O_7$: C, 52.55; H, 6.62. Found : C, 52.28; H, 6.73.

b) Reduction of I with $LiAlH_4$: To a solution of 5.5 g. of I in 80 cc. of dry ether was added 6 g. of $LiAlH_4$. Under protection from moisture, the reaction mixture was warmed under reflux for 30 hr. The excess hydride was decomposed by the dropwise addition of 200 cc. of water. The separated aqueous layer was evaporated under reduced pressure to dryness. The residue was acetylated with pyridine and acetic anhydride, and after the usual treatment, VII was obtained in 35% yield.

6-Deoxy-1,5-anhydro-D-sorbitol (VIII)——Two g. of VII was dissolved in 20 cc. of dehyd. MeOH saturated with ammonia at 0°. After 24 hr., the solvent was removed by distillation under reduced pressure and the resulted crystalline mass was recrystallized from dehyd. EtOH. Several recryst-

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13) J.B. Fraser, L.N. Owen, G. Shaw : J. Chem. Soc., 328 (1947).
14) L.J. Bellamy : "The Infra-red Spectra of Complex Molecules" p. 178 Methuen & Co. Ltd., London (1958).

allizations from EtOH gave crystalline powder, m.p. 149~150°, $[\alpha]_D^{24}$ +29 (c=1.0, MeOH). *Anal.* Calcd. for $C_6H_{12}O_4$: C, 48.64; H, 8.16. Found : C, 48.44; H, 8.24.

Sodium Metaperiodate Oxidation of (VIII)——The procedure devised by Jackson and Hudson[15] was employed. A solution of VIII (0.102 g.) was treated with 0.25*M* sodium metaperiodate solution (10 cc.) and the volume was adjusted to 50 cc. After 24 hr. at room temperature (23°), 10 cc. samples were titrated for residual periodate and formic acid. On a molar basis, VIII was found to consume 2.04 moles of oxidant with liberation of 0.98 mole of formic acid.

6-Deoxy-6-acetylthio-2,3,4-tri-O-acetyl-α-D-glucopyranosyl Bromide (X)——Ten g. of 6-deoxy-6-acetylthio-1,2,3,4-tetra-O-acetyl-β-D-glucopyranose, m.p. 130~131°, was dissolved in 50 cc. of hydrogen bromide in AcOH (ca. 30% W/W) by shaking at room temperature. The reaction mixture was allowed to stand for 2 hr., the solvent was removed under reduced pressure (40° bath).

The residual sirup was taken up in $CHCl_3$, washed with sodium bicarbonate solution and water successively, and dried over sodium sulfate. After removal of solvent by distillation under reduced pressure, the residue was dissolved in dry ether and left in refrigerator; yield, 8.5 g. Several recrystallizations from ether and petr. ether (1:3) gave needles, m.p. 96~98°, $[\alpha]_D^{23}$ +174.0 (c=1.2, $CHCl_3$). *Anal.* Calcd. for $C_{14}H_{19}O_8SBr$: C, 39.38; H, 4.47. Found : C, 39.22; H, 4.58.

1,6-Dideoxy-1,6-diacetylthio-2,3,4-tri-O-acetyl-β-D-glucopyranose (XI)——Six g. of X was added to a solution of 20 cc. of EtOH solution containing 2 g. of potassium thiolacetate, and shaken for 4 hr. at room temperature. The reaction mixture was then diluted with 100 cc. of water, and the crystals were collected, washed with water, and recrystallized from ether and petr. ether (1:5) in colorless needles, m.p. 85~87°, $[\alpha]_D^{23}$ −16.8 (c=2.4, MeOH). *Anal.* Calcd. for $C_{16}H_{22}O_9S_2$: C, 45.48; H, 5.52; S, 15.14. Found : C, 45.53; H, 5.30; S, 14.99.

6-Deoxy-6-mercapto-1-thio-D-glucose (XII)——Five g. of XI was treated with 20 cc. of dehyd. MeOH saturated with ammonia at 0°, and after standing overnight in refrigerator, the solvent was removed under reduced pressure. The slightly colored residue was triturated with EtOH, then with ether to remove acetamide. Then the residue was dissolved in small amount of water and treated with charcoal. On removal of water by distillation under reduced pressure, XII was obtained as hygroscopic sirup, $[\alpha]_D^{18}$ +4.1 (c=1.1, water). *Anal.* Calcd. for $C_6H_{12}O_4S_2$: C, 33.94; H, 5.75; S, 30.21. Found : C, 33.63; H, 5.58; S, 30.04.

6-Deoxy-6-mercapto-D-glucose Phenylosazone (VI)——a) From a Hydrolyzate of IV : A solution of 2 g. of IV in 20 cc. of 4% HCl was heated on steam-bath for 2 hr. After neutralization with sodium carbonate, the reaction mixture gave color reaction of thiol with sodium nitroferricyanide and reduced Benedict's solution different from the nature of VI. To this solution, 4 g. of phenylhydrazine hydrochloride and 8 g. of sodium acetate were added and heated on steam-bath for 1 hr. Resulted crystalline mass was filtered off and washed with cold water; yield, 0.8 g. Recrystallization from EtOH gave light yellow needles, m.p. 141~143°, $[\alpha]_D^{18}$ +42 (c=1.4, pyridine). *Anal.* Calcd. for $C_{18}H_{22}O_3N_4S$: C, 57.76; H, 5.87; N, 14.02; S, 8.56. Found : C, 58.01; H, 5.62; N, 14.46; S, 8.55.

b) From XII : VI was also obtained from 1 g. of XII, 2 g. of phenylhydrazine hydrochloride, and 4 g. of sodium acetate in 10 cc. of water in the same manner as described above.

Desulfurization of (XI) by Raney Nickel——The desulfurization was carried out in the same manner as that of III. VII was obtained in 60% yield of theoretical.

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Summary

1,6-Anhydro-1,6-sulfide-2,3,4-tri-O-acetyl-β-D-glucopyranose was synthesized by alkali-degradation and successive acetylation of 6-O-tosyl-2,3,4-tri-O-acetyl-β-D-glucopyranosyl ethylxanthate and 6-O-tosyl-1-deoxy-1-acethylthio-2,3,4-tri-O-acetyl-β-D-glucopyranose, which were prepared from 6-O-tosyl-2,3,4-tri-O-acetyl-α-D-glucopyranosyl bromide with potassium ethylxanthate and potassium thiolacetate respectively. On desulfurization of 1,6-anhydro-1,6-sulfide-2,3,4-tri-O-acetyl-β-D-glucopyranose with Raney nickel, 6-deoxy-1,5-anhydro-D-sorbitol triacetate was obtained.

1,6-Dideoxy-1,6-diacetylthio-2,3,4-tri-O-acetyl-β-D-glucopyranose was prepared from 6-deoxy-6-acetylthio-2,3,4-tri-O-acetyl-α-D-glucopyranosyl bromide, which was synthesized from 6-deoxy-6-acetylthio-1,2,3,4-tetra-O-acetyl-β-D-glucopyranose, and potassium thiolacetate. The structure was also confirmed by desulfurization with Raney nickel according to give 6-deoxy-1,5-anhydro-D-sorbitol.

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