data. The infrared spectra were determined by Mr. K. Machida and Mrs. I. Hamanaka of Kyoto University, to whom the authors are also grateful.

Summary

Amides of β-mercaptohydrocinnamic acid were prepared by the addition of hydrogen sulfide to amides of cinnamic acid. Amides of thiosalicylic acid were also prepared. Some of these mercapto-amides formed stable chelates with copper and nickel. Cobalt chelate was not stable enough to be separated in pure state. The ratio of the ligand to the metal was 1:1 in copper chelate and 2:1 in nickel chelate. It was found that these chelate compounds were S-O chelating compounds from the infrared spectra.

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UDC 547.452.07

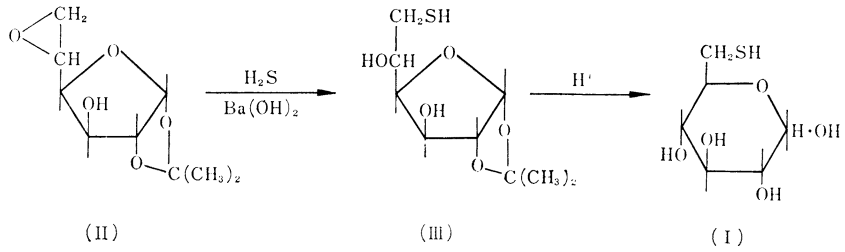
91. Masuo Akagi, Setsuzo Tejima, and Masanobu Haga : Biochemical Studies on Thiosugars. III.*1 Synthesis of 6-Deoxy-6-mercapto-D-glucose.

(*Faculty of Pharmaceutical Sciences, School of Medicine, Hokkaido University**2)

Thiosugars in which the primary hydroxyl group of sugars is substituted by the thiol group are not found in nature, however, it seems to be sure that they heve some biological activities on the basis of the rationale of structural analogue. From this point of view, the present work deals with the synthesis and characterization of 6-deoxy-6-mercapto-D-glucose (I).

Previously in 1935, Ohle and Mertens[1] reported that 6-deoxy-6-mercapto-D-glucose (I) was obtained as syrup by the addition of hydrogen sulfide to 1,2-O-isopropylidene-5,6-anhydro-α-D-glucofuranose (II) in barium hydroxide solution and acid-hydrolysis of isopropylidene group of 1,2-O-isopropylidene-6-mercapto-α-D-glucofuranose (III).

In addition, they described that (I) did not react with carbonyl reagents, such as phenylhydrazine, and that β-pentaacetate of (I) did not form corresponding glycosyl halide derivative.



(II) (III) (I)

Chart 1.

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*1 Part II : This Bulletin, **9**, 360 (1961).

*2 Nishi 5-chome, Kita 12-jo, Sapporo, Hokkaido (赤木満洲雄, 手島節三, 羽賀正信).

1) H. Ohle, W. Mertens : Ber., **68**, 2176 (1935).

Recently, Pacsu, *et al.*[2] described the Bunt's salt derivatives of carbohydrate, that is, 6-deoxy-6-sodium thiosulfato-1,2,3,4-tetra-O-acetyl-β-D-glucopyranose (IV), prepared from sodium thiosulfate and 6-deoxy-6-iodo-1,2,3,4-tetra-O-acetyl-β-D-glucopyranose (V). They hydrolyzed (IV) by 90% acetic acid after reacetylation obtained di-(6-deoxy-1,2,3,4-tetra-O-acetyl-α-D-glucopyranose)-6,6'-disulfide (VI) instead of expected 6-deoxy-6-mercapto-6-S-acetyl-1,2,3,4-tetra-O-acetyl-β-D-glucopyranose (VIII), and they did not mention about (I).

In the present work, the introduction of the thiol group into the carbohydrate residues was achieved by two methods; 1) the thiolacetyl compounds were obtained by refluxing corresponding *p*-toluenesulfonyl (tosyl) derivatives with potassium thiolacetate in acetone or ethanol according to the procedure devised by Chapman and Owen,[3] and 2) also corresponding ethylxanthate and thiouronium derivatives were prepared from 6-iodo derivatives.

At the outset, as a convenient intermediate, 6-O-tosyl-1,2,3,4-tetra-O-acetyl-β-D-glucopyranose (VII), which was prepared by the selective tosylation of glucose according to the method of Hardegger and Montavon,[4] was chosen. By refluxing of (VII) with potassium thiolacetate in acetone solution, 6-deoxy-6-mercapto-6-S-acetyl-1,2,3,4-tetyl-O-acetyl-β-D-glucopyranose (VIII), m.p. 130~131°, which was reported by Ohle and Mertens[1] of m.p. 123°, was obtained in good yield.

For the preparation of thiols, halogen derivative is more generally adopted than tosyl derivative, the tosyl derivative (VII) was converted to 1-deoxy-6-iodo-1,2,3,4-tetra-O-acetyl-β-D-glucopyranose (V)[4] by heating in acetic anhydride with sodium iodide. Similarly, (VIII) was obtained in excellent yield from (V) and potassium thiolacetate in acetone.

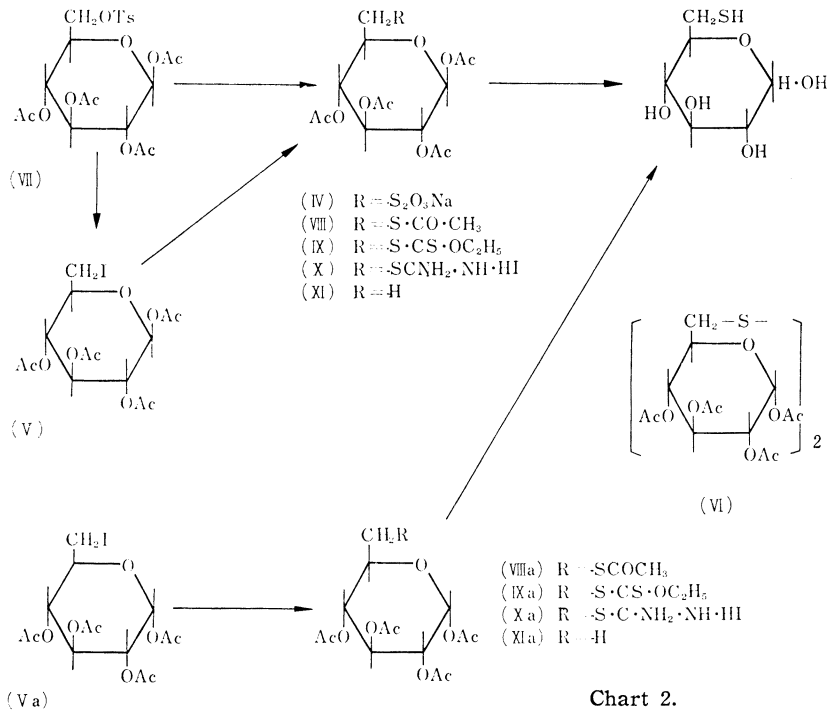

Chart 2.

2) G. Hebblethwaite, R.F. Schwenker, E. Pacsu: Proc. Cellulose Conf., 2nd. 214 (1959).
3) J.H. Chapman, L.N. Owen: J. Chem. Soc., **1950**, 579.
4) E. Hardegger, R.M. Montavon: Helv. Chim. Acta, **29**, 1199 (1946).

Besides, corresponding ethylxanthate (IX) and thiouronium (X) derivatives were prepared by heating of (V) with potassium ethylxanthate and thiourea respectively.

From (VIII), (IX), (X), and (I) was obtained as hygroscopic syrup by hydrolysis with sodium methoxide and removal of sodium with ion exchange resin.

(I) gave color reaction with sodium nitroferricyanide as thiol and reduced Fehling's solution. Contrary to the descriptions of Ohle and Mertens,[1] (I) reacted with phenylhydrazine as usual and gave phenylosazone of (I), moreover, (VIII) reacted with hydrogen bromide in acetic acid and gave 6-deoxy-6-mercapto-6-S-acetyl-2,3,4-tri-O-acetyl-α-D-glucopyranosyl bromide, which will be published in the near future. From these discrepancies the incomplete hydrolysis of isopropylidene group of (III) is indicated.

Likewise, as for α-derivatives, 6-deoxy-6-mercapto-6-S-acetyl-1,2,3,4-tetra-O-acetyl-α-D-glucopyranose (VIIIa), m.p. 103~104°, and corresponding ethylxanthate (IXa) and thiouronium (Xa) derivatives were prepared from 6-deoxy-6-iodo-1,2,3,4-tetra-O-acetyl-α-D-glucopyranose (Va)[4] in the same manner as β-anomers. These derivatives, (VIII, VIIIa, IX, IXa, X, and Xa), were easily desulfurized by Raney nickel to anomeric 6-deoxy-1,2,3,4-tetra-O-acetyl-D-glucopyranoses (XI and XIa) respectively.

For an another tosyl derivative of glucose, 1,2-O-isopropylidene-3,5-benzylidene-6-O-tosyl-α-D-glucofuranose[5] (XII) was converted to 6-deoxy-6-mercapto-6-S-acetyl-1,2-O-isopropylidene-3,5-benzylidene-α-D-glucofuranose (XIII) by refluxing with potassium thiolacetate in acetone as stated above. By treatment with dimethylsulfate and sodium hydroxide, (XIII) was easily deacetylated and methylated, and gave 6-deoxy-6-mercapto-S-methyl-1,2-O-isopropylidene-3,5-benzylidene-α-D-glucofuranose (XIV). By deacetylation with sodium methoxide, (XIII) gave 6-deoxy-6-mercapto-1,2-O-isopropylidene-3,5-benzylidene-α-D-glucofuranose (XV), which was methylated with diazomethane in ethereal solution to (XIV).

(XV) is comparatively stable and quantitatively oxidized to corresponding disulfide (XVI) by iodine. Also these derivatives (XIII, XIV, XV, and XVI) were desulfurized by Raney nickel and gave known 6-deoxy-1,2-O-isopropylidene-3, 5-benzylidene-α-D-glucofuranose (XVII).[6]

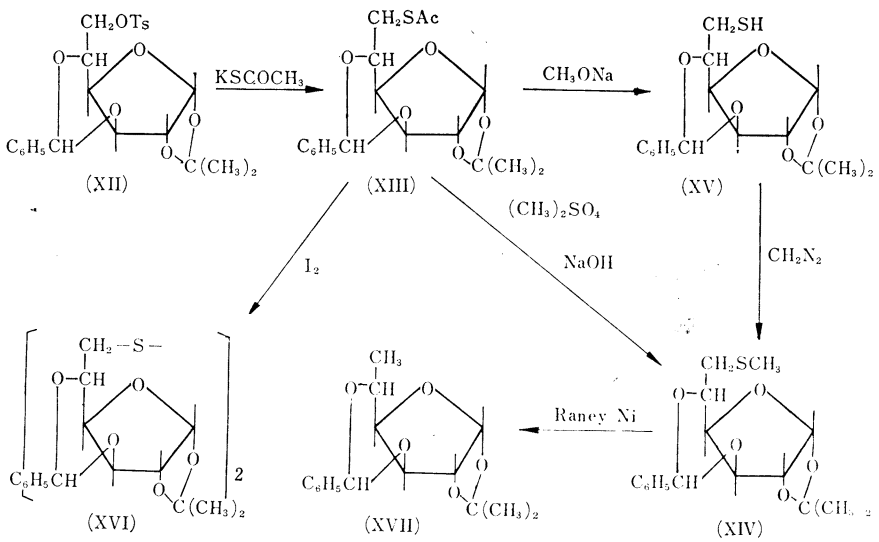

Chart 3.

5) A. S. Meyer, T. Reichstein: Helv. Chim. Acta, **29**, 139 (1946); E. J. Reist, R. R. Spencer, B. R. Baker: J. Am. Chem. Soc., **82**, 2025 (1960).

6) P. Karrer, A. Boettcher: Helv. Chim. Acta, **36**, 570 (1953).

Experimental

6-Deoxy-6-mercapto-6-S-acetyl-1,2,3,4-tetra-O-acetyl-β-D-glucopyranose (VIII)——A solution of 6.0 g. of 6-O-tosyl-1,2,3,4-tetra-O-acetyl-β-D-glucopyranose (m.p. 202~204°)[4] (VII) and 2.0 g. of potassium thiolacetate[7] (1.5 mol. equiv.) in 50 cc. of dehyd. Me_2CO was heated under reflux for 6 hr.

After removal of the precipitated potassium tosylate by filtration and washing with Me_2CO, the filtrate was concentrated in a slightly reduced pressure. The residual syrup was stirred with H_2O, several minutes later, the product solidified and washed with H_2O, and dried. Yield, 4.3 g. (90%). After recrystallization from EtOH, (VIII) was obtained as colorless crystals, m.p. 130~131°; $[\alpha]_D^{24}$ −19 (c=1.0, $CHCl_3$). *Anal.* Calcd. for $C_{16}H_{22}O_{10}S$: C, 47.29; H, 5.46; S, 7.88. Found: C, 47.72; H, 5.69; S, 7.74. IR ν_{max}^{Nujol} cm^{-1}: 1760 (acetyl CO), 1694 (S-acetyl CO).

(VIII) from 6-Deoxy-6-iodo-1,2,3,4-tetra-O-acetyl-β-D-glucopyranose (V)——A solution of 5.0 g. of (V), m.p. 148°[4] and 1.8 g. of potassium thiolacetate dissolved in 30 cc. of dehyd. EtOH was refluxed for 30 min. After treatment of reaction mixture as stated above, (VIII) was obtained in 95% yield.

6-Deoxy-6-ethoxythiocarbonylthio-1,2,3,4-tetra-O-acetyl-β-D-glucopyranose (IX)——5.0 g. of (V) and 2.6 g. of potassium ethylxanthate were refluxed in 30 cc. of Me_2CO for 30 min. After cool, the mixture was poured into 200 cc. of H_2O. The precipitate was recrystallized from EtOH to 4.2 g. of crystals, m.p. 121~123°; $[\alpha]_D^{24}$ +23.2 (c=1.1, $CHCl_3$). *Anal.* Calcd. for $C_{17}H_{21}O_{10}S_2$: C, 45.12; H, 5.35; S, 14.15. Found: C, 44.98; H, 5.60; S, 13.79.

6-Deoxy-6-mercapto-D-glucose (I)——A solution of (VIII) or (IX) (1 mole) in MeOH was treated with MeONa (1 mole) at 0° and the resulting mixture was left to stand overnight in a refrigerator. The precipitates were collected and washed with cold EtOH, which corresponded with sodium salt of (I). The solution of sodium salt in H_2O passed through a column of Amberlite IR-120 (H^+). The effluent was treated with charcoal and concentrated in a reduced pressure at 40° to colorless syrup, $[\alpha]_D^{24}$ −49.1 (c=0.8, H_2O). This syrup reduced Fehling's solution and gave color reaction as thiols, and also was obtained from thiouronium iodide (X)[4] by treatment with 2 mole equiv. of MeONa as described above. *Anal.* Calcd. for $C_6H_{12}O_5S$: C, 36.57; H, 5.01; S, 15.19. Found: C, 36.22; H, 5.24; S, 14.87.

Phenylosazone of (I)——A solution of 0.5 g. of (I), 1.0 g. of freshly distilled phenylhydrazine and 1 cc. of 50% AcOH in 15 cc. of H_2O was heated on a steam bath for 30 min. After cool, yellow precipitates were filtered off and washed with small amount of cold H_2O. Recrystallization from EtOH gave light yellow needles, m.p. 141~143° (decomp.); $[\alpha]_D^{24}$ +42.4 (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, 58.00; H, 5.61; N, 14.45; S, 8.55. By exposure to light, yellow needles changed its color and crystalline form to brown mass gradually.

6-Deoxy-6-mercapto-6-S-acetyl-1,2,3,4-tetra-O-acetyl-α-D-glucopyranose (VIIIa)——It was prepared in the same manner as described for (VIII) from 5.0 g. of 6-deoxy-6-iodo-1,2,3,4-tetra-O-acetyl-α-D-glucopyranose (Va), m.p. 180°,[4] and 1.8 g. of potassium thiolacetate, m.p. 102~104°; $[\alpha]_D^{24}$+38 (c=1.1, $CHCl_3$). *Anal.* Calcd. for $C_{16}H_{22}O_{10}S$: C, 47.29; H, 5.46; S, 7.88. Found: C, 47.71; H, 5.64; S, 7.62.

6-Deoxy-6-ethoxythiocarbonylthio-tetra-O-acetyl-α-D-glucopyranose (IXa)——From 5.0 g. of (Va) and 2.6 g. of potassium ethylxanthate, (IXa) was prepared in the same manner as (IX) to 4.4 g. (90%) of white crystals, after two recrystallizations from EtOH, m.p. 129~130°; $[\alpha]_D^{24}$+98.9 (c=0.8, $CHCl_3$). *Anal.* Calcd. for $C_{17}H_{21}O_{10}S_2$: C, 45.12; H, 5.35; S, 15.15. Found: C, 44.86; H, 5.40; S, 14.89.

Desulfurization of (VIII) by Raney Ni——A solution of 5.0 g. of (VIII) in 50 cc. of dehyd. EtOH was treated with Raney-Ni freshly prepared from 70 g. of Ni-Al alloy in EtOH and then refluxed for 3 hr. After cool, the supernatant solution was decanted and the Ni was washed three times with 50 cc. portions of EtOH. The combined decantates, after treatment with charcoal, were concentrated in a reduced pressure to colorless syrup, which crystallized by trituration with Et_2O and petr. ether. Recrystallization from Et_2O and petr. ether gave 6-deoxy-1,2,3,4-tetra-O-acetyl-β-D-glucopyranose (XI), m.p. 150~151° (literature[4] m.p. 151°), in 70% yield. $[\alpha]_D^{24}$+20 (c=1.0, $CHCl_3$). *Anal.* Calcd. for $C_{14}H_{20}O_9$: C, 50.60; H, 6.07. Found: C, 50.54; H, 6.21. From (VIIIa), 6-deoxy-tetra-O-acetyl-α-D-glucopyranose (XIa), m.p. 115~117° (literature[4] m.p. 117°), in 70% yield, was obtained in the same manner as (XI). From (IX) or (X) and (IXa) or (Xa)[4], (XI) and (XIa) were also obtained in 60~70% yield respectively.

6-Deoxy-6-mercapto-6-S-acetyl-1,2-O-isopropylidene-3,5-benzylidene-α-D-glucofuranose (XIII)——A mixture of 5.0 g. of 6-O-tosyl-1,2-O-isopropylidene-3,5-benzylidene-α-D-glucofuranose (XII),[5] m.p. 118°, and 2.0 g. of potassium thiolacetate was heated under reflux in Me_2CO for 3 hr. After treatment as described in (VIII), (XIII) was obtained as white crystals in 90% yield, m.p. 133~134°; $[\alpha]_D^{20}$+27.6 (c=1.6, $CHCl_3$). *Anal.* Calcd. for $C_{18}H_{22}O_6S$: C, 59.01; H, 6.05; S, 8.74. Found: C, 58.97; H, 6.14; S, 8.59.

7) C. Ulrich: Ann., **109**, 275 (1859).

6-Deoxy-6-mercapto-1,2-O-isopropylidene-3,5-benzylidene-α-D-glucofuranose (XV)——A solution of 3.6 g. of (XIII) in 20 cc. of MeOH containing 0.23 g. of Na (1 mol. equiv) was left to stand at room temperature for 6 hr. Then the mixture was neutralized with AcOH and 3.2 g. of colorless crystals were obtained. Recrytstallization from EtOH gave (XV), m.p. 129°; $[\alpha]_D^{20}$+16.8 (c=1.0, $CHCl_3$). (XV) gave color reaction with sodium nitroferricyanide and was not hygroscopic. *Anal.* Calcd. for $C_{16}H_{20}O_5S$: C, 59.25; H, 6.22; S, 9.87. Found: C, 59.04; H, 6.39; S, 9.90.

6-Deoxy-6-mercapto-6-S-methyl-1,2-O-isopropylidene-3,5-benzylidene-α-D-glucofuranose (XIV)——To a solution of 2.5 g. of (XIII) in 25 cc. of Me_2CO, 8 cc. of Me_2SO_4 and 18 cc. of 30% NaOH were added alternately at 50° with stirring for 1.5 hr. After heating at 70° for 15 min., the mixture was poured into 200 cc. of H_2O and neutralized with 50% AcOH. The precipitates were recrystallized to colorless crystals from EtOH, m.p. 124~126°; $[\alpha]_D^{20}$+6 (c=1.5, $CHCl_3$). (XIV) was also obtained from (XV) with CH_2N_2 in Et_2O in the usual manner. *Anal.* Calcd. for $C_{17}H_{22}O_5S$: C, 60.34; H, 6.55; S, 9.46. Found: C, 60.60; H, 6.72; S, 9.29.

Oxidation of (XV) by iodine to disulfide (XVI)——To a solution of 1.0 g. of (XV) or (XIII) in 20 cc. of 0.5*N* NaOH-EtOH the calculated amount of I_2 dissoled in EtOH was added. After 2 hr., the precipitates were filtered off and washed with H_2O and EtOH. Recrystallization from $CHCl_3$-EtOH gave white crystalline powder, m.p. 223°; $[\alpha]_D^{20}$+3 (c=1.3, $CHCl_3$). *Anal.* Calcd. for $C_{32}H_{38}O_{10}S_2$: C, 59.12; H, 5.88; S, 9.62. Found: C, 59.26; H, 6.00; S, 9.54.

Desulfurization of (XIII) and (XIV) by Raney-Ni——From (XIII) or (XIV) 6-deoxy-1,2-isopropylidene3,5-benzylidene-α-D-glucofuranose (XVII), m.p. 111°,[6] was obtained in 60~70% yield in the same manner as described for (VIII).

Summary

6-Deoxy-6-thio-D-glucose was prepared by hydrolysis of 6-deoxy-6-mercapto-6-S-acetyl-1,2,3,4-tetra-O-acetyl-β-D-glucopyranose and 6-deoxy-6-mercapto-6-S-acetyl-1,2-O-isopropylidene-3,5-benzylidene-α-D-glucofuranose which were synthesized from corresponding 6-*p*-toluenesulfonyl derivatives and potassium thiolacetone in boiling acetone.

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UDC 615.7[547.592.2]-092.21

92. Minoru Yoshimura*2 and Hisao Tsukamoto*3: Metabolism of Drugs. XXX.*1 The Biotransformation of Drugs having Cyclohexene Ring. (3). The Synthesis and Metabolism of 5-Ethyl-5-(1-cyclohexenyl)-4,6-dioxohexahydropyrimidine.

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It was shown in the previous paper on the metabolism of drugs having a cyclohexene ring that 5-ethyl-5-(1-cyclohexenyl)barbituric acid (EHB),[1,2] 1,5-dimethyl-5-(1-cyclohexenyl)barbituric acid (MHB),[3] and 2-alkyl- or 2-phenyl-2-(1-cyclohexenyl)glutarimide[4] underwent oxidation *in vivo* or *in vitro* at 3-position of the cyclohexene ring to yield oxo and hydroxyl derivatives. These drugs have a common moiety of -CO-NH-

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*1 Part XXIX: This Bulletin, **10**, 540(1962).
*2 Showa-machi, Nagasaki (吉村 実).
*3 Katakasu, Fukuoka (塚元久雄).
1) H. Tsukamoto, E. Takabatake, H. Yoshimura: This Bulletin, **2**, 201 (1954).
2) H. Tsukamoto, H. Yoshimura, S. Toki: *Ibid.*, **3**, 239 (1955).
3) H. Tsukamoto, H. Yoshimura: *Ibid.*, **3**, 364 (1955).
4) *Idem*: *Ibid.*, **9**, 584 (1961).