was eluted with the following pyridine acetate buffers (pH 5.0); 0.05*M* (400 ml.) and 0.1*M* (500 ml.). Individual fractions (10 ml.) were collected at a flow rate of 3~4 ml. per minute and absorbancy at 280 mμ was determined for each fraction. The desired material was present in the 0.1*M* eluate (tube No. 96~137) which were pooled, evaporated to a small volume and lyophilized; yield 0.12 g. (38%), $[\alpha]_D^{23}$ +16.5° (c=0.5, 1*N* HCl), R_f^1 0.49, R_f^2 1.02, ninhydrin, Pauly, Sakaguchi and Ehrlich positive spot, amino acid ratios in acid hydrolysate $His_{1.03}$ $Phe_{0.99}$ $Arg_{1.00}$ $Gly_{1.00}$ (average recovery 90%). Amino acid ratios in LAP[12] digest; $His_{1.00}$ (80% recovery) $Phe_{0.80}$ $Arg_{0.46}$. Treatment of the product (Ⅲ) (3.41 μmoles) with trypsin*5 followed by LAP[12] gave His (3.03 μmoles), Phe (2.76 μmoles), Arg (2.81 μmoles), Try (0.16 μmoles), and Gly (0.16 μmoles). *Anal.* Calcd. for $C_{34}H_{43}O_6N_{11}\cdot CH_3COOH\cdot 3H_2O$: C, 53.0; H, 6.6; N, 18.9. Found: C, 52.9; H, 6.8; N, 18.9.

This work has been supported in part by a grant from the Ministry of Education. The authors express their gratitude to Prof. S. Uyeo for his encouragement during the course of this investigation. They are indebted to the members of the Elemental Analysis Center of this University. The skillful technical assistance of Mrs. Ikeda is greatefully acknowledged.

Summary

The synthesis of two steroisomeric pentapeptides, D-histidyl-L-phenylalanyl-L-arginyl-L-tryptophylglycine and L-histidyl-L-phenylalanyl-L-arginyl-D-tryptophylglycine was described and their melanocyte-expanding activities have been assayed *in vitro*. It was observed that D-histidyl-L-phenylalanyl-L-arginyl-L-tryptophylglycine is biologically inert while L-histidyl-L-phenylalanyl-L-arginyl-D-tryptophylglycine possesses 1×10^5 MSH U/g.

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[Chem. Pharm. Bull. 13(7) 764~769 (1965)] UDC 547.452.07

100. Takao Maki, Hiroshi Nakamura, Setsuzo Tejima, and Masuo Akagi: Thiosugars. VII.*1 Synthesis of 1-Thio-2-deoxy-β-D-glucose Derivatives.

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Since several years ago, we have been working on the syntheses of sulfur containing sugar derivatives in order to find some physiologically active material among them. The antitumor activity of our preparations has been tested, and found the intraperitoneal administration of β-D-mannopyranosyl ethylxanthate[1] increases the survival time of *dd* strain of mouse inoculated with Ehrlich ascites carcinoma cells.[2]

In the meanwhile, comparatively a large amount of papers has been reported on the physiological activities of 2-deoxy-D-glucose and it is noteworthy to mention that 2-deoxy-D-glucose is an inhibitor of cancerous growth in animals,[3] antagonists in experimental cancer,[4] and an inhibitor of anaerobic bacteria[5] and influenza virus.[6]

*1 Part Ⅵ. M. Sakata, M. Haga, S. Tejima, M. Akagi: This Bulletin, **12**, 652 (1964).

*2 Nishi-5-chome, Kita-12-jo, Sapporo (楓 孝雄, 中村 博, 手島節三, 赤木満洲雄).

1) S. Tejima, T. Maki, M. Akagi: This Bulletin, **12**, 528 (1964); Y. Tsuzuki, K. Tanaka, K. Tanabe, M. Akagi, S. Tejima: Bull. Chem. Soc. Japan, **37**, 730 (1964).
2) M. Akagi, M. Haga, S. Tejima, D. Mizuno, S. Okamoto, K. Takano, Y. Hirokawa: Abstract of Papers presented at the XIVth Pharmaceutical Assembly, 81st Annual Meeting of the Pharmaceutical Society of Japan, 193 (1961).
3) J. O. Ely: J. Franklin Inst., **258**, 157 (1954); C. A., **48**, 13944 (1954).
4) B. Sokoloff, W. H. Eddy, C. C. Saelhof, J. Beach: Arch. Pathol., **59**, 729 (1955).
5) W. T. Bradner, D. A. Clarke: Cancer Research, **18**, 299 (1958).
6) E. D. Kilbourne: Nature, **183**, 271 (1959).

In view of these evidences, we assumed that sulfur containing 2-deoxy-D-glucoses might be interesting as potential antitumor or antimetabolic agents.

On the synthesis of 2-deoxy-D-glucose derivatives having thioalkyl or aryl group, several papers have been referred in the literature,[7] however, that having free sulfhydryl in carbon 1, so far as we know, has not yet been reported.

In the preceding paper from this laboratory,[8] we reported on the bromine addition compounds derived from 3,4,6-tri-O-acetyl-D-glucal (I). In this paper, in continuation of our studies on D-glucal, we describe the preparation of 1-thio-2-deoxy-β-D-glucose derivatives starting from I.

In order to get 1-thio-2-deoxy-D-glucose, first of all, the authors projected a utilization of addition reaction at the double bond in D-glucal. According to Overend, *et al.*[9] addition occurs to give methyl 2-deoxy-α-D-galactopyranoside when D-galactal and methanol are heated under acidic condition.

However, our efforts, which aimed at the formation of benzyl 1-thio-2-deoxy-D-glucosides by addition of benzyl mercaptan upon D-glucal, were failed; crystals which could be separated were dibenzyl disulfide.

On the other hand, crystals, m.p. 104~105°, $[\alpha]_D^{18}$ +164°, were separated when a mixture of I and thioacetic acid was heated under reflux for 5.5 hours in the presence of a catalytic amount of sulfuric acid, followed by evaporation of the reaction mixture under vacuum. The structure was assigned not to be 1-S-acetyl-1-thio-2-deoxy-3,4,6-tri-O-acetyl-D-glucopyranose (III or IV), but 1-S-acetyl-1-thio-2,3-didehydro-2,3-dideoxy-4,6-di-O-acetyl-α-D-*erythro*-hexose (II),*3 one of D-pseudoglucals. The experimental data

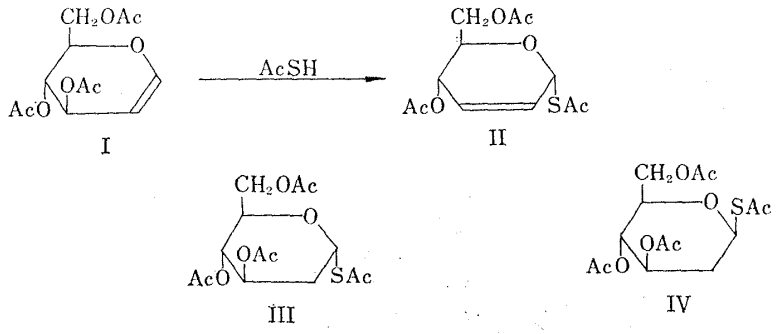

Chart 1.

which support structure II were as follows: the infrared spectrum showed an absorption at 6.02 μ which corresponds to the olefinic linkage, the elementary analysis and acetyl determination were not in agreement with a tetraacetate, but a triacetate, and reductive desulfurization of the crystals gave 1,5-anhydro-2,3-dideoxy-4,6-di-O-acetyl-D-glucitol (V)[10] in 80% yield, which was derived to crystalline 4,6-O-benzylidene compound (VI)[11] by deacetylation and benzylidation.

The nuclear magnetic resonance spectrum of II revealed two vinyl protons[12] at 5.90 p.p.m. which clearly confirms structure II.

*3 The formation and structure of II were presented at the 145th national meeting of the American Chemical Society, Sept. 10, 1963.

7) W. G. Overend: "Advances in Carbohydrate Chemistry," Vol. VIII, 45 (1953), Academic Press Inc., New York.
8) H. Nakamura, S. Tejima, M. Akagi: This Bulletin, **12**, 1302 (1964).
9) W. G. Overend, F. Shabizadeh, M. Stacey: J. Chem. Soc., **1951**, 992.
10) M. Bergmann, W. Breuers: Ann., **470**, 51 (1929).
11) R. J. Ferrier, W. G. Overend, A. E. Ryan: J. Chem. Soc., **1962**, 3667.
12) R. K. Ness, H. G. Fletcher, Jr.: J. Org. Chem., **28**, 435 (1963); Varian Associates: "High Resolution NMR Spectra Catalog," No. 210 (1962).

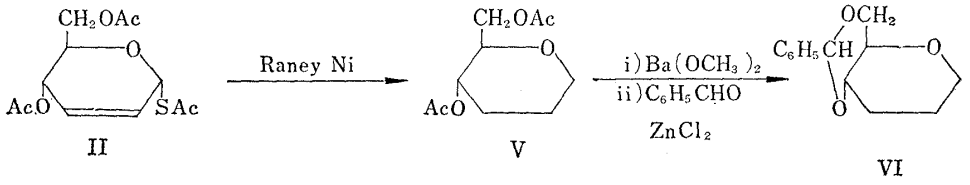

Chart 2.

On the configuration of S-acetyl in II, we are assuming to be α owing to its large positive specific rotation.

Thus, the authors clarified that an addition involving a migration of the double bond occured when I was heated with thioacetic acid. An analogous reaction has been reported by Ferrier, *et al.*[11]; the double bond migrates between carbon 2 and 3 to form *p*-nitrophenol glycoside, when I is heated with *p*-nitrophenol in benzene. According to the recent communication,[13] thioacetic acid is able to add on the double bond in 1,2-O-isopropylidene-5,6-di-deoxy-α-D-*xylo*-hexofuranose-5-ene to give 5-deoxy-6-S-acetyl-6-thio-1,2-O-isopropylidene-α-D-*xylo*-hexofuranose.

On the synthesis of 1-thio-2-deoxy-D-glucose derivatives, in the next step, our attention was turned toward a different synthetic route. It has been well known that 2-deoxy-3,4,6-tri-O-acetyl-D-glucopyranosyl bromide (VII) is a good intermediate for the preparation of nucleosides having 2-deoxy-D-glucopyranosyl residue.[14] The authors thus used VII as the starting material. Syrupy VII was prepared starting from I in a similar fashion to that used by Novák and Šorm.[15] Reaction of potassium ethylxanthate upon VII in dry acetone gave 2-deoxy-3,4,6-tri-O-acetyl-β-D-glucopyranosyl ethylxanthate (VIII), m.p. 99~100°, $[\alpha]_D^{20}$ −32°, in 65% yield. An ethanolic solution of VIII gave a strong absorption at 274 mμ, which is a characteristic of acetylated sugar xanthates, and a positive Dische test for 2-deoxy-sugars. The optical rotatory dispersion curve of VIII revealed the similarity with that of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl ethylxanthate[16] as illustrated in Fig. 1 which supports the β-configuration of the ethylxanthate group.

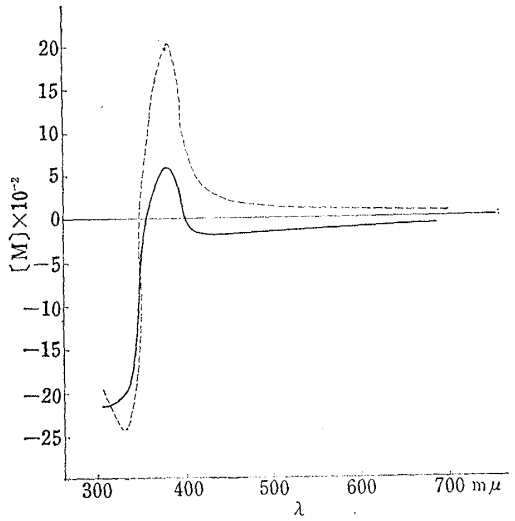

Fig. 1. Optical Rotatory Dispersion Curve

——— 2-Deoxy-3,4,6-tri-O-acetyl-β-D-glucopyranosyl ethylxanthate (VIII)
– – – – – 2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl ethylxanthate

Deacetylation of VIII with cold methanolic hydrogen chloride gave crystalline 2-deoxy-β-D-glucopyranosyl ethylxanthate (IX), m.p. 104~105°, $[\alpha]_D^{18}$ −80°, which returned to VIII in theoretical yield by acetylation with acetic anhydride and pyridine.

Treatment of VIII with cold sodium methoxide led to the formation of crystals, m.p. 114~115°, $[\alpha]_D^{15}$ +22°. The structure was assigned to be 1-thio-2-deoxy-β-D-glucose

13) D. Horton, W. N. Turner : Chem. & Ind. (London), **1964**, 76.
14) J. Davoll, B. Lythgoe : J. Chem. Soc., **1949**, 2526; G. Cooley, B. Ellis, P. Mamalis, V. Petrow, B. Sturgeon : J. Pharm. and Pharmacol., **2**, 579 (1950); J. J. Fox, L. F. Cavalieri, N. Chang : J. Am. Chem. Soc., **75**, 4315 (1953).
15) J. J. K. Novák, F. Šorm : Collection Czechoslov. Chem. Communs., **27**, 902 (1962).
16) Y. Tsuzuki, K. Tanabe, M. Akagi, S. Tejima : Bull. Chem. Soc. Japan, **37**, 162 (1964); D. Horton, M. L. Wolfrom : J. Org. Chem., **27**, 1794 (1962).

sodium salt dihydrate (X) from the experimental data mentioned below. Namely, reaction of aniline hydrochloride upon X afforded crystals (XI), m.p. 187~188° (decomp.), $[\alpha]_D^{22}$ −142° (10 min.), −100° (23 hr.) whose elementary analysis and physical constants were in agreement with that of 2-deoxy-D-glucose anilide.[17] Treatment of X with benzyl chloride in methanol gave benzyl 1-thio-2-deoxy-β-D-glucoside (XII), m.p. 96~97°, $[\alpha]_D^{21}$ −242°, in 97% yield. Acetylation of XII with acetic anhydride and pyridine gave triacetate (XIII), m.p. 60~61°, $[\alpha]_D^{18}$ −192°. The elementary analysis of XII or XIII was in agreement with that of benzyl 1-thio-2-deoxy-D-glucoside or benzyl 1-thio-2-deoxy-3,4,6-tri-O-acetyl-D-glucoside, respectively.

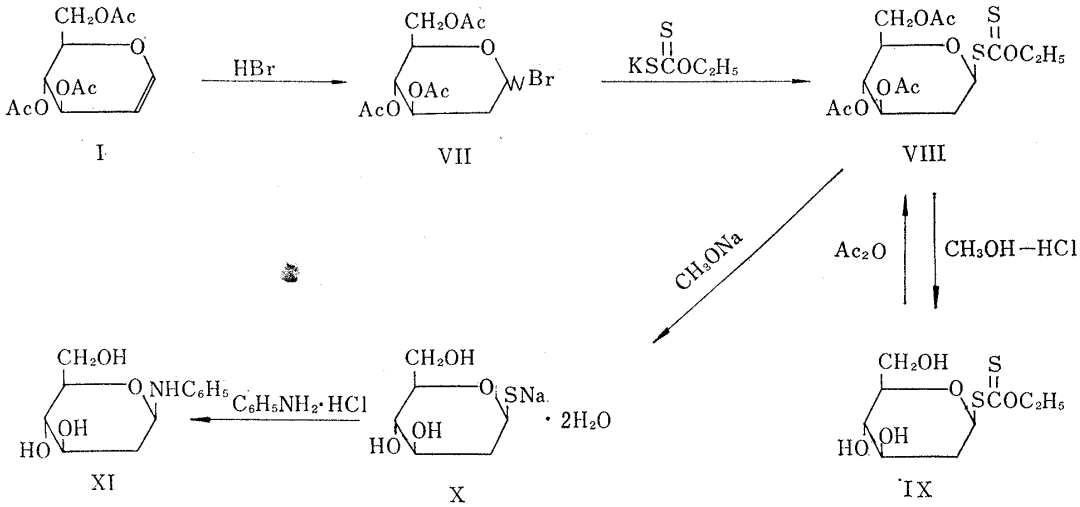

Chart 3.

Acetylatien of X with acetic anhydride and pyridine failed to give a crystalline product, but led to a syrupy acetate. The result appears to support our conclusion, as mentioned in the earlier parts of this paper, that crystalline thioacetate (II), obtained by reaction of thioacetic acid upon I, is not 1-S-acetyl-1-thio-2-deoxy-3,4,6-tri-O-acetyl-D-glucopyranoses.

The antitumor activity of VIII, IX or X is under investigation under the direction of Prof. D. Mizuno of the University of Tokyo.

Experimental

1-S-Acetyl-1-thio-4, 6-di-O-acetyl-α-D-pseudoglucal (1-S-Acetyl-1-thio-2, 3-didehydro-2, 3-dideoxy-4,6-di-O-acetyl-α-D-*erythro*-hexose) (II)——A mixture of triacetyl-D-glucal (I) (5 g.) and AcSH (4 ml.) containing 2 drops of conc. H_2SO_4 was heated under reflux for 5.5 hr. in an oil bath at 130~140°. The solution was concentrated *in vacuo* at 70° to afford syrupy residue, from which crystallization was induced by scratching the side of the flask after addition of a small amount of EtOH. Recrystallization from EtOH gave pure material (3.1 g., 58.5%), m.p. 104~105°, $[\alpha]_D^{22}$ +164° (c=0.5, $CHCl_3$), IR λ_{max}^{Nujol} μ: 5.9 (-SAc), 6.02 (-CH=CH-). *Anal.* Calcd. for $C_{12}H_{16}O_6S$: C, 49.67; H, 5.59; S, 11.13. Found: C, 49.59; H, 5.54; S, 11.25.

The NMR spectrum measured by JNM-3H-60-spectrometer (Japan Electron Optics Laboratory Co., Ltd.) in $CHCl_3$ at 60 Mc. revealed a singlet having a doublet area at 5.90 p.p.m. using tetramethylsilane as internal standard at 0.

1,5-Anhydro-2,3-dideoxy-4,6-O-benzylidene-D-glucitol (VI)——A solution of II (3 g.) in EtOH (50 ml.) was treated with freshly prepared Raney Ni (50 g. of alloy was activated) and the resulting suspension refluxed gently for 6 hr. Ni was removed by filtration and washed thoroughly with EtOH. The combined filtrate and washings were concentrated *in vacuo* at 40° to a colorless syrup (V) (1.8 g., 80%), $[\alpha]_D^{18}$ +22.1°

17) W. G. Overend, M. Stacey, J. Stanek: J. Chem. Soc., **1949**, 2841; K. Butler, S. Laland, W. G. Overend, M. Stacey: *Ibid.*, **1950**, 1433.

(c=1.4, EtOH), which did not decolorize CCl_4 containing Br_2. Bergmann and Breures[10] give $[\alpha]_D^{20}$ +2.2° (EtOH) and Ferrier, *et al.*[11] give $[\alpha]_D^{20}$ +2.6° (c=0.8, EtOH) for 1,5-anhydro-2,3-dideoxy-4,6-di-O-acetyl-D-glucitol.

Di-O-acetate (V) (0.6 g.) in MeOH (30 ml.) was deacetylated with $Ba(OMe)_2$ (0.01*N*) at 0° for 18 hr. and treated with PhCHO (30 ml.) and $ZnCl_2$ (1.0 g.) using the similar methods of Ferrier, *et al.*[11] for the preparation of 1,5-anhydro-2,3-dideoxy-4,6-O-benzylidene-D-glucitol. The product thus obtained had m.p. 136~137°. *Anal.* Calcd. for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32. Found: C, 71.04; H, 7.39.

Bergmann and Breuers[10] give m.p. 137°, Ferrier, *et al.*[11] give m.p. 135° for 1,5-anhydro-2,3-dideoxy-4,6-O-benzylidene-D-glucitol.

2-Deoxy-3,4,6-tri-O-acetyl-β-D-glucopyranosyl Ethylxanthate (VIII)——Starting from 3,4,6-tri-O-acetyl-D-glucal (I) (10 g.), syrupy 2-deoxy-3,4,6-tri-O-acetyl-D-glucopyranosyl bromide (VII), $[\alpha]_D^{20}$ +165.2° (10 min.), +105.4° (4 hr.) (c=1.12, $CHCl_3$) was prepared in a similar fashion to that used by Novák and Šorm.[15]

The bromide (VII) was dissolved in dry acetone (40 ml.) containing potassium ethylxanthate (6 g.), and the mixture was stirred for 30 min. at room temperature. After removal of the precipitated inorganic substances by filtration, the filtrate was concentrated *in vacuo* to a syrup. The residue was dissolved in $CHCl_3$ (150 ml.), washed twice with H_2O and the $CHCl_3$ layer was dried on $CaCl_2$ overnight. The solvent was removed from the filtrate *in vacuo* to afford a syrupy residue which induced to crystallize after addition of a small amount of EtOH and scratching the wall of the flask. The crystals (9.5 g., 65%) were separated by filtration and recrystallized from EtOH to give pure material, m.p. 99~100°, $[\alpha]_D^{20}$ −32° (c=1, acetylenetetrachloride), UV λ_{max}^{EtOH} mμ: 274. Its EtOH-solution showed Dische test for 2-deoxy-sugars. *Anal.* Calcd. for $C_{15}H_{22}O_8S_2$: C, 45.67; H, 5.62; S, 16.26. Found: C, 45.61; H, 5.69; S, 16.01.

The ORD (Fig. 1) was measured in tetrahydrofuran (c=0.5) at 20°.

2-Deoxy-β-D-glucopyranosyl Ethylxanthate (IX)——To an ice cold mixture of VIII (2 g.) in MeOH (12 ml.) was added MeOH (10 ml.) containing dry HCl which had previously been saturated at 0°, then left to stand in a refrigerator. After 20 hr. the solvent was removed *in vacuo* to a syrup. The residue was dissolved in dry benzene (10 ml.), the solvent was distilled off *in vacuo*, then left to stand in a vacuum desiccator to afford crystalline product. Recrystallization from EtOH-petr. ether gave pure material (1.0 g., 91%), m.p. 104~105°, $[\alpha]_D^{18}$ −80° (c=0.5, acetone). *Anal.* Calcd. for $C_9H_{16}O_5S_2$: C, 40.28; H, 6.01. Found: C, 40.50; H, 6.02.

Acetylation of IX (0.5 g.) with pyridine (4 ml.) and Ac_2O (3 ml.) for 15 hr. afforded acetate (0.67 g., 90%), m.p. 99~100°, $[\alpha]_D^{20}$ −34° (c=1, acetylenetetrachloride), after recrystallization from EtOH. The product showed no depression of melting point on admixture with VIII.

1-Thio-2-deoxy-β-D-glucose Sodium Salt Dihydrate (X)——A solution of VIII (6 g.) in $CHCl_3$ (16 ml.) was cooled to −15° and treated, under stirring and cooling with 40 ml. of an equally cold MeOH-solution of MeONa containing 0.6 g. of Na. Precipitates began to appear as the reaction took place. The reaction mixture was then left to stand in a refrigerator to complete the precipitation. The precipitates were separated by filtration, dried in the air at room temperature and recrystallized from MeOH to afford pure material (3.5 g., 95%), m.p. 114~115°, $[\alpha]_D^{15}$ +22° (c=1, H_2O). *Anal.* Calcd. for $C_6H_{11}O_4SNa \cdot 2H_2O$: C, 30.25; H; 6.34; S, 13.46. Found: C, 30.18; H, 6.46; S, 13.66.

A solution of X (0.219 g.) in 25 ml. of H_2O containing 2 ml. of 3*N* HCl mutarotated at 15° as follows: +25.1° (10 min.), +58.8° (20 hr.).

2-Deoxy-D-glucose Anilide (XI)——A mixture of X (0.5 g.), $PhNH_2 \cdot HCl$ (0.27 g.) and EtOH (5 ml.) was heated under reflux for 1 hr. After cooling, precipitates were separated by filtration, and recrystallized from EtOH to give pure material (0.25 g., 50%), m.p. 187~188° (decomp.), $[\alpha]_D^{22}$ −142° (10 min.), −97° (6 hr.), −100° (23 hr.) (c=1, pyridine). Overend, *et al.*[17] give m.p. 193~194°, $[\alpha]_D^{20}$ −138→−106° (2 days) (c=1, pyridine) and Butler, *et al.*[17] give m.p. 188~189° for 2-deoxy-D-glucose anilide. *Anal.* Calcd. for $C_{12}H_{17}O_4N$: C, 60.23; H, 7.14; N, 5.85. Found: C, 60.07; H, 7.25; N, 5.60.

Benzyl 1-Thio-2-deoxy-β-D-glucoside (XII)——A mixture of X (1 g.), $PhCH_2Cl$ (0.53 g.) and MeOH (15 ml.) was refluxed for 10 min. After removal of the precipitated inorganic substances by filtration, the solvent was distilled off *in vacuo* at 40°. The residue crystallized gradually on standing. Recrystallization from acetone-petr. ether gave pure material (1.1 g., 97%), m.p. 96~97°, $[\alpha]_D^{21}$ −242° (c=0.5, MeOH). *Anal.* Calcd. for $C_{13}H_{18}O_4S$: C, 57.76; H, 6.71; S, 11.86. Found: C, 57.69; H, 6.68; S, 11.73.

Benzyl 1-Thio-2-deoxy-3,4,6-tri-O-acetyl-β-D-glucoside (XIII)——A mixture of XII (0.5 g.), pyridine (4 ml.) and Ac_2O (3 ml.) was allowed to stand at 0° overnight. The solution was poured into ice-H_2O and extracted well with $CHCl_3$ (20 ml. × 4). The $CHCl_3$ layer was washed with ice-cold 3*N* H_2SO_4, aq. $NaHCO_3$ and H_2O respectively. The organic phase was dried over $CaCl_2$ and the solvent was removed from the filtrate to afford syrupy residue. Crystallization was induced by scratching the side of flask after trituration of the residue with a small amount of EtOH. Crystals (0.47 g., 64%) were separated by filtration and recrystallized from EtOH to give pure material, m.p. 60~61°, $[\alpha]_D^{18}$ −192° (c=1, $CHCl_3$). *Anal.* Calcd. for $C_{19}H_{24}O_7S$: C, 57.57; H, 6.10; S, 8.09. Found: C, 57.54; H, 6.01; S, 8.21.

The NMR spectrum was determined by Mr. S. Shimokawa of School of Technology, Hokkaido University, and a part of the elementary analyses was carried out by the Shimotakaido Laboratory, Kowa Co., Ltd. to all of whom the authors' thanks are due.

Summary

1-Thio-2-deoxy-β-D-glucose sodium salt dihydrate (X), m.p. 114~115°, $[\alpha]_D^{15}$ +22° was prepared starting from 3,4,6-tri-O-acetyl-D-glucal (I) *via* 2-deoxy-3,4,6-tri-O-acetyl-D-glucopyranosyl bromide (VII) and 2-deoxy-3,4,6-tri-O-acetyl-β-D-glucopyranosyl ethylxanthate (VIII). The product afforded 2-deoxy-D-glucose anilide, benzyl 1-thio-2-deoxy-β-D-glucoside, m.p. 96~97°, $[\alpha]_D^{21}$ −242°, and benzyl 1-thio-2-deoxy-3,4,6-tri-O-acetyl-β-D-glucoside, m.p. 60~61°, $[\alpha]_D^{18}$ −192°. The optical rotatory dispersion of VIII reveals the similarity with that of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl ethylxanthate, which supports the β-configuration of VIII, together with that of the compounds derived from VIII.

Heating of I with thioacetic acid for 5.5 hours in the presence of a small amount of sulfuric acid, afforded crystals, m.p. 104~105°, $[\alpha]_D^{22}$ +164°, in 60% yield. The structure was assigned to be 1-S-acetyl-1-thio-2,3-didehydro-2,3-dideoxy-4,6-di-O-acetyl-α-D-*eryhtro*-hexose (II).

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UDC 547.924.04

101. Munemitsu Tomoeda, Manabu Inuzuka, Tetsuya Furuta,[*1] and Toshitaka Koga: Studies on Conformation and Reactivity. II.[*2] The Polyphosphoric Acid-catalyzed Ring Opening of 4,5-Epoxy-3-oxo Steroids. 2. The Synthesis of 4-Ethylthio-17β-acetoxyandrost-4-en-3-one and its Analogs.[*3]

(*Faculty of Pharmacy, Kanazawa University*[*4])

In the first paper of this series,[1] it has been revealed that polyphosphoric acid (PPA) can work as an efficient catalyst, when used in the presence of suitable nucleophiles, of both normal and abnormal ring opening[*5] of 4β-, 5-epoxy-5β-cholestan-3-one (I). In acetic acid, I afforded 2α-acetoxycholest-4-en-3-one (II) as the sole and abnormal product. Ethanethiol, in marked contrast, reacted with I in dioxane affording 4-ethylthiocholest-4-en-3-one (III), as the normal product, and a further product, 3,4-bis-(ethylthio)cholesta-3,5-diene (IV). A further interesting fact was observed that ethanedithiol and 2-mercaptoethanol reacted with I, affording cholesta-3,5-dieno [3,4-*b*] dithiane (V) and its oxathiane (VI) derivative respectively.

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*2 Part I: Tetrahedron, **21**, 733 (1965).

*3 Presented at the meeting of the Kinki-Blanch of the Pharmaceutical Society of Japan, Kyoto, on 18th January, 1964, and published in part, as a communication, in this Bulletin, **12**, 383 (1964).

*4 Takara-machi, Kanazawa (友枝宗光, 犬塚 学, 古田哲弥, 古賀俊隆).

*5 For definition of the terms "normal" and "abnormal" regarding the ring opening of 4,5-epoxy-3-oxo steroids, see ref. 1.

1) Part I[*2] of this series published by M. Tomoeda, M. Ishizaki, H. Kobayashi, S. Kanatomo, T. Koga, M. Inuzuka, and T. Furuta.