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113. Takeo Naito and Mitsuji Sano: Studies on Nucleosides and Nucleotides. II.*1 Synthesis of Glycosyl-2-thiothymines from Glycosylthioureas.

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Synthesis of glucosylthymine from glucosylurea was described in Part I of this series*1 as a new method for synthesis of pyrimidine nucleosides. Based on the preliminary experiments described in Part I, examinations were made on the synthesis of glucosyl-2-thiothymine from glucosylthiourea and 1-β-D-glucopyranosyl-2-thiothymine and 1-β-D-ribofuranosyl-2-thiothymine were successfully obtained.

D-Glucosylthiourea (I), the starting material for the synthesis of 1-β-D-glucopyranosyl-2-thiothymine (Ⅷ), was prepared from D-glucose and thiourea in the presence of hydrochloric acid, in accordance with the method of Helferich.[1] The structure of this thioureide has not been described in any literature but was assumed to be 1-β-D-glucopyranosylthiourea by analogy with the structure of D-glucosylurea clarified in the preceding work.*1 As a first step prior to pyrimidine cyclization of the thioureide (I), protection of the hydroxyls in the sugar portion by acetylation was attempted by treatment with acetic anhydride and pyridine but, contrary to the case of D-glucosylurea, pentaacetate (Ⅳ) of m.p. 175° was obtained instead of the objective tetraacetate (Ⅱ). The acetylation was attempted in various ways and the method used by Sakami[2] for acetylation of the hydroxyl alone in hydroxylated amino acid was adopted. Acetylation with a mixture of acetic anhydride, glacial acetic acid, and perchloric acid finally afforded the desired tetraacetate (Ⅱ) of m.p. 171~173°. The fact that there had been no structural change by this treatment was confirmed by the formation of (Ⅳ) from (Ⅱ) by further acetylation and formation of (I) by deacetylation of (Ⅱ) and (Ⅳ). Attempt was made to obtain further proof of the structure of (Ⅱ) by its derivation to 1-(tetra-O-acetyl-D-glucosyl)urea (Ⅲ). Micheel[3] had converted 1-(poly-O-acetylglucosyl)-3-acylthiourea to urea derivative with mercury oxide and Fischer[4] used mercury oxide and ammonium isothiocyanate in deriving glucosylthiourea to glucosylurea, while Haring[5] converted 1-(poly-O-acetylglucosyl)-3-alkylthiourea to urea derivative by treatment with silver nitrate. These methods were tried in conversion of (Ⅱ) to (Ⅲ) but all ended in the recovery of the starting material. However, the same treatment of the monobenzoate (Ⅴ), m.p. 149.5~150.5°, obtained by benzoylation of (Ⅱ), showed that the reaction proceeded only in the case of silver nitrate and the corresponding urea derivative (Ⅵ), m.p. 218~220°, was obtained. This substance (Ⅵ) was identified with the monobenzoate of 1-(tetra-O-acetyl-β-D-glucopyranosyl)urea (Ⅲ), synthesized in the preceding work.*1 It has therefore been established that (Ⅱ) is 1-(tetra-O-acetyl-β-D-glucopyranosyl)thiourea and (I) is 1-β-D-glucopyranosylthiourea.

For the pyrimidine cyclization of (Ⅱ), condensation with 2-methyl-3-methoxyacryloyl chloride was carried out in chloroform, with pyridine as the deacidification agent. The intermediate in this reaction, 1-(tetra-O-acetyl-β-D-glucopyranosyl)-3-(2-methyl-3-methoxyacryloyl)thiourea (Ⅶ), was difficult to crystallize and was immediately warmed with

*1 Part I: This Bulletin, **9**, 703(1961).
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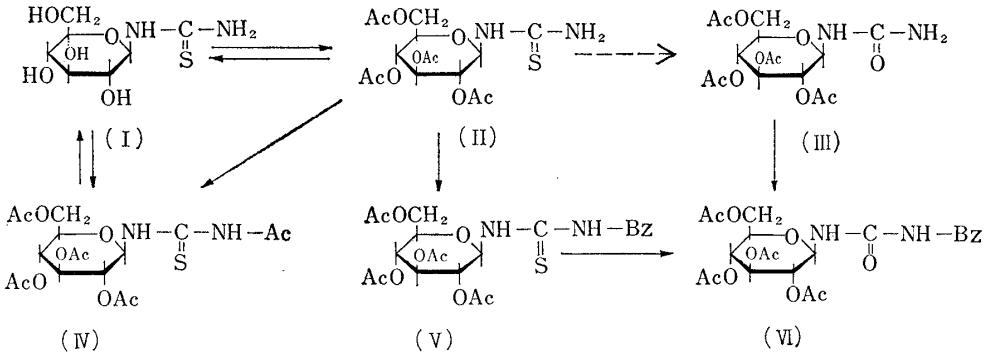
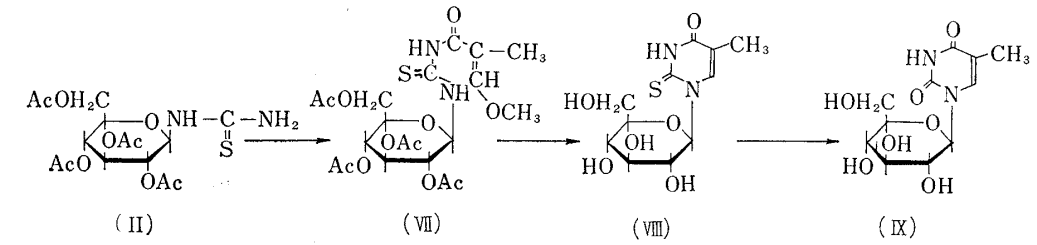
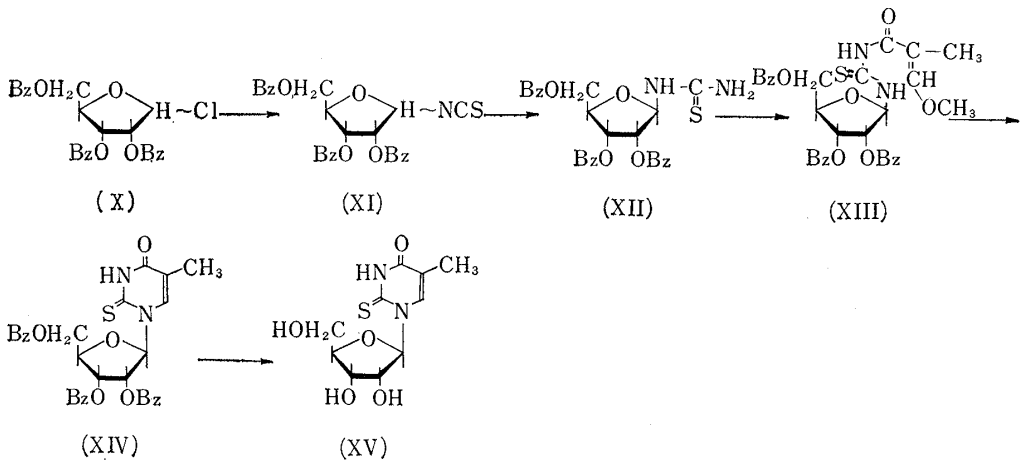
1) B. Helferich: Ber., **56**, 59 (1926).
2) W. Sakami: J. Biol. Chem., **144**, 203 (1942).
3) F. Micheel: Ber., 88, 481 (1955).
4) F. Fischer: *Ibid.*, **47**, 1377 (1914).
5) K.M. Haring: J. Am. Chem. Soc., **55**, 395 (1933).



dilute ammonia water to effect cyclization. The product so obtained was purified through chromatography according to the method of Stambaugh[6] and 1-β-D-glucopyranosyl-2-thiothymine (Ⅷ) of m.p. 226~228° was obtained. The structure of this substance was established by its treatment with monochloroacetic acid and identity of its product with 1-β-D-glucopyranosylthymine (Ⅸ), m.p. 266~267°, obtained in the preceding work.*[1]





Synthesis of 1-β-D-ribofuranosyl-2-thiothymine was then carried out. 1-(Tri-O-benzoyl-β-D-ribofuranosyl)thiourea (XII), the starting material for this synthesis, was prepared from tri-O-benzoyl-D-ribofuranosyl isothiocyanate (XI). Reaction of tri-O-benzoyl-D-ribofuranosyl chloride (X), obtained by the usual method, with silver isothiocyanate in toluene or with potassium thiocyanate in acetone or acetonitrile afforded a substance showing infrared spectrum with a characteristic absorption at 2000 cm^{-1}. This substance was obtained in a syrupy state and could not be crystallized but it was a ssumed to be the objective isothiocyanate (XI) and not thiocyanate because Ettlinger,[7] Lieber,[8] and Williams[9] showed that isothiocyanate compound possessed a broad absorption band of extremely

6) R.L. Stambaugh : J. Chromatog., 3, 22 (1960).
7) M.G. Ettlinger : J. Am. Chem. Soc., 77, 1831 (1955).
8) E. Lieber : Spectrochim. Acta, 13, 296 (1959).
9) D. Williams : J. Chem. Phys., 8, 513 (1940).

strong intensity at around 2100 cm^{-1} due to non-symmetric stretching vibration of N=C=S bond and that this band is clearly different from the strong absorption band at around 2140 cm^{-1} in thiocyanate compounds due to C≡N bond. For the sake of comparison, infrared spectrum was measured of tetra-O-acetyl-β-D-glucopyranosyl-isothiocyanate and thiocyanate as similar compounds and, as shown in Fig. 1, the spectra were found to be clearly different. The band at 2000 cm^{-1} in the substance obtained as above had shifted to a somewhat lower wave-number region but it could be assigned to the stretching vibration of N=C=S, and the substance was considered to be the objective (XI). The reaction of (XI) with ammonia afforded 1-(tri-O-benzoyl-D-ribofuranosyl)thiourea (XII), m.p. 163~164°.

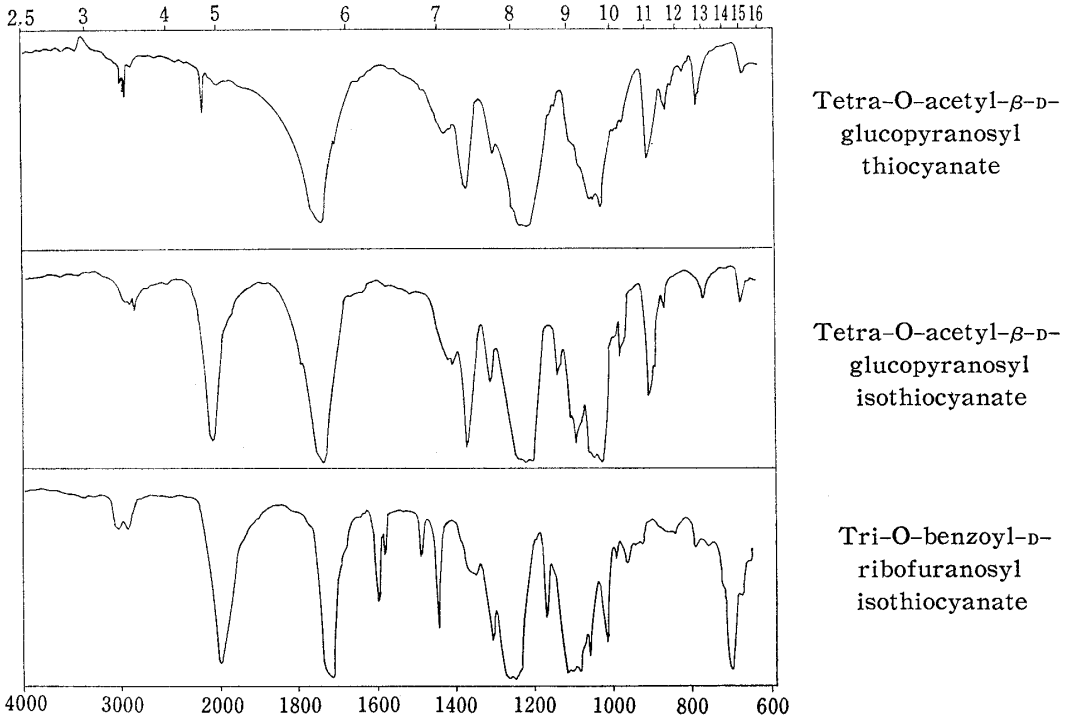


Fig. 1. Infrared Absorption Spectra of Thiocyanate and Isothiocyanate Derivatives (KBr disk)

For the synthesis of (XV) from (XII), condensation of (XII) and 2-methyl-3-methoxyacryloyl chloride was carried out in chloroform in the presence of pyridine and the intermediate (XIII) was obtained in amorphous state. Pyrimidine cyclization of this product, in the presence of trimethylamine, and purification through chromatography afforded a substance (XIV) of m.p. 156~158°, which was identified with 1-(tri-O-benzoyl-β-D-ribofuranosyl)-2-thiothymine, prepared by the method of Shaw.[10] Its debenzoylation finally gave the objective 1-β-D-ribofuranosyl-2-thiothymine (XV). These results showed that the configuration at C-1 of thioureide (XII) is a β-type.

The foregoing experiments have revealed that glycosylthiourea, irrespective of the ring structure of the sugar, undergoes pyrimidine cyclization as in the case of glycosylurea and forms pyrimidine nucleoside.

Experimental

1-D-Glucopyranosylthiourea (I)——Prepared according to the report of Helferich.[1] Colorless prisms, m.p. 207~210°(decomp.).

10) G. Shaw : J. Chem. Soc., **1958**, 2294.

1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)thiourea (II)——To a mixture of Ac_2O (56 cc.) and AcOH (20 cc.), 60% $HClO_4$ (8 cc.) and powdered D-glucosylthiourea (5 g.) were added at 0°. After stirring for 30 min. at room temperature, the mixture was poured into ice-water (300 g.), and neutralized with aqueous $NaHCO_3$. The separated crystalline substance was filtered off and washed with cold water. Crude product, dried in a desiccator, was recrystallized from AcOEt to (II) (10.7 g. of 63%) as colorless prisms, m.p. 171~173°, $[\alpha]_D^{25}$ +8.68°(c=0.69, $CHCl_3$). *Anal.* Calcd. for $C_{15}H_{22}O_9N_2S$: C, 44.33; H, 5.46; N, 6.89. Found: C, 44.61; H, 5.54; N, 6.84.

3-Acetyl-1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)thiourea (IV)——(a) A mixture of finely powdered D-glucopyranosylthiourea (20 g.), pyridine (120 cc.), and Ac_2O (70 cc.) was stirred for 4 days at room temperature. After filtering a small amount of unreacted thiourea, the filtrate was evaporated *in vacuo* to give a gummy residue. This was extracted with $CHCl_3$ and washed with aqueous $NaHCO_3$ and water. The dried $CHCl_3$ solution was evaporated *in vacuo*, leaving of syrup which provided crystals (26 g.) on allowing to stand in Et_2O. Recrystallization from AcOEt-petr. ether gave colorless needles, m.p. 173~175°. *Anal.* Calcd. for $C_{17}H_{24}O_{10}N_2S$: C, 45.44; H, 5.35; N, 6.25. Found: C, 45.41; H, 4.94; N, 6.31.

(b) A mixture of Ac_2O (10 cc.), anhyd. $ZnCl_2$ (0.5 g.), and (II) (0.5 g.) was heated for 2 hr. on a boiling water bath. After evaporating the excess Ac_2O *in vacuo*, the residue was poured into cold water neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The evaporated residue of $CHCl_3$ solution, dried with Na_2SO_4, gave crystalline solid by trituration with petr. ether. The product was crystallized from AcOEt-petr. ether to colorless needles (0.4 g.), m.p. 173~175°. This was identical with (IV) prepared by method (a) and undepressed on admixture.

Deacetylation of 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)thiourea——To a solution of (II) (0.5 g.) in dehyd. MeOH (10 cc.), Na (2 mg.) was added and refluxed for 30 min. on a water bath. The separated crystalline product was filtered and washed with MeOH. Colorless prisms, m.p. 205~208°(decomp.), were obtained as a first crop. Yield, 220 mg. (92%). The mixed melting point with (I) was not depressed.

Deacetylation of 3-Acetyl-1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)thiourea——A solution of (IV) (0.5 g.) and Na (2 mg.) in MeOH (10 cc.) was treated after the manner described above. Colorless prisms, m.p. 205~208°(decomp.). Yield, 200 mg. (75%). The mixed melting point with (I) was not depressed.

3-Benzoyl-1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)thiourea (V)——(II) (0.4 g.) was dissolved in 2.5 cc. of $CHCl_3$, dried over P_2O_5, and pyridine (0.12 cc.) and BzCl (0.17 g.) were added to this solution. The mixture was allowed to stand overnight at room temperature and 10 cc. of $CHCl_3$ was added at the end of this time. After successive washing with $NaHSO_4$, $NaHCO_3$ solutions, and water, the dried solution was evaporated, leaving a gummy residue with which provided crystalline solid on trituration with petr. ether. This was recrystallized from EtOH to colorless needles (0.35 g., 69%), m.p. 149.5~150.5°, $[\alpha]_D^{25}$ −2.23°(c=0.897, $CHCl_3$). *Anal.* Calcd. for $C_{22}H_{26}O_{10}N_2S$: C, 51.76; H, 5.13; N, 5.49. Found: C, 51.67; H, 5.13; N, 5.46.

3-Benzoyl-1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)urea (VI)——Prepared according to the report of Helferich and Kosche,[1] colorless needles, m.p. 218~220°. Reported[1] m.p. 211~212°. *Anal.* Calcd. for $C_{22}H_{26}O_{11}N_2$: C, 53.43; H, 5.30. Found: C, 53.34; H, 5.03.

Conversion of 3-Benzoyl-1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)thiourea to 3-Benzoyl-1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)urea (VI)——A hot solution of 0.1 g. of (V) in 2 cc. of EtOH and a solution of 0.1 g. of $AgNO_3$ in 0.5 cc. of water were mixed and heated on a water bath at 50~60°. After 5 min. 0.1*N* NaOH was added to neutralized HNO_3 liberated from $AgNO_3$. This promoted the coagulation of Ag_2S and helped to prevent HNO_3 from hydrolyzing acetyl groups of the sugar. The solution was heated until Ag_2S coagulated. It was then cooled and filtered. The filtrate was concentrated to dryness *in vacuo* and added with 3 cc. of water. Undissolved precipitate was filtered, washed with water, and the desulfurized ester was obtained in 72% yield (70 mg.). Crude product was recrystallized from EtOH to colorless needles, m.p. 218~220°. This was identical with (VI), m.p. 218~220°, and undepressed on admixture.

1-β-D-Glucopyranosyl-2-thiothymine (VIII)——The suspended (II) (2.2 g.) in dehyd. $CHCl_3$ (15 cc.) was mixed with 0.65 g. of pyridine and 0.9 g. of 2-methyl-3-methoxyacryloyl chloride, the mixture was allowed to stand overnight at room temperature and then refluxed for 4 hr. on a water bath. After successive washing with $NaHSO_4$, $NaHCO_3$ solution, and H_2O, the $CHCl_3$ solution was dried over Na_2SO_4 and evaporated *in vacuo*, leaving 3.5 g. of a yellowish brown syrup. The syrup was again dissolved in 20 cc. of $CHCl_3$ and this solution was added slowly to the $CHCl_3$ layer on the top of a silica gel column which had been prepared by pouring a slurry of 100~200 mesh silica gel (125 g.) in $CHCl_3$ into a column (3.5×23 cm.).

The column was eluted with 500 cc. of $CHCl_3$, 2000 cc. of $CHCl_3$-AcOEt (17:3), and 1000 cc. of $CHCl_3$-AcOEt (1:1). Total of 134 fractions of 25-cc. each were taken by means of an automatic fraction collector. The effluents were examined by ultraviolet rays (2536 Å). The fractions (29 to 41)

containing the main product were combined and evaporated *in vacuo* to yield 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(2-methyl-3-methoxyacryloyl)thiourea (Ⅶ) (0.9 g.) as pale yellowish amorph. Analytical sample was further purified by means of chromatography on alumina column, eluted with AcOEt. UV. $\lambda_{max}^{H_2O}$ mμ : 267, 289. λ_{max}^{EtOH} mμ : 261, 287. *Anal.* Calcd. for $C_{20}H_{28}O_{11}N_2S$: C, 47.61; H, 5.59; N, 5.55. Found : C, 47.88; H, 5.75; N, 5.33.

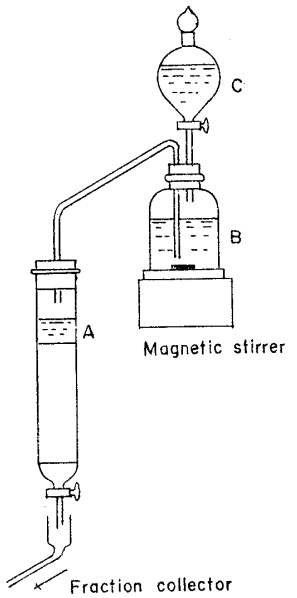


Fig. 2.

Apparatus for Gradient Elution

The amorphous (Ⅶ) (4.1 g.) was mixed with 300 cc. of 3.3% NH_4OH and heated with stirring for 1.5 hr. on a boiling water bath. The reaction mixture was treated with a little charcoal and evaporated *in vacuo*, leaving 3.5 g. of a syrup. This syrup was purified by means of chromatography on activated charcoal column which had been prepared as follows : Apparatus used for charcoal chromatography consisted of a 5 cm. (diameter) chromatographic column "A" and two 1000-cc. bottles: "B" and "C," as shown in Fig. 2. The aqueous acid solution (pH 2.0) containing a syrupy compound was adsorbed on a column consisting of charcoal (70 g.) and cellulose powder (70 g.) in tube "A" and eluted slowly (1.6 cc./min.). The column was washed with distilled water until the washing became neutral to litmus. The elution of the adsorbed compounds was carried out as follows. 200 cc. of water was added on charcoal column in tube "A", and 800 cc. of water was added to the mixing bottle "B." The volume and concentration of solvents added to the bottle "C" were as follows : First 500 cc. water, second 1000 cc. conc. NH_4OH-EtOH-H_2O (5:1:13), third 2000 cc. conc. NH_4OH-EtOH-H_2O (5:5:13).

Total of 120 fractions of 25-cc. each was taken by means of an automatic fraction collector. Each fraction absorbing ultraviolet ray (2536 Å) was submitted to paper partition chromatographic examination using Toyo Roshi No. 50 filter paper, developed by the ascending method with upper layer of MeCOEt. As a result, it was seen that the main product eluted in fraction Nos. 55～61 (Rf 0.17). The fractions (55 to 61) were combined and evaporated to dryness *in vacuo*. The residue was recrystallized from MeOH to colorless prisms (0.70 g.), m.p. 226～228°, $[\alpha]_D^{25}$ +14.5° (c=0.87, H_2O), UV : $\lambda_{max}^{H_2O}$ 282 mμ (log ε 4.19). *Anal.* Calcd. for $C_{11}H_{16}O_6N_2S$: C, 43.42; H, 5.30; N, 9.21. Found: C, 43.48; H, 5.45; N, 8.96.

Conversion of 1-β-D-Glucopyranosyl-2-thiothymine (VIII) into 1-β-D-Glucopyranosylthymine (IX) ——A solution of (Ⅷ) (0.2 g.), $CH_2ClCOOH$ (4 g.), and H_2O (40 cc.) was refluxed for 6 hr., and the product was separated by charcoal chromatography as shown in Fig. 2. The reaction mixture was absorbed on a column consisting of charcoal (5 g.) and cellulose powder (5 g.) in tube "A" (2-cm. diameter). The column was washed with distilled water until the washing became neutral. The elution of the adsorbed compounds was carried out as follows : 50 cc. of water was added to the charcoal column in tube "A" and 50 cc. of water was added to "B." The volume and concentration of solvents added to "C" were as follows : First 300 cc. conc. NH_4OH-EtOH-H_2O (5:1:13), second 600 cc. conc. NH_4OH-EtOH-H_2O (5:5:13).

Total of 82 fractions of 12-cc. each were taken. Each fraction absorbing ultraviolet ray (2536 Å) was submitted to paper partition chromatographic examination using Toyo Roshi No. 50 filter paper, developed by the ascending method with water-saturated iso-BuOH. Fraction Nos. 24～31 (containing (IX), Rf 0.11) were collected, and the product was evaporated, and the residue was recrystallized from EtOH to colorless prisms, m.p. 264～266°, yield, 0.17 g. (69%), UV : $\lambda_{max}^{H_2O}$ 264 mμ

(log ε 3.99). This was identical with 1-β-D-glucopyranosylthymine prepared in earlier work*1 and undepressed on admixture.

2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl isothiocyanate (XI)——1-O-Acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (5.0 g.) was suspended in dehyd. Et_2O, saturated with HCl at 0°, and kept at 0° for 10 days. Et_2O and HCl were removed in a reduced pressure at 5°. The residual gum was treated twice with benzene and once with toluene, followed by evaporation. There was finally no odor of AcOH. The clear gum was dissolved in toluene (30 cc.), freshly prepared AgNCS (3.3 g.) was added, and the mixture stirred under reflux for 2.5 hr. The solid was removed and washed with toluene. The combined filtrate and washings were evaporated to a gum, which did not crystallize. Pale yellowish gum, yield, 5.2 g. IR $\nu_{N=C=S}$ 2000 cm^{-1} (film).

1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)thiourea (XII)——To a solution of syrupy 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl isothiocyanate (5.2 g.) in $CHCl_3$ (10 cc.), 3 cc. of MeOH-NH_4OH (0.8 g. of NH_3 contai ned) was added with stirring at 0°. After 30 min., solvents and NH_3 were immediately removed in a reduced pressure at 5°. The residual syrup was dissolved in MeOH and recovered by evaporation. Crystallized from MeOH the thiourea (3.8 g., 73%) had m.p. 158~161° and recrystallized from MeOH to colorless needles, m.p. 163~164°; $[\alpha]_D^{25}$ −44.8° (c=0.89, $CHCl_3$). *Anal.* Calcd. for $C_{27}H_{24}O_7N_2S$: C, 62.30; H, 4.65; N, 5.38. Found: C, 62.38; H, 4.59; N, 5.18.

1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-2-thiothymine (XIV)——The suspended (XII) (2.0 g.) in dehyd. $CHCl_3$ (15 cc.) was mixed with pyridine (0.6 g.) and 2-methyl-3-methoxyacryloyl chloride (0.7 g.), the mixture was allowed to stand overnight at room temperature, and then refluxed for 2.5 hr. on a water bath. After successive washing with $NaHSO_4$ $NaHCO_3$ solution, and water, the $CHCl_3$ solution was dried over Na_2SO_4, and evaporated *in vacuo*, leaving a yellowish syrup. The syrup was again dissolved in $CHCl_3$ (20 cc.) and this solution was added slowly to the $CHCl_3$ layer on the top of a silica gel column which had been prepared by pouring a slurry of 100~200 mesh silica gel (130 g.) in $CHCl_3$ into a column (3.5×25 cm.).

The column was eluted with $CHCl_3$ (1000 cc.), $CHCl_3$-AcOEt (9:1) (1500 cc.). Total of 100 fractions of 25 cc. each were taken and the effluents were detected by ultraviolet absorption. The main fractions (54 to 69) were combined and evaporated *in vacuo* to yield 1-(2,3,5-tri-O-benzoyl-D-ribofuranosyl)-3-(2-methyl-3-methoxyacryloyl)thiourea (XIII) (2.0 g.) as pale yellowish amorph. *Anal.* Calcd. for $C_{32}H_{30}O_9N_2S$: C, 62.18; H, 4.85; N, 4.52. Found: C, 63.61; H, 4.45; N, 4.85.

A solution of (XIII) (1.8 g.) and Et_3N (2.0 g) in AcOEt (50 cc.) was refluxed for 1.5 hr. on a water bath, then cooled, washed with 3% HCl (3×20 cc.) and water (3×20 cc.), dried over Na_2SO_4, and evaporated *in vacuo* to a syrup. This syrup was dissolved in $CHCl_3$ (10 cc.) and then purified by column chromatography over silica gel (50 g.) (2-cm. diameter).

Total of 130 fractions of 25-cc. each were taken, the main fractions (82 to 87) were collected, and solvent was evaporated *in vacuo*. The syrupy residue was dissolved in MeOH (5 cc.) and allowed to stand for several hours. The crystalline product (70 mg.) was recrystallized from MeOH to colorless needles, m.p. 156~158°. This was identified with (XIV) prepared by Shaw, *et al.*,[10] and undepressed on admixture.

1-β-D-Ribofuranosyl-2-thiothymine (XV)——Prepared according to the report of Shaw, *et al.*[10] Yield, 30 mg. from 0.2 g. of (XIV). Colorless needles (from EtOH), m.p. 215~217°, $[\alpha]_D^{28}$ +30.5° (c=0.85, H_2O). *Anal.* Calcd. for $C_{10}H_{14}O_5N_2S$: C, 43.80; H, 5.15. Found: C, 43.55; H, 5.23.

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Summary

Synthesis of glycosyl-2-thiothymine from glycosylthiourea was carried out. Acetylation of 1-β-D-glucopyranosylthiourea with acetic anhydride, glacial acetic acid, and perchloric acid was found to give 1-(tetra-O-acetyl-β-D-glucosyl)thiourea and it was condensed with 2-methyl-3-methoxyacryloyl chloride. Cyclization of its product afforded 1-β-D-glucopyranosyl-2-thiothymine. In a similar manner, thiourea, prepared from tri-O-benzoyl-D-ribofuranosyl chloride through isothiocyanate, afforded 1-β-D-ribofuranosyl-2-thiothymine by the same method. The structure of all the compounds synthesized was established.

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