

[Chem. Pharm. Bull.]
29(8) 2188-2192(1981)

Studies on Nucleoside Analogs. XXI. A Convenient Synthesis of 1,2,4-Triazole-5-thione Glycosides¹⁾

HARUO OGURA,* HIROSHI TAKAHASHI, and OSAMU SATO

*School of Pharmaceutical Sciences, Kitasato University, 5-9-1
Shirokane, Minato-ku, Tokyo 108, Japan*

(Received December 15, 1980)

The reaction of glycosyl isothiocyanates (**1a—c**) with acyl or aroyl hydrazine, followed by treatment with $\text{Ac}_2\text{O}-\text{H}_3\text{PO}_4$, afforded 1,2,4-triazole-5-thione glycosides (**20a**, **21a—c**, **22a**) in fair yields. Attempts to prepare 1,2,4-triazole glycoside analogs with acetic anhydride or sodium methoxide failed. The reaction of glycosyl-2-(phenyl- or pyrid-2-ylhydrazine)thiocarboxamides (**6a**, **7a**) with phosgene in pyridine or triethylamine gave thiadiazole-5-thiones (**8a**, **9a**) instead of 1,2,4-triazole glycosides.

Keywords—glycosyl isothiocyanate; N-glycosyl-2-substituted hydrazine thiocarboxamide; N-glycosylamino-4-substituted 1,3,4-thiadiazol-5-one; 1,2,4-triazole-5-thione glycoside; dehydration reaction

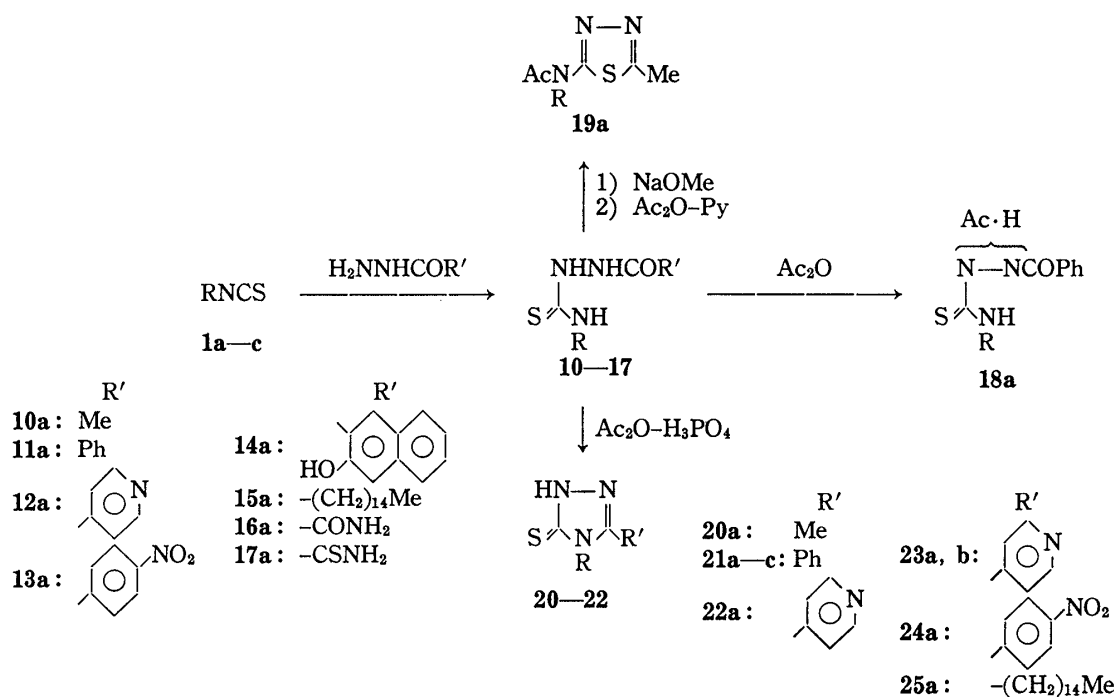
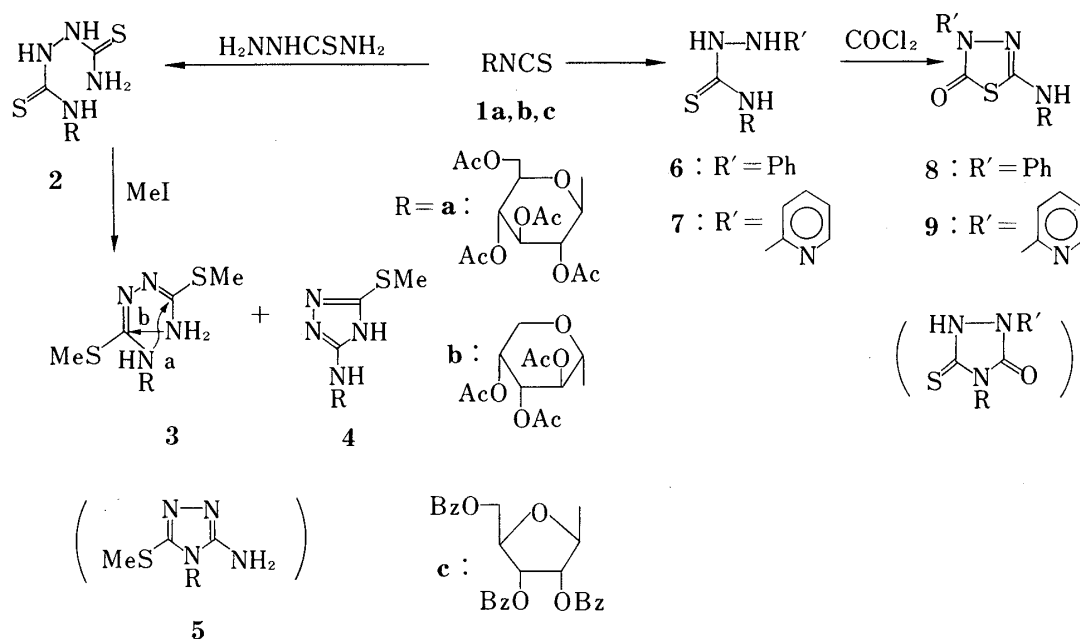
Previously, we have reported the synthesis of nucleoside analogs from glycosyl isothiocyanate.²⁾ It is known that 1,2,4-triazole³⁾ and 1,2,3-triazole glycoside⁴⁾ have biological activities; among them, Virazole showed the highest anti-viral activities.⁵⁾

In this paper, we describe a convenient and general synthetic method for 1,2,4-triazole glycoside analogs through the reaction of glycosyl isothiocyanates with hydrazine, followed by a dehydration reaction. The reaction of 2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl isothiocyanate (**1a**) with thiosemicarbazide in acetonitrile (MeCN) gave N-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)-2,5-thiobiurea (**2a**) in good yield. Altland and Graham⁶⁾ found that 1,6-dialkyl-2,5-thiobiureas cyclized under basic conditions to form 1,2,4-triazoline-3-thiones. Treatment of **10a** with methanolic sodium methoxide,⁷⁾ followed by acetylation with acetic anhydride (Ac_2O)-pyridine, gave 2,2-acetyl(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)-amino-5-methyl-1,2,4-thiadiazole (**19a**) instead of 4-glycosyl-1,2,4-triazole-5-thione (**20a**). We have reported a cyclodesulfurization reaction of thioureido compounds⁸⁾ using methyl iodide-triethylamine. Treatment of **2a** with $\text{MeI}-\text{NEt}_3$, followed by chromatography on silica gel, gave 3-glucopyranosylamino-5-thiomethoxy-1,2,4-triazole (**4a**) in 3:4 ratio. The former (**3a**) was easily converted into the cyclized product (**4a**) by heating in an appropriate solvent. The nuclear magnetic resonance (NMR) spectrum of **3a** showed a sharp singlet peak at δ 2.43 due to the SCH_3 protons. The NMR spectrum of **4a** showed a singlet peak at δ 2.58 which was assigned to the SCH_3 protons. In this experiment, the 1,2,4-triazole glycoside (**5a**) was not isolated.

A one-carbon insertion reaction of N-glycosyl-2-(phenyl- or 2-pyridylhydrazine)thiocarboxamides (**6a**, **7a**) with phosgene-ether solution gave glycosylamino-4-phenyl- or glycosylamino-4-(pyrid-2-yl)-1,3,5-thiadiazol-5-ones (**8a**, **9a**) in fair yields after chromatography.

We then investigated the cyclization reaction of N-glycosyl-2-(benzoylhydrazine)thiocarboxamides (**10a—c**) under acidic conditions. Treatment of **10a** in Ac_2O under stirring at room temperature or heating gave two N-acetyl compounds after chromatography.

When the N-glycosyl-2-(benzoylhydrazine)thiocarboxamide (**11a**) was treated with polyphosphoric acid (PPA) at 60 °C for 2 h, a 1,2,4-triazole-5-thione glycoside (**20a**) was obtained in 45% yield along with the starting material. On increasing the reaction temperature to 80–85 °C, the cyclized product (**20a**) was obtained in 67% yield together with decomposed products. In order to find mild dehydration conditions, we examined the dehydration reaction



using Ac_2O -phosphoric acid (H_3PO_4). Treatment of **10a** with Ac_2O - H_3PO_4 (20:1) under ice cooling afforded **20a** in 92% yield. Similar treatment of N-glycosyl-2-substituted hydrazine thiocarboxamides (**10a**, **11a-c**, **12a**) yielded the corresponding 1,2,4-triazole-5-thione glycosides (**20a**, **21a-c**, **22a**) in good yields.

The deacetylation of some product was carried out in the usual way. Treatment of the protected 1,2,4-triazole-5-thione glycosides with methanolic sodium methoxide, followed by neutralization with Dowex ion-exchange resin (H^+ form), afforded free 1,2,4-triazole-5-thione glycosides (**23a**, **b**, **24a**, **25a**) in good yields.

Experimental

All melting points are uncorrected. IR spectra were measured with a JASCO A-2 spectrometer and NMR spectra on a Varian T-60 spectrometer. Tetramethylsilane was used as an internal reference. Mass spectra (MS) were measured with a JMS-D-100 spectrometer using a direct inlet system at 75 eV. Optical rotations were measured in CHCl_3 solution in a 50 mm cell with a JASCO DIP-181 automatic polarimeter.

1-(2,3,4,6-Tetra-O-acetyl- β -D-glucopyranosyl)-2,5-thiobiurea (2a)—A mixture of **1a** (389 mg, 0.001 mol) and thiosemicarbazide (91 mg, 0.001 mol) in dry benzene (30 ml) was refluxed for 6 h and then allowed to stand at room temperature. The separated crystals were collected by filtration and recrystallized from Et_2O – EtOH (1:1) to give colorless fine needles. Yield: 465 mg (97%), mp 172–175°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3570, 3450, 3270 (NH_2 , NH), 1740 (OCOCH_3), 1620, 1220, 1035. NMR ($\text{DMSO}-d_6$) δ : 5.85 (1H, t, 1'-H), 7.60 (2H, bs, $\text{NH} \times 2$). MS (m/z): 446 ($\text{M}^+ - \text{H}_2\text{S}$). Anal. Calcd for $\text{C}_{16}\text{H}_{24}\text{N}_4\text{O}_9\text{S}_2$: C, 39.99; H, 5.03; N, 11.66. Found: C, 40.02; H, 5.42; N, 11.70.

1-(2,3,4,6-Tetra-O-acetyl- β -D-glucopyranosyl)-2,5-di-S-methylthiobiurea (3a) and 3-(2,3,4,6-Tetra-O-acetyl- β -D-glucopyranosyl)amino-5-thiomethoxy-1,2,4-triazole (4a)—MeI (2 ml) and NEt_3 (2 ml) were added dropwise at room temperature to a stirred solution of **2a** (480 mg, 0.001 mol) in tetrahydrofuran (THF). After the reaction mixture had been stirred for 10 h, the solvent was evaporated off under reduced pressure to give a brownish residue. The residue was dissolved in CHCl_3 (50 ml), washed with H_2O and dried over MgSO_4 . Removal of the solvent left a slightly yellow residue which was chromatographed on silica gel with benzene–acetone. Elution with benzene–acetone (19:1) gave 150 mg (30%) of **3a** as colorless needles. Recrystallization from Et_2O –*n*-hexane (1:1) afforded **3a** as colorless fine needles, mp 140–142°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3350, 3300 (NH_2 , NH), 1740 (OCOCH_3), 1200, 1010. $[\alpha]_D^{25} - 15^\circ$ ($c=1.0$). Anal. Calcd for $\text{C}_{18}\text{H}_{28}\text{N}_4\text{O}_9\text{S}$: C, 42.51; H, 5.55; N, 11.02. Found: C, 42.47; H, 5.53; N, 11.08. NMR (CDCl_3) δ : 2.43 (6H, s, $\text{Me} \times 2$), 7.14 (1H, d, $J=8.0$ Hz, 1'-H). Elution with benzene–acetone (4:1) gave 200 mg (43%) of **4a** as colorless needles. Recrystallization from Et_2O –*iso*- Pr_2O (2:1) gave **4a** as colorless prisms, mp 159–162°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3350, 3300 (NH_2 , NH), 1740 (OCOCH_3), 1600, 1030. MS (m/z): 460 (M^+). $[\alpha]_D^{25} + 14^\circ$ ($c=1.0$). Anal. Calcd for $\text{C}_{17}\text{H}_{24}\text{N}_4\text{O}_9\text{S}$: C, 44.34; H, 5.25; N, 12.17. Found: C, 44.36; H, 5.20; N, 12.22.

2,2-Acetyl(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)amino-5-methyl-1,3,4-thiadiazole (19a)—A solution of **10a** (463 mg, 0.001 mol) in MeOH – NaOMe (10 ml) was stirred for 2 h under cooling in an ice bath. The reaction solution was neutralized with ion-exchange resin (Dowex 50W-X8, H^+ -form) and filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue was treated with Ac_2O (2 ml) and dry pyridine (2 ml). After being stirred for 6 h at room temperature, the mixture was poured into ice water and extracted with CHCl_3 (100 ml). The extract was washed with sat. NaHCO_3 solution and H_2O and dried over MgSO_4 . Removal of the solvent by evaporation left a brownish residue, which was chromatographed on silica gel. Elution with benzene–acetone (97:3) gave 360 mg (74%) of **19a** as slightly yellow crystals. Recrystallization from CCl_4 – CHCl_3 (3:1) gave **19a** as colorless fine needles, mp 177–168°C. $[\alpha]_D^{25} + 19^\circ$ ($c=1.0$). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1740 (OCOCH_3), 1610, 1370, 1230, 1040. NMR (CDCl_3) δ : 2.30 (3H, s, NCOCH_3), 2.64 (3H, s, $-\text{S}=\text{CCH}_3$). MS (m/z): 487 (M^+). Anal. Calcd for $\text{C}_{19}\text{H}_{25}\text{N}_3\text{O}_{10}\text{S}$: C, 46.81; H, 5.17; N, 8.62. Found: C, 46.93; H, 5.23; N, 8.65.

2-(2,3,4,6-Tetra-O-acetyl- β -D-glucopyranosyl)amino-4-phenyl-1,3,4-thiadiazol-5-one (8a) and 2-(2,3,4,6-Tetra-O-acetyl- β -D-glucopyranosyl)amino-4-(pyrid-2-yl)-1,3,4-thiadiazol-5-one (9a)—A 30% COCl_2 – Et_2O solution was added dropwise to an Et_2O solution of **6a** (0.001 mol) and dry pyridine (0.5 ml) under cooling in an ice bath. After being stirred for 30–50 min, the reaction solution was washed with H_2O and dried over MgSO_4 . Removal of the solvent by evaporation left a slightly brownish residue, which was chromatographed on silica gel. From the eluate with CHCl_3 , 500 mg (96%) of **8a** was obtained as a slightly yellow syrup. *Rf* 0.45 [silica gel, benzene–acetone (3:2)]. $[\alpha]_D^{25} + 13^\circ$ ($c=1.0$). Anal. Calcd for $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_{10}\text{S}$: C, 50.47; H, 4.81; N, 8.03. Found: C, 50.32; H, 4.75; N, 8.09. MS (m/z): 523 (M^+). A 30% CO – Et_2O solution was added to a solution of **7a** (0.001 mol) and dry pyridine (0.5 ml) in Et_2O (10 ml) under cooling and the reaction solution was treated as described above for **8a**. From the eluate with benzene–acetone (97:3), 498 mg (95%) of **9a** was obtained as a slightly brownish syrup. *Rf* 0.55 [silica gel, benzene–acetone (5:1)], $[\alpha]_D^{25} + 8^\circ$ ($c=1.0$). Anal. Calcd for $\text{C}_{21}\text{H}_{24}\text{N}_4\text{O}_{10}\text{S}$: C, 48.09; H, 4.61; N, 10.68. Found: C, 48.16; H, 4.80; N, 10.60. MS (m/z): 524 (M^+).

N-(2,3,4,6-Tetra-O-acetyl- β -D-glucopyranosyl)-2-(acetylbenzoylhydrazine)thiocarboxamides (18a)—A solution of N-glycosyl-2-(benzoylhydrazine)thiocarboxamide (**10a**; 445 mg, 0.001 mol) in Ac_2O (10 ml) or Ac_2O (5 ml)–dry pyridine (5 ml) was stirred for 24 h at room temperature. The reaction solution was poured into ice water and extracted with benzene. The organic layer was washed with sat. NaHCO_3 solution, and H_2O and dried over MgSO_4 . Removal of the solvent by evaporation under reduced pressure left a syrup, which was chromatographed on silica gel. The eluate with benzene–acetone (19:1) gave 369 mg (65%) of the first band product. *Rf* 0.56 [silica gel, benzene–acetone (4:1)], IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3150, 3000, 1740, 1510, 1420, 1360, 1220. NMR (CDCl_3) δ : 2.30 (3H, s, NCOCH_3), 5.80 (1H, t, 1'-H), 11.45 (1H, d, $J=8.0$ Hz, 1'-NH).

The eluate with benzene–acetone (17:3) gave 130 mg (23%) of the second band product. *Rf* 0.32 [silica gel, benzene–acetone (4:1)]. IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 3150, 3000, 1740, 1510, 1360, 1210. NMR (CDCl_3) δ : 2.22 (3H, s, NCOCH_3), 5.65 (1H, t, 1'-H), 8.12 (1H, bs, NH), 11.60 (1H, d, $J=8.0$ Hz, 1'-NH).

N-Glycosyl-2-(substituted hydrazine)thiocarboxamides (10—17)—a) A mixture of 2,3,4-tri-O-acetyl- α -D-arabinopyranosyl isothiocyanate (317 mg, 0.001 mol) or 2,3,5-tri-O-benzoyl- β -D-ribofuranosyl isothiocyanate (503 mg, 0.001 mol) and an acyl or aroyl hydrazine (0.001 mol) in MeCN (20—50 ml) was refluxed for 2—10 h then allowed to stand at room temperature. The reaction solution was concentrated under reduced pressure to give a residue, which was chromatographed on silica gel. Elution with benzene-acetone (97:3) gave the cyclized product in 93—97% yields.

10b: Yield: 359 mg (93%), mp 111—114°C [Et₂O-CCl₄ (2:1)]. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3200 (NH), 1740 (OCO-CH₃). *Anal.* Calcd for C₁₄H₂₁N₃O₈S: C, 42.96; H, 5.41; N, 10.74. Found: C, 42.90; H, 5.38; N, 10.82. MS (*m/z*): 373 (M⁺ - H₂O).

11b: Yield: 400 mg (93%), mp 170—173°C [Et₂O-benzene (3:2)]. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3300 (NH), 1740 (OCOCH₃), 1600, 750 (Ph). *Anal.* Calcd for C₁₉H₂₃N₃O₈S: C, 50.33; H, 5.11; N, 9.27. Found: C, 50.32; H, 5.07; N, 9.32. MS (*m/z*): 435 (M⁺ - H₂O).

12b: Yield: 441 mg (97%), mp 207—210°C [iso-Pr₂O-CHCl₃ (1:1)]. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3300 (NH), 1740 (OCOCH₃), 1680 (CONH). *Anal.* Calcd for C₁₈H₂₂N₄O₈S: C, 47.57; H, 4.88; N, 12.33. Found: C, 47.60; H, 4.84; N, 12.27. MS (*m/z*): 436 (M⁺ - H₂O).

10c: Yield: 500 mg (87%). *Rf* 0.32 [benzene-acetone (4:1)]. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3250 (NH), 1720 (OCOPh). *Anal.* Calcd for C₂₉H₂₇N₃O₈S: C, 60.30; H, 4.71; N, 7.28. Found: C, 60.35; H, 4.73; N, 7.25. [α]_D²⁰ +36° (*c*=1.0).

11c: Yield: 588 mg (92%), mp 175—176°C [Et₂O-iso-Pr₂O (1:1)]. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3300 (NH), 1720 (OCOPh), 1600, 750 (Ph). *Anal.* Calcd for C₃₄H₂₉N₃O₈S: C, 63.84; H, 4.57; N, 6.57. Found: C, 63.90; H, 4.55; N, 6.57. [α]_D²⁰ +9° (*c*=1.0).

b) A mixture of 2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl isothiocyanate (389 mg, 0.001 mol) and an acyl or aroyl hydrazine (0.001 mol) in MeCN (20 ml) or benzene (20 ml) was refluxed for 3 h and treated as described for a) (Table I).

TABLE I. N-Glycosyl-2-(substituted hydrazine)thiocarboxamides (10a—17a)

Compd. No.	Yield (%)	mp (°C) or <i>R_f</i>	IR $\nu_{\text{max}}^{\text{KBr}}$ cm ⁻¹	Formula	Analysis (%)			MS (<i>m/z</i>)
					Calcd (Found)			
					C	H	N	
10a	90	Syrup 0.32 ^{a)}	3350, 1740	C ₁₇ H ₂₅ N ₃ O ₁₀ S	44.06 (44.30)	5.44 5.38	9.07 9.15)	445 (M ⁺ - H ₂ O)
11a	94	127—130	3350, 1740, 1620, 1550, 1100, 750	C ₂₂ H ₂₇ N ₃ O ₁₀ S	50.28 (50.32)	5.00 5.08	8.00 8.12)	507 (M ⁺ - H ₂ O)
12a	95	170—175	3200, 1740, 1680, 1580	C ₂₁ H ₂₆ N ₄ O ₁₀ S	47.91 (47.96)	4.98 4.94	10.64 10.60)	508 (M ⁺ - H ₂ O)
13a	93	90—93	3300, 1740, 1600, 1350	C ₂₂ H ₂₆ N ₄ O ₁₂ S	46.31 (46.52)	4.59 4.63	9.82 9.78)	512 (M ⁺ - H ₂ O)
14a	92	140—142	3350, 3300, 1740, 1600	C ₂₆ H ₂₉ N ₃ O ₁₁ S	52.79 (52.75)	4.94 4.96	7.10 7.14)	573 (M ⁺ - H ₂ O)
15a	87	Syrup 0.65 ^{a)}	3350, 1740	C ₃₁ H ₄₉ N ₃ O ₉ S	58.20 (58.18)	7.72 7.76	6.57 6.64)	621 (M ⁺ - H ₂ O)
16a	65	188—191	3200, 1740, 1720, 1640	C ₁₆ H ₂₄ N ₄ O ₁₀ S	41.38 (41.42)	5.21 5.30	12.06 12.12)	446 (M ⁺ - H ₂ O)
17a	77	172—175	3570, 3450, 1740, 1620	C ₁₆ H ₂₄ N ₄ O ₉ S ₂	39.99 (40.02)	5.03 5.42	11.66 11.70)	462 (M ⁺ - H ₂ O)

a) TLC [silica gel, benzene-acetone (3:2)].

4-Glycosyl 1,2,4-Triazole-5-thione (20a, 21a—c, 22c)—a) A solution of 11a (524 mg, 0.001 mol) in PPA (5 ml) was heated at 60°C under N₂ in an oil bath. After 50 min, crushed ice was added to the reaction solution, which was then extracted with CHCl₃. The organic layer was washed with sat. NaHCO₃ solution, and H₂O, and dried over MgSO₄. Removal of the solvent by evaporation gave a brownish residue. The residue was then chromatographed on silica gel. Elution with benzene-acetone (97:3) afforded **20a** as colorless needles. Yield: 164 mg (37%), mp 171—172°C [Et₂O-iso-Pr₂O (1:1)]. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3300 (NH), 1740 (OCOCH₃), 1230, 1040. NMR (CDCl₃) δ : 6.58 (1H, bs, NH), 2.52 (3H, s, 3-Me). MS (*m/z*): 445 (M⁺). *Anal.* Calcd for C₁₇H₂₃N₃O₉S: C, 45.84; H, 5.20; N, 9.44. Found: C, 45.87; H, 5.25; N, 9.38.

21a: Yield: 228 mg (45%). *Rf* 0.51 [silica gel, benzene-acetone (4:1)]. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3250 (NH), 1740 (OCOCH₃), 1580, 750 (Ph). NMR (CDCl₃) δ : 6.03 (1H, bs, NH), 7.20—7.40 (5H, m, Ph). MS (*m/z*): 507 (M⁺).

b) A mixture of 10a (465 mg, 0.001 mol) in PPA (5 ml) was heated at 80—85°C in an oil bath. After 2.5 h, the reaction mixture was treated as described for a) to provide 340 mg (67%) of **20a**.

c) H_3PO_4 (0.5 ml) was added to a solution of N-glycosyl-2-(substituted hydrazine)thiocarboxamide (10a, 11a—c, 16a; 0.001 mol) in Ac_2O (10 ml) under cooling. After 2—4 h, the reaction solution was poured into ice water and extracted with CHCl_3 . The organic layer was treated as described for a).

20a: Yield: 481 mg (95%).

21a: Yield: 480 mg (92%).

21b: Yield: 395 mg (91%), mp 105—107°C [Et_2O -benzene (1:1)]. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3300 (NH), 1740 (OCOCH_3), 1530, 750 (Ph). NMR (CDCl_3) δ : 6.47 (1H, bs, NH), 7.19—7.92 (5H, m, Ph). MS (m/z): 435 (M^+). Anal. Calcd for $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}_7\text{S}$: C, 52.41; H, 4.86; N, 9.65. Found: C, 52.38; H, 4.90; N, 9.68.

21c: Yield: 531 mg (95%). Rf 0.47 [silica gel, benzene-acetone (3:2)]. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3250 (NH), 1720 (OCOPh), 1605, 750 (Ph). $[\alpha]_D^{17} - 58^\circ$ ($c=1.0$). Anal. Calcd for $\text{C}_{29}\text{H}_{25}\text{N}_3\text{O}_7\text{S}$: C, 62.24; H, 4.50; N, 7.51. Found: C, 62.20; H, 4.56; N, 7.48.

22a: Yield: 390 mg (88%), mp 161—163°C [Et_2O -benzene (3:2)]. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3300 (NH), 1740 (OCOCH_3). Anal. Calcd for $\text{C}_{17}\text{H}_{22}\text{N}_3\text{O}_9\text{S}$: C, 45.94; H, 4.99; N, 9.45. Found: C, 45.87; H, 4.93; N, 4.50. MS (m/z): 444 (M^+).

4-Glycosyl-3-substituted 1,2,4-Triazole-5-thione (23a, b, 24a, 25a)—A solution of a 4-acetylglucosyl-3-substituted 1,2,4-triazole-5-thione (0.001 mol) in MeOH - MeONa (10 ml) was stirred for 0.5—1 h under ice cooling. The solution was neutralized by stirring it with ion-exchange resin [Dowex 50W-X8 (H^+ form)], then the resin was filtered off and washed with MeOH (5 ml). The filtrate was evaporated to dryness under reduced pressure below 40°C. The residue was crystallized from EtOH to give 23a as a colorless syrup, or 23b, 24a, 25a as colorless needles.

23a: Yield: 313 mg (92%). $[\alpha]_D^{22} - 13^\circ$ ($c=1.0$, MeOH). IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 3400, 1610, 1540, 1220, 1050. Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{N}_4\text{O}_5\text{S}$: C, 45.88; H, 4.74; N, 16.45. Found: C, 45.80; H, 4.70; N, 16.45.

23b: Yield: 288 mg (93%), mp 166—168°C. $[\alpha]_D^{22} - 24^\circ$ ($c=1.0$, MeOH). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3450, 1605, 1540, 1220, 1050. Anal. Calcd for $\text{C}_{12}\text{H}_{14}\text{N}_4\text{O}_4\text{S}$: C, 46.45; H, 4.55; N, 18.05. Found: C, 46.48; H, 4.60; N, 18.20.

24a: Yield: 357 mg (93%), mp 81—84°C. $[\alpha]_D^{22} - 15^\circ$ ($c=1.0$, MeOH). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3450, 3300, 1605, 740. Anal. Calcd for $\text{C}_{14}\text{H}_{16}\text{N}_4\text{O}_7\text{S}$: C, 43.75; H, 4.20; N, 14.58. Found: C, 43.70; H, 4.25; N, 14.62.

25a: Yield: 449 mg (95%), mp 84—87°C. $[\alpha]_D^{22} - 13^\circ$ ($c=1.0$, MeOH). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3300, 1240, 1050. Anal. Calcd for $\text{C}_{23}\text{H}_{43}\text{N}_3\text{O}_5\text{S}$: C, 58.32; H, 9.15; N, 8.87. Found: C, 58.60; H, 9.20; N, 8.85.

Acknowledgement This work was supported in part by a Grant-in-Aid for Cancer Research (55-16) from the Ministry of Health and Welfare, Japan.

References and Notes

- 1) The previous series entitled "C-Nucleoside Synthesis" has been followed by the present series "Studies on Nucleoside Analogs." This also constitutes Part XL in a series entitled "Studies on Heterocyclic Compounds." Previous paper (Part XX): H. Ogura, H. Takahashi, and O. Sato, *Chem. Pharm. Bull.*, **29**, 1838 (1981).
- 2) H. Takahashi, N. Nimura, and H. Ogura, *Chem. Pharm. Bull.*, **27**, 1130, 1147 (1979); H. Takahashi, K. Takeda, N. Nimura, and H. Ogura, *Chem. Pharm. Bull.*, **27**, 1143 (1979).
- 3) G.L. Szekeres, J.T. Witkowski, and R.K. Robins, *J. Carbohydr. Nucleosides Nucleotides*, **4**, 147 (1977); M.S. Szekeres and E.F. Nowoswait, *J. Org. Chem.*, **42**, 1109 (1977); R.D. Youssefyeh, J.P. Verheyden, and J.G. Moffatt, *J. Org. Chem.*, **44**, 1301 (1979).
- 4) J.A. Montgomery, A.T. Shortnacy, and H.J. Thomas, *J. Med. Chem.*, **17**, 1197 (1974).
- 5) J.T. Witkowski, R.K. Robins, R.W. Sodwell, and L.N. Simon, *J. Med. Chem.*, **15**, 1150 (1972).
- 6) H.W. Altland and P.A. Graham, *J. Heterocycl. Chem.*, **15**, 377 (1978).
- 7) F. Kurzer and J.L. Secker, *Tetrahedron*, **33**, 1999 (1977); R. Esmail and F. Kurzer, *Tetrahedron*, **33**, 2007 (1977).
- 8) H. Ogura, H. Takahashi, and E. Kudo, *J. Carbohydr. Nucleosides Nucleotides*, **5**, 329 (1978); H. Takahashi, N. Nimura, and H. Ogura, *Chem. Pharm. Bull.*, **27**, 1153 (1979).