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Studies on Nucleoside Analogs. XXII. Reactions of Glycosyl Isothiocyanates: Syntheses of Glycosylamino-1,2,3-thiadiazoles and 1,2,4,6-Thiatriazine-S-oxide Glycosides

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The reactions of glycosyl isothiocyanates (**1a**—**c**) with diazomethane or ethyl diazoacetate gave the corresponding glycosylamino-1,2,3-thiadiazoles (**2a**—**c** or **3a**, **b**). Attempted ring transformation of **2** under thermal or basic conditions failed. Similar treatment of D-gluconyl isothiocyanate (**1d**) with diazomethane afforded D-gluco-pent-1-yl oxathiazolone (**5d**) in good yield. The reactions of **1a**—**c** with acetoamidine or formamidine hydrochloride under basic conditions gave the corresponding N-glycosyl-N′-acetoamidino- or N-glycosyl-N′-formamidinothiocarboxamides (**6a**—**c**; **7a**, **c**). Subsequent treatment of **6b**, **c** and **7a**, **c** with thionyl chloride under basic conditions afforded the corresponding 1,2,4,6-thiatriazine-S-oxide glycosides (**8a**—**c**; **9a**, **c**) in good yields. Attempted transformation of **8** to 1,2,4-triazole glycoside (**10**) was unsuccessful.

Keywords——glycosyl isothiocyanate; D-gluconyl isothiocyanate; diazomethane; ethyl diazoacetate; glycosylamino-1,2,3-thiadiazole; 1,2,4,6-thiatriazine-S-oxide glycoside; N-glycosyl-N′-acetoamidinothiocarboxamide; N-glycosyl-N′-formamidinothiocarboxamide; thionyl chloride

We have reported a convenient synthetic method for nucleoside analogs using glycosyl isothiocyanates as starting materials, *e.g.*, glycosylaminoisothiazoles, glycosylaminoisothiazolo[3,4-*d*]pyrimidines,[2] glycosylaminopyrazolo[3,4-*d*]pyrimidines,[3] and glycosylaminotheophylline.[4]

In the present paper, we wish to describe the reactions of D-glycosyl or D-gluconyl isothiocyanate with diazo compounds or amidines.

Synthesis of Glycosylamino-1,2,3-thiadiazoles and Their Derivatives

Treatment of glycosyl isothiocyanates (**1a**—**c**) with an excess of diazomethane (CH_2N_2) under cooling for 4 h gave the corresponding 5-glycosylamino-1,2,3-thiadiazoles (**2a**—**c**) in 84—95% yields after chromatography. The infrared (IR) spectra of these products showed NH bands at 3350—3250 cm^{-1} instead of isothiocyanate bands. The nuclear magnetic resonance (NMR) spectra of **2a**—**c** showed a doublet at δ 6.25—7.75 due to the NH proton and a singlet at δ 8.00—8.02 which was assigned to the proton at the 4 position. The physical data for **2a**—**c** are summarized in Table I. Similar treatments of **1a**, **b** with ethyl diazoacetate in dioxane under reflux for 24—48 h afforded the corresponding 4-carboethoxy-5-glycosylamino-1,2,3-thiadiazoles (**3a**, **b**) in 30—42% yields with 52—60% recoveries of the starting material. In the case of the reaction between glycosyl isothiocyanates and diazo compounds, 1,2,3-triazole glycoside (**4**) was not isolated and 5-glycosylamino-1,2,3-thiadiazoles (**2a**—**c**; **3a**, **b**) were obtained in good yields.

Recently, transformation of 5-alkyl-1,2,3-thiadiazoles into 5-alkylthio-1,2,3-triazoles has been reported by Masuda *et al.*[5] We investigated the ring transformation under thermal or basic conditions. When **2a** was treated with Na_2CO_3 under heating, the reaction solution discolored (dark brown) and it decomposed gradually, giving no desired products. Heating of **2a** in xylene or dimethyl sulfoxide (DMSO), or without solvent gave no characterizable products and 12% of the starting material was recovered.

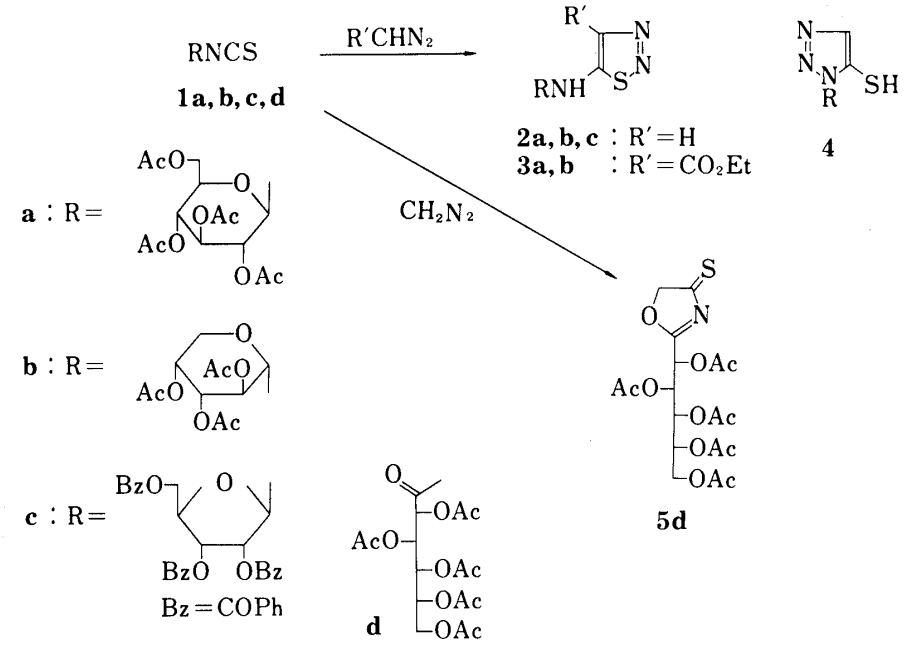

Chart 1

Table I. 5-Glycosylamino-1,2,3-thiadiazoles (**2a**—**c** and **3a**, **b**)

Compd. No.	Yield (%)	*Rf* or mp (°C)	IR ν_{max}^{KBr} cm^{-1}	NMR ($CDCl_3$, δ) Heterocyclic moiety	UV λ_{max}^{MeOH} nm (log ε)	Formula	Analysis (%) Calcd (Found) C H N	MS (*m/z*)
2a	95	0.60[a]	3350, 1740, 1210, 1040	6.30 (1H, d, J= 8.0 Hz, NH), 8.00 (1H, s, 4-H)	289(3.8) 265(3.4) 223(3.4)	$C_{16}H_{21}O_9N_3S$	44.55 4.91 9.74 (44.50 4.87 9.82)	431(M^+)
2b	92	0.69[a]	3300, 1740, 1210, 1045	6.25 (1H, d, J= 8.0 Hz, NH), 8.00 (1H, s, 4-H)	290(3.8) 265(3.4) 226(3.3)	$C_{13}H_{17}O_7N_3S$	43.45 4.77 11.69 (43.37 4.78 11.73)	359(M_+)
2c	84	0.42[b]	3250, 1710, 1580, 745	6.75 (1H, d, J= 8.0 Hz, NH), 8.02 (1H, s, 4-H)	292(3.9) 283(3.9) 276(3.9) 229(4.6)	$C_{28}H_{23}O_7N_3S$	61.64 4.25 7.70 (61.70 4.32 7.74)	
3a	42	0.37[b]	3370, 1740, 1220, 1050	1.43 (3H, t, Me), 4.46 (2H, m, CH_2), 11.00 (1H, bs, NH)		$C_{19}H_{25}N_3O_{11}S$	45.33 5.01 8.35 (45.40 5.08 8.40)	503(M^+)
3b	30	123—125	3350, 1740, 1210, 1045	1.42 (3H, t, Me), 4.45 (2H, m, CH_2), 11.05 (1H, bs, NH)		$C_{16}H_{21}O_9N_3S$	44.55 4.91 9.74 (44.60 4.85 9.70)	431(M^+)

a) TLC [silica gel, benzene–acetone (3:2)].
b) TLC [silica gel, benzene–acetone (5:1)].

2,3,4,5,6-Penta-*O*-acetyl-D-gluconyl isothiocyanate (**1d**), prepared from 2,3,4,5,6-penta-*O*-acetyl-D-gluconyl chloride according to our method,[6] was treated with excess CH_2N_2 in ether at room temperature to give 2-(D-*gluco*-pent-1-yl)-4-oxathiazolone (**5d**) in 92% yield.

Synthesis of 1,2,4,6-Thiatriazine-S-oxide Glycosides

We have shown that a one-carbon insertion reaction of glycosyl isothiobiurets or N-glycosyl-N'-guanidylthiocarboxamides with triethyl orthoformate gives 5-azathiocytosine glycosides and related *s*-triazine glycosides.[7] A similar reaction of N-glycosyl-N'-acetoamidinothiocarboxamides did not occur and the starting material was recovered because of thermal dissociation.[8]

Stirring of mixtures of **1a—c** and acetoamidine hydrochloride in acetonitrile (MeCN) solution in the presence of dry pyridine or triethylamine (NEt_3) afforded the corresponding N-glycosyl-N′-acetoamidinothiocarboxamides (**6a—c**) after chromatography on silica gel. Similar treatment of **1a** and **c** with formamidine hydrochloride gave the corresponding N-glycosyl-N′-formamidinothiocarboxamides (**7a, c**) in good yields.[9]

Next, we attempted to prepare thiatriazine-*S*-oxide glycosides from the N-glycosyl-N′-acetoamidinothiocarboxamides. Treatment of **8a—c** and **7a, c** with thionyl chloride in $CHCl_3$ solution under cooling gave the corresponding 1,2,4,6-thiatriazine-*S*-oxide glycosides (**8a—c**; **9a, c**) in good yields (Table II). The NMR spectra of **8a—c** showed a singlet at δ 2.02—2.48 due to the methyl protons and a broad singlet at δ 7.08—7.50 which was assigned to the NH proton. In the mass spectra, the M-SO]$^+$ fragment appeared.

TABLE II. 2-Glycosyl-1,2,4,6-thiatriazine-S-oxides (**8a—c** or **9a, c**)

Compd. No.	Yield (%)	*Rf* or mp (°C)	IR ν_{max}^{KBr} cm^{-1}	NMR ($CDCl_3$, δ) Me or H	NMR ($CDCl_3$, δ) NH	Ms (*m/z*) or $[\alpha]_D^{16}$ (*c* 1.0, MeOH)	Formula	Analysis (%) Calcd (Found) C	H	N
8a	95	157—161 Colorless needles	3300, 1740, 1610, 1220, 1050	2.48(s)	7.08(bs)	445 (M–SO]$^+$) −18°	$C_{17}H_{23}N_3O_{10}S_2$	41.38 (41.52	4.70 4.72	8.51 8.60)
8b	92	134—135 Colorless fine needles	3300, 1740, 1605, 1220, 1040	2.46(s)	7.50(bs)	373 (M–SO]$^+$) −47°	$C_{14}H_{19}N_3O_8S_2$	39.90 (39.95	4.54 4.60	9.97 9.94)
8c	90	0.60[a]	3300, 1710, 1610, 1580, 1210, 750	2.02(s)	—	445 (M-base]$^+$) −83°	$C_{29}H_{25}N_3O_8S_2$	57.32 (57.40	4.15 4.23	6.92 6.88)
9a	93	147—150 Colorless needles	3300, 1740, 1610, 1220, 1050	8.20	7.10	431 (M–SO]$^+$)	$C_{16}H_{21}N_3O_{10}S_2$	40.08 (40.13	4.41 4.55	8.76 8.80)
9c	87	160—163 Colorless	3250, 1710, 1610, 1580, 1220, 750	8.35	—	445 (M–SO]$^+$)	$C_{28}H_{23}N_3O_8S_2$	56.65 (56.68	3.91 3.87	7.08 7.12)

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

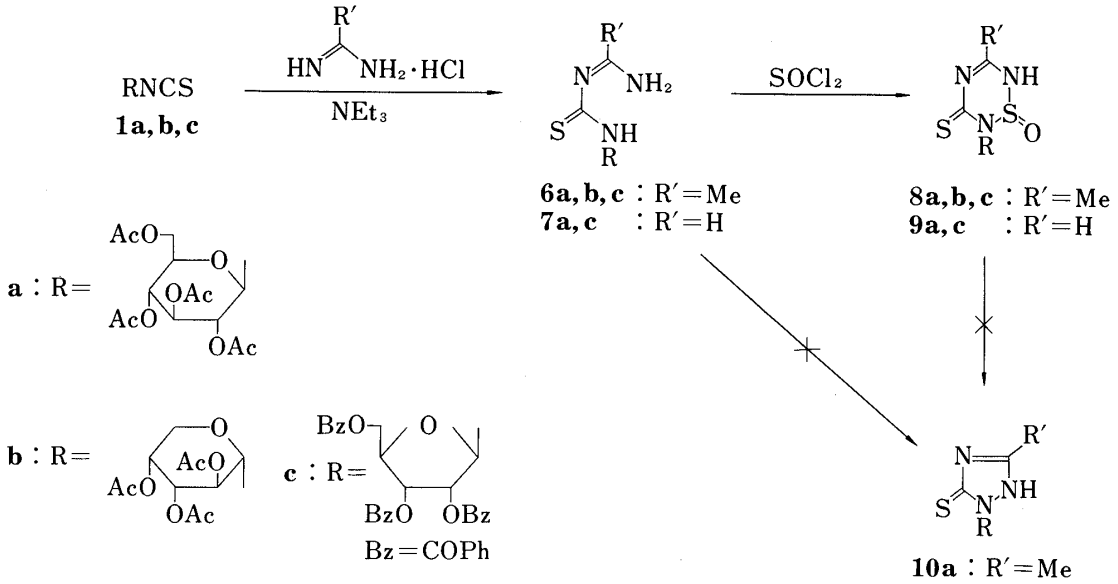

Chart 2

Ring construction of the thiatriazine-S-oxide glycosides under thermal or basic conditions was attempted. Refluxing of **8a, b** in dry xylene did not give 1,2,4-triazole glycoside (**10a**),[9] and the starting material was recovered. Heating of **8a** in dry pyridine at 60—80 °C for 2 h did not afford the desired product **10a**; the reaction solution discolored (dark brown) and many spots were detected on thin-layer chromatography (TLC).

In conclusion, attempted ring transformation from thiatriazine-S-oxide glycosides to triazole glycosides was unsuccessful.

Experimental

All melting points are uncorrected. Thin-layer chromatography (TLC) was performed on silica gel (Kieselgel, Merck). Infrared (IR) spectra were measured with a JASCO A-2 spectrometer. The nuclear magnetic resonance (NMR) spectra were measured with a Varian T-60 spectrometer and tetramethylsilane was used as an internal reference. Mass spectra (MS) were determined with a JMS-D-100 spectrometer using a direct inlet system at 75 eV.

5-Glycosylamino-1,2,3-thiadiazoles (2a—c) (See Table I)——CH_2N_2–Et_2O solution (15 ml) was added to a solution of **1a, b,** or **c** (0.001 mol) in dry Et_2O (100 ml) under ice-cooling. The reaction solution was stirred for 2 h and stirring continued for 2 h at room temperature. Removal of the solvent by evaporation left a slightly brownish residue, which was chromatographed on silica gel with benzene–acetone. From the eluate with benzene–acetone (49: 1, v/v), **2a, b,** or **c** was obtained as slightly yellow syrup. Crystallization from benzene–iso-Pr_2O (1: 2, v/v) gave **2a** or **c** as colorless fine prisms. In the case of **1b, 2b** was obtained as a colorless syrup.

4-Carboethoxy-5-glycosylamino-1,2,3-thiadiazoles (3a, b) (See, Table I)——A solution of **1a** or **b** (0.001 mol) and ethyl diazoacetate (170 mg, 0.001 mol) in dry pyridine (10 ml) was refluxed for 24—48 h. Removal of the solvent by evaporation left a slightly yellow syrup, which was chromatographed as described for **2a—c**. Elution with benzene–acetone (97: 3, v/v) provided a colorless syrup. In the case of **1b**, a trace of benzene was added to the syrup and the mixture was left in a freezer overnight. Separated crystals were collected by filtration and recrystallized from CCl_4–EtOH (2: 1, v/v) to **3b** as colorless needles.

2-(1,2,3,4,5-Penta-O-acetyl-D-gluco-pent-1-yl)-4-oxathiazolone (5b)——Excess CH_2N_2 in Et_2O (20 ml) was added to an Et_2O solution of **1d** (447 mg, 0.001 mol) under ice-cooling. After being stirred for 3 h, the reaction solution was further stirred for 6 h at room temperature. The resulting solution was washed with H_2O and dried over $MgSO_4$. Removal of the solvent by evaporation left a slightly yellow residue which was chromatographed on silica gel. From the eluate with benzene, **5d** was obtained as colorless needles. Recrystallization from *n*-hexane–Et_2O (2: 1, v/v) gave **5d** (415 mg, 92%) as colorless fine needles, mp 95—96°C. IR ν_{max}^{KBr} cm^{-1}: 1740 ($OCOCH_3$), 1220, 1050. *Anal.* Calcd for $C_{18}H_{23}O_{11}NS$: C, 46.85; H, 5.02; N, 3.04. Found: C, 46.80; H, 5.09; N, 2.98. NMR ($CDCl_3$) δ: 3.70 (2H, s, 5-H_2), MS (*m/z*): 461 (M^+).

N-Glycosyl-N′-acetoamidinothiocarboxamides (6a—c) and N-Glycosyl-N′-formamidinothiocarboxamides (7a, c)——These compounds were prepared by the reported procedure, by the reaction of glycosyl isothiocyanates (**1a—c**) with acetoamidine hydrochloride or formamidine hydrochloride.[9]

2-Glycosyl-5-methyl-1,2,4,6-thiatriazine-S-oxides (8a—c) and 2-Glycosyl-1,2,4,6-thiatriazine-S-oxides (9a, c) (Table II)——a) Thionyl chloride (1—2 ml) in $CHCl_3$ (2 ml) was added dropwise to a stirred solution of **6a—c** (0.001 mol) in $CHCl_3$ (30 ml) solution under cooling. After 10—20 min, the reaction solution was washed with H_2O and saturated $NaHCO_3$ solution, and dried over $MgSO_4$. Removal of the solvent by evaporation left a brownish residue, which was chromatographed on silica gel. Elution with $CHCl_3$–acetone (97: 3, v/v) gave the desired product (**8a, b,** or **c**).

b) Thionyl chloride (2 ml) in $CHCl_3$ (2 ml) was added dropwise to a stirred solution of **7a** or **c** (0.001 mol) in $CHCl_3$ (20 ml) under cooling. After 15—30 min, the resulting solution was washed with H_2O and saturated $NaHCO_3$ solution, and dried over $MgSO_4$. Removal of the solvent by evaporation left a slightly yellow residue, which was treated as described for a).

Attempted Ring Construction——a) A solution of **8a** (0.001 mol) in dry xylene (10 ml) was refluxed for 2 h. The reaction solution was concentrated under reduced pressure to give a syrup, which was identical with the starting material.

b) A solution of **8a** (493 mg, 0.001 mol) in dry pyridine (0.5 ml) was heated at 60—80°C for 2 h. Removal of the solvent under reduced pressure gave a dark brownish residue. There were many spots on TLC.

c) Thionyl chloride (1 ml) was added to a solution of **7a** (447 mg, 0.001 mol) and dry pyridine (0.2 ml) in dry benzene (20 ml). The reaction solution was stirred for 1 h at room temperature, refluxed for 3 h, and then treated as described above for **8a** to give a brownish residue. Chromatography on silica gel with benzene-acetone (97: 3, v/v) gave **8a** (170 mg) as colorless needles.

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References and Notes

1) This work was presented at the 100th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1980: This constitutes Part XLI in a series entitled "Studies on Heterocyclic Compounds:" Previous paper (Part XXI): H. Ogura, H. Takahashi, and O. Sato, *Chem. Pharm. Bull.*, in press.
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