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A One-Step Synthesis of Glycosylaminoisothiazolo[3,4-*d*]pyrimidines and Glycosylaminoisothiazoles[1)]

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The reaction of glycosyl isothiocyanates (**5a**—**c**) with 2-aminopyridine or 2-amino-4-picoline gave N-glycosyl-N′-(pyrid-2-yl)thioureide (**6a**) or N-glycosyl-N′-(4-methylpyrid-2-yl)thioureide (**6b**), respectively, in good yields; cyclized products were not obtained. On the other hand, the reaction of glycosyl isothiocyanates (**5a**—**c**) with ethyl 3-aminocrotonate yielded ethyl 3-amino-2-glycosylthiocarbamoylcrotonates (**7a**—**c**) and glycosylaminoisothiazoles (**8a**—**c**). A similar reaction between **5a**—**c** and 6-amino-1,3-dimethyluracil afforded glycosylaminoisothiazolo[3,4-*d*]pyrimidines (**10a**—**c**) in excellent yields.

Keywords——glycosyl isothiocyanate; enamine; glycosylaminoisothiazolo[3,4-*d*]-pyrimidines; glycosylaminoisothiazoles; HSAB principle

The reaction of alkyl isocyanates or isothiocyanates with enamines,[3)] *e.g.*, to yield thiopyrimidine, has been reported by Lamon[4)] and Behrend *et al.*[5)]

Recently, we reported the synthesis of nucleoside analogs from glycosyl isothiocyanates as starting materials.[6)] In the present paper, we describe the synthesis of nucleoside analogs through a reaction of glycosyl isothiocyanates (**5a**—**c**) with enamines such as ethyl 3-aminocrotonate (**1**) and 6-amino-1,3-dimethyluracil. Behrend and Hesse[5)] reported that the reaction of methyl isothiocyanate with ethyl 3-aminocrotonate afforded 3,4-dimethyl-2-thiopyrimidin-6-one (**2**) and iminoacetomaloester methylthioamide (**3**). In our experiments, 3,4-dimethyl-2-thiopyrimidin-6-one, ethyl-2-methylthiocarbamoylcrotonate, and an unknown compound were isolated as crystals after chromatography on silica gel. The nuclear magnetic resonance

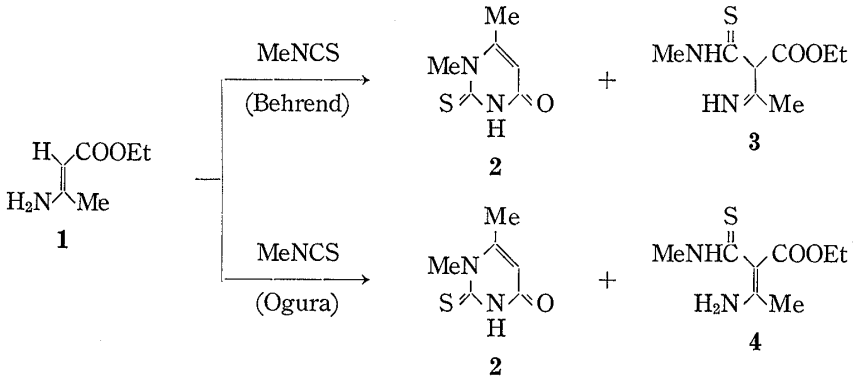

Chart 1

1) This constitutes Part XXIX in a series entitled "Studies on Heterocyclic Compounds." Previou spaper (Part XXVIII): H. Takahashi, N. Nimura, and H. Ogura, *Chem. Pharm. Bull.* (Tokyo), **27**, 1143 (1979).
2) Location: *5-9-1 Shirokane, Minato-ku, Tokyo 108, Japan.*
3) A. Gilbert, "Enamines: Synthesis, Structure, and Reactions," Marcel Dekker Inc., New York and London, 1969.
4) R.W. Lamon, *J. Heterocyclic Chem.*, **5**, 837 (1968).
5) R. Behrend, F. Meyer, and Y. Buchholz, *Ann. Chem.*, **314**, 200 (1901); R. Behrend and P. Hesse, *Ann. Chem.*, **329**, 341 (1903).
6) H. Ogura and H. Takahashi, *Heterocycles*, **6**, 1633 (1977); **8**, 125 (1977); H. Ogura, H. Takahashi, and N. Nimura, *Nucleic Acids Res.*, **S2**, 7 (1976).

(NMR) spectrum of 3,4-dimethyl-2-thiopyrimidin-6-one (**2**) showed a singlet peak at δ 5.80 which was assigned to 5-H of the pyrimidine ring. Two singlets appeared at δ 2.14 and at δ 3.50 due to the methyl group and the N-methyl group at the 4-position. In the NMR spectrum of ethyl 2-methylthiocarbamoylcrotonate (**4**), amino protons appeared as a broad δ 3.50 due to the methyl group and the N-methyl group at the 4-position. In the NMR spectrum of ethyl 2-methylthiocarbamoylcrotonate (**4**), amino protons appeared as a broad singlet at δ 7.60. The molecular ion was observed at *m/e* 202 (54%). These data and elemental analysis confirmed the structure.

This experiment suggested the possibility that thiopyrimidine glycoside might be formed from the reaction of **5a** and **1** in the absence of solvent, but in fact glycosylaminoisothiazole was obtained in low yield.

Treatment of 2-aminopyridine and 2-amino-4-picoline with **5a** in benzene under reflux gave N-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-N′-(pyrid-2-yl)thioureide (**6a**) and N-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-N′-(4-methylpyrid-2-yl)thioureide (**6b**), respectively, in good yields; cyclized products were not obtained. A similar treatment of **5a**—**c** with ethyl 3-aminocrotonate in benzene under reflux or at room temperature for 1 hr yielded ethyl 3-amino-2-glycosylthiocarbamoylcrotonates (**7a**—**c**) and 4-carboethoxy-5-glycosylamino-3-methylisothiazoles (**8a**—**c**), respectively, after chromatography (Tables I and II). The former compounds (**7**) were easily cyclized to afford the latter (**8**). The ring-opened intermediates (**7a**—**c**) showed a doublet at δ 9.92—11.88 due to NH and a broad singlet at δ 8.85—10.80 due to NH_2.

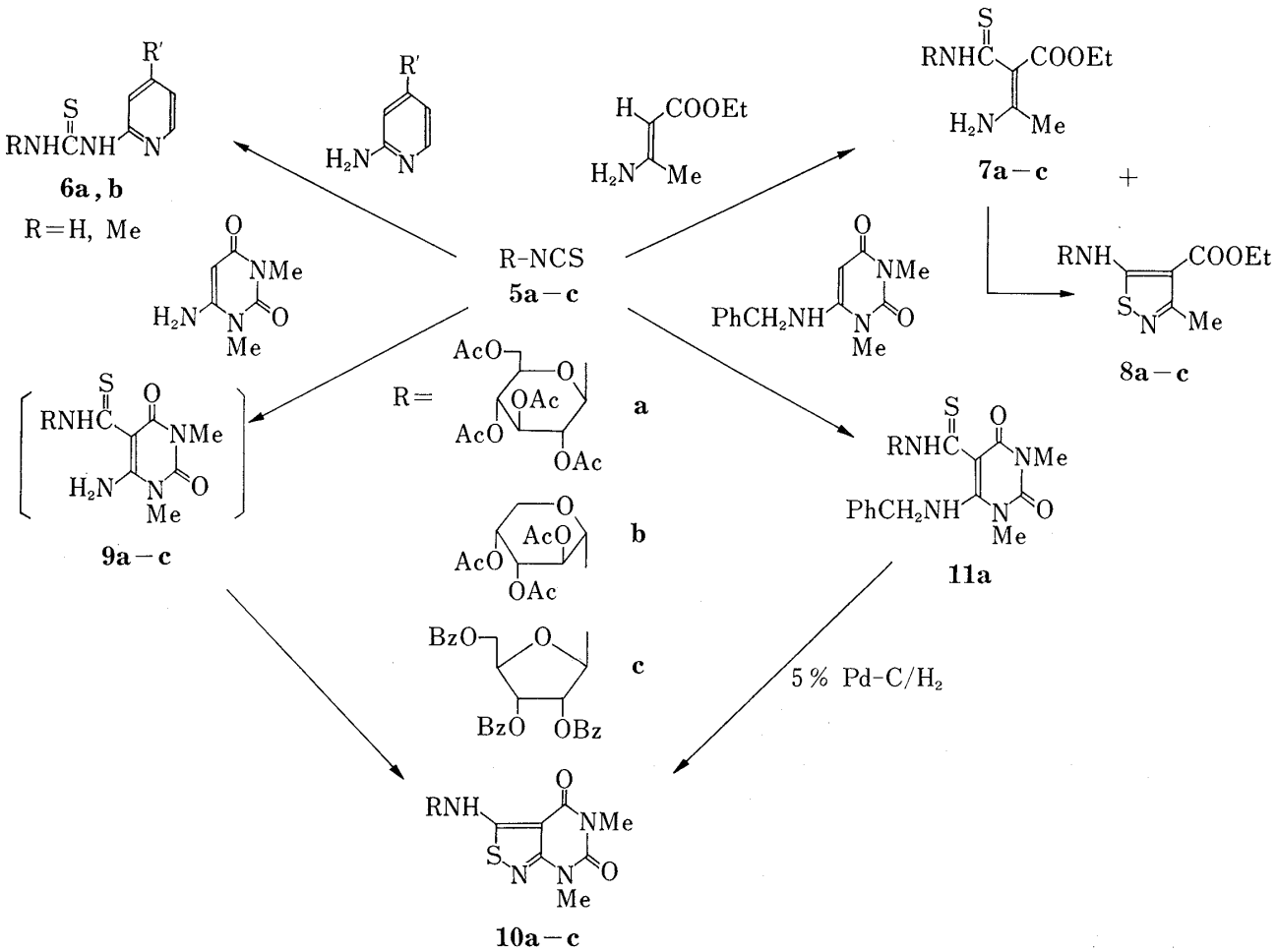

Chart 2

TABLE I. Ethyl 3-Amino-2-glycosylthiocarbamoylcrotonate (**7a—c**)

Compd. No.	mp (°C)	Yield (%)	IR ν_{max}^{KBr} cm^{-1}	UV $\lambda_{max}^{Dioxane}$ nm (log ε)
7a	164—165	34	3300, 1740, 1650, 1600, 1200, 1010	224(4.3), 271(4.0), 388(2.6)
7b	Syrup[a]	42	3300, 1740, 1220, 1090	224(4.3), 269(4.0), 388(2.6)
7c	Syrup[b]	32	3400, 1710, 1610, 1220, 1100, 750	228(4.6), 275(4.3), 385(2.6)

Compd. No.	NMR ($CDCl_3$, δ) heterocyclic moiety	MS (*m/e*) Found (Calcd)	Formula	Analysis (%) Calcd. (Found) C	H	N
7a	1.20 (3H, t, Me), 2.20 (3H, s, Me), 4.22 (2H, q, CH_2), 10.80 (2H, bs, NH_2), 11.88 (1H, d, J=8.0 Hz, NH)	518.028 (518.028)	$C_{21}H_{30}N_2O_{11}S$	48.64 (48.68	5.83 5.80	5.40 5.44)
7b	1.25 (3H, t, Me), 2.20 (3H, s, Me), 4.20 (2H, q, CH_2), 8.85 (2H, bs, NH_2), 10.02 (1H, d, J=8.0 Hz, NH)	446.135 (446.136)	$C_{18}H_{26}N_2O_9S$	48.42 (48.38	5.87 5.90	5.90 6.32)
7c	1.18 (3H, t, Me), 2.22 (3H, s, Me), 4.10 (2H, q, CH_2), 8.98 (2H, bs, NH_2), 9.92 (1H, d, J=8.0 Hz, NH)	632.182 (632.183)	$C_{33}H_{32}N_2O_9S$	62.65 (62.73	5.10 5.24	4.43 4.60)

a) TLC (silica gel) *Rf* 0.73 (benzene–acetone=5:1).
b) TLC (silica gel) *Rf* 0.65 (benzene–acetone=3:2).

TABLE II. 4-Carboethoxy-5-glycosylamino-3-methylisothiazole (**8a—c**)

Compd No.	mp (°C)	Yield (%)	IR ν_{max}^{KBr} cm^{-1}	UV $\lambda_{max}^{Dioxane}$ nm (log ε)
8a	Syrup[a]	68	3300, 1740, 1650, 1200, 1020	223(3.3), 273(4.1), 380(2.6)
8b	123—124	47	3300, 1740, 1210, 1020	225(3.4), 273(4.1), 382(2.7)
8c	Syrup[b]	57	3350, 1710, 1605, 1260, 1100, 710	230(4.5), 275(4.5), 380(2.7)

Compd. No.	NMR($CDCl_3$, δ) heterocyclic moiety	MS (*m/e*) Found (Calcd)	Formula	Analysis (%) Calcd. (Found) C	H	N
8a	1.30 (3H, t, Me), 3.70 (3H, s, Me), 4.20 (2H, q, CH_2), 9.50 (1H, d, J=8.0 Hz, NH)	516.140 (516.141)	$C_{21}H_{28}N_2O_{11}S$	48.83 (48.95	5.46 5.42	5.42 5.47)
8b	1.32 (3H, t, Me), 3.70 (3H, s, Me), 4.22 (2H, q, CH_2), 9.82 (1H, d, J=8.0 Hz, NH)	444.110 (444.110)	$C_{18}H_{24}N_2O_9S$	48.64 (48.70	5.44 5.50	6.30 6.34)
8c	1.20 (3H, t, Me), 3.74 (3H, s, Me), 4.10 (2H, q, CH_2), 9.90 (1H, d, J=8.0 Hz, NH)	630.167 (630.167)	$C_{33}H_{30}N_2O_9S$	62.85 (62.97	4.79 4.82	4.44 4.40)

a) TLC (silica gel) *Rf* 0.52 (benzene–acetone=5:1).
b) TLC (silica gel) *Rf* 0.68 (benzene–acetone=3:2).

A similar treatment of **5a**—**c** with 6-amino-1,3-dimethyluracil in DMF solution at 70—80° for 4 hr gave 3-glycosylamino-5,7-dimethylisothiazolo[3,4-*d*]pyrimidin-4,6-diones (**10a**—**c**) in good yields (Table III). The infrared (IR) spectra of **10a**—**c** showed no absorption at 2000—2100 cm^{-1}, indicating the absence of the isothiocyanate group. The NMR spectra of **10a**—**c** showed a sharp singlet at δ 3.18—3.48 due to NMe. The ultraviolet (UV) spectra showed bands at 310 and 314 nm due to the isothiazole ring.[7]

In order to confirm the reaction mechanism, the reaction of **5a** with 6-benzylamino-1,3-dimethyluracil was carried out and gave N-glycosyl-N′-(6-benzylamino-1,3-dimethyl-2,4-dioxopyrimidin-5-yl)thioureide (**11a**) in 94% yield. Hydrogenation of **11a** using 5% Pd-C in MeOH afforded 3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-5,7-dimethylisothiazolo[3,4-*d*]-pyrimidin-4,6-dione (**10a**) in 23% yield after chromatography. The reaction of glycosyl isothiocyanate with enamine suggested the reaction route shown in Chart 3; the isothiocyanate group

Table III. 3-Glycosylamino-5,7-dimethylisothiazolo[3,4-*d*]pyrimidin-4,6-dione (**10a**—**c**)

Compd No.	mp (°C)	Yield (%)	IR ν_{max}^{KBr} cm^{-1}	UV $\lambda_{max}^{Dioxane}$ nm (log ε)
10a	156—158	96	3350, 1740, 1610, 1210, 1120	221(4.2), 258(4.4), 276(4.3), 314(4.4)
10b	143—144	92	3350, 1740, 1610, 1210, 1110	224(4.0), 259(4.2), 271(4.1), 314(4.2)
10c	Syrup[a]	94	3400, 1710, 1610, 1260, 1120, 750	230(4.5), 260(4.2), 277(4.2), 310(4.2)

Compd. No.	NMR (DMSO-d_6, δ) heterocyclic moiety	MS (*m/e*) Found (Calcd)	Formula	Analysis (%) Calcd. (Found) C	H	N
10a	3.20, 3.38 (6H, s, $(NMe)_2$), 12.80 (1H, d, J=8.0 Hz, NH)	542.133 (542.132)	$C_{21}H_{26}N_4O_{11}S$	46.49 (45.92)	4.83 (4.68)	10.33 (11.89)
10b	3.30, 3.48 (6H, s, $(NMe)_2$), 13.35 (1H, d, J=8.0 Hz, NH)	470.110 (470.111)	$C_{18}H_{22}N_4O_9S$	45.96 (45.92)	4.71 (4.68)	11.91 (11.89)
10c	3.18, 3.45 (6H, s, $(NMe)_2$), 13.45 (1H, d, J=8.0 Hz, NH)	445.128 (445.129) M-base^{+}	$C_{33}H_{28}N_4O_9S$	60.36 (60.32)	4.30 (4.32)	8.53 (8.50)

a) TLC (silica gel) *Rf* 0.56 (benzene–acetone=3:2).

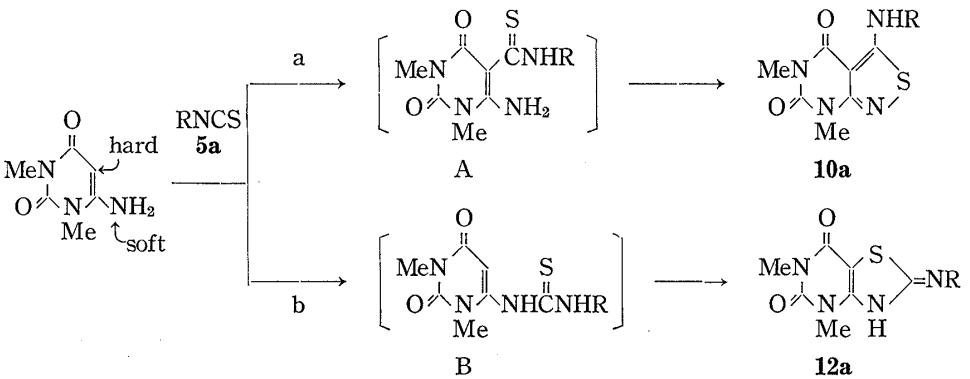

Chart 3

7) R. Niess and H. Eilingsfeld, *Liebigs Ann. Chem.*, **1974**, 2019; Y. Furukawa, O. Miyashita, and S. Shima, *Chem. Pharm. Bull.* (Tokyo), **24**, 970 (1976); Y. Furukawa and S. Shima, *Chem. Pharm. Bull.*, (Tokyo), **24**, 979 (1976).

of **5a**—**c** attacks the 5-position (hard site) and not the 6-amino group (soft site) in DMF or MeCN solution. On the other hand, a similar treatment of 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl isothiocyanate (**5a**) with 6-amino-1,3-dimethyluracil in THF solution at room temperature afforded two products. The major product was 3-glycosylamino-5,7-dimethylisothiazolo[3,4-*d*]pyrimidin-4,6-dione (**10a**) and the minor product was 2-glycosyliminothiazolo[4,5-*d*]pyrimidin-4,6-dione (**12a**).

Based on the HSAB principle,[8] a possible mechanism for the reaction of **5a** with 6-amino-1,3-dimethyluracil, which has two electrophilic centers,[9] C-5 and 6-NH_2, might be as follows. The isothiocyanate group of **5a** should undergo initial addition at the hard site (C-5 position) to give the thiocarbamoyluracil (A) as an intermediate, followed by oxidative ring closure to afford **10a** (pathway a). The formation of the minor product (**12a**) can be understood if it is assumed that the isothiocyanate group of **5a** attacks the soft site (6-NH_2) (pathway b).

Experimental

Reaction of Ethyl 3-Aminocrotonate with Methyl Isothiocyanate——A mixture of MeNCS (0.7 g, 0.01 mol) and ethyl 3-aminocrotonate (1.2 g, 0.01 mol) was heated at 140—145° for 1 hr or at 70—75° for 5 hr. After cooling, the separated crystals were collected by filtration and 1.1 g (57%) of 3,4-dimethyl-2-thiopyrimidin-6-one (**2**) was obtained as fine yellow needles after recrystallization from MeOH. mp 258—260° (reported mp 271—273°[5]). IR ν_{max}^{KBr} cm^{-1}: 3360 (NH), 1640 (CONH). *Anal.* Calcd. for $C_6H_8N_2OS$: C, 46.14; H, 5.16; N, 17.93. Found: C, 46.07; H, 5.18; N, 17.90. NMR ($CDCl_3$) δ: 5.80 (1H, s, 5-H), 3.50 (3H, s, NMe), 2.14 (3H, s, Me). MS *m/e*: 156 (M^+). The filtrate was evaporated down under reduced pressure to yield a brownish residue, which was chromatographed on silica gel with CCl_4–$CHCl_3$. Elution with CCl_4–$CHCl_3$ (2:3) gave 0.64 g (32%) of ethyl 3-amino-2-methylthiocarbamoylcrotonate (**4**) as colorless crystals. Recrystallization from CCl_4–$CHCl_3$ (1:2) gave **4** as colorless fine needles. mp 84—85°. IR ν_{max}^{KBr} cm^{-1}: 3400 (NH_2), 3280 (NH), 1720 (ester), 1680 (CSNH). *Anal.* Calcd. for $C_8H_{14}N_2O_2S$: C, 47.50; H, 6.98; N, 13.85. Found: C, 47.48; H, 6.92; N, 13.88. NMR ($CDCl_3$) δ: 1.40 (3H, t, Me), 2.52 (3H, s, Me), 3.00 (3H, d, NMe), 4.32 (2H, q, CH_2), 7.60 (2H, bs, NH_2), MS *m/e*: 202 (M^+). Elution with $CHCl_3$ gave 120 mg of an unknown product as colorless crystals. Recrystallization from ether gave colorless plates. mp 138—139°. IR ν_{max}^{KBr} cm^{-1}: 3240, 2350, 1650. NMR (DMSO-d_6) δ: 2.85, 3.20 (6H, d), 3.75 (2H, s), 6.89, 10.12 (2H, bs, $(NH)_2$). *Anal.* Found: C, 31.50; H, 6.92; N, 3.42. MS *m/e*: 146.

N-Glycosyl-N′-(pyrid-2-yl)thioureide (6a) and N-Glycosyl-N′-(4-methylpyrid-2-yl)thioureide (6b)——A mixture of 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl isothiocyanate (**5a**; 389 mg, 0.001 mol) and 2-aminopyridine (94 mg, 0.001 mol) or 2-amino-4-picoline (108 mg, 0.001 mol) in dry benzene (20 ml) was refluxed for 3 hr and allowed to stand at room temperature. The separated crystals were collected, and recrystallization from benzene gave **6a** or **6b** as colorless needles. **6a**: Yield 454 mg (94%). mp 172—174°. IR ν_{max}^{KBr} cm^{-1}: 3350, 1740, 1605, 1580, 1200, 1025. *Anal.* Calcd. for $C_{20}H_{25}N_3O_9S$: C, 49.68; H, 5.21; N, 8.69. Found: C, 49.64; H, 5.16; N, 8.72. NMR ($CDCl_3$) δ: 9.52 (1H, bs, NH), 12.85 (1H, d, J=8.0 Hz, NH). MS *m/e*: 483 (M^+). **6b**: Yield 417 mg (84%). mp 184—185°. IR ν_{max}^{KBr} cm^{-1}: 3350, 1740, 1600, 1580, 1220, 1025, 750. *Anal.* Calcd. for $C_{21}H_{27}N_3O_9S$: C, 50.70; H, 5.47; N, 8.45. Found: C, 50.90; H, 5.27; N, 8.40 NMR ($CDCl_3$) δ: 2.32 (3H, s, Me), 6.62, 6.80, 8.02 (3H, m, pyridine ring), 9.35 (1H, bs, NH), 12.95 (1H, d, J=8.0 Hz, NH), MS *m/e*: 497 (M^+).

4-Carboethoxy-5-glycosylamino-3-methylisothiazole (8a—c) and Ethyl 3-Amino-2-glycosylthiocarbamoylcrotonate (7a—c) (Tables I and II)——A solution of **5a**, **b** or **c** (0.001 mol) and ethyl 3-aminocrotonate (129 mg, 0.001 mol) in MeCN (10 ml) was stirred for 24 hr at room temperature. The reaction solution was evaporated down under reduced pressure to give a residue which was chromatographed on silica gel with CCl_4–$CHCl_3$. Elution with CCl_4–$CHCl_3$ (3:2) gave **8a** or **8c** as a colorless syrup, or **8b** as colorless needles. From the eluate with CCl_4–$CHCl_3$ (4:1) **7a** was obtained as colorless fine needles, or **7b** or **c** as a colorless syrup.

3-Glycosylamino-5,7-dimethylisothiazolo[3,4-*d*]pyrimidin-4,6-dione (10a—c) (Table III)——a) A mixture of **5a** or **b** (0.01 mol) and 6-amino-1,3-dimethyluracil (1.7 g, 0.01 mol) in DMF (10—20 ml) was warmed at 70—80° for 3—4 hr. After cooling, the reaction mixture was poured into ice-water to give **10a** or **b** as colorless needles.

b) A solution of **5c** (2.5 g, 0.005 mol) and 6-amino-1,3-dimethyluracil (0.78 g, 0.005 mol) in MeCN (20 ml) was refluxed for 3 hr. The solvent was removed under reduced pressure to give a slightly yellow

8) Tse-Lok Ho, "Hard and Soft Acids and Bases Principle on Organic Chemistry," Academic Press., New York, 1977.

9) G.B. Bennett, W. Ronald, J. Shimpson, R.B. Mason, R.J. Strohchein, and R. Manskhani, *J. Org. Chem.*, **42**, 221 (1977).

syrup, which was chromatographed on silica gel using CCl_4–$CHCl_3$. Elution with CCl_4–$CHCl_3$ (9: 1) afforded **10c** as a colorless syrup.

Reaction of 5a with 6-Amino-1,3-dimethyluracil in THF Solution——A mixture of **5a** (389 mg, 0.001 mol) and 6-amino-1,3-dimethyluracil (170 mg, 0.001 mol) in THF (30 ml) was stirred at room temperature for 35 hr. The separated crystals were collected by filtration and 40 mg (7.3%) of **12a** was obtained as colorless fine needles after recrystallization from MeOH, mp 171—173°. IR ν_{max}^{KBr} cm^{-1}: 3270 (NH), 1740 (ester), 1645 (CONH), 1575, 1210, 1020. *Anal.* Calcd. for $C_{21}H_{26}N_4O_{11}S$: C, 46.49; H, 4.83; N, 10.33. Found: C, 46.53; H, 4.78; N, 10.30. NMR (DMSO-d_6) δ: 3.18, 3.35 (6H, s, $(NMe)_2$), 8.54 (1H, bs, NH). MS *m/e* for $C_{21}H_{26}N_4O_{11}S$: Calcd. 542.132. Found: 542.130. UV λ_{max}^{MeOH} nm (log ε): 223 (4.5), 272 (4.5), 293 (4.0). The filtrate was concentrated under reduced pressure to give a syrup. DMSO (3 ml) was added to the syrup and the solution was poured into ice-water to give **10a** as colorless fine needles in 88% yield.

N-(2,3,4,6-Tetra-*O*-acetyl-*β*-D-glucopyranosyl)-N′-(6-benzylamino-1,3-dimethyl-2,4-dioxopyrimidin-5-yl)thioureide (11a) and Its Catalytic Hydrogenation——A mixture of **5a** (389 mg, 0.001 mol) and 6-benzylamino-1,3-dimethyluracil (245 mg, 0.001 mol) in dry benzene (30 ml) was refluxed for 2 hr. The reaction solution was concentrated under reduced pressure to give a colorless syrup. The syrup was chromatographed on silica gel with CCl_4–$CHCl_3$ (3: 2) to give 600 mg (94%) of **11a** as colorless fine needles. mp 136—138°. *Anal.* Calcd. for $C_{28}H_{34}N_4O_{11}S$: C, 52.99; H, 5.40; N, 8.83. Found: C, 52.97; H, 5.37; N, 8.43. IR ν_{max}^{KBr} cm^{-1}: 3050 (NH), 1740 (ester), 1700 (CSNH), 1620 (phenyl), 750. NMR ($CDCl_4$) δ: 4.60 (2H, d, J=6.0 Hz, $NHC\underline{H}_2$), 6.00 (1H, t, 1-H), 12.98 (1H, d, J=8.0 Hz, 1-NH), 13.30 (1H, t, J=6.0 Hz, $N\underline{H}CH_2$). MS *m/e*: 634 (M^+).

A solution of **11a** (400 mg, 0.0006 mol) in MeOH (100 ml) was hydrogenated over 5% Pd-C (0.5 g). After removal of the catalyst by filtration, the filtered solution was concentrated under reduced pressure to give a syrup. The syrup was chromatographed on silica gel with $CHCl_3$–acetone (7: 3) to give 124 mg (23%) of **10a** as colorless needles.