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Studies on Nucleoside Analogs. XIX. Reaction of D-Gluconyl Isothiocyanate with Diamines or Enamines[1]

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The reaction of phenylacetyl isothiocyanate (**1a**) with diamines afforded 1-substituted 3-phenylacetyl thiourea (**3a**—**d**) in good yields. Attempted ring closure of these products under thermal or basic conditions was unsuccessful. However, treatment of **3a** with Ac_2O–H_3PO_4 at room temperature gave the cyclized product (**5a**). Similar reaction of D-gluconyl isothiocyanate (**1b**) with *o*-phenylenediamine (**2a**) or diaminopyrimidines (**2b, c, e, f**) gave the D-*gluco*-pentyl benzotriazepine-2-thione (**7a**) or D-*gluco*-pentyl pyrimidotriazepine-2-thiones (**7b, c, e, f**), respectively, in fair yields. Treatment of **1b** with ethyl 3-aminocrotonate or 6-amino-1,3-dimethyluracil afforded D-*gluco*-pentyl thiopyrimidine (**8b**) or D-*gluco*-pentyl pyrimido[4,5-*d*]pyrimidine (**9b**), respectively.

Keywords——phenylacetyl isothiocyanate; D-gluconyl isothiocyanate; D-*gluco*-pentyl benzotriazepine-2-thione; D-*gluco*-pentyl pyrimidotriazepine-2-thione; D-*gluco*-pentyl thiopyrimidine; D-*gluco*-pentyl pyrimido[4,5-*d*]pyrimidine

We have reported syntheses of glycosylaminoisothiazoles, glycosylaminoisothiazolo[3,4-*d*]-pyrimidines,[2] and glycosylaminotheophylline[3] through the use of glycosyl isothiocyanates with enamines or diamines.

In this paper, we wish to report a one-step synthesis of D-*gluco*-pentyl pyrimidotriazepine or D-*gluco*-pentyl thiopyrimidine by the reaction between D-gluconyl isothiocyanate and enamines or diamines.

We first investigated the possibility that 1,3,5-triazepine-2-thione derivatives might be prepared by the reaction of phenylacetyl isothiocyanate (**1a**)[4] with diamines, followed by dehydration. The reaction of **1a** with *o*-phenylenediamine (**2a**) or diaminomaleonitrile (**2d**) in benzene solution under reflux gave *o*-aminophenyl-3-phenylacetyl thiourea (**3a**) or 2-amino-1,2-dicyanoethenyl-3-phenylacetyl thiourea (**3d**), respectively, in good yield. Similar treatment of **1a** with 5,6-diamino-1,3-dimethyluracil (**2b**) or 4,5-diamino-2,6-dimercaptopyrimidine (**2c**) in dimethylformamide (DMF) yielded 6-amino-1,3-dimethyl-2,4-dioxopyrimidin-5-yl- (**3b**) or 4-amino-2,6-dimercaptopyrimidin-5-yl-3-phenylacetylthiourea (**3c**), respectively, in 74—92% yield. The nuclear magnetic resonance (NMR) spectra of **3a** and **3d** showed a broad singlet at δ 4.78—6.78 due to the NH_2 protons. The amino proton signals in the NMR spectra of **3b** and **3c** are summarized in Table I. Attempted preparation of **3a**—**c**, and **3f** under thermal conditions in the presence of zinc chloride[5] failed, and the starting materials were recovered. Treatment of **3b** with ammonium hydroxide[6] gave 1-(6-amino-1,3-dimethyl-2,4-dioxopyrimidin-5-yl)thiourea (**4a**) in quantitative yield. However, **3b** was treated with acetic anhydride-phosphoric acid or formic acid[7] at room temperature to afford the cyclized product (**5a**) in 74% yield.

Application of this reaction to D-gluconyl isothiocyanate (**1b**) gave the desired product. 2,3,4,5,6-Penta-O-acetyl-D-gluconyl isothiocyanate, prepared from 2,3,4,5,6-penta-O-acetyl-D-gluconyl chloride according to our method,[8] was treated diamines (**2a**—**c**) in MeCN or DMF for 24 h to give the corresponding 1,3,5-triazepine-2-thiones (**7a**—**f**) in good yields after chromatography.

The thione–thiol tautomerism of 3-aryl-2-indolinethiones has been studied by Hino *et al.*[9] Morton and Stubb reported the ultraviolet (UV) absorption of some sulfur compounds.[10]

TABLE I. I-Substituted-3-phenylacetyl Thioureides (**3a—d**)

Compd. No.	Yield (%)	mp (°C)	IR ν_{max}^{KBr} cm^{-1}	NMR (DMSO-d_6, δ)	Mass (m/z)	Formula	Analysis (%) Calcd / Found C	H	N
3a	96	149—150	3370, 1680, 1600, 1590, 740, 695	3.80 (2H, s, CH_2), 4.78 (2H, bs, NH_2), 7.32 (5H, s, Ph), 6.40—7.30 (4H, m, Ph), 11.80, 11.94, (2H, bs, NH×2)	258 (M^+)	$C_{15}H_{15}ON_4S$	63.13 (63.08	5.30 5.50	14.73 14.48)
3b	92	232—233	3325, 1690, 1600, 740, 695	3.13, 3.32 (6H, s, NMe×2), 3.78 (2H, s, CH_2), 6.82 (2H, bs, NH_2), 7.28 (5H, s, Ph), 11.16, 11.72 (2H, bs, NH×2)	347 (M^+)	$C_{15}H_{17}O_3N_5S$	51.86 (51.70	4.93 4.90	20.16 20.08)
3c	74	259—260 (dec.)	3370, 1680, 1600, 1590, 700, 690	3.72 (2H, s, CH_2), 6.90 (2H, bs, NH_2) 11.30, 11.72 (2H, bs, NH×2), 12.60 (2H, bs, SH×2)	274 (M^+-Ph)	$C_{13}H_{13}ON_5S_3$	44.43 (44.25	3.73 3.70	19.93 19.82)
3d	82	180—183 (dec.)	3325, 3250, 2050, 1670, 1580, 710	3.78 (2H, s, CH_2), 6.78 (2H, bs, NH_2), 6.45—7.28 (5H, m, Ph), 12.60 (1H, bs, NH)	285 (M^+)	$C_{13}H_{11}ON_5S$	54.72 (54.58	3.89 3.95	24.55 24.60)

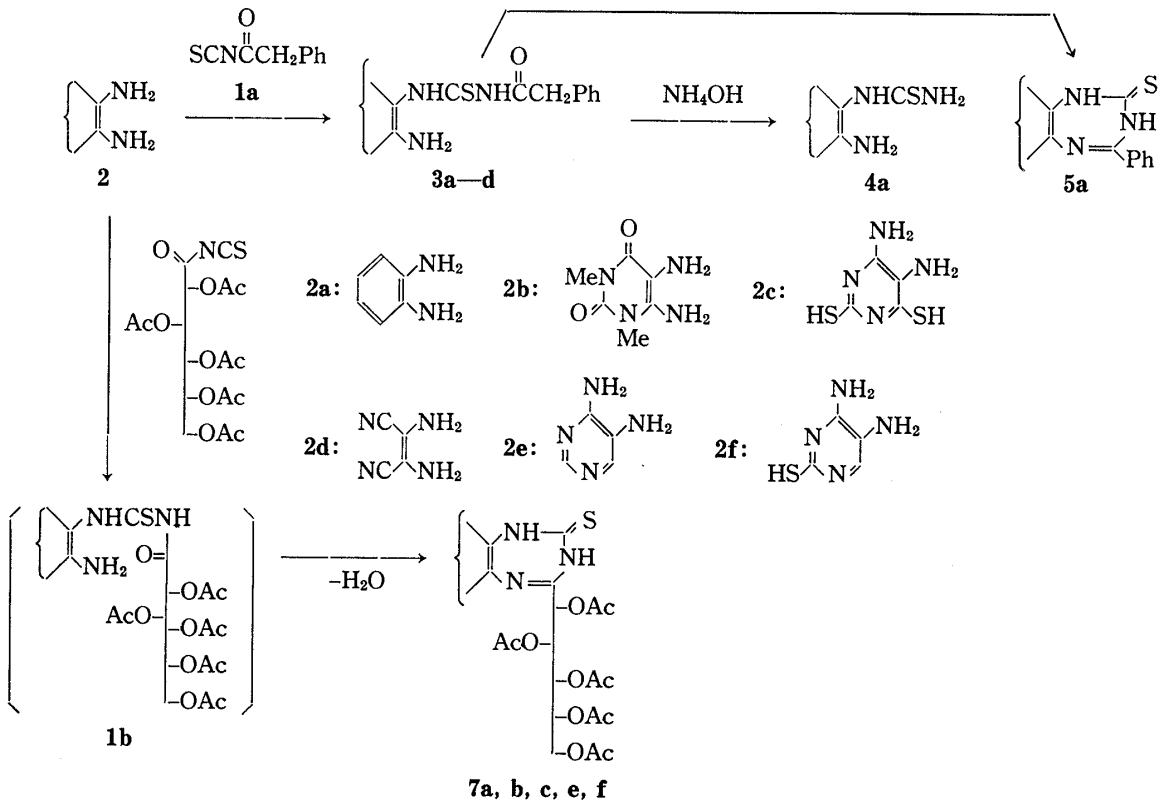


Chart 1

TABLE II. D-Gluconyl 1,3,5-Triazepine-2-thiones (**7a, b, c, e, f**)

Compd. No.	Yield (%)	mp (°C)	IR ν_{max}^{KBr} cm^{-1}	UV λ_{max}^{MeOH} nm (log ε)	NMR (δ, $CDCl_3$) Heterocyclic moiety	Formula	Analysis (%) Calcd (Found) C	H	N
7a	92	Syrup[a]	3300, 1740, 1630, 1610, 1580, 1220, 1020, 750, 695	229(4.2) 284(4.0)	7.20—6.60 (4H, m, Ph), 11.42, 9.65 (2H, bs, NH×2)	$C_{23}H_{27}O_{10}N_3S$	51.39 (51.52	5.06 5.32	7.82 7.50)
7b	87	124—125	3300, 1740, 1650, 1630, 1220, 1120	220(4.1) 270(4.2)	3.48, 3.32 (6H, s, Me_2), 10.00, 10.80 (2H, bs, NH×2)	$C_{21}H_{29}O_{12}N_5S$	43.82 (43.60	5.08 5.12	12.17 12.22)
7c	76	120—121	3300, 1740, 1640, 1220, 1120	219(3.8) 274(4.3) 333(4.1)	6.50 (1H, s, SH), 10.20, 10.90 (2H, bs, NH×2)[b]	$C_{21}H_{25}O_{10}N_5S_3$	41.79 (41.50	4.17 4.20	11.60 11.72)
7e	90	107—109	3300, 1740, 1620, 1210, 1140	219(4.1) 280(3.9)	8.30, 7.98 (2H, s, 2-H, 6-H), 11.15, 12.20 (2H, bs, NH×2)	$C_{21}H_{25}O_{10}N_5S$	46.75 (46.97	4.67 4.63	12.98 12.75)
7f	70	117—119	3300, 1740, 1650, 1220, 1100	221(3.7) 241(3.6) 288(3.6) 337(3.2)	8.00 (1H, s, 6-H), 10.05, 10.95 (2H, bs, NH×2)[b]	$C_{21}H_{25}O_{10}N_5S_2$	44.13 (44.10	4.41 4.52	12.25) 12.51)

a) TLC (silica gel) *Rf* 0.68 [benzene–acetone (3: 2)].
b) In DMSO-d_6.

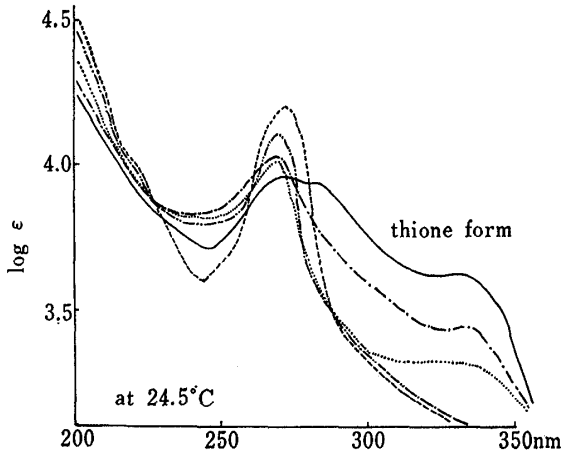


Fig. 1

UV λ_{max} nm (log ε): MeOH (----); 220 (4.1) 270 (4.2), MeOH: dioxane (1: 5) (·····); 269 (4.1) 339 (3.2), MeOH: dioxane (1: 1) (—··—); 219 (4.0) 268 (4.2), MeOH: dioxane (1: 9) (—·—·); 268 (4.0) 334 (3.4), dioxane (——); 271 (4.0) 283 (4.0) 336 (3.6).

Prototropic tautomerism of 2-substituted 5-mercapto-*s*-triazolothiadiazine was reported by Spinner.[11] In order to obtain information on the thione–thiol equilibrium in compound **7b**, UV spectra were measured in various solvents. The absorption curves are shown in Fig. 1. The circular dichroism (CD) curves of **7b** in various solvents are shown in Fig. 2. A methanolic solution of **7b** showed a strong negative Cotton effect at 283 nm, which was explained in terms of the presence of the thiol form (**7b'**), and a weak negative one at 330 nm, indicating the presence of the thione form. In changing from a polar solvent to a non-polar solvent (dioxane), the intensities of the bands were found to be reversed. The CD curves of **7a**, **e** and **7f** changed similarly in going from a protic solvent such as methanol (Fig. 3). These results suggest that the thione form predominates in non-polar solvents.

Next, we investigated the reaction of **1b** with enamines, ethyl 3-aminocrotonate and 6-amino-1,3-dimethyluracil. Treatment of **1b** with ethyl 3-aminocrotonate in ether solution at room temperature gave D-*gluco*-pentyl thiopyrimidine (**8b**) in 98% yield. Similarly. **1b** was treated with 6-amino-1,3-dimethyluracil to give D-*gluco*-pentyl pyrimido[4,5-*d*]pyrimidine (**9b**) in 96% yield. The infrared (IR) spectra of these products (**8b** and **9b**) showed NH bands at around 3300—3400 cm^{-1} instead of isothiocyanate bands (2000—2100 cm^{-1}). The NMR spectrum of **8b** showed a singlet at δ 2.14 due to the 4-Me group of the pyrimidine ring. In compound **9b**, two singlets appeared at δ 3.38 and 3.55, which were assigned to the N-methyl group.

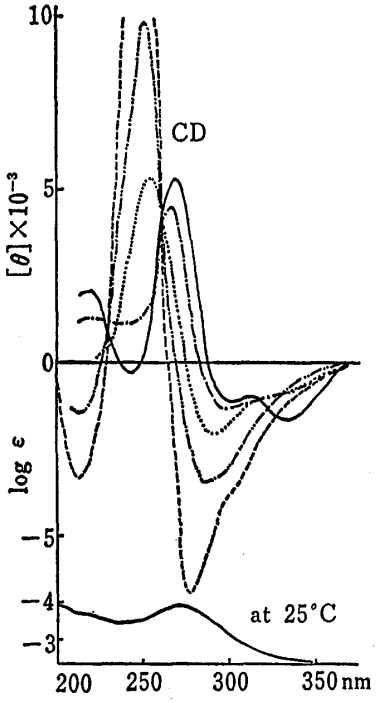
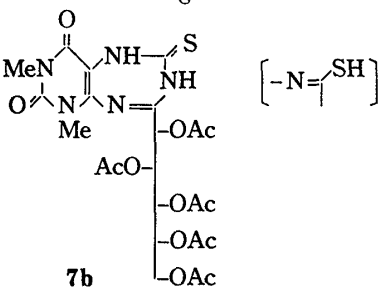
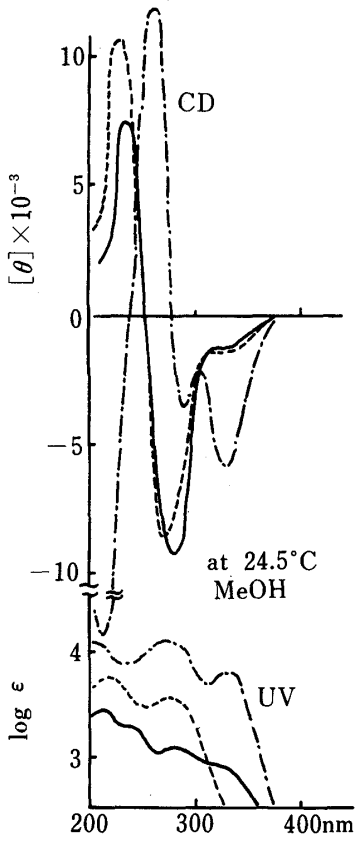


Fig. 2



7b

MeOH (-----): $[\theta]_{316}=-3491$, $[\theta]_{253}=16537$, $[\theta]_{283}=-6707$,
dioxane (——): $[\theta]_{321}=2189$, $[\theta]_{270}=5373$, $[\theta]_{301}=-1228$, $[\theta]_{336}=-1782$.
MeOH: dioxane (1:1): (—·—), (1:5); (·····), (1:9): (—·—·).



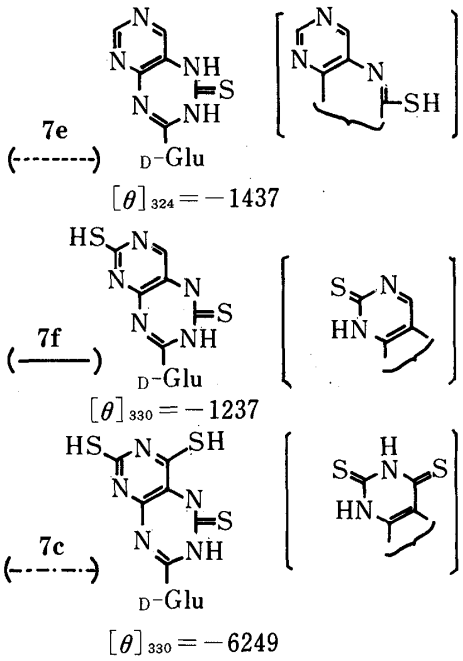
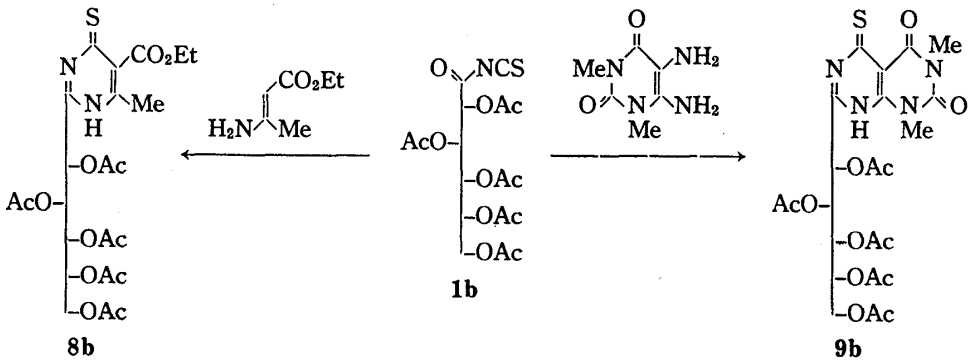


Fig. 3



8b 1b 9b

Chart 2

Experimental

All melting points are uncorrected. IR spectral measurements were performed with a JASCO A-2 spectrometer. NMR spectra were measured with a Varian T-60 spectrometer, using tetramethylsilane as an internal reference. Mass spectra (MS) were determined with a JMS-D-100 spectrometer at 75 eV by the direct inlet system.

Phenylacetyl Isothiocyanate (1a)——This compound was prepared by a procedure similar to that reported by Smith and Kan.[4] Under dry N_2, AgSCN (16.5 g, 0.1 mol) was added to a solution of phenylacetyl chloride (9 g, 0.1 mol) in dry toluene (200 ml). The reaction solution was heated at 100°C for 3 h and filtered. The filtrate was treated with charcoal and concentrated under reduced pressure to give phenylacetyl isothiocyanate (**1a**). Yield: 15 g (84%), bp 85—90°C/0.2—0.3 mmHg (reported[4] bp 83—91°C/0.3 mmHg). IR ν_{max}^{film} cm^{-1}: 1970 (NCS), 1075 (CO), 1590, 1580, 1100, 700.

1-Substituted 3-Phenylacetyl Thiourea (3a—d) (Table I)——Phenylacetyl isothiocyanate (**1a**: 1.8 g, 0.01 mol) was added dropwise to a solution of **2a, b,** or **2c** (0.01 mol) in dry benzene (20 ml). After being refluxed for 0.5 h, the reaction solution was allowed to stand at room temperature. The separated crystals were collected by filtration and recrystallized from benzene or benzene–MeOH (9: 1) to give **3a, b,** or **3c** as colorless crystals in 90—95% yield. In the case of diaminomaleonitrile (**2d**), anhydrous THF was used as a solvent instead of benzene. After being stirred for 10 min at room temperature, the reaction became brownish in color and yellow crystals were obtained.

1-(6-Amino-1,3-dimethyl-2,4-dioxopyrimidin-5-yl)thiourea (4a)——**3b** was treated according to the method reported by Goerdeler and Poland.[6] A solution of **3b** (347 mg, 0.001 mol) in 28% NH_4OH (10 ml) was warmed at 50—60°C for 0.5 h, then allowed to stand at room temperature. The separated crystals were collected by filtration, and recrystallized from MeOH to give **4a** as colorless fine needles, mp 280—282°C. IR ν_{max}^{KBr} cm^{-1}: 3350 (NH_2, NH), 1690 (CON=). NMR (DMSO-d_6) δ: 3.15, 3.30 (6H, s, NMe_2), 6.80, 10.30 (4H, bs, $NH_2\times2$), 11.20 (1H, s, NH). MS (*m/z*): 229 (M^+). *Anal.* Calcd for $C_7H_{11}O_2N_5S$: C, 36.67; H, 4.84; N, 30.55. Found: C, 36.80; H, 4.67; N, 30.47.

1,2,3,4,5-Penta-O-acetyl-D-*gluco*-pentyl-1,3,5-triazepine-2-thiones (7a, b, c, e, f) (Table II)——A mixture of **1b** (450 mg, 0.001 mol) and diamine (0.001 mol) in dry benzene, THF, or DMF (5010 ml) was heated at 70—85°C for 3—10 h under N_2. The reaction solution was concentrated under reduced pressure to give a residue. The residue was chromatographed on silica gel with $CHCl_3$–acetone. Elution with $CHCl_3$–acetone (97: 3) gave **7a** as a colorless syrup. In the case of diaminopyrimidine, the reaction solution was poured into ice-water and the separated crystals were collected by filtration. Recrystallization from MeOH or MeOH–EtOH (1: 3) gave **7b, f** as colorless needles, or **7c, e** as slightly yellow powders.

5-Carboethoxy-6-methyl-2-(1,2,3,4,5-penta-O-acetyl-D-*gluco*-pentyl)pyrimidine-4-thione (8b)——A mixture of **1b** (447 mg, 0.001 mol) and ethyl 3-aminocrotonate (129 mg, 0.001 mol) in dry ether (10 ml) or MeCN (10 ml) was stirred for 2 h at room temperature. The reaction solution was concentrated to 1/5 volune and the mixture was left in a freezer overnight. Separated crystals were collected by filtration and recrystallized from ether–petroleum ether (1: 1) to give 547 mg (98%) of **8b** as fine colorless needles. mp 69—72°C. IR ν_{max}^{KBr} cm^{-1}: 3400 (NH), 1740 ($OCOCH_3$), 1640 (CSNH), 1210, 1130, 750. NMR ($CDCl_3$) δ: 2.05, 2.10, 2.16 (15H, s, $OAc\times5$), 2.14 (3H, s, =CMe), 1.20 (3H, t, $-CH_2C\underline{H}_3$), 3.52 (2H, q, $-C\underline{H}_2-CH_3$), 11.40 (1H, bs, NH). Mass (*m/z*): 558 (M^+). *Anal.* Calcd for $C_{23}H_{30}O_{12}N_2S$: C, 49.46; H, 5.41; N, 5.02. Found: C, 49.53; H, 5.46; N, 5.05.

2-(1,2,3,4,5-Penta-O-acetyl-D-*gluco*-pentyl)-4,6-dimethyl-5,7-dioxo-4,5,6,7-tetrahydropyrimido[4,5-d]-pyrimidine-8-thione (9b)——A mixture of **1b** (447 mg, 0.001 mol) and 6-amino-1,3-dimethyluracil (170 mg, 0.001 mol) in dry DMF (5 ml) or DMA (5 ml) was stirred for 30 h at room temperature, then poured into ice-water to give **9b** as colorless needles. Recrystallization from EtOH gave **9b** as colorless fine needles. Yield: 560 mg (96%), mp 160—161°C. IR ν_{max}^{KBr} cm^{-1}: 3400 (NH), 1740 ($OCOCH_3$), 1630 (CONH), 1220, 1120. *Anal.* Calcd for $C_{23}H_{28}O_{12}N_4S$: C, 47.26; H, 4.83; N, 9.58. Found: C, 47.32; H, 4.80; N, 9.52. NMR (DMSO-d_6) δ: 2.35, 2.10, 2.05, 2.03 (15H, s, $OAc\times5$), 3.38, 3.55 (6H, s, $NMe\times2$), 4.40, 4.15 (2H, dd, 6-H), 5.10 (1H, m, 5-H), 5.30—5.80 (2H, m, 4-H), 5.38 (1H, d, $J=4.0$ Hz, 2-H), 11.15 (1H, bs, NH). MS (*m/z*): 584 (M^+).

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References and Notes

1) This series of papers is a continuation of a series entitled "C-Nucleoside Synthesis:" this also constitutes Part XXXVIII in a series entitled "Studies on Heterocyclic Compounds." Previous paper (Part XVIII): H. Ogura, M. Sakaguchi, T. Okamoto, K. Gonda, and S. Konda, *Heterocycles*, **12**, 359 (1979).
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