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Cyclodesulfurization Reaction of Glycosyl Thioureides[1]

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Reactions of glycosyl isothiocyanates (**1a**, **b**, **c**) with diamines such as *o*-phenylenediamine, 2,3-diaminopyridine or 5,6-diamino-1,3-dimethyluracil gave the corresponding glycosyl thioureides in good yields. Glycosyl thioureides were converted into N-glycosylaminobenzimidazoles (**5a**, **b**, **c**), N-glycosyl-3-deazapurine (**6a**) or N-glycosylaminotheophyllines (**7a**, **b**, **c**) in excellent yields through a cyclodesulfurization reaction.

Keywords——glycosyl isothiocyanate; glycosyl thioureide; cyclodesulfurization reaction; N-glycosylaminobenzimidazole; N-glycosylaminotheophylline; S-methylisourea

Recently, Tweit[3] reported that a reaction of 2-mercaptoaniline and isothiocyanate gave N-substituted 2-aminobenzothiazole, thioureide and disulfide. Matsui *et al.*[4] reported that a reaction of *o*-phenylenediamine with ethoxycarbonyl isothiocyanate in the presence of heavy metal ions afforded aminobenzimidazole. Omar *et al.*[5] reported a new synthesis of N-substituted 2-aminobenzimidazole *via* N-(2-aminophenyl)-N′-substituted thiourea using DCC as a cyclodesulfurization agent. More recently, we found that alkylating agents, MeI and NEt_3, were useful reagents for cyclization reactions.[6] A similar method was used for the synthesis of wyosine[7] and some model compounds.[8] We reported syntheses modified nucleoside analogs using glycosyl isothiocyanates as starting materials.[9] In this paper, we describe a convenient synthetic method for nucleoside analogs utilizing a cyclodesulfurization reaction of glycosyl thioureides.

Mixtures of glycosyl isothiocyanates (**1a**—**c**) and *o*-phenylenediamine in benzene under reflux for 3 hr gave N-glycosyl-N′-(*o*-aminophenyl)thioureides (**2a**—**c**) in good yields (Table I). The nuclear magnetic resonance (NMR) spectra of **2a**—**c** showed a doublet peak at δ 6.60—6.70 (J=8.0 Hz) which was assigned to the NH group. Another NH proton was observed at δ 7.82—8.60 as a broad singlet. These NH signals disappeared on addition of D_2O.

Similar treatments of **1a**—**c** and 2,3-diaminopyridine or 5,6-diamino-1,3-dimethyluracil in acetonitrile (MeCN) or tetrahydrofuran (THF) under reflux for 2—4 hr afforded N-glycosyl-N′-(2-aminopyrid-3-yl)thioureides (**3a**—**c**) or N-glycosyl-N′-(6-amino-1,3-dimethyl-2,4-dioxopyrimidin-5-yl)thioureides (**4a**—**c**), respectively (Tables II and III). The NMR spectra of

1) This constitutes Part XXX in a series entitled "Studies on Heterocyclic Compounds." Previous paper: H. Takahashi, N. Nimura, and H. Ogura, *Chem. Pharm. Bull.* (Tokyo), **27**, 1147 (1979); a preliminary report of the present work has appeared in *a*) H. Ogura, H. Takahashi, K. Takeda, M. Sakaguchi, N. Nimura, and H. Sakai, *Heterocycles*, **3**, 1129 (1975); *b*) H. Ogura and H. Takahashi, *Heterocycles*, **8**, 125 (1977).

2) Location: *5-9-1 Shirokane, Minato-ku, Tokyo 108, Japan.*

3) R.C. Tweit, *J. Heterocycl. Chem.*, **7**, 687 (1970).

4) T. Matsui, M. Nagano, J. Tobitsuka, and K. Oyamada, *Yakugaku Zasshi*, **93**, 977 (1973).

5) A.M-.M.E. Omar, M.S. Habib, and O.M. Aboulwafa, *Synthesis*, **1977**, 864.

6) See 1).

7) S. Nakatsuka, T. Ohgi, and T. Goto, *Tetrahedron Lett.*, **1978**, 2579.

8) K. Ienaga and W. Pfleiderer, *Tetrahedron Lett.*, **1978**, 1447.

9) H. Ogura and H. Takahashi, *Heterocycles*, **6**, 1633; **8**, 125 (1977); H. Ogura, H. Takahashi, and M. Sakaguchi, *Nucleic Acids Res.*, **S5**, 251 (1978); H. Ogura, H. Takahashi, and E. Kudo, *J. Carbohydr. Nucleosides Nucleotides*, **5**, 329 (1978).

4a—c showed a broad singlet at δ 6.35—6.50 due to the amino group at the 6-position of the pyrimidine ring. N-Methyl signals appeared at δ 3.10—3.30 and δ 3.34—3.51 as singlets. 1-NH proton and another NH proton appeared at δ 7.12—7.27 and δ 8.18—8.50, respectively.

We investigated the cyclodesulfurization reaction using the reported method.[4] Treatment of **2a** with lead acetate or mercuric oxide (yellow) in MeOH, followed by acetylation with acetic anhydride, afforded N-acetylaminobenzimidazole as a major product together with the desired product, N-glycosylaminobenzimidazole, in poor yield.

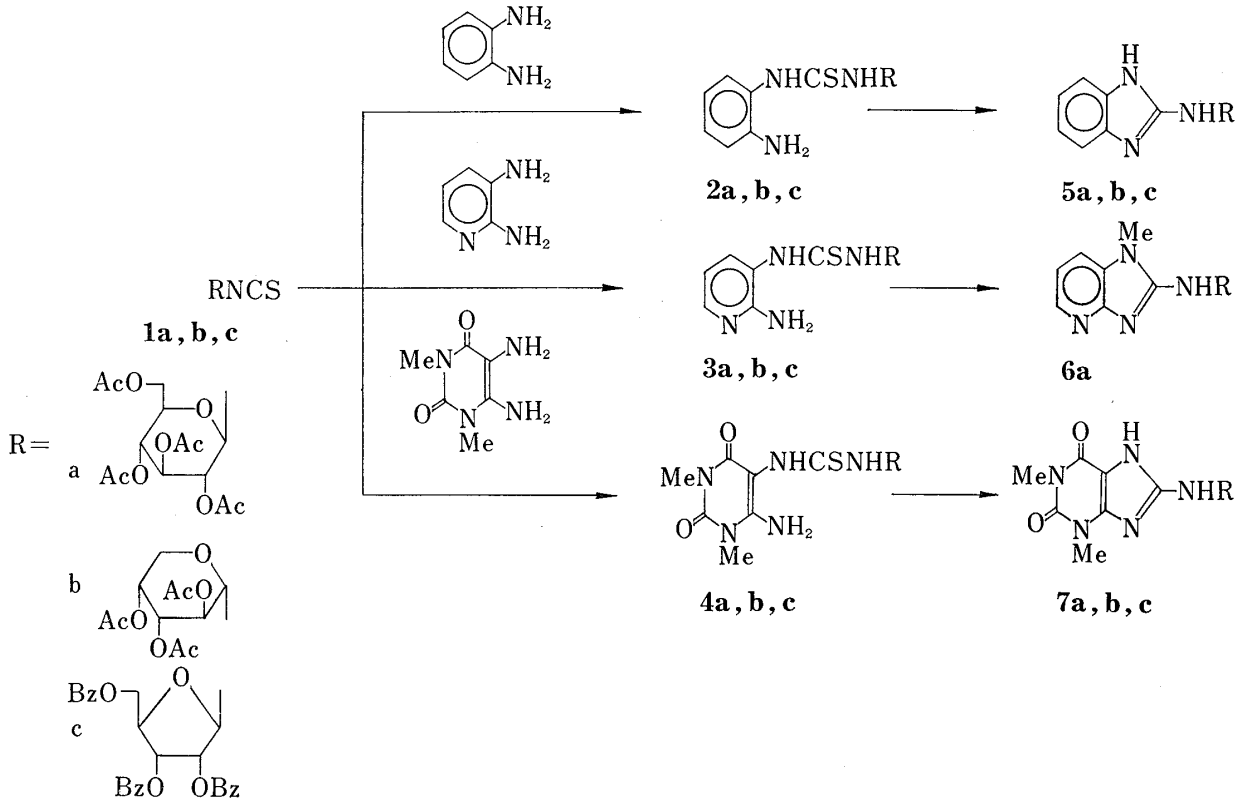

Chart 1

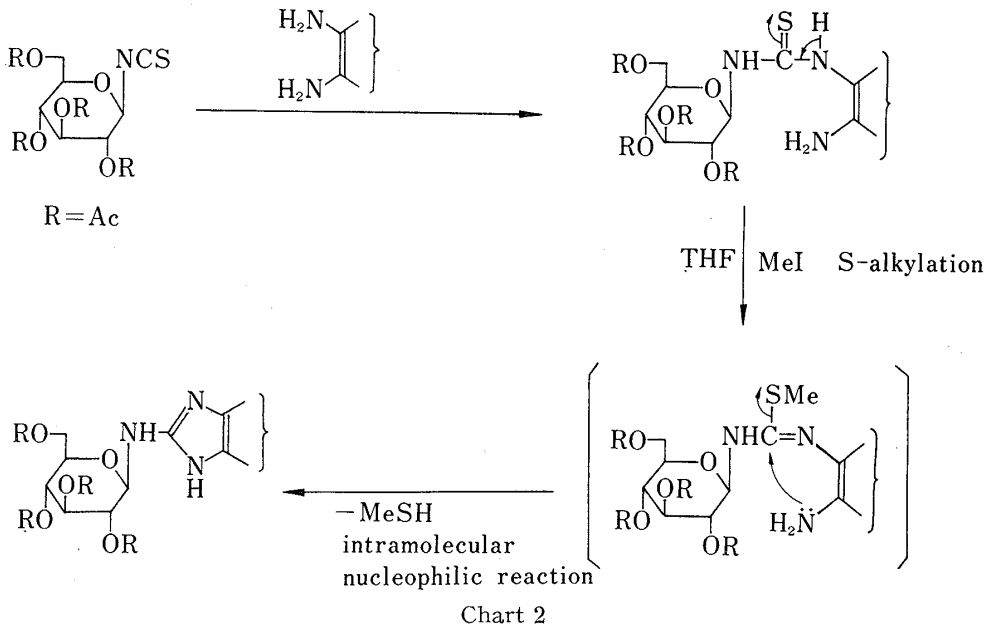

Chart 2

In our experiments, reactions of **2a—c** and **3a** with methyl iodide in the presence of triethylamine gave N-glycosylaminobenzimidazoles (**5a—c**) and N-glycosyl-3-deazapurine (**6a**), respectively, in excellent yields. Similar reactions of **4a—c** and methyl iodide in THF solution yielded **7a—c** in 90—95% yields (Table V). The NMR spectra of 8-glycosylaminotheophyllines (**7a—c**) showed the presence of an NH proton on the anomeric carbon at δ 8.15—8.28. The assignment of N(7)–H on the theophylline moiety was confirmed on the basis of NMR data of theophylline derivatives[10] and polyhydroxyalkyl theophylline.[11]

The mechanism is shown in Chart 2. The reaction takes place *via* an initial nucleophilic attack at the isothiocyanate group and gives glycosyl thioureides. Methyl iodide attacks the sulfur atom of glycosyl thioureide, leading exclusively to the S-methyl isourea in THF solution. Subsequent elimination of methyl mercaptan takes place to afford the fused imidazole glycosides.

Experimental

All melting points are uncorrected. Infrared (IR) spectral measurements were performed with a JASCO A-2 infrared 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. Ultraviolet (UV) spectra were measured with Hitachi 340 spectrometer.

N-(*o*-Aminophenyl)-N′-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)thioureide (**2a**)——A mixture of 2,3,-4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl isothiocyanate (**1a**; 390 mg, 0.001 mol) and *o*-phenylenediamine (110 mg, 0.001 mol) in dry benzene (20 ml) was refluxed for 3 hr on a water bath and then allowed to stand at room temperature. The crystals that separated were collected by filtration and recrystallized from benzene to give colorless fine needles (Table I).

Table I. N-Glycosyl-N′-(*o*-aminophenyl)thioureide(**2a—c**)

Compd. No.	mp (°C)	Yield (%)	IR ν_{max}^{KBr} cm^{-1}	UV λ_{max}^{MeOH} nm (log ε)	NMR (δ, $CDCl_3$) heterocyclic moiety	Analysis (%) Calcd.	Found
						$C_{21}H_{27}N_3O_9S$	
2a	179—182	97	3400, 3300, 3250, 1740, 1610, 740	240(4.5), 295(4.4)	6.70 (1H, d, J=8.0 Hz, 1-NH), 6.80—7.40 (4H, m, Ph), 8.10 (1H, bs, NH)	C 50.70 H 5.47 N 8.45 (M^+, *m/e* 497)	50.45 5.53 8.32
						$C_{18}H_{23}N_3O_7S$	
2b	126—130	92	3400, 3300, 3250, 1740, 1600, 750	242(4.6), 299(4.0)	6.60 (1H, d, J=8.0 Hz, 1-NH), 6.82—7.40 (4H, m, Ph), 7.82 (1H, bs, NH)	C 50.82 H 5.45 N 9.88 (M^+, *m/e* 425)	50.78 5.60 9.85
						$C_{33}H_{20}N_3O_7S$	
2c	Syrup[a]	95	3450, 3300, 1710, 1610, 1600, 750	231(4.7), 282(3.9), 301(3.9)	6.64 (1H, d, J=8.0 Hz, 1-NH), 8.60 (1H, bs, NH)	C 64.80 H 4.78 N 6.87	64.75 4.82 6.92

a) TLC (silica gel) *Rf* 0.52 (benzene/acetone=3:2).

N-(*o*-Aminophenyl)-N′-(2,3,4-tri-*O*-acetyl-*α*-D-arabinopyranosyl)thioureide (**2b**)——A mixture of 2,3,4-tri-*O*-acetyl-*α*-D-arabinopyranosyl isothiocyanate (**1b**; 320 mg, 0.001 mol) and *o*-phenylenediamine (110 mg, 0.001 mol) in dry benzene (20 ml) was refluxed for 1 hr, then evaporated to dryness under reduced pressure. The residue was chromatographed on silica gel. Elution with CCl_4–$CHCl_3$ (1:9) gave a colorless syrup, which was crystallized from benzene–ether (1:1) to give **2b** as colorless needles (Table I).

N-(*o*-Aminophenyl)-N′-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)thioureide (**2c**)——A mixture of 2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl isothiocyanate (**1c**; 503 mg, 0.001 mol) and *o*-phenylenediamine (110 mg, 0.001 mol) in dry benzene (15 ml) was refluxed for 2 hr, then concentrated under reduced preseure to give a

10) L.-M. Twanmoch, H.B. Wood, and J.S. Driscoll, *J. Heterocycl. Chem.*, **10**, 187 (1973).
11) H. Ogura, H. Takahashi, and M. Sakaguchi, *Heterocycles*, **3**, 93 (1975); K. Gonda, S. Koga, M. Sakaguchi, Y. Miyata, H. Ogura, and T. Okamoto, *Yakugaku Zasshi*, **98**, 708 (1978).

slightly yellow residue. The residue was treated as described above for **2b**. Elution with $CHCl_3$–acetone (97: 3) gave **2c** as a colorless syrup (Table I).

N-(2-Aminopyrid-3-yl)-N′-glycosylthioureide (3a, b, c) (Table II)——Mixtures of **1a, b, c** (0.001 mol) and 2,3-diaminopyridine (109 mg, 0.001 mol) in MeCN (20 ml) were refluxed for 5—6 hr, then evaporated to dryness under reduced pressure. The residues were chromatographed on silica gel with $CHCl_3$–acetone (9: 1) to give **3a, b, c**, respectively as crystalline solids in 94—97% yields.

Table II. N-Glycosyl-N′-(2-aminopyrid-3-yl)thioureide (3a—c)

Compd. No.	mp (°C)	Yield (%)	IR ν_{max}^{KBr} cm^{-1}	NMR (δ, $CDCl_3$) heterocyclic moiety	Analysis (%) Calcd.	Found
					$C_{20}H_{26}N_4O_9S$	
3a	194—195	95	3500, 3350, 3300, 1740, 1610, 1520, 1250, 1120, 780	6.50 (1H, d, J=8.0 Hz, 1-NH), 6.62, 7.72—7.93 (3H, m, pyridine ring), 7.68 (2H, bs, NH_2)	C 48.19	48.13
					H 5.26	5.32
					N 11.24	11.20
					(M^+, m/e 498)	
					$C_{17}H_{22}N_4O_7S$	
3b	142—143	97	3450, 3300, 1740, 1610, 1540, 1220, 1120, 780, 760	7.10—8.30 (3H, m, pyridine ring), 9.18 (2H, bs, NH_2), 9.70 (1H, bs, NH), 12.30 (1H, d, J=8.0 Hz, 1-NH)[a]	C 47.88	47.85
					H 5.20	5.16
					N 13.14	13.18
					(M^+, m/e 426)	
					$C_{32}H_{28}N_4O_7S$	
3c	99—103	94	3500, 3450, 3300, 1710, 1620, 1590, 1210, 1110, 780	6.47 (1H, d, J=8.0 Hz, 1-NH), 8.02 (2H, bs, NH_2)	C 62.74	62.70
					H 4.61	4.58
					N 9.15	9.14

a) in DMSO-d_6.

N-(6-Amino-1,3-dimethyl-2,4-dioxopyrimidin-5-yl)-N′-glycosylthioureide (4a, b, c) (Table III)——a) A mixture of **1a** or **b** (0.001 mol) and 5,6-diamino-1,3-dimethyluracil (170 mg, 0.001 mol) in MeCN or THF (20 ml) was refluxed for 2—3 hr, then allowed to stand at room temperature. The crystals that separated were collected by filtration and recrystallized from benzene–MeCN (5: 2) to give **4a** or **b** as fine needles.

Table III. N-Glycosyl-N′-(6-amino-1,3-dimethyl-2,4-dioxopyrimidin-5-yl)thioureide(4a—c)

Compd. No.	mp (°C)	Yield (%)	IR ν_{max}^{KBr} cm^{-1}	NMR (δ, $CDCl_3$) heterocyclic moiety	Analysis (%) Calcd.	Found
					$C_{21}H_{20}N_5O_{11}S$	
4a	145—147	95	3400, 3300, 3250, 1740, 1690, 1210, 1115, 750	3.30, 3.40 (6H, s, $(NMe)_2$), 6.35 (2H, bs, NH_2), 7.12 (1H, d, J=8.0 Hz, 1-NH), 8.30 (1H, bs, NH)	C 45.08	45.13
					H 5.22	5.20
					N 12.52	12.56
					(M^+, m/e 559)	
					$C_{18}H_{25}N_5O_9S$	
4b	167—170	95	3400, 3300, 3200, 1740, 1620, 1500, 1210, 1160, 760	3.29, 3.51 (6H, s, $(NMe)_2$), 6.42 (2H, bs, NH_2), 7.27 (1H, d, J=8.0 Hz, 1-NH), 8.18 (1H, bs, NH)	C 44.35	44.30
					H 5.17	5.21
					N 14.37	14.40
					(M^+, m/e 487)	
					$C_{33}H_{31}N_5O_9S$	
4a[a]	193—197	94	3450, 3300, 1710, 1630, 1610, 1580, 1210, 1150, 760	3.10, 3.34 (6H, s, $(NMe)_2$), 6.50 (2H, bs, NH_2), 8.50 (1H, bs, NH)	C 58.83	58.85
					H 4.64	4.70
					N 10.40	10.42

a) UV $\lambda_{max}^{Dioxane}$ nm (log ε): 231 (5.0), 263 (3.8), 284 (3.5).

b) A mixture of **1c** (500 mg, 0.001 mol) and 5,6-diamino-1,3-dimethyluracil (170 mg, 0.001 mol) in MeCN (20 ml) was treated as described above for **2a** or **b**. The reaction solution was concentrated to 1/4 volume and poured into ice-water to yield crude crystals. Recrystallization from benzene–MeCN (9: 1) afforded **4c** as colorless fine needles.

N-(2,3,4,6-Tetra-*O*-acetyl-*β*-D-glucopyranosyl)aminobenzimidazole (5a)——A solution of **2a** (500 mg, 0.001 mol) and $Pb(OAc)_2$ (379 mg, 0.001 mol) in MeOH (10 ml) was refluxed for 3 hr. After filtration, the

solvent was removed under reduced pressure to give a slightly yellow syrup. The syrup was acetylated with Ac_2O (5 ml) and pyridine (5 ml) at room temperature for 20 hr. The reaction solution was poured into ice-water and extracted with $CHCl_3$ (30 ml). The organic layer was washed with 5%-$NaHCO_3$, H_2O and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a residue, which was chromatographed on silica gel with CCl_4–$CHCl_3$. From the eluate with CCl_4–$CHCl_3$ (19: 1) N-acetylaminobenzimidazole was obtained in 87% yield and further elution with CCl_4–$CHCl_3$ (3: 7) gave **5a** in 7% yield.

N-Glycosylaminobenzimidazole (5a, b, c) and N-Glycosylaminotheophylline (7a, b, c) (Tables IV and V)—To a solution of **2a**, **b** or **c**, or **4a**, **b** or **c** (0.001 mol) in MeOH (10 ml), MeI (1—3 ml) was added dropwise at room temperature. The reaction solution was stirred for 30 min and then gently refluxed for 3 hr on a water bath. Removal of the solvent by evaporation left residue, which was chromatographed on silica gel with $CHCl_3$–acetone. From the eluate with $CHCl_3$–acetone (97: 3), **5a**, **b** or **c**, or **7a**, **b** or **c**, respectively, was obtained as a colorless syrup. Crystallization from benzene or MeOH gave **5b** or **c**, or **7a**, **b** or **c** as colorless fine needles.

Table IV. N-Glycosylaminobenzimidazole (**5a—c**)

Compd. No.	mp (°C)	Yield (%)	IR ν_{max}^{KBr} cm^{-1}	UV λ_{max}^{MeOH} nm (log ε)	NMR (δ $CDCl_3$) heterocyclic moiety	Analysis (%) Calcd. Found
5a	Syrup[a]	96	3300, 1740, 1620, 1590, 1580, 1210, 1120, 760	246(4.8), 280(4.0), 285(4.0)	6.95 (1H, bs, NH), 6.85—7.40 (4H, m, Ph)	$C_{21}H_{25}N_3O_9$ C 54.43 54.38 H 5.44 5.50 N 9.07 9.12 (M^+, *m/e* 463)
5b	152—153	90	3300, 1740, 1610, 1580, 1220, 1120, 760	242(4.0), 248(4.8), 282(4.1), 287(4.1)	6.87 (1H, d, J=8.0 Hz, 1-NH), 7.86 (1H, bs, NH), 6.80—7.42 (4H, m, Ph)	$C_{18}H_{21}N_3O_7$ C 55.24 55.27 H 5.41 5.36 N 10.74 10.76 (M^+ m, *m/e* 391)
5c	118—121	92	3250, 1710, 1690, 1620, 1580, 1210, 1140, 740	230(4.5), 280(3.8), 297(3.9)	6.35 (1H, bs, NH)	$C_{33}H_{27}N_3O_7$ C 68.62 68.57 H 4.71 4.76 N 7.28 7.32

a) TLC (silica gel) *Rf* 0.52 (benzene/acetone=3: 2).

Table V. N-Glycosylaminotheophylline (**7a—c**)

Compd. No.	mp (°C)	Yield (%)	IR ν_{max}^{KBr} cm^{-1}	UV λ_{max}^{MeOH} nm (log ε)	NMR (δ, $CDCl_3$) heterocyclic moiety	Analysis (%) Calcd. Found
7a	263—265	86	3450, 3400, 1740, 1630, 1580, 1240, 1140, 740	216(4.5), 290(4.3)	3.20, 3.32 (6H, s, $(NMe)_2$), 8.15 (1H, d, J=8.0 Hz, 1-NH), 11.82 (1H, bs, NH)	$C_{21}H_{27}N_5O_{11}$ C 48.00 48.06 H 5.18 5.14 N 13.33 13.30 (M^+, *m/e* 525)
7b	213—214	90	3450, 3250, 1740, 1690, 1620, 1580, 1210, 1140, 740	212(4.5), 289(4.3)	3.53, 3.57 (6H, s, $(NMe)_2$), 8.28 (1H, d, J=8.0 Hz, 1-NH), 11.75 (1H, bs, NH)	$C_{18}H_{23}N_5O_9$ C 47.68 47.64 H 5.11 5.17 N 15.45 15.42 (M^+, *m/e* 453)
7c	Syrup[a]	92	3450, 3250, 1710, 1690, 1620, 1580, 1210, 1120, 760	231(5.0), 282(3.8), 302(3.7)	3.15, 3.48 (6H, s, $NMe)_2$), 11.55 (1H, bs, NH)	$C_{33}H_{29}N_5O_9$ C 61.97 61.95 H 4.57 4.60 N 10.95 10.98

a) TLC (silica gel) *Rf* 0.62 (benzene/acetone=3: 2).

N-(2,3,4,6-Tetra-*O*-acetyl-*β*-D-glucopyranosyl)amino-3-deazapurine (6a)——To a solution of **3a** (500 mg, 0.001 mol) in THF (20 ml), an excess of MeI (3 ml) and NEt_3 (3 ml) was added dropwise and the mixture was stirred for 1 hr at room temperature. The reaction mixture was then refluxed for 3 hr and evaporated to dryness under reduced pressure. The residue was dissolved in $CHCl_3$ (100 ml), washed with H_2O and dried over $MgSO_4$. Removal of the solvent by evaporation gave a residue, which crystallized from ether to afford fine needles in 95% yield, mp 230—232°. *Anal.* Calcd. for $C_{21}H_{26}N_4O_9$: C, 52.72; H, 5.48; N, 11.71. Found: C, 52.76; H, 5.52; N, 11.74. IR ν_{max}^{KBr} cm^{-1}: 3430 (NH), 1740 (ester), 1630 (C=N), 1580, 790, 760. NMR ($CDCl_3$) δ: 4.31 (3H, s, NMe), 7.39 (1H, t, 5-H), 7.99 (1H, d, J=6.0 Hz, 4-H), 8.30 (1H, d, J=8.0 Hz, 6-H). MS *m/e* 478 (M^+).