Synthesis of 6-(2-Amino-2-deoxy-β-D-glucopyranosylamino)- and 6-(β-D-Glucopyranosylamino)purine

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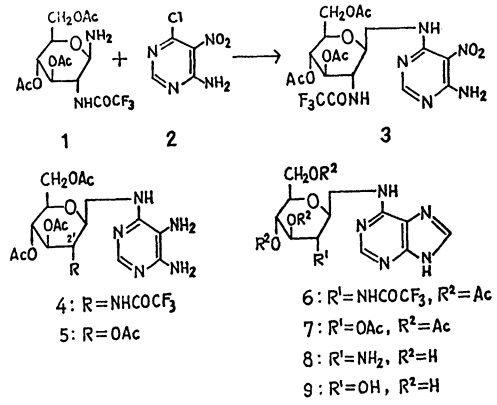
6-(β-Glycosylamino)purines have been synthesized in good yields by condensation of 4-amino-5-nitro-6-chloropyrimidine with masked glycosylamines followed by hydrogenation of nitro group, cyclization with triethyl orthoformate and removal of protecting groups.

Since kinetin[1] and zeatin,[2] factors inducing cell division, were discovered, many related compounds such as 6-acylaminopurines,[3] reversed nucleosides,[4] and modified nucleosides,[5] have been synthesized. Furthermore, 6-(aminoheptosylamino)purine was found in septacidin,[6] an antifungal and cytotoxic antibiotic. In order to investigate further the structure-activity relationships, we have synthesized the title compounds.

The synthesis of 6-(glycosylamino)purines has rarely been reported. The elegant synthesis of reversed nucleosides by Leonard and Carraway[4] involved condensation of a 9-masked derivative of 6-chloropurine with a masked derivative of 5-amino-5-deoxyribose. Ikehara and Tada[7] found that carbon disulfide ring-closure of 6-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamino)-4,5-diaminopyrimidine gave a mixture of masked derivatives of 9-(β-D-glucopyranosyl)purine and 6-(β-D-glucopyranosyl)purine.

For the preparation of 6-substituted purines, the condensation of 6-chloropurine[8] or 6-mercaptopurine[1,9] with an amine, and the direct alkylation of adenine derivatives[1] have been developed. Our attempts to prepare 6-(glycosylamino)purines by these procedures were unsuccessful. However, we have found that the 6-(β-glycosylamino)purines could be synthesized in good yields by condensation of 4-amino-6-chloro-5-nitropyrimidine with masked glycosylamines followed by cyclization with triethyl orthoformate.

We have prepared 6-(2-amino-2-deoxy-β-D-glucopyranosylamino)purine (**8**) as an aminonucleoside (Scheme 1). In this synthesis, the base-labile *N*-trifluoroacetyl group was used for the protection of the amino group of the sugar. Ikehara and Tada[7] discussed the formation of N^6-glucosyladenine together with N^9-isomer and ascribed it to the presence of hydrogen bond between the 2′-*O*-acetyl and 6-NH group of pyrimidine base. Since the *N*-trifluoroacetyl group is known to be less participating, we were interested in the influence of this function on the ring-closure.



Scheme 1

3,4,6-Tri-*O*-acetyl-2-deoxy-2-trifluoroacetamido-β-D-glucopyranosyl azide[10,11] was hydrogenated with Raney nickel to give the glycosylamine (**1**) in high yield. Condensation of **1** with 4-amino-6-chloro-5-nitropyrimidine[12] (**2**) in dioxane afforded 6-(3,4,6-tri-*O*-acetyl-2-deoxy-2-trifluoroacetamido-β-D-glucopyranosylamino)-4-amino-5-nitropyrimidine (**3**) in a 58% yield. Catalytic reduction with Raney nickel then gave 6-(3,4,6-tri-*O*-acetyl-2-deoxy-2-trifluoroacetamido-β-D-glucopyranosylamino)-4,5-diaminopyrimidine (**4**). Cyclization of **4** with triethyl orthoformate and acetic anhydride afforded, in a 66% yield, 6-(3,4,6-tri-*O*-acetyl-2-deoxy-2-trifluoroacetamido-β-D-glucopyranosylamino)purine (**6**), which, after removal of the protecting groups by treatment with methanolic ammonia at room temperatures, led to 6-(2-amino-2-deoxy-β-D-glucopyranosylamino)purine (**8**) in a 39% overall yield from **1**.

Next, we prepared 6-(β-D-glucopyranosylamino)-purine (**9**) by the analogous procedure. 6-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosylamino)-4,5-diaminopyrimidine (**5**) was prepared by the method described by Ikehara and Tada,[7] and, in the present paper, we have described purification of this compound and its physical properties. Cyclization of **5** with triethyl

Table 1. Ultraviolet spectral data

Compounds	λ_{max} mμ	($\varepsilon \times 10^{-3}$)
3	325.5	(16.3)[a]
4	286.5	(6.56)[a]
5	286	(8.4)[a]
6	263.5	(19.5)[a]
7	263	(16.4)[a]
8	271.5	(21.0)[b]
	262	(18.45)[c]
	271	(18.4)[d]
9	273	(17.5)[b]
	263	(16.4)[c]
	272	(14.3)[d]

a) MeOH, b) 0.01 M HCl, c) Water, d) 0.01 M NaOH.

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Table 2. Physical properties and elemental analyses

Compound	Mp, °C	Formula	Calcd, %			Found, %			Yield %	$[\alpha]_D$[a]
			C	H	N	C	H	N		
3	245	$C_{18}H_{21}N_6O_{10}F_3$	40.16	3.93	15.62	40.26	4.27	16.00	58	−27.4 (*c* 0.55) m
4	122—135	$C_{18}H_{23}N_6O_8F_3$	42.52	4.53	16.54	42.28	4.80	16.29	96	−4.3 (*c* 0.9) m
5	113—115	$C_{18}H_{25}N_5O_9$	47.47	5.49	15.38	47.30	5.63	15.62	95.5	−12.0 (*c* 2.0) c
6	169—170	$C_{19}H_{21}N_6O_8F_3$	44.02	4.05	16.22	44.13	3.98	16.37	66	−4.9 (*c* 1.0) m
7	193—194	$C_{19}H_{27}N_5O_9$	48.61	5.80	14.92	48.88	5.75	14.54	60	−22.0 (*c* 0.5) m
8	225(dec)	$C_{11}H_{16}N_6O_4$	44.59	5.44	28.60	44.73	5.66	28.20	84	−70.0 (*c* 1.1) w
9	223(dec)	$C_{11}H_{15}N_5O_5$	44.44	5.09	23.56	44.50	5.33	23.53	70	−48.5 (*c* 1.0) w

a) Determined at room temperatures, m: methanol, c: chloroform, w: water

or thoformate and acetic anhydride gave, in a 60% yield, 6-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamino)purine (**7**), which, after deblocking, gave **9** in a 33% overall yield from **2**.

The above-mentioned yields of **6** and **7** suggested that the hydrogen bonding of 2′-*O*-acyl or 2′-*N*-acyl group with 6-NH group in the pyrimidine compounds (**4**, **5**) did not exert substantial influence on the ring-closure with triethyl orthoformate.

The structure and stereochemistry of the above-described products have been confirmed by UV (Table 1), IR and NMR spectral studies.

Experimental

*3,4,6-Tri-O-acetyl-2-deoxy-2-trifluoroacetamido-β-D-glucosylamine (**1**).* A solution of 3,4,6-tri-*O*-acetyl-2-deoxy-2-trifluoroacetamido-β-D-glucopyranosyl azide[11] (2.66 g, 6.24 mmol) in ethyl acetate (50 ml) was shaken with Raney nickel (W-2, 2 ml) and hydrogen (55 kg/cm²) at room temperatures for 18 hr. The catalyst was filtered off, and the filtrate was evaporated to dryness *in vacuo*. The residue was crystallized from 2-propanol-ethyl acetate (1 : 1) to yield 2.39 g (5.97 mmol, 96.5%) of **1** as needles; mp 174—176 °C, $[\alpha]_D^{15}$ −20.2° (*c* 1.12, MeOH) [lit,[11] mp 158 °C, $[\alpha]_D^{22}$ −14.4° (*c* 0.6, MeOH)]; ν_{max}^{KBr} (cm⁻¹), 1750, 1710 (-$COCH_3$, -$COCF_3$), 1230 (C-O-C); tlc, R_f 0.75 (benzene-ethyl acetate 1 : 6).

*6-(3,4,6-Tri-O-acetyl-2-deoxy-2-trifluoroacetamido-β-D-glucopyranosylamino)-4-amino-5-nitropyrimidine (**3**).* To a solution of **1** (2.22 g, 5.55 mmol) in anhydrous dioxane (5 ml) and triethylamine (0.77 ml, 5.55 mmol), a suspension of 4-amino-6-chloro-5-nitropyrimidine[12] (**2**) in anhydrous dioxane (30 ml) was added with stirring. The mixture was heated at 60—65 °C for 15 hr and filtered. The filtrate was evaporated to dryness *in vacuo*. The residue (3.78 g) was chromatographed on a column (3×38 cm) of silica gel (100 g, Wakogel C-200) and eluted with ether. The fractions containing **3** were combined and evaporated to dryness *in vacuo*. The residue was crystallized from ethanol to give **3** (1.73 g, 58%) as needles; ν_{max}^{KBr} (cm⁻¹), 1760, 1715 (-$COCH_3$, -$COCF_3$), 1625, 1595 (-C=N-), 1525, 1370 (-NO_2), 1235 (C-O-C); tlc R_f 0.6 (ethyl acetate-benzene 3 : 1).

*6-(3,4,6-Tri-O-acetyl-2-deoxy-2-trifluoroacetamido-β-D-glucosylamino)-4,5-diaminopyrimidine (**4**).* A sample of **3** (1.24 g, 2.31 mmol) was hydrogenated in the presence of Raney nickel as described in the preparation of **5**. The catalyst was filtered off and the filtrate was evaporated to dryness *in vacuo* to give a colorless glass of **4** (1.11 g, 96%); ν_{max}^{KBr} (cm⁻¹), 1760, 1740 (-$COCH_3$, -$COCF_3$), 1650, 1600 (-C=N-); tlc R_f 0.2 (ethyl acetate).

*6-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosylamino)-4,5-diaminopyrimidine (**5**).* A sample of 6-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamino)-4-amino-5-nitropyrimidine[7] (1.52 g, 3.15 mmol) was dissolved in anhydrous methanol (55 ml) at 60 °C and cooled. To the solution Raney nickel (3.8 ml, W-2) was added and the mixture was shaken with hydrogen (hydrogen pressure 60 kg/cm²) at room temperature for 6 hr. The catalyst was filtered off and washed with methanol. The filtrate and washings were combined and evaporated to dryness *in vacuo*. The resulting solid (1.37 g) was crystallized from ethyl acetate to give colorless needles of **5** (1.01 g, 95.5%); ν_{max}^{KBr} (cm⁻¹), 3380 (-NH), 1750 (-$COCH_3$), 1660, 1630, 1595 (-C=N-); tlc R_f 0.5 (ethyl acetate-ethanol 6 : 1).

*6-(3,4,6-Tri-O-acetyl-2-deoxy-2-trifluoroacetamido-β-D-glucopyranosylamino)purine (**6**).* A solution of **4** (1.26 g, 2.31 mmol) in triethyl orthoformate and acetic anhydride (11.2 ml, 1 : 1) was refluxed for 85 min and the reaction mixture was evaporated to sirup *in vacuo*. The residue was chromatographed on a column (2.8×24 cm) of silica gel (70 g, Wakogel C-200) and eluted with ethyl acetate-ethanol (20 : 1). Fractions containing the product of R_f 0.5 (tlc, ethyl acetate-ethanol 20 : 1) were combined and evaporated to dryness. The residue was crystallized from ethyl acetate-isopropyl ether (1 : 1) to yield **6** (0.792 g, 66%) as colorless needles; ν_{max}^{KBr} (cm⁻¹), 1760 1725 (-$COCH_3$, -$COCF_3$), 1625, 1600 (-C=N-), 1245 (C-O-C); tlc R_f 0.5 (ethyl acetate-ethanol 6 : 1), 0.3 (ethyl acetate).

*6-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosylamino)purine (**7**).* A solution of **4** (1.733 g, 3.82 mmol) in triethyl orthoformate and acetic anhydride (19 ml, 1 : 1) was heated at 125 °C (bath temperature) for 1.5 hr and the solution was evaporated to dryness *in vacuo*. The residue was chromatographed on a column of silica gel (50 g, Wakogel C-200) and eluted with benzene-ethanol (9 : 1). Fractions containing of the product of R_f 0.35 (tlc, benzene-ethanol 9 : 1) were combined and evaporated to dryness *in vacuo* to give **7** (1.074 g, 60%) as colorless needles, which were recrystallized from ethyl acetate; ν_{max}^{KBr} (cm⁻¹), 3430 (-NH), 1760 (-$COCH_3$), 1625, 1600 (-C=N-), 1060, 1035 (C-O-C); NMR (DMSO-d_6), δ 8.70 (1H s, purine H_2), 8.64 (1H d, J=8—9 Hz, purine C_6-NH), 8.50 (1H s, purine H_8), 5.85 (1H d, J=8—9 Hz, $C_{1'}$-H), 2.02 (3H s, -$OCOCH_3$), 1.97 (6H s, -$OCOCH_3$), 1.88 (3H s, -$OCOCH_3$); tlc R_f 0.35 (benzene-ethanol 9 : 1), 0.30 (ethyl acetate).

*6-(2-Amino-2-deoxy-β-D-glucopyranosylamino)purine (**8**).* A portion of **6** (0.60 g, 1.16 mmol) was treated with saturated methanolic ammonia (35 ml) at room temperature for 5 days. The solution was evaporated to dryness *in vacuo*. The resulting solid was recrystallized from water-ethanol to give 6-(2-amino-2-deoxy-β-D-glucopyranosyl)purine (**8**) (290 mg, 84%) as colorless needles; ν_{max}^{KBr} (cm⁻¹), 3380, 3320,

3180 (-NH, -OH), 1635, 1595 (-C=N-), 1105, 1080, 1057, 1048, 1026 (C-O-C); NMR (DMSO-d_6), δ 8.27 (1H s, purine H_2), 8.17 (1H s, purine H_8), 8.01 (1H d, J=9 Hz, purine C_6-NH), 5.43 (1H d, J=9 Hz, $C_{1'}$-H); tlc R_f 0.2 (*n*-butanol-water 86 : 14).

*6-(β-D-Glucopyranosylamino)purine (**9**).* A solution of **7** (335 mg, 0.715 mmol) in anhydrous methanol (35 ml) was saturated at 0 °C with dry ammonia. After storage in a refrigerator for 18 hr, the solution was evaporated to dryness *in vacuo*. The residue was recrystallized from water-ethanol to give 6-(β-D-glucopyranosylamino)purine (**9**) (148 mg, 70%) as colorless needles; ν_{max}^{KBr} (cm^{-1}), 3400, 3350, 3140 (-NH, -OH), 1625, 1600 (-N=C-), 1105, 1080, 1070 (C-O-C) NMR (DMSO-d_6), δ 8.26 (1H s, purine H_2), 8.17 (1H s, purine H_8), 7.84 (1H d, J=8.5 Hz, purine C_6-NH), 5.52 (1H broad, $C_{1'}$-H); tlc R_f 0.17 (*n*-butanol saturated with 2 M ammonia).

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