Studies on Imidazole Derivatives and Related Compounds. 4. Synthesis of *O*-Glycosides of 4-Carbamoylimidazolium-5-olate

Y. Tarumi*, Y. Takebayashi and T. Atsumi

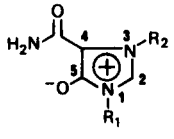
Takarazuka Research Center, Pharmaceuticals Research Laboratory,
Sumitomo Chemical Co., 2-1, 4-chome, Takatsukasa, Takarazuka-shi,
Hyogo-ken, 665 Japan

Received January 24,1984

Ribosylation of trimethylsilyl derivative of 1-(4-nitrobenzyl)-5-carbamoylimidazolium-4-olate (**5**) with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose in the presence of stannic chloride and trimethylsilyl trifluoromethanesulfonate afforded no 5-*O*-glycosides but N-1 ribosylated compound (**6**). However, 5-*O*-riboside (**7a**) and its orthoamide derivative (**8**) were given by glycosylation of tri-*n*-butylstannyl derivative of **5** with 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl chloride in the presence of silver trifluoromethanesulfonate. This procedure was successfully applied to other sugars and 5-*O*-glucuronide (**11**), a possible metabolite of **1** *in vivo*, was obtained as one of the 5-*O*-glycoside derivatives.

J. Heterocyclic Chem., **21**, 849 (1984).

Cytostatic and antitumor activities of 4-carbamoylimidazolium-5-olate (**1**) [1a-d], the aglycone of bredinin (**2a**) [1a], have encouraged us to undertake the synthesis and biological evaluation of novel nucleosides of **1**. We have already reported the syntheses of N-1 nucleosides (**2b**) and N-3 nucleosides (**2c**) of **1** [2] (Figure 1), but glycosylation at 5-*O* position which is a reactive site of **1** has not yet been achieved.



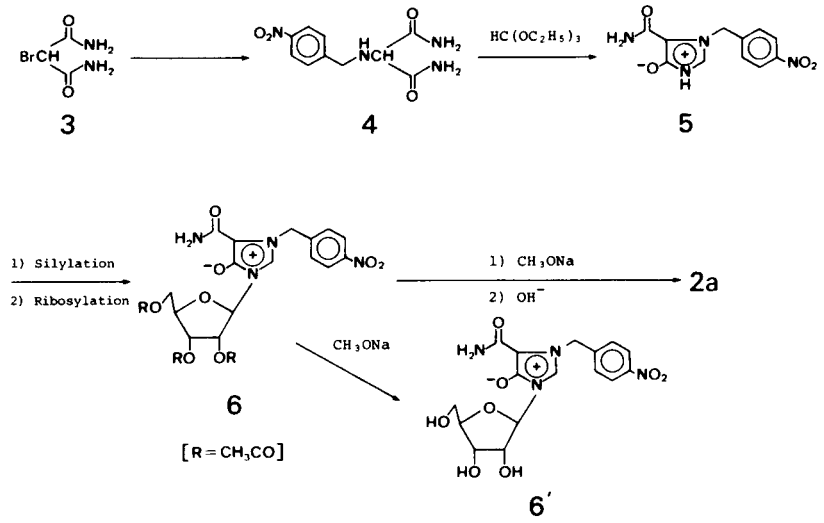
1 : $R_1=R_2=H$

2 a: R_1=1-β-D-Ribofuranosyl, $R_2=H$
b: R_1=Sugar moiety, $R_2=H$
c: $R_1=H$, R_2=Sugar moiety

Figure 1

Meanwhile, it is known that there exists high levels of β-glucuronidase in human cancer cells [3]. Taking this observation into consideration, we were interested in the synthesis of 5-*O*-glucuronide of **1**, which is expected to be selectively activated and to afford **1** in tumor cells. Furthermore, formation of 5-*O*-glucuronide of **1** may be assumed as one of metabolites of **1** *in vivo*. The purpose of the present investigation is to prepare these 5-*O*-glycosides of **1**.

Protection at N-3 position of **1** with 4-nitrobenzyl group was attempted to prevent the production of N-3 nucleosides (**2c**) which was observed in condensation of trimethylsilyl derivatives of **1** with peracyl sugars in the presence of trimethylsilyl trifluoromethanesulfonate (TMS triflate) [2]. 3-(4-Nitrobenzyl) derivative (**5**) was prepared by condensation of 2-bromopropanediamide (**3**) with 4-nitrobenzylamine in dry ethanol, followed by treatment of the resultant 2-(4-nitrobenzylamino)propanediamide (**4**) with triethyl orthoformate and a catalytic amount of *p*-toluenesulfonic acid as shown in Sheme 1.



3 4 5 6 6'

Scheme 1

Glycosylation of **5** is represented by ribosylation as follows. We treated trimethylsilyl derivative of **5**, prepared by refluxing a mixture of **5** and hexamethyldisilazane in xylene, with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose in the presence of TMS triflate, but we could not observe the formation of any products. Contrary to this result, glycosylation smoothly proceeded by addition of stannic chloride to the above reaction mixture. However we only obtained the unexpexted product, 4-carbamoyl-3-(4-nitrobenzyl)-1-(2,3,-5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazolium-5-olate (**6**) in a yield of 76%. The structure of **6** was unambiguously verified by leading it to bredinin (**2a**) (Scheme 1).

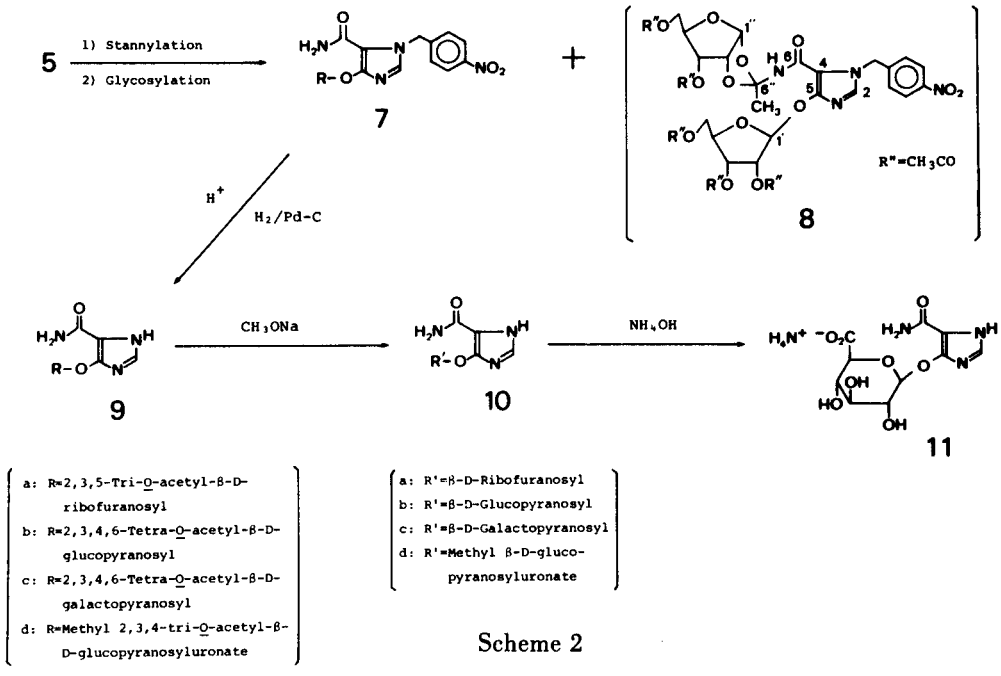
At first, catalytic hydrogenolysis was tried to remove the 4-nitrobenzyl group, but the reaction was so slow that the aimed compound was not obtained. But hydrolysis of **6** to obtain deacylated nucleoside (**6'**) unexpectedly gave the fully deprotected product, *i.e.*, bredinin (**2a**) as follows. Compound **6** was treated with sodium methoxide in dry methanol and after the solvent was evaporated, the residual oil was dissolved in a small amount of water. The strongly alkaline aqueous solution was charged on the column of cation exchange resin (H^+ form) and the column was eluted with water to afford **2a** in 54% yield. As the deprotection at N-3 was supposed to occur in the alkaline aqueous solu-

Table 1

Analytical Data for Glycoside Derivatives of **1** and its Related Compounds

Compound No.	Mp, °C (solvent) [a]	Yield, %	$[\alpha]_D^{25}$, °	Formula (molecular Weight)		Analysis, % C	H	N	Mass (m/e)
4	178-179 (MeOH)	77.9		$C_{10}H_{12}N_4O_4$ (252.23)	Calcd.	47.62	4.80	22.22	208 (M^+-$CONH_2$)
					Found	47.70	4.83	22.17	151,136,121 106
5	266 dec (MeOH-H_2O)	96.8		$C_{11}H_{10}N_4O_4$ (262.22)·½H_2O	Calcd.	48.71	4.09	20.66	262, 245, 219
					Found	48.91	4.03	20.77	136, 106, 90
6	84-96 (Et_2O)	75.6	−11.9 (c = 0.1, MeOH)	$C_{22}H_{24}N_4O_{11}$ (520.46)·½H_2O	Calcd.	49.90	4.76	10.58	520, 478, 447
					Found	50.29	4.92	10.30	259, 139, 97
6'	221 dec (MeOH-H_2O)	81.4	−42.6 (c = 0.1, MeOH)	$C_{15}H_{18}N_4O_8$ (394.35)	Calcd.	48.73	4.60	14.21	394, 324, 219
					Found	48.45	4.65	14.02	136, 106
7a	155.5-156.5 (EtOH)	48.6 (33.1) [b] (24.0) [c]	−11.7 (c = 0.09, MeOH)	$C_{22}H_{24}N_4O_{11}$ (520.44)·½H_2O	Calcd.	49.90	4.76	10.58	520, 490, 447
					Found	50.09	4.63	10.60	388, 318, 288
7b	100-102 (EtOH-IPE)	92.7	−28.0 (c = 0.05, MeOH)	$C_{25}H_{28}N_4O_{13}$ (592.51)·½H_2O	Calcd.	49.92	4.86	9.32	592, 519, 446
					Found	50.12	4.81	9.23	331, 262
7c	111 (EtOH-IPE)	65.1	−7.1 (c = 0.1, MeOH)	$C_{25}H_{28}N_4O_{13}$ (592.51)·½H_2O	Calcd.	49.92	4.86	9.32	592, 533, 331
					Found	49.85	4.90	9.02	169, 127
7d	119-123 (DEE)	71.7	−14.1 (c = 0.09, MeOH)	$C_{24}H_{26}N_4O_{13}$ (578.50)·¼H_2O	Calcd.	49.06	4.63	9.54	518 (M^+-60)
					Found	49.42	4.61	9.43	458, 257, 197
8	163-164 (MeOH)	37.9	+41.7 (c = 0.01, MeOH)	$C_{33}H_{38}N_4O_{18}$ (778.69)	Calcd.	50.90	4.92	7.20	778, 519, 460
					Found	50.70	4.81	7.17	450, 259, 136
9a	132-133.5 ($CHCl_3$-IPE)	61.8	−18.7 (c = 0.05, MeOH)	$C_{15}H_{19}N_3O_9$ (385.33)	Calcd.	46.75	4.97	10.91	385, 259, 139
					Found	46.54	5.08	10.58	127, 97
9b	237-238 (EtOH-IPE)	79.5	−35.6 (c = 0.09, MeOH)	$C_{18}H_{23}N_3O_{11}$ (457.39)·2/5EtOH	Calcd.	47.45	5.38	8.83	457, 331, 271
					Found	47.08	5.13	8.50	216, 169, 127
9c	234.5-235 ($CHCl_3$-MeOH)	92.3	−17.2 (c = 0.1, MeOH)	$C_{18}H_{23}N_3O_{11}$ (457.39)·¼H_2O	Calcd.	46.80	5.13	9.10	457, 331, 169
					Found	46.89	5.10	9.15	127, 109
9d	216-216.5 dec (EtOH)	93.0	−22.5 (c = 0.1, MeOH)	$C_{17}H_{21}N_3O_{11}$ (443.38)·¼H_2O	Calcd.	45.59	4.84	9.38	443, 383, 323
					Found	45.67	4.81	9.32	257, 197, 155
10a	167 dec (H_2O)	93.1	+13.7 (c = 0.1, H_2O)	$C_9H_{13}N_3O_6$ (259.22)·3/5H_2O	Calcd.	40.03	5.30	15.56	
					Found	39.62	4.90	15.35	
10b	157 dec (Me_2CO)	90.0	−28.1 (c = 0.1, H_2O)	$C_{10}H_{15}N_3O_7$ (289.24)·½H_2O	Calcd.	40.27	5.41	14.09	
					Found	40.38	5.43	13.97	
10c	130 dec (MeOH-Me_2CO)	78.8	+4.1 (c = 0.1, H_2O)	$C_{10}H_{15}N_3O_7$ (289.24)·½MeOH ·½H_2O	Calcd.	40.13	5.77	13.37	
					Found	39.90	5.68	13.33	
10d	146 dec (IPA-MeOH)	92.7	−20.5 (c = 0.1, H_2O)	$C_{11}H_{15}N_3O_8$ (317.26)·½H_2O)	Calcd.	40.49	4.94	12.88	
					Found	40.61	5.05	12.68	
11	185 dec (MeOH)	82.0	−30.3 (c = 0.05, H_2O)	$C_{10}H_{16}N_4O_8$ (320.27)·1/5MeOH ·3/2H_2O	Calcd.	34.64	5.64	15.84	
					Found	34.75	5.35	15.59	

[a] MeOH: Methanol, IPE: Diisopropyl ether, EtOH, Ethanol, Me_2CO: Acetone, DEE: Diethyl ether. [b] The yield obtained when **8** was isolated together with **7a**. [c] The yield obtained by acid hydrolysis of **8**.



Scheme 2

tion, the methanolic reaction mixture was neutralized by use of the dried cation exchange resin to give **6'** successfully in a yield of 81%.

As the desired 5-*O*-riboside was not obtained by use of TMS derivative of **5**, we tried the condensation of tri-*n*-butylstannyl one with 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl chloride [4] in the presence of silver triflate expecting the substitution at 5-*O*-position (Scheme 2). A solution of two molar equivalent of 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl chloride to **5** in nitromethane was added to a solution of silver triflate in nitromethane in the presence of 1,1,3,3-tetramethylurea at −15° to form 2,3,5-tri-*O*-acetyl-D-ribofuranosyl triflate and silver chloride [5]. Then a solution of stannyl derivative of **5**, which was prepared by refluxing a mixture of **5** and bis(tri-*n*-butyltin)oxide in dry benzene, was added to the slurry of the above reaction mixture. This mixture was naturally warmed up to room temperature from −15° over five hours. After completion of the glycosylation, the solution was concentrated to provide the residue, which was submitted to silica gel column chromatography to afford 5-*O*-riboside (**7a**) in a yield of 49%.

Catalytic hydrogenolysis of **7a** over 10% palladium on charcoal as a catalyst in the presence of an equal amount of *N*-hydrochloric acid gave **9a** successfully as shown in Scheme 2. The results of elemental and mass spectroscopic analyses proved **7a** and **9a** to be monoribosylated products (Table 1).

The structural assignment of **7a** and **9a** was based on their uv spectroscopic study. We have studied on the uv spectra of some alkyl derivatives of **1** and found some spectral characteristics; 5-*O*-substituted derivatives have one band (227-268 nm), while 5-*O*-nonsubstituted ones have two bands (275-287 nm and 230-246 nm) [6]. The spectra of **7a** and **9a** are essentially identical with those of the following two 5-*O*-substituted derivatives, 1-methyl-4-methoxy-1*H*-imidazole-5-carboxamide (**12**) and 4(5)-methoxy-1*H*-imidazole-5(4)-carboxamide (**13**), respectively (Table 2).

Monitoring of the ribosylation of **5** by tlc showed two major products, but **7a** was only isolated by silica gel column chromatography. Acidic degradation of another product due to triflate may occur during separation. After completion of the ribosylation, an equimolar amount of sodium bicarbonate in water was added to neutralize the reaction mixture and the organic layer was submitted to the silica gel column chromatography. Two kinds of products, **7a** and **8** were obtained in yields of 33% and 38%, respectively (Scheme 2).

The structure of **8** was determined as follows. 1) The results of elemental analysis and molecular ions in mass spectra proved **8** to be di-ribosylated product. 2) The carbonyl absorption of **8** in the ir spectrum supported the secondary amide structure (1680 and 1535 cm^{-1} in nujol). 3) In the ^{13}C nmr spectrum the peaks for the orthoamide structure CH_3-C≡ (25.6 and 112.7 ppm, respectively) [7] and upfield shift (−2.3 ppm) of the peak for C_6 were observed (Table 3). 4) Similarly, in the ^1H nmr spectrum a sharp singlet peak (3H) (1.74 ppm) for the methyl group of the orthoamide structure and a slightly broad singlet peak (1H) (7.64 ppm; disappeared by the addition of deuterium

Table 2

Ultraviolet Spectra of Glycoside Derivatives of **1**

Compound No.	Neutral (H_2O)	Acidic (aq *N*-HCl)	Basic (aq *N*-NaOH)
	λ max (nm) ($\epsilon \times 10^{-3}$)	λ max (nm) ($\epsilon \times 10^{-3}$)	λ max (nm) ($\epsilon \times 10^{-3}$)
5	277 (19.6)	273 (14.1)	285 (20.3)
	240 (sh) [a]	240 (sh)	
6	280 (4.8)	281 (4.8)	274 (20.3)
	245 (sh)	245 (sh)	
6′	279 (20.6)	279 (20.0)	273 (22.7)
	245 (sh)	245 (sh)	
7a	256 (16.7)	262 (13.3)	[b]
7b	252 (17.2)	253 (14.2)	255 (17.2)
7c	252 (14.5)	253 (10.5)	256 (11.7)
7d	253 (16.1)	253 (13.2)	250 (16.5)
8	258 (19.5)	257 (14.6)	[b]
9a	250 (13.4)	241 (9.7)	265 (13.3)
9b	248 (13.5)	231 (9.0)	264 (14.5)
9c	248 (12.8)	234 (8.4)	264 (13.5)
9d	247 (13.2)	230 (9.3)	264 (13.9)
10a	251 (11.8)	242 (8.1)	265 (11.6)
10b	248 (11.8)	241 (8.4)	265 (12.5)
10c	249 (11.4)	242 (8.2)	264 (11.9)
10d	248 (12.8)	228 (9.2)	264 (13.2)
11	251 (13.3)	229 (10.0)	264 (14.2)
12	258 (12.2)	243 (9.3)	258 (12.1)
13	256 (13.3)	241 (10.5)	268 (13.5)

[a] Shoulder. [b] Decomposed.

Table 3

^{13}C and ^{1}H NMR Chemical Shifts [a] for Glycoside Derivatives of **1** and its Related Compounds

Compound No.	^{13}C Chemical Shifts (ppm)						^{1}H Chemical Shifts (ppm) [b]		
	C-2	C-4	C-5	C-6	C-1′	$CH_2C_6H_5$-NO_2	C-2-H	C-1′-H [c]	CH_2-C_6H_5-NO_2
5	130.6	99.9	157.2	161.8		49.7	8.12		5.63
6	127.4	98.0	155.5	161.6	85.4	50.8	8.65	5.86 (d, J = 3.1 Hz)	5.73
6′	127.3	98.3	156.0	161.9	87.2	50.7	8.64	5.57 (d, J = 4.6 Hz)	5.70
7a	136.4	105.4	153.3	160.2	102.6	48.9	7.83	6.26 (s)	5.66
7b	136.3	105.6	153.2	160.0	96.3	48.9	7.86	6.01 (d, J = 8.1 Hz)	5.65
7c	136.4	105.5	153.3	160.0	96.7	48.9	7.98	6.07 (d, J = 7.8 Hz)	5.77
7d	136.4	105.5	153.1	160.0	95.9	49.0	7.86	6.11 (d, J = 7.9 Hz)	5.64
8	137.0	105.3	153.4	157.9	102.2	49.0	7.87	6.17 (s)	5.57
	(C_6'':112.7, C_6''-CH_3:25.6, C_1'':105.3) [d]						[C_1''-H:5.89(d, J = 3.5 Hz), C_6''-CH_3:1.74, N*H:7.65*] *[C]*		
9a	132.5	106.7	151.6	160.2	102.8		7.43	6.21 (s)	
9b	132.6	106.9	151.8	160.0	96.6		7.46	5.94 (d, J = 7.8 Hz)	
9c	132.5	106.6	151.8	160.0	97.0		7.46	5.89 (d, J = 7.5 Hz)	
9d	132.6	106.8	151.5	159.9	96.2		7.48	6.06 (d, J = 7.7 Hz)	
10a	133.0	107.4	152.9	161.0	105.9		7.41	5.94 (s)	
10b	132.6	107.3	153.2	160.9	100.5		7.38	5.30 (d, J = 4.3 Hz)	
10c	132.5	107.0	153.2	160.6	100.9		7.43	5.30 (d, J = 5.7 Hz)	
10d	132.6	106.8	152.7	160.4	99.9		7.41	5.40 (d, J = 6.6 Hz)	
11	132.6	108.3	152.9	160.5	101.7		7.46	5.08 (d, J = 4.8 Hz)	

[a] In δ units in deuteriodimethyl sulfoxide with TMS as internal standard. [b] The proton bonded to C-2 and benzylmethylene protons were observed as singlet. [c] d: doublet, s: singlet. [d] Numbering of the each atoms is shown in scheme 2.

oxide) for the secondary amide proton were observed. 5) The uv spectra of **7a** and **8** were essentially identical to each other. 6) 5-*O*-Monoribosylated compound, **7a** was obtained in 24% yield by mild acidic hydrolysis of **8** in aqueous dioxane. The poor yield is due to the acidic cleavage of 5-*O*-glycosidic bond.

From these results, the structure of **8** was identified as the orthoamide derivative of **7a** as shown in Scheme **2**.

The procedure for 5-*O*-glycosylation, in which the reaction mixture was not neutralized with the addition of base, was also applied to other sugars to afford 5-*O*-substituted derivatives (**7b-d**) (Scheme 2). The nitrobenzyl group of these 5-*O*-glycosides was easily removed by catalytic hydrogenolysis to give per-acyl 5-*O*-glycosides (**9b-d**). The acyl groups of sugar moieties of **9a-d** were removed by alcoholysis with sodium methoxide to provide free 5-*O*-glycosides (**10a-d**). Furthermore, methyl glucuronate (**10d**) was treated with ammonium hydroxide to afford free 5-*O*-glucuronate (**11**) as shown in Sheme 2). The analytical data, uv spectral data and nmr chemical shifts of these glycosides were shown in Tables 1, 2 and 3, respectively.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ultraviolet absorption spectra were obtained on a Shimadzu UV-300 spectrophotometer. Nuclear magnetic resonance spectra were measured in DMSO-d_6 on JEOL FX-100 FT-NMR spectrometer at 99.60 (^{1}H) and 25.20 (^{13}C) MHz using tetramethylsilane as internal standard. Electron impact mass spectra were determined on a Shimadzu LKB-9000 mass spectrometer operating at 12 and 70 eV and specific rotations on a JASCO DIP-181 digital polarimeter. Melting points, recrystallization solvents and analytical data for glycoside derivatives of **1** and its related compounds are listed in Table 1.

2-(4-Nitrobenzyl)aminopropanediamide (**4**).

To a suspension of 14.969 g (82.7 mmoles) of **3** in 200 ml of dry ethanol, were added 11.6 ml (82.9 mmoles) of triethylamine and 11.922 g (82.7 mmoles) of 4-nitrobenzylamine. The mixture was stirred for two hours under reflux and then allowed to cool to room temperature. The crystals that separated were collected by filtration, and washed with ethanol and diisopropylether to give 16.254 g (78%) of **4**, mp 176-177.5.

1-(4-Nitrobenzyl)-5-carbamoylimidazolium-4-olate (**5**).

A mixture of 50.446 g (0.200 moles) of **4**, 760 mg (4.00 mmoles) of *p*-toluenesulfonic acid monohydrate, 177.8 g (1.20 moles) of triethyl orthoformate and 1.30 l of dry ethanol was stirred for three hours under reflux. The mixture was allowed to cool to room temperature. The precipitates were collected by filtration, and washed with ethanol and diisopropylether to provide 50.780 g (97%) of **5**, mp 258° dec.

4-Carbamoyl-3-(4-nitrobenzyl)-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazolium-5-olate (**6**).

A mixture of 7.870 g (30.0 mmoles) of **5**, 21.80 g (135 mmoles) of hexamethyldisilazane, 80 mg (0.60 mmoles) of anhydrous ammonium sulfate and 60 ml of dry xylene was refluxed for one and a half hours to provide a clear solution. The solution was concentrated to dryness *in vacuo* and the residue was dissolved in 120 ml of dry 1,2-dichloroethane. To the solution were added, 9.550 g (30.0 mmoles) of 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose, 3.15 ml (27.0 mmoles) of stannic chloride and 0.55 ml (3.0 mmoles) of TMS triflate. The reaction mixture was stirred for one hour at room temperature and further for one hour at 60°, and then it was allowed to cool to room temperature. To this mixture were added, 11.6 g of sodium bicarbonate, 200 ml of methanol and 200 ml of water. The reaction mixture was stirred for half an hour and then the organic solvent was evaporated *in vacuo* to afford the suspension. The residual suspension was extracted with chloroform and the organic layer was dried over anhydrous sodium sulfate. After the removal of the solvent *in vacuo*, the oily residue was chromatographed on a column of silica gel. The column was eluted with chloroform/methanol (50:1). The fractions containing **6** were concentrated *in vacuo* and the residue was futher purified with reversed phase chromatography using connected three columns of silica gel (Merck; RP-8, B size). Elution with methanol/water/acetic acid (40:60:1) gave 11.800 g (76%) of **6**.

4-Carbamoyl-1-β-D-ribofuranosylimidazolium-5-olate(bredinin) (**2a**) from **6**.

To a solution of 1.040 g (2.00 mmoles) of **6** in 20 ml of dry methanol was added 1.730 g (8.00 mmoles) of 25% (w/w) sodium methoxide in methanol under ice-cooling. The reaction mixture was stirred for half an hour at room temperature, and then the solvent was evaporated *in vacuo*. The residue was dissolved in a small amount of water and charged on a column of cation exchange resin (Dowex 50 × 4, H^+ form), and the column was eluted with water. Fractions containing **2a** were combined and evaporated to give 280 mg (54%) of **2a**, which showed an identical ir spectrum with that of commercially available bredinin.

4-Carbamoyl-3-(4-nitrobenzyl)-1-β-D-ribofuranosylimidazolium-5-olate (**6'**).

To a solution of 5.205 g (10.0 mmoles) of **6** in 600 ml of dry methanol was added 8.650 g (40.0 mmoles) of 25% (w/w) sodium methoxide in methanol under ice-cooling. The reaction solution was stirred for half an hour at room temperature and then neutralized with 62 ml of cation exchange resin (Dowex 50 × 4, H^+ form) which was repeatedly washed with dry methanol. The resin was filtered off and washed with water. The filtrate and washings were combined, and the mixture was concentrated to give an oily residue, which was washed and triturated with methanol to provide 3.21 g (81%) of **6'**.

The three examples given below are representative for preparation of compounds **7a-d**, **9a-d** and **10a-d**, respectively.

1-(4-Nitrobenzyl)-4-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyloxy)-1*H*-imidazole-5-carboxamide (**7a**) and 1-(4-Nitrobenzyl)-4-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyloxy)-1*H*-imidazole-5-*N*-{2-methyl-3',5'-di-*O*-acetyl-D-ribofurano[1',2':4,5]1,3-dioxolan-2-yl}carboxamide (**8**).

(A) Without Neutralization of the Reaction Mixture to Give Only **7a**.

A solution of 2.500 g (7.85 mmoles) of 1,2,3,5-*O*-acetyl-β-D-ribofuranose in 16 ml of dry methylene chloride was rapidly saturated with anhydrous hydrogen chloride at 0° and was kept at the same temperature for two and a half hours while slowly bubbling dry hydrogen chloride gas through the solution. The solvent was then removed *in vacuo* at room temperature, and the residue was co-evaporated with dry xylene for three times and dissolved in 5 ml of dry methylene chloride. This solution was added dropwise to the solution of 2.020 g (7.86 mmoles) of silver triflate and 1.06 ml (7.86 mmoles) of 1,1,3,3-tetramethylurea in 35 ml of dry nitromethane at −20°. To this reaction mixture at the same temperature was further added the solution of 3.90 mmoles of tri-*n*-butylstannyl derivative of **5** in 20 ml of dry benzene, which was prepared by refluxing the mixture of 1.022 g (3.90 mmoles) of **5**, 2.324 g (3.90 mmoles) of bis(tri-*n*-butyltin)oxide and 20 ml of dry benzene for one hour. The reaction mixture was naturally warmed up to room temperature while being stirred for 17 hours and filtered over celite. The filtrate was concentrated *in vacuo* and the residual oil was chromatographed on a column of silica gel. Elution with methylene chloride/acetone (5:1) gave 986 mg (49%) of **7a**, mp 153-156.5°.

(B) With Neutralization of the Reaction Mixture to Give Both **7a** and **8**.

The reaction mixture which was obtained by the same manner described above was filtered over celite and concentrated *in vacuo* to remove methylene chloride. To the residual solution, were added 150 ml of benzene and a solution of 819 mg (7.86 mmoles) of sodium bicarbonate in 70 ml of water under ice-cooling. The organic layer was separated and washed with saturated aqueous sodium chloride for three times, and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residual oil was triturated with diethyl ether to give 2.384 g of a mixture of **7a** and **8**. The mixture was readily separated by column chromatography using silica gel and elution with methylene chloride/acetone (5:1) provided 831 mg (33%) of **7a** and 1.421 g (38%) of **8**.

(C) Partial Acid Hydrolysis of **8** to Provide **7a**.

A mixture of 156 mg (0.20 mmoles) of **8**, 0.2 ml of *N*-hydrochloric acid and 4 ml of 1,4-dioxane was stirred at ambient temperature for two and a half hours. To the reaction mixture was added an excess of sodium bicarbonate and then was filtered over celite. The filtrate was concentrated and the residual glass was chromatographed on a column of silica gel. Elution with methylene chloride/acetone (3:1) provided 25.0 mg (24%) of pure **7a**, which showed an identical ^{1}H nmr spectrum with that of the authentic sample prepared from **5**.

4(5)-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyloxy)-1*H*-imidazole-5(4)-carboxamide (**9a**).

A solution of 729 mg (1.40 mmoles) of **7a** in 60 ml of tetrahydrofuran was hydrogenated in the presence of 300 mg of 10% palladium on charcoal and 2.52 ml (2.52 mmoles) of *N*-hydrochloric acid for five hours. After neutralization by addition of 1 g of sodium bicarbonate, the excess sodium bicarbonate and the catalyst were filtered off. The filtrate was concentrated *in vacuo* and the residue was chromatographed on a column of silica gel. Elution with chloroform/methanol (15:1) gave 333 mg (62%) of **9a**, mp 131-134.5°.

4(5)-β-D-Ribofuranosyloxy-1*H*-imidazole-5(4)-carboxamide (**10a**).

To a solution of 1.156 g (3.00 mmoles) of **9a** in dry methanol was added 684 mg (12.00 mmoles) of 95% sodium methoxide. The mixture was stirred at room temperature for half an hour, and then the solvent was evaporated *in vacuo* to provide a white solid. The residual solid was dissolved in a small amount of water and charged on the column of cation exchange resin (Dowex 50 × 4; NH_4^+ form, 500 ml). Elution with water gave 724 mg (93%) of **10a**.

4(5)-(Ammonium β-D-Glucopyranosyloxyuronate)-1*H*-imidazole-5(4)-carboxamide (**11**).

To a solution of 635 mg (2.00 mmoles) of **10d** in 12 ml of methanol and 8 ml of water was added 2.2 ml of 28% aqueous ammonium hydroxide. The mixture was stirred at room temperature for 24 hours, and then concentrated to dryness *in vacuo*. The residue was triturated with methanol. The crystals were collected by filtration and washed with diethyl ether to provide 500 mg (78%) of **11**, mp 185° dec.

REFERENCES AND NOTES

[1a] K. Mizuno, M. Tsujino, M. Takada, M. Hayashi, K. Atsumi, K. Asano and T. Matsuda, *J. Antibiotics*, **27**, 775 (1974); [b] M. Fukui, M. Inaba, S. Tsukagoshi and Y. Sakurai, *Cancer Res.*, **42**, 1098 (1982); [c] M. Inaba, M. Fukui, N. Yoshida, S. Tsukagoshi and Y. Sakurai, *ibid.*, **42**, 1103 (1982); [d] N. Yoshida, M. Nakamura, M. Fukui, S. Morisada, S. Ogino, M. Inaba, S. Tsukagoshi and Y. Sakurai, *ibid.*, in press.

[2] Y. Tarumi, K. Moriguchi and T. Atsumi, *J. Heterocyclic Chem.*, in press.

[3] G. J. Dutton, "Glucuronic Acid", Academic Press, New York, 1966, Chapter 4.

[4] R. A. Earl and L. B. Towonsend, *J. Carbohydr. Nucleosides Nucleotides*, **1**, 177 (1974).

[5] S. Hanessian and J. Banoub, *Carbohydr. Res.*, **53**, C13 (1977).

[6] Y. Tarumi and T. Atsumi, *J. Heterocyclic Chem.*, **20**, 875 (1983).

[7] F. Seela, U. Lupke and D. Hasselmann, *Chem. Ber.*, **113**, 2808 (1980). The peak for the tetra-substituted carbon of the orthoamide structure C_6H_5-C≡ was reported to appear at 114.4 ppm in DMSO-d_6.