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Synthetic Studies on Amino-sugars from Pyridines. III. Synthesis of 1-O-Methyl-5-benzamido-5-deoxy-*dl*-idopiperidinose[1]

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1-O-Methyl-5-benzamido-5-deoxy-*dl*-idopiperidinose was synthesized from the dihydropyridine derivative (**1**) by stereoselective introduction of the hydroxyl function.

In the previous paper,[3] we already reported the synthetic conversion of a dihydropyridine (**1**) to a derivative of 5-amino-5-deoxyglucose (**2**), which was correlated to an antibiotic, nojirimycin (**3**). From this experience, together with the result of the synthetic study of 5-amino-5-deoxypentose[4] described in the preceding report, we acquired the knowledge that the introduction of a hydroxyl function into the double bonds of dihydropyridines could be progressed stepwise and in a stereoselective manner. In the present work, we tried the inversion of the stereochemistry concerning the hydroxyl-equivalent substituent on the piperidine ring and wish to report the synthesis of 1-O-methyl-5-benzamido-5-deoxy-*dl*-

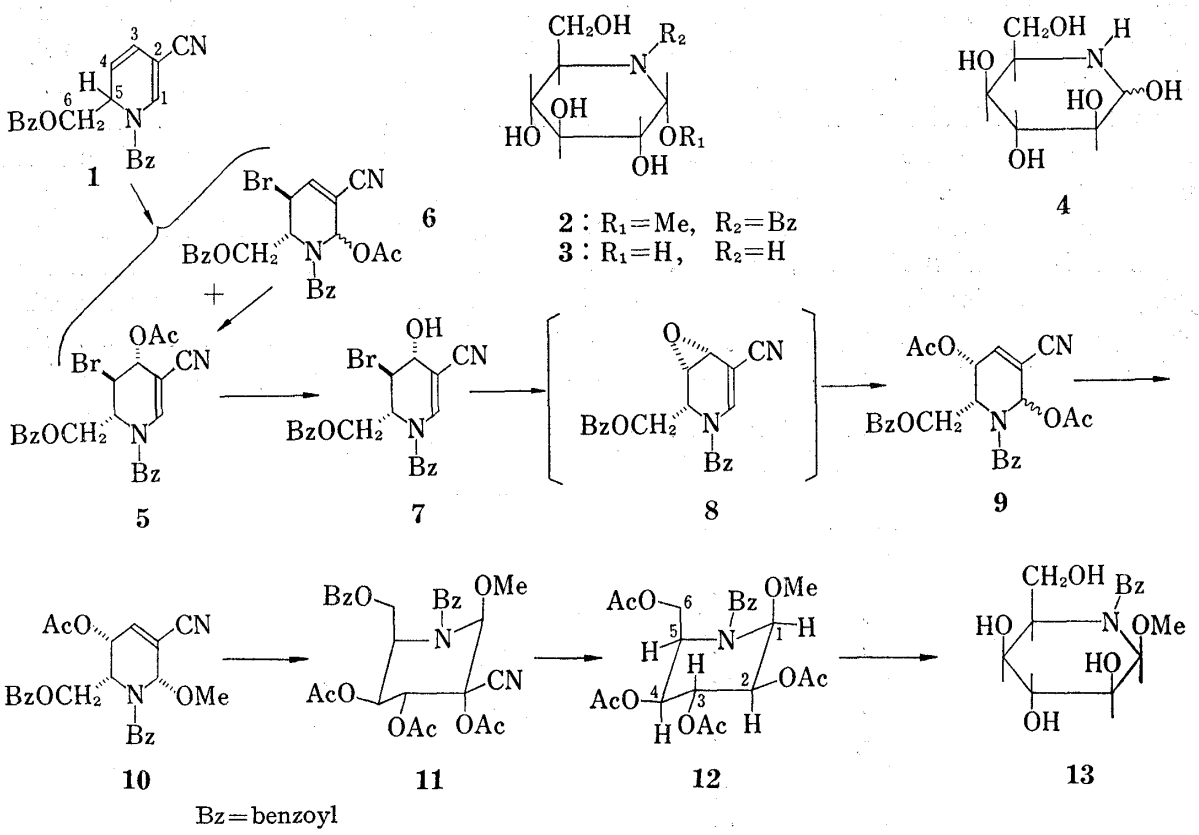

Chart 1

1) M. Natsume and M. Wada, Abstr. Papers, 1st Symposium on the Progress of Syntheses and Reactions, 135 (1974).
2) Location: *Tamagawa 2-28-10, Setagaya-ku, Tokyo, 158, Japan.*
3) M. Natsume and M. Wada, *Chem. Pharm. Bull.* (Tokyo), **23**, 2567 (1975).
4) M. Natsume and M. Wada, *Chem. Pharm. Bull.* (Tokyo), **24**, 2651 (1976).

idopiperidinose (**13**). Idopiperidinose (**4**) is an amino-sugar, which is different from nojirimycin (**3**) in the configuration of all secondary hydroxyl groups, and was studied once by Paulsen and his collaborators as a representative of 5-amino-5-deoxyhexoses.[5]

The photo-adduct dibenzoate (**1**), whose formation was described in our previous paper,[3] was oxidized with N-bromosuccinimide (NBS) in glacial acetic acid and the resulting mixture was separated into two products (**5** and **6**) by preparative thin-layer chromatography. Judging from their nuclear magnetic resonance (NMR) spectra, **5** was a normal oxidation product having the proton signal of C-3[6] at δ 5.60, whereas **6** exhibited the corresponding proton at a much lower field (δ 7.00) and furthermore possessed an additional proton signal as a singlet at δ 7.30, which was assignable to H_1 of **6**. These data suggested that **6** had a new double bond, which was formed by subsequent reaction steps of the attack of bromonium ion to the double bond between C-3 and C-4, followed by allylic rearrangement of the other double bond to 2—3 position, accompanied by the introduction of an acetoxyl group to C-1. The same NBS oxidation was carried out in deuterated acetic acid and the reaction course was checked by NMR spectrum using H_3 signals of **5** and **6** as indices of formation of the both compounds. As the result, simultaneous formation of these was observed from the beginning and the production ratio of **5** and **6** was found to be approximately 1:2 at the end of the reaction. **6** was converted to **5** in 72% yield when it was heated in acetic acid for a short time and this experiment not only supported the proposed structure for **6** but enabled us to simplify the oxidation reaction with NBS, so that the reaction mixture after NBS treatment was directly heated with acetic acid to obtain pure **5** in 73% yield.

In order to obtain the C-4 oxygen function in *cis* relationship to the neighboring benzoyloxymethyl group, we planned the synthetic route by way of an epoxide (**8**) and this was achieved by the following procedure. Only the acetoxyl group in **5** was selectively hydrolyzed with diluted perchloric acid in 67.5% yield and the resulting bromohydrin derivative (**7**) was refluxed with silver oxide[7] in anhydrous ether. The epoxide was too unstable to be isolated in a pure state that it was treated at once with acetic anhydride and sodium acetate in benzene solution. The product (**9**) obtained in 60% yield from **7** was the same type of compound as **6** and showed in its NMR spectrum a vinyl proton signal at δ 6.78 and a proton signal of C-1 position at δ 7.08, whose values were quite similar to those of **6**. The acetoxyl group at C-1 was involved in the moiety of α-carbinolamine diacylate and therefore the unstable acetoxyl group could be replaced by a methoxyl function in 69% yield for the convenience of the further oxidation step, when **9** was heated in methanol in the presence of *p*-toluene-

Table I. NMR Spectral Data of 1-O-Methyl-5-benzamido-5-deoxy-*dl*-idopiperidinose Tetraacetate (**12**)

Protons	δ	Shape	J(Hz)
H_1	5.63	d	4
H_2	4.94	dd	10, 4
H_3	5.76	t	10
H_4	5.16	dd	10, 6
H_5	4.78—5.03	m	
H_6	4.44	d	8[a]
H_6'	4.45	d	6[a]
OMe	3.31	dif. s	
OAc	2.02	s	
	2.03(9H)	s	

a) $J_{66'}$ value is uncertain.

5) H. Paulsen and K. Todt, *Chem. Ber.*, **99**, 3450 (1966).
6) Sugar numbering is used in this paper.
7) P.G. Stevens, *J. Am. Chem. Soc.*, **54**, 3732 (1932).

sulfonic acid. Stereochemistry of the methoxyl group was uncertain at this stage and concluded to be as shown by the precise examination of an NMR spectrum of **12**. Oxidation of **10** with potassium permanganate or osmium tetroxide took place opposite to the acetoxyl group and, after acetylation, **11** was produced in 68% yield in either case. In the NMR spectrum of **11**, 10 Hz of the spin-spin coupling constant between H_3 and H_4 supported the above stereoselective course of dihydroxylation reactions. As in the case of the nojirimycin derivative,[3] hydrolysis with sodium methoxide was applied to **11** in order to obtain a ketone compound as an intermediate and then this was subjected to the sodium borohydride reduction, followed by acetylation to afford **12** in 63% yield. In its NMR spectrum (Table I), the proton signal at C-2 position appeared as a double doublet with the coupling constants of 10 Hz (J_{23}) and 4 Hz (J_{12}) and this fact clearly demonstrated that the newly formed acetoxyl group was oriented equatorially in relation of *trans* to the adjacent acetoxyl function, whereas *cis* to the methoxy group at C-1 position. Further, the proximity of H_3 and H_6 was proved by the observation of the nuclear Overhauser effect and these evidences, together with other coupling constant values, agreed well with the conformation (**12**) for the piperidinose derivative. Therefore, the acetyl-free compound (**13**), mp 159—160°, obtained by a mild alkaline hydrolysis of **12** was 1-O-methyl-5-benzamido-5-deoxy-*dl*-idopiperidinose.

Experimental

All melting points were taken on Yanagimoto micro-melting point apparatus and are not corrected. Infrared (IR) spectra were recorded on Hitachi 215 spectrophotometer and NMR spectra were determined on Varian A-60 A instrument using tetramethylsilane as an internal standard. Preparative thin-layer chromatography (prep-TLC) was carried out with Merck Silica Gel PF_{254}.

NBS Oxidation of 1——i) A mixture of dibenzoate (**1**) (322 mg) and NBS (216 mg) in AcOH (8 ml) was allowed to stand at room temperature for 3 hr. AcOH was evaporated in a reduced pressure, the residue was dissolved in CH_2Cl_2, washed with sat. $NaHCO_3$–H_2O, and dried over Na_2SO_4. Removal of the solvent afforded colorless oil (570 mg), which was separated by preparative thin-layer chromatography (prep-TLC) to obtain **5** and **6** in the order of decreasing *Rf* values. **5** (200 mg, 44%), as colorless syrup. *Anal.* Calcd. for $C_{23}H_{19}O_5N_2Br$: C, 57.15; H, 3.96; N, 5.80. Found: C, 57.21; H, 4.07; N, 5.83. IR ν_{max}^{KBr} cm^{-1}: 2216, 1753, 1726, 1692, 1626. NMR δ ($CDCl_3$): 1.95 (3H, s, OAc), 4.43 (1H, dd, J=11, 9.5 Hz, H_6), 4.65 (1H, dd, J=11, 7 Hz, H_6'), 4.78 (1H, t, J=2 Hz, H_4), 5.32 (1H, br t, J=*ca.* 8 Hz, H_5), 5.60 (1H, dd, J=2, 1.5 Hz, H_3). **6** (235 mg, 52%), colorless syrup. *Anal.* Calcd. for $C_{23}H_{19}O_5N_2Br$: C, 57.15; H, 3.96; N, 5.80. Found: C, 56.88; H, 4.13; N, 5.90. IR ν_{max}^{KBr} cm^{-1}: 2236, 1758, 1728, 1678. NMR δ ($CDCl_3$): 1.98 (3H, s, OAc), 4.52 (2H, d, J= 7.5 Hz, $-CH_2-$), 4.85 (1H, dd, J=6, 1.5 Hz, H_4), 5.28 (1H, br t, J=*ca.* 7.5 Hz, H_5), 7.00 (1H, br d, J=6 Hz, H_3), 7.30 (1H, s, H_1).

A solution of **6** (81 mg) in AcOH (1.5 ml) was heated at 70° for 50 min, evaporated *in vacuo* to dryness, and the yellow oil obtained was purified by prep-TLC (CH_2Cl_2) to yield **5** (58 mg, 72%).

ii) A mixture of **1** (284 mg) and NBS (204 mg) in AcOH (5 ml) was treated as above and the reaction mixture (476 mg) was dissolved in AcOH (3 ml) and warmed at *ca.* 80° for 1 hr. AcOH was evaporated *in vacuo*, the residue was dissolved in CH_2Cl_2, washed with sat. $NaHCO_3$–H_2O, and dried over Na_2SO_4. Removal of CH_2Cl_2 gave 367 mg of an oil, which was purified by prep-TLC (CH_2Cl_2) to obtain a colorless syrup of **5** (292 mg, 73%).

Partial Hydrolysis of 5——A solution of **5** (888 mg) dissolved in a mixture of 70% $HClO_4$ (4 ml) in acetone (13 ml) and H_2O (3 ml) was refluxed for 1.5 hr and most of acetone was evaporated in a reduced pressure. The residue was dissolved in 10% MeOH–CH_2Cl_2, washed with sat. $NaHCO_3$–H_2O, and dried over Na_2SO_4. The brown oil obtained by evaporation of the solvent, was purified by prep-TLC (1% MeOH–CH_2Cl_2) to yield bromohydrin (**7**) (546 mg, 67.5%) as colorless glassy substance. *Anal.* Calcd. for $C_{21}H_{17}O_4N_2Br$: C, 57.16; H, 4.88; N, 6.35. Found: C, 57.17; H, 4.58; N, 6.70. IR ν_{max}^{KBr} cm^{-1}: 3425, 2223, 1728, 1688 (sh), 1623. NMR δ (C_6D_6–$CDCl_3$=4: 1): 3.48—3.95 (1H, br s, OH), 4.15—4.40 (2H, m, H_3 and H_4), 4.40 (1H, dd, J=11, 6 Hz, H_6), 4.67 (1H, dd, J=11, 7.5 Hz, H_6'), 5.35 (1H, br t, J=*ca.* 7 Hz, H_5).

Conversion of 7 to 9——A mixture of bromohydrin (**7**) (133 mg) and Ag_2O (292 mg) in anhyd. ether (40 ml) was stirred under reflux for 9 hr in N_2 atmosphere. Silver salt was removed by filtration and evaporation of the solvent afforded epoxide (**8**) (108 mg) as colorless oil. NMR δ ($CDCl_3$): 3.57 (1H, d, J=4.5 Hz, H_3), 3.83 (1H, t, J=4.5 Hz, H_4), 4.48 (1H, dd, J=11, 8 Hz, H_6), 4.70 (1H, dd, J=11, 5 Hz, H_6'), 5.26 (1H, ddd, J=8, 5, 4.5 Hz, H_5). A mixture of the epoxide (108 mg), NaOAc (203 mg), and Ac_2O (5 ml) in dry benzene (10 ml) was stirred under reflux for 30 min. It was evaporated to dryness *in vacuo* and the residue was dissolved in CH_2Cl_2, washed with sat. $NaHCO_3$–H_2O and dried over Na_2SO_4. Removal of the solvent gave a crystalline solid, which was recrystallized from MeOH to yield **9** (84 mg, 60%). An analytical sample was

obtained by further recrystallization from MeOH as colorless prisms, mp 184—185°. *Anal.* Calcd. for $C_{25}H_{22}O_7N_2$: C, 64.93; H, 4.80; N, 6.60. Found: C, 65.18; H, 4.82; N, 6.47. IR ν_{max}^{KBr} cm^{-1}: 2245, 1762, 1728, 1676. NMR δ ($CDCl_3$): 1.83 (3H, s, OAc), 2.08 (3H, s, OAc), 4.26 (1H, dd, J=11, 6.5 Hz, H_6), 4.66 (1H, dd, J=11, 8 Hz, H_6'), 5.25 (1H, br q, J=*ca.* 7 Hz, H_5), 5.80 (1H, ddd, J=6.5, 1.5, 1.5 Hz, H_4), 6.78 (1H, q, J=1.5 Hz, H_3), 7.08 (1H, t, J=1.5 Hz, H_1).

Replacement of OAc in 9 by OMe——A solution of **9** (111 mg) in MeOH (5 ml) was refluxed in the presence of *p*-toluenesulfonic acid monohydrate (9 mg) for 35 min. MeOH was evaporated, the residue was taken up in CH_2Cl_2, and the extract was washed with sat. $NaHCO_3$–H_2O, dried over Na_2SO_4, and evaporated. The crystalline solid was purified by recrystallization from MeOH to give **10** (72 mg, 69%) and further recrystallization from MeOH afforded an analytical sample as colorless prisms, mp 178—179°. *Anal.* Calcd. for $C_{24}H_{22}O_6N_2$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.08; H, 5.09; N, 6.48. IR ν_{max}^{KBr} cm^{-1}: 1747, 1735, 1661. NMR δ ($CDCl_3$): 2.34 (3H, s, OAc), 3.56 (3H, s, OMe), 4.58 (1H, d, J=8 Hz, H_6), 4.60 (1H, d, J=6 Hz, H_6'), 4.85 (1H, br q, J=*ca.* 6 Hz, H_5), 5.67 (1H, ddd, J=6.5, 2, 2 Hz, H_4), 6.02 (1H, br s, H_1), 6.64 (1H, br s, H_3).

OsO_4 Oxidation of 10——A solution of **10** (137 mg) in pyridine (2 ml) was treated with OsO_4 (84 mg) at room temperature for 16 hr. After removal of pyridine in a reduced pressure, the residue was dissolved in CH_2Cl_2–MeOH and H_2S gas was bubbled under ice-cooling for 2 hr. A solid was filtered off and the filtrate was evaporated *in vacuo*. The crude diol obtained here was acetylated with Ac_2O (1.5 ml) in pyridine (2 ml) at room temperature for 4.5 hr. The crystalline solid, which was obtained by usual work-up, was purified by recrystallization from MeOH to afford **11** (103 mg) as slightly yellow prisms. Purification of the solid from the mother liquor by prep-TLC afforded 14 mg of **11** (total yield, 67%). An analytical sample was obtained by recrystallization from MeOH once more as colorless prisms, mp 218—219°. *Anal.* Calcd. for $C_{28}H_{28}O_{10}N_2$: C, 60.86; H, 5.11; N, 5.07. Found: C, 60.91; H, 5.18; N, 5.18. IR ν_{max}^{KBr} cm^{-1}: 1776 (sh), 1762, 1717, 1677. NMR δ ($CDCl_3$): 1.97 (3H, s, OAc), 2.17 (3H, s, OAc), 2.24 (3H, s, OAc), 3.64 (3H, s, OMe), 4.67 (1H, d, J=7.5 Hz, H_6), 4.68 (1H, d, J=5 Hz, H_6'), 5.07 (1H, br q, J=*ca.* 6 Hz, H_5), 5.39 (1H, dd, J=10, 6.5 Hz, H_4), 6.07 (1H, d, J=10 Hz, H_3), 6.23 (1H, br s, H_1).

$KMnO_4$ Oxidation of 10——A solution of $KMnO_4$ (46 mg) in 50% aqueous MeOH (2 ml) was added to a solution of **10** (110 mg) in MeOH (2 ml) under ice-cooling. After 2 min, sat. $NaHSO_3$–H_2O was added to the reaction mixture and filtered. The filtrate was evaporated *in vacuo* to give the crude diol, which was acetylated with Ac_2O (2 ml) in pyridine (3 ml) at room temperature for 5.5 hr. The crystalline solid obtained by the usual work-up was purified by recrystallization from MeOH to afford **11** (95 mg, 68%) as colorless prisms, mp 215—218°.

1-O-Methyl-5-benzamido-5-deoxy-*dl*-idopiperidinose Tetraacetate (12)——A methanolic solution of NaOMe prepared from Na (25 mg) and anhyd. MeOH (2 ml) was added to a solution of **11** (95 mg) in MeOH (10 ml) under ice-cooling. After being kept standing under cooling for 2.5 hr, $NaBH_4$ (33 mg) was added to the reaction mixture and it was allowed to stand at 3° for 17 hr. The mixture was neutralized with AcOH, evaporated in a reduced pressure, and the residue was acetylated with Ac_2O (1.5 ml) in pyridine (2 ml) at room temperature for 16 hr. The crystalline solid obtained in a usual manner was recrystallized from MeOH to afford **12** (47 mg, 63%) as colorless prisms, mp 166°. *Anal.* Calcd. for $C_{22}H_{27}O_{10}N$: C, 56.77; H, 5.85; N, 3.01. Found: C, 56.98; H, 6.07; N, 3.15. IR ν_{max}^{KBr} cm^{-1}: 1751, 1655.

1-O-Methyl-5-benzamido-5-deoxy-*dl*-idopiperidinose (13)——To a solution of **12** (24 mg) in MeOH (3 ml), 10% KOH–H_2O (0.03 ml) was added under ice-cooling and the resulting mixture was kept to stand under cooling for 2.5 hr. After neutralization with ion-exchanger resin (Amberlite IR-120B, H^+ form, 1.5 ml), evaporation of the solvent gave a crystalline solid, which was recrystallized from MeOH–ether to afford 2 mg of **13** as slightly yellow prisms, mp 159—161°. IR ν_{max}^{KBr} cm^{-1}: 1632. *Anal.* Calcd. for $C_{14}H_{19}O_6N$: 56.56; H, 6.44; N, 4.71. Found: C, 56.28; H, 6.37; N, 4.66.

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