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Aminosugars. XVIII. Synthesis of 3-Acetamido-3,5-dideoxy-D-ribose*[1]

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3-Acetamido-3,5-dideoxy-1,2-*O*-isopropylidene-α-D-ribofuranose (**5**) was synthesized through two pass-ways: 1) starting from 3-acetamido-3-deoxy-1,2-*O*-isopropylidene-α-D-allofuranose which is obtained from D-glucose, through five steps; periodate oxidation, hydrogenation, 5-*O*-tosylation, 5-iodination and hydrogenation: 2) starting from 1,2-*O*-isopropylidene-3,5-di-*O*-tosyl-α-D-xylofuranose through four steps; 5-iodination, hydrogenation, 3-amination and *N*-acetylation. Total yields in the two pass-ways were 12.7% and 7.6% from the parent aldoses, respectively. Hydrolysis of **5** gave the titled compound as a sirup, which was converted to the crystalline osazone. The structure and conformation of intermediates in these syntheses were examined by NMR spectroscopy.

Since 3-amino-3-deoxy-D-ribose has been found as a component of puromycin[1)] and synthesized,[2–4)] a numerous homologues of pentoses and hexoses have been reported,[5)] but 3-amino-3,5-dideoxy-D-ribose is not yet described in literatures. As an intermediate for a total synthesis of kasugamine,[6)] the authors synthesized 3-acetamido-3,5-dideoxy-D-ribose (**9**) by two pass-ways.

Results and Discussion

Lemieux and Chu[3)] have synthesized 3-amino-3-deoxy-D-ribose hydrochloride from 3-acetamido-3-deoxy-1,2;5,6-di-*O*-isopropylidene-α-D-allose[7)] which is derived from 1,2 ; 5,6-di-*O*-isopropylidene-3-*O*-tosyl-α-D-glucofuranose, by partial hydrolysis to the corresponding 1,2-*O*-isopropylidene derivative (**1**), and followed by periodate oxidation, hydrogenation and hydrolysis. In this process, the authors have improved the condition of partial hydrolysis, and newly isolated 5,6-di-*O*-acetate of **1** and 3-acetamido-3-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranose (**2**) as a crystalline form. Tosylation of **2** in pyridine gave the corresponding 5-*O*-tosylate (**3**) in 68% yield, which was then converted into the 5-iodo-5-deoxy derivative (**4**) in a quantitative yield by heating at 110°C for 2 hr with sodium iodide in acetonitrile. Hydrogenation of **4** in the presence of Raney nickel and triethylamine gave the corresponding 5-deoxy derivative (**5**) in 91% yield.

As another method for the preparation of **5**, 1,2-*O*-isopropylidene-3,5-di-*O*-tosyl-α-D-xylofuranose[8)] (**6**) was treated with sodium iodide at 90°C for 20 hr in acetonitrile to give the corresponding 5-iodo-5-deoxy derivative (**7**) in 70% yield. Hydrogenation of **7** in the presence of Raney nickel gave in 70% yield the corresponding 5-deoxy derivative (**8**), which was then converted to **5** by heating with anhydrous hydrazine at 140°C, followed by hydrogenation and *N*-acetylation. Total yield of **5** in the two pass-ways mentioned above were 12.7% and 7.6% from D-glucose and D-xylose, respectively. Treatment of **5** with 60% acetic acid at 95°C for 3 hr gave **9** as a sirup in 95% yield. Crystallization of *N*-phenyl-glycosylamine of **9** was failed, but, further reaction of phenylhydrazine gave the corresponding osazone (**10**) as an yellow crystals.

Lemieux and Chu[3)] have corrected the misunderstanding on the configuration of the 3-amino group of **1**[7)] by comparison of X-ray powder photograph and IR spectrum of 3-amino-3-deoxy-D-ribose hydrochloride with that of the corresponding natural product, however, the structure of new compounds obtained here were proved by NMR spectra. As representative examples, the spectrum

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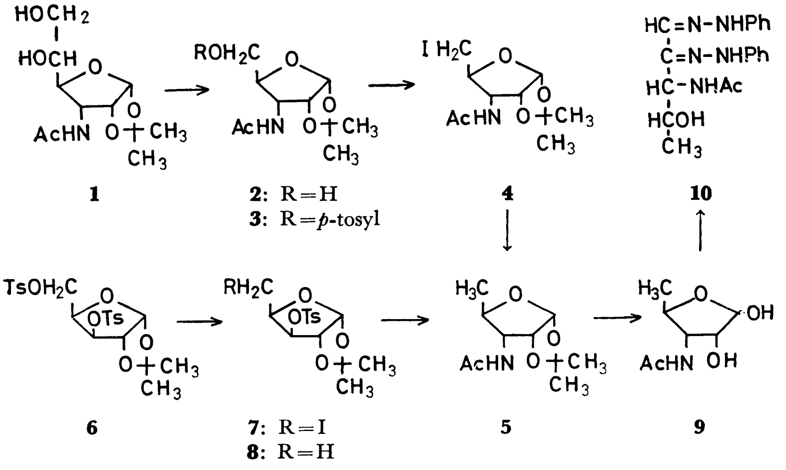

Table 1. First-order analysis of NMR spectra of 5-deoxy-1,2-*O*-isopropylidene-α-D-ribose and -D-xylose derivatives

Compound	Chemical shifts (τ), Coupling constants (Hz), and Dihedral angles[13]				
	H_1	H_2	H_3	H_4	H_5
4	4.16 (d) $J_{1,2}=4.0$ (47°)	5.36 (t) $J_{2,3}=4.7$ (43°)	5.82 (sex.) $J_{3,4}=9.0^{*2}$ (161°)	6.27 (sep.) $J_{4,5}=3.3$ $J_{4,5'}=6.6$	6.55 (q.), 6.75 (q) $J_{5,5'}=11.0$
5	4.21 (d) $J_{1,2}=4.0$	5.46 (t) $J_{2,3}=4.2$ (46°)	5.97 (sex.) $J_{3,4}=8.8^{*2}$ (159°)	6.16 (m) $J_{4,5}=5.8$	8.72 (d)
7	4.07 (d) $J_{1,2}=4.0$	5.21 (d) $J_{2,3}=0$ (80°)	5.10 (d) $J_{3,4}=2.8$ (55°)	5.58 (sep.) $J_{4,5}=6.0^{*3}$ $J_{4,5'}=9.0$	6.84 (q), 7.01 (q) $J_{5,5'}=10.0^{*3}$
8	4.15 (d) $J_{1,2}=4.0$	5.39 (d) $J_{2,3}=0$	5.36 (d) $J_{3,4}=2.8$	5.68 (m) $J_{4,5}=6.4$	8.86 (d)

*2 In both cases, $J_{3,NH}=9.0$.

*3 At 80°C, these coupling constants changed to $J_{4,5}=5.7$, $J_{4,5'}=7.7$ and $J_{5,5'}=10.5$.

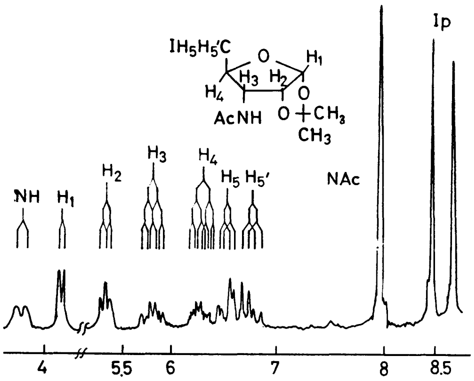

Fig. 1. NMR spectrum of 3-acetamido-3,5-dideoxy-5-iodo-1,2-*O*-isopropylidene-α-D-ribofuranose (**4**) (100 MHz, $CDCl_3$)

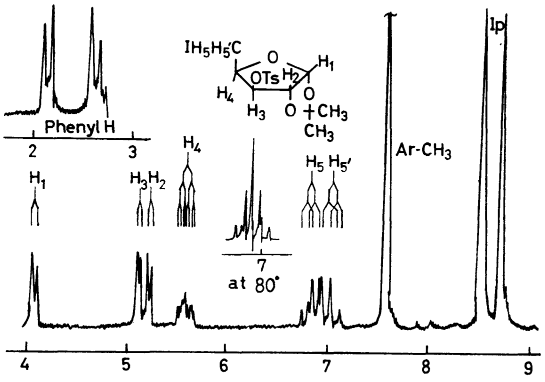

Fig. 2. NMR spectrum of 5-deoxy-5-iodo-5-iodo-1,2-*O*-isopropylidene-3-*O*-(*p*-toluenesulfonyl)-α-D-xylofuranose (**7**) (100 MHz, $CDCl_3$).

of **4** and **7** were shown in Figs. 1 and 2, and some NMR data were summarized in Table 1, in order to compare the conformation of *cis*-fused five-membered ring of 1,2-*O*-isopropylidene-α-D-xylose with that of α-D-ribose. The dihedral angles of ring protons in the both indicate that the conformation of the furanose ring is a twist in which C_2 and C_3 atoms are displaced in opposite senses from the plane of the other ring atoms, as was shown by several workers by use of α-D-glucofuranose[9,10] and others.[11,12] Comparison of (H_3–H_4) dihedral angle of **4** and **7** with that of the individual planer conformation indicate that the displacement of C_3 in **7** is rather larger than that of **4**. This fact suggests that the nonbonded interaction between *cis*-oriented C_3-*O*-tosyl and C_4-iodomethyl groups effects simply in the former, while that of endo-C_3-acetamido and gauche C_4-iodomethyl or endo-methyl of isopropylidene groups behave reversely in the latter. It is noteworthy that the chemical shift of ring protons in **4** and **7** are to be shifted commonly to lower field than that of **5** and **8**, and that of H_3 in **7** and **8** are markedly shifted due to the inductive effect of the C_3-*O*-tosyl group. The higher shift of H_5 protons in **7** and **8** than that of **4** and **5** will be attributed to the anisotropic effect of the benzene ring.

On the other hand, the remarkable difference in the coupling constant of $J_{4,5}$ and $J_{4,5}'$ between **4** and **7** makes us deduce a hindered rotation of C_4–C_5 bond of **7**. The appearance of H_5 proton signals of **7** measured at 80°C changed markedly as was shown in Fig. 2, and the coupling constants approached to that of **4** (Table 1), while no change was observed in the case of **4**. A more detailed study along with such a line may offer a valuable information on rotational isomers.

Experimental

The solutions were evaporated under diminished pressure at a bath temperature not exceeding 45°C. All melting points are uncorrected. Optical rotations were measured in a 0.5-dm tube, with a Carl Zeiss Photoelectric Precision Polarimeter. The NMR spectra were taken in deuteriochloroform solution with a JNM-4H-100 MHz Spectrometer, using tetramethylsilane as an internal standard.

3-Acetamido-3-deoxy-1,2-*O*-isopropylidene-α-D-allofuranose (1). A solution of 3-acetamido-3-deoxy-1,2;5,6-di-*O*-isopropylidene-α-D-allofuranose[7] (42 g, 139 mmol) in 0.2 N-hydrochloric acid solution (300 m*l*) of acetone - water (1 : 1 in volume) was maintained at 20—23°C for 1.5 hr, and then neutralized with sodium hydrogencarbonate (6 g), concentrated to a sirup. The sirup was extracted with methanol, the methanol solution was treated with active carbon, and then addition of ether to it gave colorless crystals (29.5 g) in 81% yield. $[\alpha]_D^{23}$ + 158.3° (*c* 1.08, methanol); mp 154—155°C (lit,[3] 154—156°C). NMR: τ 8.63, 8.43 (two s, C–CH_3), 7.92 (s, NAc), 5.34 (t, H_2), 4.11 (d, H_1, *J*=4.0 Hz), 3.60 (d, NH, *J*=9.0 Hz).

This compound was acetylated to the corresponding di-*O*-acetate by acetic anhydride and pyridine in an usual manner. Mp 163—164°C; $[\alpha]_D^{23}$ + 66.6° (*c* 0.80, chloroform).

Found: C, 52.24; H, 6.51; N, 4.11%. Calcd for $C_{15}H_{23}NO_8$: C, 52.17; H, 6.71; N, 4.06%.

3-Acetamido-3-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranose (2). To a solution of **1** (20.4 g, 75 mmol) in 100 m*l* of water was added sodium periodate (18 g, 84.5 mmol) in water (200 m*l*), and the solution was left to stand at room temperature for 2 hr, concentrated to 50 m*l*, then filtered. The filtrate was treated with sodium borohydride (1.6 g, 42.5 mmol) for 2 hr, and concentrated to a sirup which was crystallized from ethanol. Yield, 16.5 g (94.8%); mp 148—149°C; $[\alpha]_D^{23}$ + 151.2° (*c* 0.915, methanol); NMR: τ 8.65, 8.45 (two s, C–CH_3), 7.95 (s, NAc), 4.16 (d, H_1, *J*=3.5 Hz), 3.72 (d, NH, *J*=8.0 Hz).

Found: C, 51.76; H, 7.22; N, 5.83%. Calcd for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06%.

This compound was converted to the corresponding 5-*O*-acetate by acetic anhydride and pyridine in an usual manner, which showed mp 132—133°C; $[\alpha]_D^{23}$ + 73° (*c* 1.0, chloroform); NMR: τ 8.66, 8.45 (two s, C–CH_3), 7.97 (s, NAc), 7.93 (s, OAc), 4.17 (d, H_1, *J*=3.8 Hz), 3.94 (d, NH, *J*=9.2 Hz).

Found: C, 52.85; H, 7.02; N, 5.20%. Calcd for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01; N, 5.13%.

3-Acetamido-3-deoxy-1,2-*O*-isopropylidene-5-*O*-(*p*-toluenesulfonyl)-α-D-ribofuranose (3). To a solution of **2** (8 g, 34.6 mmol) in dry pyridine (20 m*l*) was added *p*-toluenesulfonyl chloride (15 g, 78.9 mmol), and the reaction mixture was heated at 60°C for 10 min, allowed to stand overnight at room temperature, then poured into ice-water. The resultant solution was extracted three times with chloroform, and the combined extracts were washed with aqueous sulfuric acid, sodium hydrogencarbonate and then water, dried over anhydrous sodium sulfate, and concentrated to give a pale yellow sirup in 79% (10.5 g) yield. $[\alpha]_D^{23}$ + 52.6° (*c* 1.25, chloroform), NMR: τ 8.70, 8.51 (two s, C–CH_3), 8.02 (s, NAc), 7.57 (s, aromatic CH_3), 4.27 (d, H_1, *J*=4.0 Hz), 3.55 (d, NH, *J*=7,5 Hz).

Found: C, 52.86; H, 6.05; N, 3.67%. Calcd for $C_{17}H_{23}NO_7S$: C, 52.98; H, 6.02; N, 3.64%.

3-Acetamido-3,5-dideoxy-5-iodo-1,2-*O*-isopropylidene-α-D-ribofuranose (4). A solution of **3** (10.5 g, 27.3 mmol) and sodium iodide (8 g, 53.3 mmol) in acetonitrile (100 m*l*) was heated in a sealed tube at 110°C for 24 hr, and then concentrated, extracted three times with chloroform. The combined extracts were washed with water, dried over anhydrous sodium sulfate, concentrated to give a pale yellow sirup which crystallized from ether as needles. Yield, 8.0 g (99%); mp 134.5—135.5°C; $[\alpha]_D^{23}$ +38.1° (*c* 0.756, chloroform).

Found: C, 35.14; H, 4.36; N, 4.21%. Calcd for $C_{10}H_{16}INO_4$: C, 35.20; H, 4.69; N, 4.10%.

3-Acetamido-3,5-dideoxy-1,2-*O*-isopropylidene-α-D-ribofuranose (5). a) A solution of **4** (8 g, 26.7 mmol) in ethanol (100 m*l*) was hydrogenated at 40 atm pressure for 20 hr in the presence of Raney nickel (10 g) and triethylamine (2 m*l*). The reaction mixture was filtered, and the filtrate was concentrated to give a sirup which crystallized spontaneously. The crystals were purified two times by crystallization from ether - petroleum ether. Yield, 5.2 g (91%);

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mp 98—101°C; $[\alpha]_D^{23}$ +87.8° (*c* 2.12, methanol).

Found: C, 55.92; H, 7.70; N, 6.57%. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51%.

b) A mixture of **8** (14.3 g, 47.3 mmol) and anhydrous hydrazine (150 m*l*) was heated in an oil bath at 140°C for 20 hr, and the solution was evaporated. The residue was dissolved in ethanol (100 m*l*), hydrogenated in the presence of Raney nickel at 40 atm pressure for 10 hr, and then filtered. The filtrate was evaporated to a sirup, and the dried sirup was acetylated with acetic anhydride (10 m*l*) and pyridine (10 m*l*). The reaction mixture was poured into ice-water, concentrated to a sirup, and then extracted three times with chloroform. The combined extracts were washed with a small amount of aqueous sulfuric acid, sodium hydrogen carbonate, and then water, dried over anhydrous sodium sulfate, concentrated to a sirup which crystallized from ether. Yield, 1.7 g (22.6%); mp 98—100°C.

5-Deoxy-5-iodo-1,2-*O*-isopropylidene-3-*O*-(*p*-toluenesulfonyl)-α-D-xylofuranose (7). A Solution of 1,2-*O*-isopropylidene-3,5-di-*O*-(*p*-toluenesulfonyl-α-D-xylofuranose)[8] (92 g, 184 mmol) and sodium iodide (42 g, 280 mmol) in acetonitrile (1 *l*) was refluxed for 150 hr at ordinary atmosphere, concentrated, and then extracted with chloroform. The extracts were washed with water, dried over anhydrous sodium sulfate, concentrated to dryness to give a pale yellow sirup. Yield, 79 g (89%); $[\alpha]_D^{23}$ −65.5° (*c* 2.0, chloroform). This sirup was analyzed without further purification.

Found: C, 40.02; H, 4.44; S, 7.32%. Calcd for $C_{15}H_{19}IO_6S$: C, 39.66; H, 4.22; S, 7.05%.

5-Deoxy-1,2-*O*-isopropylidene-3-*O*-(*p*-toluenesulfonyl)α-D-xylofuranose (8). A solution of **7** (79 g, 174 mmol) in methanol (200 m*l*) was hydrogenated at 100 atm pressure for 24 hr in the presence of Raney nickel(70 g) and triethylamine (12 m*l*). The reaction mixture was filtered, and the filtrate was concentrated to dryness, extracted with chloroform. The extracts were washed with water, dried over anhydrous sodium sulfate, and concentrated to give a sirup which couldn't be crystallized, and therefore, analyzed without further purification. Yield, 37.2 g (65%); $[\alpha]_D^{23}$ −16.8° (*c* 1.70, chloroform).

Found: C, 54.95; H, 6.27; S, 9.46%. Calcd for $C_{15}H_{20}O_6S$: C, 54.87; H, 6.14; S, 9.76%.

3-Acetamido-3,5-dideoxy-D-ribose (9). A solution of **5** (0.9 g, 4.16 mmol) in 60% acetic acid (30 m*l*) was heated at 80°C for 3 hr, decolorized with active carbon, and concentrated to a sirup which couldn't be crystallized. Yield, 0.7 g (96%); $[\alpha]_D^{23}$ +65.1°—+63.2° (*c* 1.09, for 12 hr in methanol).

As an crystalline derivative, the corresponding osazone (**10**) was prepared as follows: the above sirup (0.7 g, 4 mmol) and phenylhydrazine (2 g, 18.5 mmol) in 60% acetic acid (20 m*l*) was heated at 90°C for 2 hr and then concentrated to a sirup which crystallized after two days. The yellow crystals were recrystallized from ethanol-ether. Yield, 1.35 g, (95%); mp 215—216°C; $[\alpha]_D^{23}$ −7.36° (*c* 1.06, methanol).

Found: C, 64,60; H, 6.51; N, 19.35%. Calcd for $C_{19}H_{23}N_5O_2$: C, 64.57; H, 6.56; N, 19.82%.

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