[Chem. Pharm. Bull. 16(5) 962—964 (1968)]

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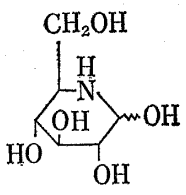
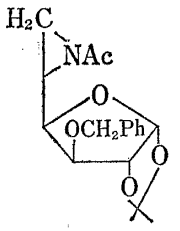
Synthesis of Nojirimycin, D-Glucopiperidinose

In the course of studies on 5,6-epimino carbohydrates,[1] we have synthesized a monosaccharide antibiotic, nojirimycin (I), which was produced by some strains of *Streptomyces* and indicated activity against a drug-resistant strain of *Shigella flexneri*, *Sarcina lutea* and *Xanthomonas oryzae*.[2]

5,6-Acetylepimino-3-O-benzyl-5,6-dideoxy-1,2-O-isopropylidene-β-L-idofuranose[1] (II) was treated with acetic acid at 60° to be converted easily, in a good yield, into a syrupy 5-



I



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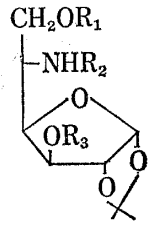
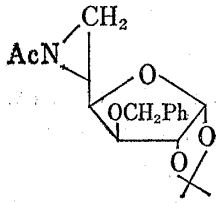
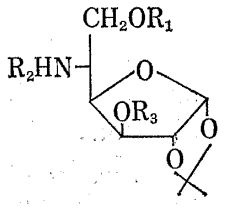


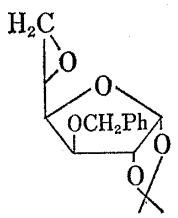
III : $R_1=R_2=Ac, R_3=CH_2Ph$
IV : $R_1=H, R_2=Ac, R_3=CH_2Ph$
V : $R_1=R_2=R_3=H$



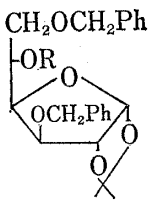
VI



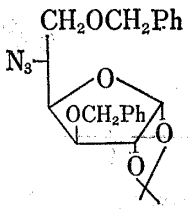
VII : $R_1=R_2=Ac, R_3=CH_2Ph$
VIII : $R_1=R_2=R_3=H$



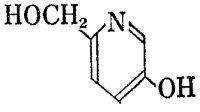
IX



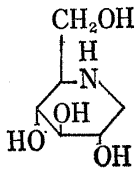
X : R=H
XI : R=Ts



XII



XIII



XIV

1) H. Saeki, T. Iwashige, and E. Ohki, *Chem. Pharm. Bull.* (Tokyo), **16**, 188 (1968).
2) *a*) N. Ishida, K. Kumagai, T. Niida, T. Tsuruoka, and H. Yumoto, *J. Antibiotics* (Tokyo), Ser A, **20** (2), 66 (1967); *b*) S. Inouye, T. Tsuruoka, and T. Niida, *J. Antibiotics* (Tokyo), Ser A, **19** (6), 288 (1966).

acetamido-6-acetoxy compound (III), which was deacetylated with sodium methoxide to give 5-acetamido-3-O-benzyl-5-deoxy-1,2-O-isopropylidene-β-L-idofuranose (IV), mp 143—144°, $[\alpha]_D^{20}$ −7.4° (c=5.3, $CHCl_3$) (*Anal.* Calcd. for $C_{18}H_{25}O_6N$: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.33; H, 7.23; N, 4.05). The structure of IV was confirmed by hydrogenation of IV, followed by saponification with barium hydroxide solution to give 5-amino-5-deoxy-1,2-O-isopropylidene-β-L-idofuranose (V), mp 185° (reported mp 178°[3a]; mp 176—179°[3b]). (*Anal.* Calcd. for $C_9H_{17}O_5N$: C, 49.30; H, 7.82; N, 6.39. Found: C, 49.00; H, 7.89; N, 6.47.), which was identified with the sample synthesized by the known method.[3a] This fact indicated that the attack of an acetate ion on the 5,6-epimino ring of II was uniquely effected at the terminal position.

Similar to the case of II, treatment of 5,6-acetylepimino-3-O-benzyl-5,6-dideoxy-1,2-O-isopropylidene-α-D-glucofuranose[1] (VI) with acetic acid afforded a crystalline 5-acetamido-6-acetoxy compound (VII), mp 123.5—124.5°, $[\alpha]_D^{21}$ −25.9° (c=6.6, $CHCl_3$) (*Anal.* Calcd. for $C_{20}H_{27}O_7N$: C, 61.05; H, 6.92; N, 3.56. Found: C, 61.01; H, 6.98; N, 3.75.). Hydrogenation of VII over palladium-charcoal, followed by saponification with barium hydroxide solution, gave 5-amino-5-deoxy-1,2-O-isopropylidene-α-D-glucose (VIII), mp 125—126°, $[\alpha]_D^{20}$ −17.0° (c=1.1, H_2O) (Lit. mp 86°,[4] $[\alpha]_D^{25}$ −12.2°[5]) (*Anal.* Calcd. for $C_9H_{17}O_5N$: C, 49.30; H, 7.82; N, 6.39. Found: C, 49.64; H, 7.79; N, 6.39.). The structure of VIII was also confirmed by identification with the sample synthesized by a modification of Whistler's procedure;[5] treatment of 5,6-anhydro-3-O-benzyl-1,2-O-isopropylidene-β-L-idofuranose[6] (IX) with sodium benzylate, followed by tosylation of the resulting 3,6-dibenzyloxy compound (X), mp 74.5° (reported mp 89—90°[5]) (*Anal.* Calcd. for $C_{23}H_{28}O_6 \cdot \frac{1}{2}H_2O$: C, 67.46; H, 7.15. Found: C, 67.57; H, 6.99.), afforded a crystalline 3,6-dibenzyloxy-5-tosyloxy compound (XI), mp 88—89°, $[\alpha]_D^{20}$ −13.7° (c=2.6, $CHCl_3$) (Lit. mp 75—76°, $[\alpha]_D^{20}$ −15.3°[5]) (*Anal.* Calcd. for $C_{30}H_{34}O_8S$: C, 64.97; H, 6.18; S, 5.78. Found: C, 65.02; H, 6.21; S, 5.78.). XI was further treated with sodium azide, giving 5-azido-3,6-di-O-benzyl-5-deoxy-1,2-O-isopropylidene-α-D-glucose (XII), mp 69°, $[\alpha]_D^{20}$ −36.9° (c=2.9, $CHCl_3$) (*Anal.* Calcd. for $C_{23}H_{27}O_5N_3$: C, 64.92; H, 6.40; N, 9.88. Found: C, 64.83; H, 6.50; N, 9.97.), which hydrogenated over palladium-charcoal at 70—80° and 70 kg/cm² to give VIII.

VIII was quite unstable to acids; it was found that a reaction product obtained by a preliminary treatment of VIII with acids exhibited absorption maxima at 225—226 mμ, 289—290 mμ (in dil. HCl) and 245 mμ, 302—303 mμ (in dil. NaOH), suggesting the presence of a pyridine derivative (XIII) or the likes, which would be the same compound obtained by acid treatment of nojirimycin.[2b] However, hydrolysis of VIII was successful by protecting O- and N-functions with easily-removable trifluoroacetyl group before acid treatment; treatment of VIII with trifluoroacetic anhydride in acetonitrile without bases to easily gave a syrupy trifluoroacetate which showed no hydroxyl absorption in its infrared spectrum. Hydrolysis of the trifluoroacetate with 0.1 N diluted hydrochloric acid at 70—80° for 1 hr, followed by removal of the protective group by basification to pH 7—8 with Dowex 1×4 (OH^-), afforded, in a good yield, an amorphous D-glucopiperidinose (I). The analytical sample, mp 105° (decomp., softening at 95°), $[\alpha]_D^{20}$ +63° (c=1.2, H_2O) (*Anal.* Calcd. for $C_6H_{13}O_5N$: C, 40.22; H, 7.31; N, 7.82. Found: C, 40.82; H, 6.97; N, 7.86.), purified by passing through a column of Dowex 1×2(OH^-), was identified with the authentic sample of nojirimycin by comparison of infrared spectra and thin-layer chromatography. Moreover, hydrogenation of I over

3) *a*) R.E. Gramera, R.M. Bruce, S. Hirase, and R.L. Whistler, *J. Org. Chem.*, **28**, 1401 (1963); *b*) H. Paulsen and K. Todt, *Chem. Ber.*, **99**, 3450 (1966).

4) Professor Whistler (private communication) said that the melting point of VIII recorded[5] was listed incorrectly. Our sample of VIII was identified with the sample sent from him by mixed melting point test, and infrared spectrometry.

5) R.L. Whistler and R.E. Gramera, *J. Org. Chem.*, **29**, 2609 (1964).

6) A.S. Meyer and T. Reichstein, *Helv. Chim. Acta*, **29**, 152 (1946).

platinum gave a deoxy-compound (XIV), mp 195°, $[\alpha]_D^{20}$ +43.1° (c=1.4, H_2O) (reported mp 195°, $[\alpha]_D^{21}$ +47°[2b]), which was also identical with the sample derived from the natural antibiotic by comparison of infrared spectra and mixed melting point test. The synthesized nojirimycin (I) also showed the same activity against *Sarcina lutea* and *Xanthomonas oryzae*.

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7) According to Dr. Ito's personal communication, his group has accomplished independent synthesis of nojirimycin from D-glucose (S. Inouye, T. Tsuruoka, T. Ito, and T. Niida, *Tetrahedron*, **24**, 2125 (1968)).