

A Synthesis of Streptozotocin Derivatives

Tetsuo SUAMI and Tomoya MACHINAMI

Department of Applied Chemistry, Faculty of Engineering, Keio University, Koganei-shi, Tokyo

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In connection with a previous paper,¹⁾ biologically active streptozotocin derivatives have been prepared in our laboratory.

Streptozotocin is an antibiotic produced by *streptomyces achromogenes* var. 128, which shows wide antimicrobial and antitumor activities.²⁻⁵⁾ The structure has been established to be *N*-carbamyl-*N'*-methyl-*N'*-nitroso- β -D-glucosamine.⁶⁻⁷⁾

In the present paper, a preparation of methyl glycosides of streptozotocin by a two-step reaction will be described. Methyl β -D-glucosaminide hydrochloride (III) was prepared by the method of Neuberger and Rivers,⁸⁾ and then it was treated with methyl isocyanate under the presence of silver carbonate to give methyl *N*-carbamyl-*N'*-methyl- β -D-glucosaminide (IV).

Nitrosation of IV was carried out with sodium nitrite in aqueous acetic acid to give methyl *N*-carbamyl-*N'*-methyl-*N'*-nitroso- β -D-glucosaminide (V) as needle crystals of mp 149°C (dec.) in 70% yield.

Starting from methyl *N*-carbobenzyloxy- α -D-glucosaminide (VII),⁹⁾ methyl *N*-carbamyl-*N'*-methyl-*N'*-nitroso- α -D-glucosaminide (X) of mp 133°C was obtained in 33% yield by an analogous reaction process.

A mixture of V and X (XV) was also prepared by an analogous process in 28% yield, beginning with methyl *N*-carbobenzyloxy-D-glucosaminide (XII).

The three compounds: V, X and XV, were fairly active against Ehrlich ascites tumor.

Experimental

A melting point was determined on a Mitamura Riken micro hot stage. A melting point marked with an asterisk was measured in a liquid bath and uncorrected. The infrared spectra were determined in potassium bromide discs. The proton magnetic resonance (pmr) spectra were measured at 60 MHz with a Varian A-60D instrument and the peak position was expressed in τ -values.

Methyl *N*-Carbobenzyloxy- β -D-glucosaminide (II). The compound was prepared by the method of Neuberger and Rivers⁸⁾ in a yield of 15.2% from *N*-carbobenzyloxy-D-glycosamine (I).⁹⁾ Mp 166—

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***N'*-nitroso- α -D-glucosaminide (XI).** A 102 mg portion of X was acetylated analogously as described in the preparation of VI and the reaction mixture was poured into ice and water to give 116 mg (78.3%) of crystals, mp 114–115°C. Recrystallization from ethanol afforded pale yellow crystals melting at 115.5°C. IR: 1750(OAc), 1715(C=O), 1530(NH), 1480(N–NO) and 870 cm⁻¹ (α -anomeric C–H).¹⁰ PMR (in CDCl₃): τ 5.01 (one proton doublet, $J_{1,2}$ =3.7 Hz, H₁); 6.45 (O–CH₃); 6.72 (N–CH₃); 7.77, 7.85, 7.91 (singlets, three protons, three protons and three protons, OAc).

Found: C, 45.04; H, 5.87; N, 10.23%. Calcd for C₁₅H₂₃N₃O₁₀: C, 44.44; H, 5.72; N, 10.37%.

Methyl *N*-Carbobenzyloxy-D-glucosaminide (XII). A mixture of I (1.78 g) in methanol (150 ml) and dry Amberlite IR-120(H⁺) (18 ml) was heated under reflux for 2.5 hr. After the resin was removed by filtration, the filtrate was evaporated under reduced pressure. The residue was crystallized from ethanol to give 1.11 g (60.0%) of the product, mp 149–153°C, $[\alpha]_D^{25} + 33.0^\circ$ (c 2.5, pyridine). The compound consisted of 48% of α -anomer and 52% of β -anomer.

Methyl D-Glucosaminide hydrochloride (XIII). A 400 mg sample of XII was treated analogously as described above to give 162 mg (57.8%) of the product, mp 147–157°C (dec.). The product showed two spots at R_f 0.53 and 0.48 in a paper chromatogram in

a solvent system of *n*-butanol : pyridine : water (6 : 4 : 3).

Methyl *N*-Carbamyl-*N'*-methyl-D-glucosaminide (XIV). A 400 mg portion of XIII was treated with methyl isocyanate as described above to give 240 mg (55.3%) of the product, mp 233–235°C. Recrystallization from aqueous ethanol afforded an analytically pure sample, mp 234.5–236°C.

Found: C, 43.39; H, 7.23; N, 11.30%. Calcd for C₉H₁₈N₂O₆: C, 43.19; H, 7.25; N, 11.20%.

Methyl *N*-Carbamyl-*N'*-methyl-*N'*-nitroso-D-glucosaminide (XV). A 180 mg sample of XIV was treated with nitrous acid as described above to give 172 mg (88.9%) of the crude product. Recrystallization from ethanol afforded needle crystals, mp 117–121°C (dec.), mp* 59°C (dec.). $[\alpha]_D^{25} - 19.6^\circ$ (c 0.5, water). The product consisted of 97% of β -anomer, since the β -anomer crystallized preferentially.

Found: C, 39.26; H, 6.26; N, 14.74%. Calcd for C₉H₁₇N₃O₇: C, 38.71; H, 6.09; N, 15.05%.

Antitumor activity. A detail of the antitumor activities of V, X and XV against Ehrlich mouse ascites tumor will be reported elsewhere.

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