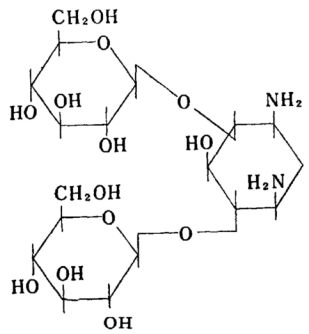
Synthesis of 4,6-Di-(D-glucopyranosyl)-deoxystreptamine

By Sumio UMEZAWA and Yukio ITO

(Received August 9, 1961)

Recently, it has been shown that a essential group for antibiotic character of neomycin[1], kanamycin[2] and paromomycin[3] belongs to the glucosides of deoxystreptamine, however, synthesis of the allied glucosides has not been reported as yet*. In continuation of our work[2d] on kanamycin, we have synthesized 4, 6-di-(β-D-glucopyranosyl)deoxystreptamine (IV).



1) F. A. Kuehl, M. N. Bishop and K. Folkers, *J. Am. Chem. Soc.*, **73**, 881 (1951); K. L. Rinehart and P. W. K. Woo, ibid., **83**, 643 (1961).

2) a) H. Umezawa, K. Maeda, M. Murase and H. Mawatari, *J. Antibiotics (Japan), Ser. A*, **11**, 163 (1958). b) M. J. Cron, O. B. Fardig, D. L. Johnson, D. F. Whitehead, I. R. Hooper and R. U. Lemieux, *J. Am. Chem. Soc.*, **80**, 4115 (1958). c) H. Ogawa, T. Ito, S. Kondo and S. Inoue, *J. Antibiotics (Japan), Ser. A*, **11**, 169 (1958); *Bull. Agr. Chem. Soc. Japan*, **23**, 289 (1959). d) S. Umezawa, Y. Ito and S. Fukatsu, *J. Antibiotics (Japan), Ser., A*, **11**, 162 1958); This Bulletin, **32**, 81 (1959).

3) T. S. Haskell, J. C. French and Q. R. Bartz, *J. Am. Chem. Soc.*, **81**, 3483 (1959).

* It should be noted that a related compound, *O*-(β-D-2-amino-2-deoxyglucopyranosyl) derivative of *d*, *l*-*trans*-2-aminocyclohexanol was synthesized: T. Suami and S. Umezawa, This Bulletin, to be published.

Addition of excess carbobenzoxychloride in toluene to an aqueous solution of deoxystreptamine made alkaline with sodium hydroxide gave, in 48% yield, *N*, *N'*-dicarbobenzoxydeoxystreptamine (I), m. p. 233~235°C. Found: C, 62.06; H, 6.23; N, 6.55. Calcd. for $C_{22}H_{26}O_7N_2$: C, 61.38; H, 6.09; N, 6.51%.

N, *N'*-Dicarbobenzoxydeoxystreptamine (I) failed to react with acetobromoglucose in benzene, chloroform, dioxane or dimethylformamide, however, it has been found that the condensation proceeded in nitromethane. To a suspension of I (1.63 mmol.) in nitromethane was added acetobromoglucose (5.35 mmol.) and powdery mercuric cyanide (5.5 mmol) and the suspension was stirred for twenty-four hours at 27°C. Extraction with chloroform followed by evaporation of the solvent gave a crude product, which was recrystallized from absolute ethanol to afford, in 76% yield, *N*, *N'*-dicarbobenzoxy-4,6-di-(tetraacetyl-D-glucosyl)deoxystreptamine (II), m. p. 253~254°C, $[\alpha]_D^{17.5}$ −9.6° (*c* 1.965, chloroform). Found: C, 54.83; H, 5.53; N, 2.85. Calcd. for $C_{50}H_{62}O_{25}N_2$: C, 55.05; H, 5.73; N, 2.57%.

Infrared spectrum: ν_{max}^{Nujol} 3480, 3340 (OH, NH); 1760 (acetyl C=O); 1700 (C=O in $OCOCH_2C_6H_5$); 1520 (CONH); 1220; 1160, 1075 (glucoside); 1035 (alicyclic secondary alcohol); 903 (β-glucoside); 733, 695 (monosubstituted benzene).

Hydrolysis of II (1.0 g.) with methanolic ammonia at room temperature followed by evaporation in vacuo and washing with ethyl acetate gave a crude product, which was recrystallized from water-dioxane-ethanol (5:1:10) to afford colorless needles (0.38 g.) of *N*, *N'*-dicarbobenzoxy-4,6-di-(D-glucosyl) deoxystreptamine (III), m.p. 288~290°C (decomp.), $[\alpha]_D^{17.5}$ −5.67° (*c* 1.43, pyridine). Found: C, 54.16; H, 6.06; N, 3.81. Calcd. for $C_{34}H_{46}N_2O_{17}$: C, 54.11; H, 6.14; N, 3.71%. Infrared spectrum: ν_{max}^{Nujol} 3350, 1700, 1545, 1295, 1230, 1165, 1075, 1035, 890, 735, 695 cm^{-1}.

Hydrogenolysis of III (0.5 g.) with palladium catalyst in water-dioxane (1:1) followed by evaporation in vacuo and washings with dioxane, ether and ethanol gave a crude product, which was recrystallized from water-ethanol to afford colorless crystals of 4,6-di-(β-D-glucosyl)deoxystreptamine (IV), $[\alpha]_D^{20}$ −4.69° (*c* 1.01, water). The product darkened and decomposed at about 190~230°C. Found: C, 43.91; H, 7.26; N, 5.37. Calcd. for $C_{18}H_{34}O_{13}N_2$: C, 44.43; H, 7.06; N, 5.76%. Infrared spectrum: ν_{max}^{Nujor} 3340, 1600 (NH_2), 1165, 1075, 1035, 890 cm^{-1}.

The positions of attachment of two D-glucoses to deoxystreptamine was substantiated by periodate oxidation of 4,6-di-(tetraacetyl-D-glucosyl)deoxystreptamine diacetate (V), which was obtained by hydrogenolysis of II with palladium catalyst in dioxane-acetic acid-water. The compound decomposed at about 270°C (darkening at about 180°C). Found: C, 48.62; H, 6.46; N, 3.14. Calcd. for $C_{34}H_{50}N_2O_{21}\cdot 2CH_3CO_2H$: C, 48.40; H, 6.21; N, 2.97%.

Upon oxidation with sodium periodate in aqueous 50% dioxane for twenty-nine hours, V did not consume the oxidant, while, in parallel experiments, methyl α-D-glucoside and β-pentaacetyl-D-glucose consumed 1.97 and 0.1 mol. of the oxidant respectively. The glucosidic linkages in III or IV are therefore on C-4 and C-6 of deoxystreptamine.

Infrared spectra of the products (III, IV) showed absorption at 890 cm^{-1} which is characteristic of β-glucosidic linkage, Moreover, a rough calculation** of the anomeric contribution (A) of the glucosidic linkages in IV gave a negative value (−13141), the presence of two β-linkages being suggested.

The structure of IV has a close resemblance to that of kanamycin, however, there is a characteristic difference regarding the configuration of anomeric carbon atoms. IV showed no antibiotic activity. The syntheses of allied compounds containing α-linkages of amino sugars are in progress.

The authors are indebted to Mr. S. Nakada for the microanalyses.

Department of Applied Chemistry
Faculty of Engineering
Keio University, Tokyo

** By substitution of 2B (24000) of D-glucose into the equation $[M]_D=2A+2B$: $-2281=2A+24000$.