Tetrahedron Letters No. 15, pp 1417 - 1420, 1974. Pergamon Press. Printed in Great Britain.

SYNTHESIS OF STREPTOLIDINE (ROSEONINE, GEAMINE)*

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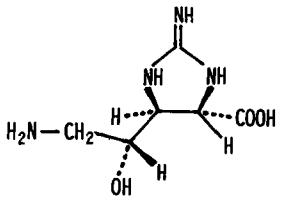
(Received in Japan 23 February 1974; received in UK for publication 4 March 1974)

Streptolidine is a guanidino amino acid widely distributed as an amino acid component in a number of *streptomyces* antibiotics. This amino acid was first isolated from the hydrolyzate of streptothricin and streptolin[1], and thereafter roseonine from roseothricin[2] as well as geamine from geomycin[3] were identified as the same amino acid. The chemical structure of the amino acid was correctly elucidated by Carter et al[4], and its absolute stereochemistry was recently established by X-ray crystallography as mentioned in 1[5].



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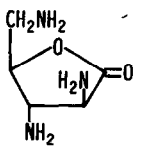

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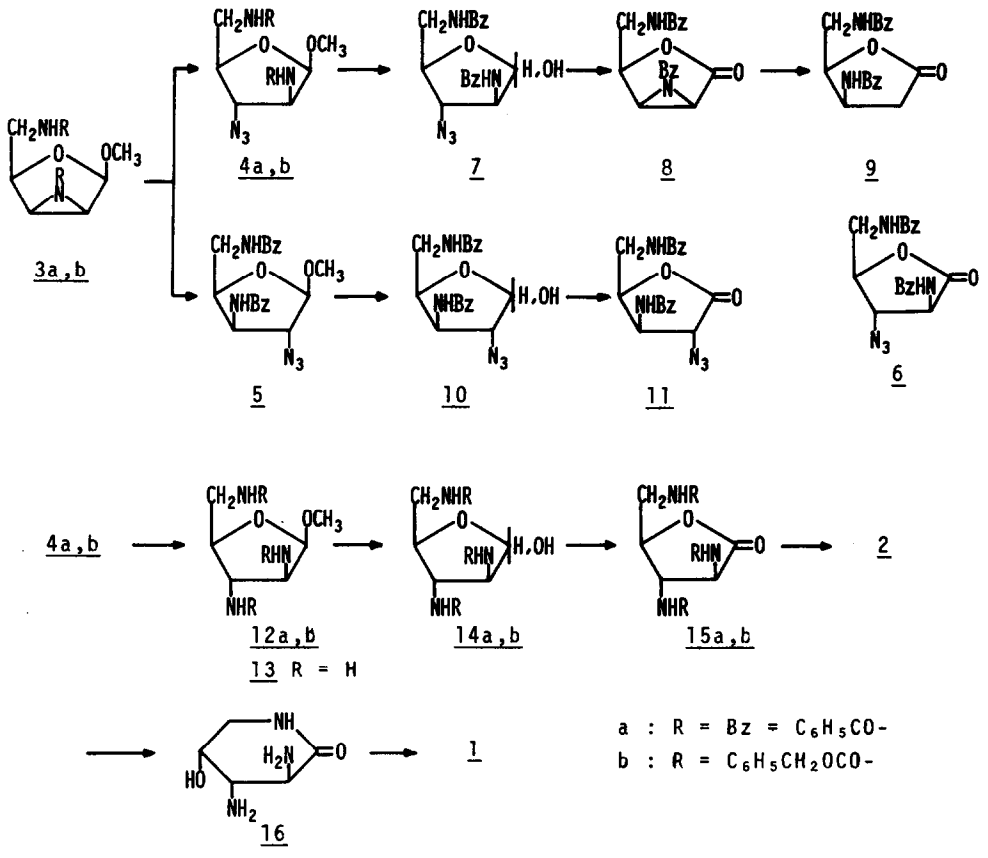
For the purpose of a total synthesis of streptolidine involving three asymmetric centers in its molecule, we adopted a rather novel approach to a polyamino acid of a definite configuration from a natural pentose. A synthesis of the key intermediate, triamino lactone 2, was performed by sterically selective conversion of hydroxyl groups of D-ribose to the corresponding amino groups. Hildesheim et al prepared two isomers of monoazido dibenzamido trideoxypentose (4a, 5) from D-ribose through azidolysis of an epimino derivative 3a[6]. They tentatively assigned each isomer to arabino (4a) and xylo (5) type structure respectively. Oxidation of C-1 in 4a to carboxyl group would be expected to lead to the desired intermediate 2 after several steps of required



transformations.

However, in an attempt to convert 4a into lactone 6, oxidation of 7 with CrO_3-pyridine afforded an epimino derivative 8 (mp 196-197°C, 73%) as a main product unexpectedly. The structure of 8 was confirmed by a conversion to 9 (mp 212-213°C; 52%; NMR: δ2.5 (1H d, J=10 Hz), 2.7 ppm (1H q, J=5, 10 Hz) in $CDCl_3$) on catalytic hydrogenation. The formation of the epimino ring in 8 is obviously resulted from an elimination of the azido group with a participation of the neighboring benzamido group. On the other hand, oxidation of 10 obtained by hydrolysis of another isomer 5, with CrO_3-pyridine, afforded an azido lactone 11 (mp 164-166°C (dec.), 67%; ν_{max} 2130, 1790 cm^{-1}) without elimination of the azido group. There was a doubt raised about the assignment of the structures of

4a and 5, since it is known in general that an α-azido group to a carbonyl group is rather unstable under an alkaline condition contrary to our observation. Therefore, the structural assignment for each series was reexamined as follows. Decoupling experiments on the lactone 11 showed that a doublet signal at δ4.12 ppm (1H, J=10 Hz) changed to a singlet when the signal at δ5.25 ppm (1H, quartet-like) coupling further with a NH proton at δ9.07 ppm (d, J=9 Hz) was irradiated. This result indicated clearly that the signal at δ4.12 ppm should be due to the proton on C-2 and the structure of this lactone must be represented as α-azido structure of xylo type as shown in 11 in accordance with Hildesheim's assignment, although explicit NMR analyses for 4a and 5 were not possible.

In order to avoid the undesirable formation of the epimino ring, in the arabino type series leading to the required intermediate 2, the azido group on C-3 in 4a was then reduced prior to the oxidation of C-1. The reduction product was benzoylated to 12a and then converted to lactone 15a through cleavage of the glycoside linkage and oxidation successively. However, a tribenzoyl derivative 15a thus obtained was found to resist against the removal of benzoyl group either on acidic hydrolysis or methanolysis giving a complex mixture of products. From this result, use of benzyloxycarbonyl group instead of benzoyl group as an amino protection seemed to be more promissing. A dibenzyloxycarbonyl derivative of the starting epimino compound 3b (mp 114-115°C) prepared from D-ribose in a similar manner to that for the benzoyl derivative, was then treated with sodium azide in DMF at 90°C to give 4b (mp 103.5-105°C, 46%). In this case, a single isomer of the arabino type was obtained as product. Catalytic hydrogenation of 4b afforded a triamino compound 13 as trihydrochloride (mp 240°C (dec.), 82%). A fact that benzoylation of 13 gave 12a obtained above, guarantees the assignment of the arabino type structures to 4b and 13. The triamino compound 13 was again benzyloxycarbonylated to 12b (mp 202-203°C, 77%), and then the glycoside linkage was cleaved by hydrolysis. In this hydrolysis, care was taken to avoid the removal of benzyloxycarbonyl group by employing a condition of refluxing 12b in 2N toluenesulfonic acid-dioxane, to yield about 35% of 14b (mp 211-212°C) accompanied with 40% of the unchanged 12b.

The product 14b thus obtained was oxidized with CrO_3 in acetic acid to give

15b (52%), which was then treated with HBr in acetic acid to afford trihydrobromide of the desired key intermediate 2 (mp 103°C (dec.), quantitatively). This hydrobromide 2 was converted to a free lactam 16 in an aqueous solution by adding 1N NaOH and then treated directly with cyanogen bromide at room temperature. In this reaction, the amino group on C-5 in the lactam form was advantageously protected for guanidination, and a selective formation of the guanidine ring between C-2 and C-3 was prompted. Finally, the reaction product was subjected to Dowex-50 x 8 (NH_4^+ form) column after hydrolysis of the lactam by refluxing in 6N HCl. Elution with 0.2N NH_4OH afforded fairely pure streptolidine 1, which was isolated as bis-4-hydroxyazobenzene-4'-sulfonate dihydrate (7.5% from 2, mp 250-254°C(dec.), $[\alpha]_D^{21}$ +20.5° (c 0.29, CH_3OH); natural salt: mp 250-254°C (dec.), $[\alpha]_D^{19}$ +22.1° (c 0.29, CH_3OH)). The IR spectra of both the above salt and dihydrochloride, mobilities on paper chromatography and paper electrophoresis, as well as elution time on amino acid analysis of the synthetic product were all identical with those of natural streptolidine.

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* This work was presented at the 17th Symposium on the Chemistry of Natural Products, Tokyo, Japan, October, 1973; p 221.

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