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SYNTHESIS OF ROSEONINE (STREPTOLIDINE), A GUANIDINO-AMINO ACID COMPONENT OF STREPTOTHRICIN GROUP ANTIBIOTICS[1]

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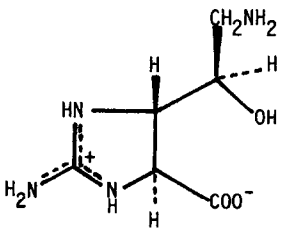
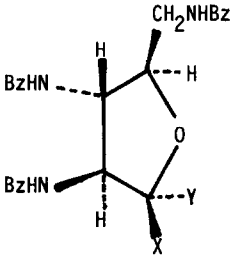
Roseonine[2] is a unique guanidino-amino acid isolated from acid hydrolyzates of antibiotic roseothricin which is produced by Streptomyces roseochromogenus. It was shown to be identical[3] with streptolidine[4] obtained from streptothricin, and geamine[5] from geomycin, and is also found in other streptothricin group antibiotics. Its structure was disputed for some time,[2,3,6] but one proposed by Carter et al.[3] has been generally accepted. The structure including absolute configuration was finally determined as I by X-ray analysis by Bycroft and King[7] in 1972. A total synthesis of roseonine described in this communication confirmed the structure and the absolute configuration that were determined by the X-ray analysis.

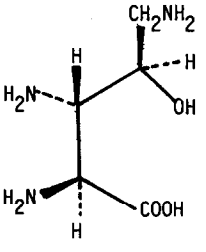


roseonine (streptolidine)
(I)



(II) X=OMe, Y=H

(III) X, Y > =O



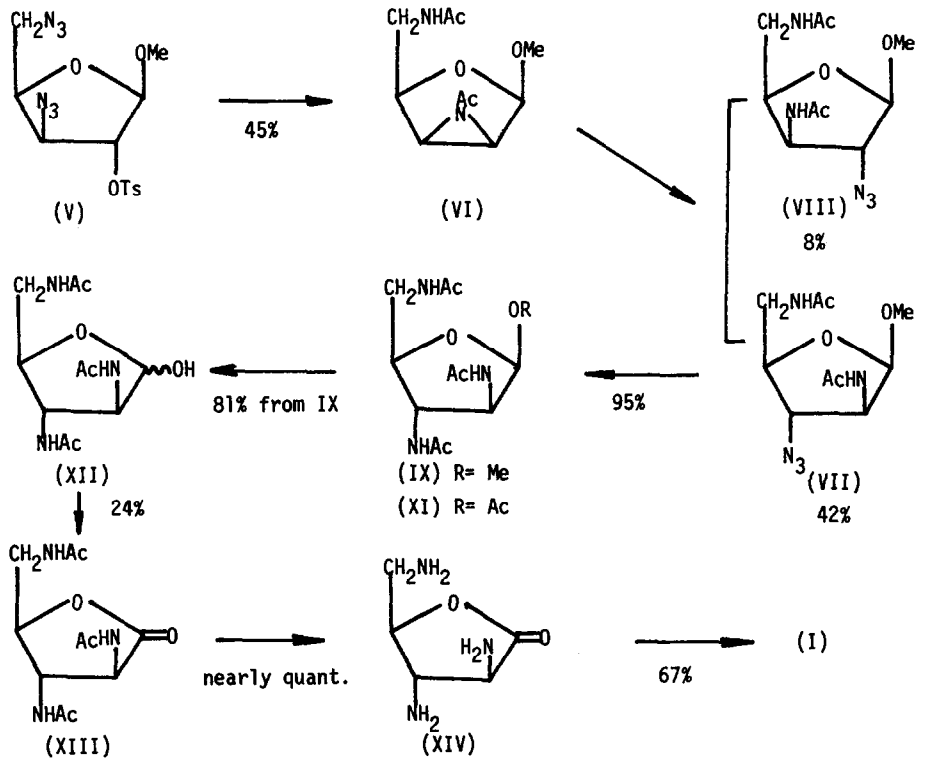
(IV)

Hildesheim et al.[8] synthesized the tribenzamide (II) from D-ribose. Resemblance of its stereochemistry to that of roseonine (I) is apparent and hence we first attempted to synthesize I from II. Hydrolysis of the glycosidic linkage of II followed by chromic acid oxidation afforded the tribenzamido lactone (III), mp 236-237°,[9] in 71% yield. However, acid hydrolysis (6N HCl) of the lactone to triaminocarboxylic acid (IV) was extremely difficult; two benzamido groups were easily hydrolyzed, but the third one could not be removed without

extensive decomposition. This difficulty was overcome by replacing the benzoyl groups by acetyl groups; the hydrolysis was accomplished in a nearly quantitative yield.

The diazide (V) was synthesized from D-ribose according to Hildesheim et al.[8] $LiAlH_4$ reduction of V in THF followed by acetylation with Ac_2O in MeOH at room temp. afforded the acetylaziridine (VI)[10] as a syrup. Treatment of VI with NaN_3 in DMF at 140° for 45 min gave a mixture from which the 3-azidoarabinoside (VII),[11] mp 141°,[9] and 2-azidoxyloside (VIII),[12] mp 114-114.5°, were isolated in yields of 42% and 8%, respectively, by silica gel column chromatography. Catalytic hydrogenation of VII over Pd-C in MeOH followed by acetylation with Ac_2O in MeOH afforded the triacetamidoarabinoside (IX),[13] mp 293-294.5°.[9] Similarly, triacetamidoxyloside (X),[14] mp 203-205°,[9] was obtained from VIII in 98% yield. Since acid hydrolysis of the glycosidic linkage of IX was always accompanied by a partial hydrolysis of the amide linkages, the following sequence of reactions was carried out. Hydrolysis of IX with aq CF_3COOH at 100° for 60 min followed by acetylation with Ac_2O and pyridine yielded the acetyl β-arabinoside (XI),[15] mp 217-220°,[9] which on treatment with MeONa in MeOH at room temp. gave the arabinose (XII), amorphous powder, mp 226-230° (dec). The anomeric hydroxyl group of XII was oxidized by CrO_3 in acetic acid in the presence of catalytic amounts of conc. H_2SO_4 to give the triacetamido-γ-lactone (XIII) as a sole product (tlc), but its purification by means of silica gel chromatography was difficult because it was always accompanied with Cr^{+3} complex. Purification of XIII could be done satisfactorily by passing it through a column containing a mixture of Amberlite IRC-50 (H type) and IR-4B (free). The γ-lactone (XIII)[16] thus obtained was a hygroscopic powder, mp 125-130°. Hydrolysis of XIII was carried out by heating it in 6N HCl under Ar atmosphere at 100° for 1 hr. Evaporation of the hydrolyzate gave the triamino-γ-lactone (XIV)[17] as a hygroscopic solid. It gave only one ninhydrin-positive spot on ppc at Rf=0.10 (n-BuOH:AcOH:H_2O=4:1:3); nmr spectrum showed no acetyl signal. The lactone (XIV) was treated with poly-Hünig-base (diisopropylaminomethylpolystyrene)[18] and excess $BrCN$[3] in aq MeOH at room temp. until the reaction mixture showed negative ninhydrin test. The mixture was filtered and evaporated to dryness, and the residue was heated with 6N HCl at 100° under Ar atmosphere for 20 min. After evaporation, the residue, which gave only one ninhydrin-positive spot on ppc whose Rf was identical with that of natural roseonine, was purified by paper chromatography to give roseonine 2HCl (I) as a glassy solid; amino acid analysis using an automatic amino acid analyzer showed only one peak at the position identical

with that of natural roseonine; its nmr spectrum taken in D_2O was also identical with that of the natural amino acid. Further identifications were made as follows. Roseonine dipicrate, mp 210-215° (dec),[9] and 2,4-dinitrophenylroseonine, mp 221-227° (dec), were prepared and no mp depressions were observed on each of them by admixture with the corresponding roseonine dipicrate, mp 208-212° (dec),[2] and DNP-roseonine, mp 226-229° (dec),[19] prepared from the natural amino acid. The ir spectra of each pair of the derivatives of synthetic and natural roseonine were superimposable. Identity of $[\alpha]_D$ values of synthetic (+10.6° in 0.1N HCl) and natural roseonine dipicrate (+11.4° in 0.1N HCl) indicates that the synthetic and natural amino acids have the same absolute configuration as shown in I.



REFERENCES AND FOOTNOTES

1) S. Kusumoto, S. Tsuji and T. Shiba reported preliminarily a synthesis of roseonine at 17th Symposium on the Chemistry of Natural Products (Oct. 18, 1973, Tokyo), where we also announced the results described in this paper.

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3) H. E. Carter, C. C. Sweeley, E. E. Daniels, J. E. McNary, C. P. Schaffner, C. A. West, E. E. van Tamelen, J. R. Dyer and H. A. Whaley, J.Amer.Chem. Soc., 83, 4296 (1961).

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9) Satisfactory elemental analysis was obtained.

10) (VI): m/e 228 (M^+); $[\alpha]_D$= +0.42° ($CHCl_3$); δ (ppm, $CDCl_3$) 5.00 (H-1), 3.36 (H-2), 3.26 (H-3), 4.08 (H-4), 3.69 (H-5), 1.98 and 2.17 (2 Ac), 3.52 (MeO), 6.30 (NH); $J_{1,2}$=1.3 Hz, $J_{2,3}$=5.0, $J_{3,4}$=1.5.

11) (VII): $[\alpha]_D$= -2.46° ($CHCl_3$); ν 2100 cm^{-1}; δ (ppm, $CDCl_3$) 4.86 (H-1), 4.61 (H-2), 3.82 (H-3), 3.89 (H-4), 3.48 (H-5), 2.03 and 2.06 (2 Ac), 3.45 (MeO), 6.42 (NH); $J_{1,2}$=5.0 Hz, $J_{2,3}$=8.0, $J_{2,NH}$=8.0.

12) (VIII): $[\alpha]_D$= -93.2° ($CHCl_3$); ν 2100 cm^{-1}; δ (ppm, $CDCl_3$) 4.87 (H-1), 3.82 (H-2), 4.68 (H-3), 4.32 (H-4), 3.08 and 3.85 (H-5), 2.01 and 2.05 (2 Ac), 3.43 (MeO), 6.20 and 6.70 (2 NH); $J_{1,2}$=1.5 Hz, $J_{2,3}$=3.5, $J_{3,NH}$=9.6, $J_{3,4}$=6.0, $J_{4,5}$=6.0, $J_{5,5'}$=15.0.

13) (IX): m/e 287 (M^+); $[\alpha]_D$= -0.84° ($CHCl_3$-MeOH, 4:1); δ (ppm, $CDCl_3$-CD_3OD, 1:1) 4.87 (H-1), 3.92 (H-4), 1.99 and 2.02 (3 Ac); $J_{1,2}$=4.0 Hz, $J_{3,4}$=7.0.

14) (X): $[\alpha]_D$= -1.19° ($CHCl_3$-MeOH, 4:1); δ (ppm, $CDCl_3$-CD_3OD, 1:1) 4.84 (H-1), 3.40 (H-5), 1.99 and 2.03 (3 Ac), 3.42 (MeO); $J_{1,2}$=1.8 Hz.

15) (XI): $[\alpha]_D$=-1.2° ($CHCl_3$-MeOH, 4:1); ν 1750 cm^{-1}; δ (ppm, $CDCl_3$ contg. trace CD_3OD) 6.18 (H-1), 4.52 (H-2), 4.26 (H-3), 3.91 (H-4), 3.40 (H-5), 2.12 (OAc), 1.96, 1.97 and 1.99 (3 NAc); $J_{1,2}$=4.0 Hz, $J_{2,3}$=3.0, $J_{2,NH}$=9.6, $J_{3,4}$=7.5, $J_{3,NH}$=9.6, $J_{4,5}$=7.0.

16) (XIII): m/e 271 (M^+); ν 1780 cm^{-1}; δ (ppm, D_2O) 2.08 (Ac), 2.06 (2 Ac).

17) The lactone (XIV as hydrochloride) showed a strong ir band at 1800 cm^{-1}, but its picrate prepared by neutralizing with Amberlite IR-45 followed by treatment with picric acid showed neither the lactone nor the carboxylic acid band. It is therefore suggested that the γ-lactone and the δ-lactam are interconvertible each other by change of pH.

18) The γ-lactone may be converted in this stage to the δ-lactam, the formation of which would interpret the exclusive formation of the five-membered, rather than six-membered, guanidine ring.

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