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ABSOLUTE CONFIGURATION OF BLASTICIDIN S

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In the works on the chemistry of blasticidin S (I), a methabolite of Streptomyces griseochromogenes, we have demonstrated its unique structural feature which consists of a new nucleoside cytosinine (II) and a new amino acid, blastidic acid (III)[1-4] on the basis of chemical reactions and spectral evidences.

Taking account of various biological activities together with the biogenetic interest of the antibiotic, the absolute configuration of I has to be made clear.

This communication deals with chemical evidences which allow the assignment of a β-configuration to the anomeric center in II and an L-configuration to the amino acid (III); consequently, the absolute configuration can be represented by I.*

II was esterified with methanolic hydrogen chloride to the methyl ester dihydrochloride[3] (IV), which was converted to the

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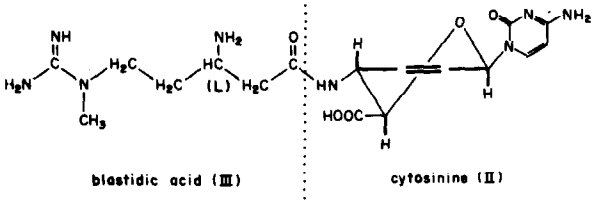
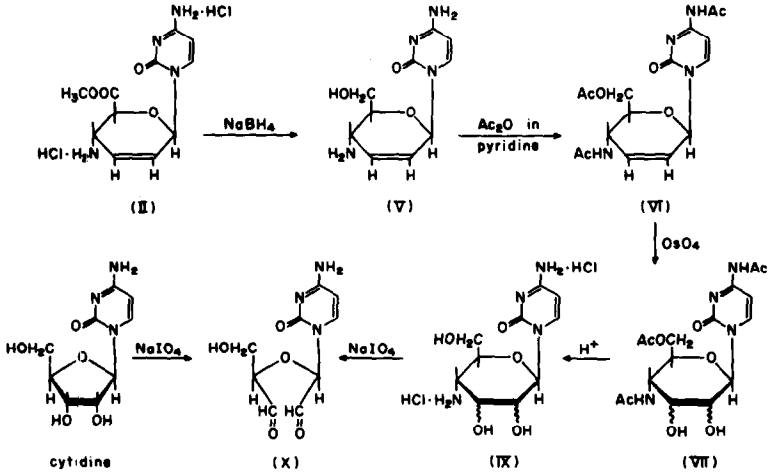
* These data were reported at the Symposium on the Physiologically Active Substances and Natural Products, the Annual Meeting of the Agricultural Chemical Society of Japan held in Kyoto, April 2, 1966.



Absolute Configuration of Blasticidin S (I)



alcohol (V), $C_{10}H_{14}O_3N_4$, m.p. 186-187.5° (dec.), by the action of sodium borohydride.

Acetylation of V with acetic anhydride in pyridine afforded the crystalline triacetate (VI), $C_{10}H_{11}O_3N_4 \cdot (CH_3CO)_3$, m.p. 234-235° (dec.). Hydroxylation of VI with osmium tetroxide in pyridine gave the diol triacetate (VII) as an amorphous powder which was deacetylated with 0.5 N methanolic sodium methoxide to the crystalline 4-N-acetyl compound (VIII), $C_{10}H_{15}O_5N_4 \cdot (CH_3CO)$, m.p. 211-212°. Deacetylation of VIII with 1 N hydrochloric acid under reflux furnished an amino-triol dihydrochloric (IX),* $C_{10}H_{16}O_5N_4 \cdot 2HCl$, m.p. 234-235° (dec.), which was converted to its crystalline dipicrate, $C_{10}H_{16}O_5N_4 \cdot 2(C_6H_3O_7N_3)$ m.p. 219-221° (dec.).

Periodate oxidation of IX resulted in the consumption of two equivalents of the oxidant within an hour, and the cleaved product was precipitated with picric acid as a crystalline mass. Recrystallization of the mass from hot water gave fine needles of the dialdehyde picrate (X), $C_9H_{11}O_5N_3 \cdot C_6H_3O_7N_3$, m.p. 235-237° (dec.), $(\alpha)_D^{20}$ + 50.8 (c=1 in pyridine). X was identical in every respect to the picrate of α-(cytosine-3)-α'-hydroxymethyl-diglycollic dialdehyde derived from periodate oxidation of cytidine reported by Davoll et al.[5]

The foregoing data establishes firmly the configuration of anomeric center of II as β.

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* The configuration of IX will be presented in the next report of this series.

With regard to the configurational structure of the sugar moiety in II, viz, the configuration of C-4 and C-5 has been established in the previous paper.[3] From the n.m.r. spectral evidence,[3] the protons at C-4 and C-5 were determined to be axial-axial and formation of erythro-β-hydroxy-D-aspartic acid after the oxidative cleavage of double bond by O_3 provided an unequivocal evidence for C-4 (S), C-5 (S) configurations and settled the sugar for D-series accordingly.* These accumulated data clarified the complete structure of cytosinine to be 1-(1'-cytosinyl)-4-amino-1,2,3,4-tetradeoxy-β-D-erythro-hex-2-ene uronic acid.

The configuration of III is most important and of interest in connection with the biological activity of the antibiotic and also with the biogenetic occurrence of this new β-amino acid.

Hitherto, several new amino acids had been isolated as structural components of antibiotics,[7] notably, 3,6-diaminohexanoic acid (β-lysine), a component of viomycin,[8] streptothricin,[9] streptoline,[10] has been shown to possess an L-configuration.

The n-π^* transition of a carboxyl group in amino acids were observed near 220 mμ and the relation between the configuration and the rotatory dispersion curves of α-amino acids were well established.[11] Recently, Kjær et al.[12] had described an

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* Recently, Fox et al.[8] have reported on the structure of blasticidin S based on our misassignment of the configuration of erythro-β-hydroxy-D-aspartic acid; this has been revised in our full paper.[3]

extension of this result to ω-substituted-α-amino acids including L-arginine and L-lysine and had observed well developed positive Cotton effects in acidic solution.

It seems possible therefore, to extend the ORD method for configurational analysis of ω-substituted-β-amino acids after comparative observation of a series of compounds with known configurations.

As shown in FIG. 1, an enantiomeric pair of 3,5-diamino valeric acid,* having the carbon skeleton of III, exhibited almost symmetrical ORD curves with positive (L-form) and negative (D-form) Cotton effects (extremum at 223mμ) in 3 N hydrochloric acid. Furthermore, L-3,7-diaminoheptylic acid and β-lysine showed positive Cotton effects in accordance with their L-configuration. These results indicate that the method is applicable to β,ω-diamino acids homologues.

The positive Cotton effect exhibited by III measured under the same condition clearly showed that blastidic acid had an L-configuration.

On the basis of these evidences, the absolute configuration of blasticidin S was elucidated to be 1-(1'-cytosinyl)-4-{L-3'-

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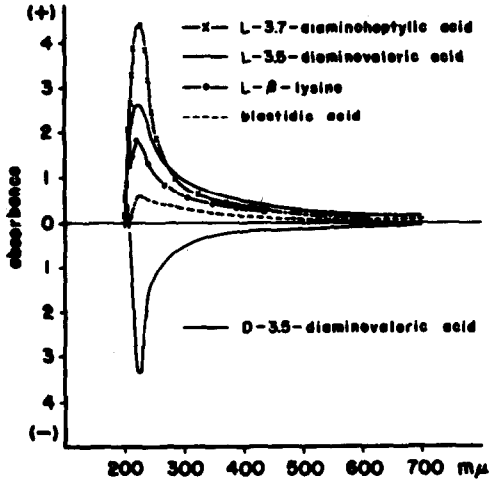
* The sample of β-lysine was obtained by the hydrolysis of viomycin according to Haskell's[8] procedure. D-and L-3,5-diamino valeric acid, L-3,7-diaminoheptylic acid were synthesized from optically pure D-or L-glutamic acids and L-lysine respectively and the structures of these synthetic compounds were confirmed by n.m.r. spectra and elementary analyses. Although the optical purity of each compounds were not confirmed they were optically active. The synthesis and physicochemical properties of these amino acids will be reported in the next papers of this series.

amino-5-(1"-N-methylguanidino)-valerylamino}-1,2,3,4-tetradeoxy-β-D-erythro-hex-2-ene uronic acid, (I).

FIG. I. Rotatory Dispersion Curves of Biostidic Acid and its Homologues



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