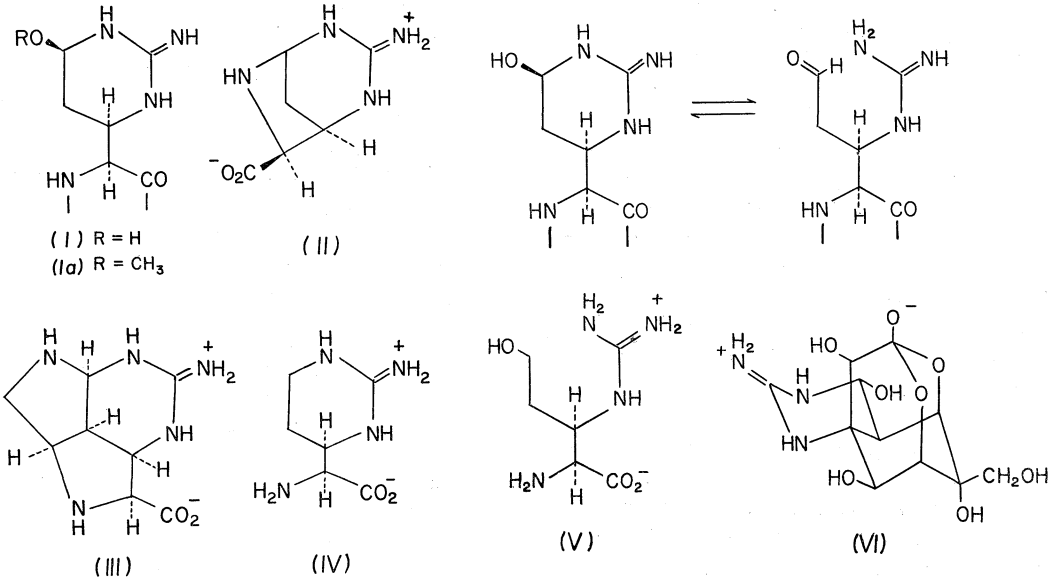
Communication to the editors

THE STRUCTURE, STEREOCHEMISTRY AND REACTIONS OF THE GUANIDINE MOIETY OF VIOMYCIN

Sir:

Recently we presented evidence to suggest that the tuberculostatic antibiotic viomycin contains the unit I[1]. More recently several papers[2,3,4] have lent support to this proposal and we present here the evidence allowing a complete stereochemical assignment, together with a summary of the remarkable chemical reactivity of this unit.



Ion exchange chromatography (Dowex 50 W×8) of the acid hydrolysate (10 N hydrochloric acid, reflux for 24 hours) of viomycin afforded two basic amino acids, viomycidine and a small amount of a compound which we have termed viocidic acid. Viomycidine was characterised as its crystalline monohydrochloride m. p. 200~204°C and our spectral and chemical data were in accord with the structure II proposed by BUCHI and RALEIGH[5]. Viocidic acid was characterised as its dipicrate m.p. 173~175°C. Found: C 35.2, H 2.7, N 22.8. $C_8H_{13}N_5O_2 \cdot (C_6H_3N_3O_7)_2$ requires C 35.8, H 2.7, N 22.7 %. Dihydrochloride m. p. 210~212°C (decomp.) Found: C 31.7, H 5.5, N 23.4. $C_8H_{13}N_5O_2 \cdot 2HCl \cdot H_2O$ requires C 31.6, H 5.6, N 23.1 $[\alpha]_D^{22}$ −51° (*c* 0.08, in H_2O). It gave a yellow ninhydrin reaction and a negative SAKAGUCHI test. Potentiometric titration showed the presence of one carboxyl group $pK_a' < 2.0$ and three basic functions of pK_a' 5.8, 6.8 and >12.0. The complete structure and absolute chirality of the dihydrobromide of viocidic acid have been determined by X-ray crystallography and are as shown in III. The mode of formation of viocidic acid is yet uncertain but probably involves a reaction of the unit I which is a potential enamine with a breakdown product of the chromophoric unit[6] of the antibiotic.

On the basis of structure III we tentatively assigned the absolute chirality, as shown, for viomycidine II and the unit I at the α and β centres. Recently two X-ray crystallographic analyses of viomycidine have been reported[2,8] confirming the proposed structure and one[8] confirming also our assignment of the absolute chirality.

Catalytic reduction of viomycin hydrochloride with PtO_2 in 3 N hydrochloric acid, followed by acid hydrolysis afforded no

viomycidine but instead capreomycidine IV isolated as the free base m.p. 195°C (decomp.) $[\alpha]_D^{22.5}$ −22.7° (*c* 0.17, in H_2O) identical (i. r., n. m. r., t. l. c. and o. r. d.) with an authentic sample isolated from the acid hydrolysate of capreomycin[7]. We have in addition confirmed the gross structure of capreomycidine by total synthesis[4] and the above correlation with viomycidine establishes the absolute chirality.

In a recent communication MAEDA and TAKITA[3] reported the isolation of a 'dihydroviomycidine' from the acid hydrolysate of the sodium borohydride reduction product of viomycin which they claimed to be epi-capreomycidine. Their spectral and chromatographic data for this compound were not in accord with those observed for our synthetic epi-capreomycidine[4] and on the basis of their evidence we suggested the alternative formulation V. More recently they have presented further results corroborating this structure[8].

The above observation together with the fact that viomycin gives a positive SAKAGUCHI reaction provide evidence that the unit I in solution is in equilibrium with the corresponding aldehyde form. This allows an assignment of the chirality of the guanidine carbinol centre in I since the molecule can be expected to adopt the most favourable configuration at this centre, *i.e.* the hydroxyl group in a pseudo-equatorial position.

Mild base hydrolysis of viomycin with 0.1 N NaOH at 100°C for 20 hours gave on ether extraction a good yield of 2-amino-pyrimidine m. p. 127~128°C completely identical with an authentic sample. Since viomycidine was not present in the total hydrolysate of the resultant peptides it followed that the 2-aminopyrimidine must have been dried from the guanidine moiety.

It is evident that methylviomycin, formed by heating viomycin with methanol, is an O-methyl derivative of the guanidine-carbinol system (Ia, chirality at the carbinol centre not defined). The extraordinary reactivity of I is paralleled in the properties of the neurotoxin, tetrodotoxin[9] VI, the only other known naturally occurring compound possessing this unit.

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