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THE CHROMOPHORE AND PARTIAL STRUCTURE OF VIOMYCIN

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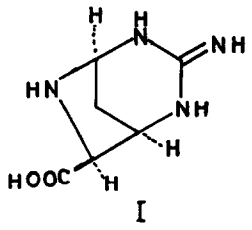
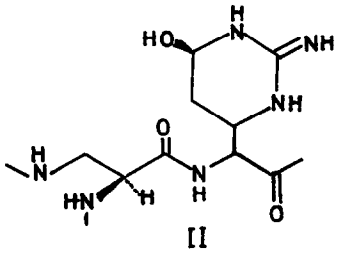
The tuberculostatic antibiotic viomycin[1] affords on complete acid hydrolysis the amino acids L-serine, L-α,β-diaminopropionic acid, L-β-lysine, and viomycidine (ratio 2:1:1:1 respectively), together with carbon dioxide, ammonia, urea and traces of glycine.[2] In a recent communication[3] we presented evidence to suggest that the basic amino acid viomycidine[4,5] (I) is an artefact derived from the unit (II) present in the intact antibiotic. In addition we were able to demonstrate kinetically that urea was probably involved in the chromophore of viomycin, and earlier structural suggestions[6,7] that the guanidine unit was incorporated in the viomycin chromophore were invalidated.



I

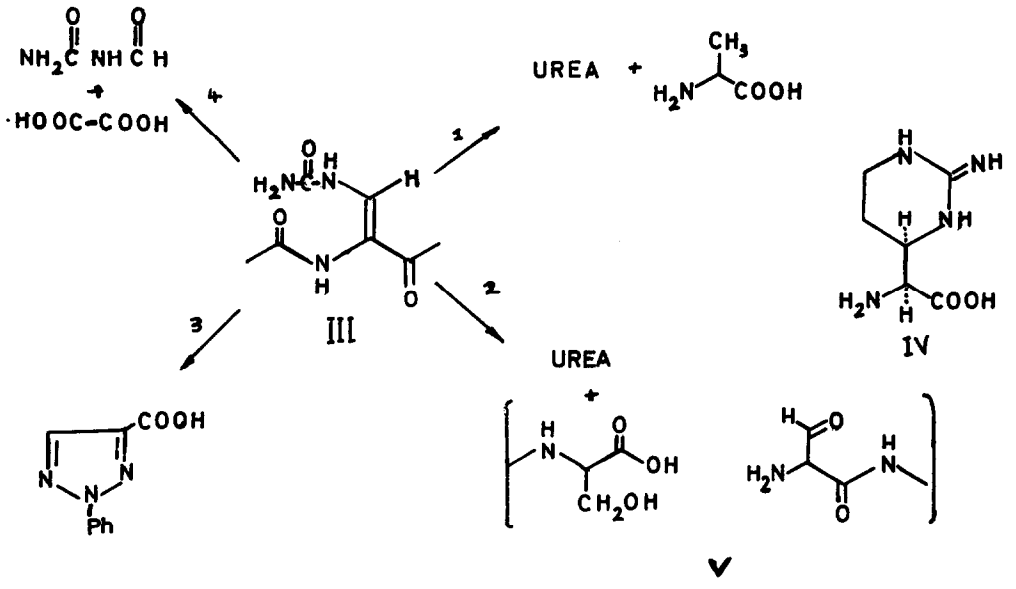


II

We now propose that the unit (III) is responsible for the ultraviolet absorption of viomycin. The chemical evidence on which this formulation is based is summarised in Fig. 1. Hydrogenation of viomycin, under strictly defined conditions, afforded urea and a perhydro derivative possessing no chromophore and yielding on acid hydrolysis the amino acids L-serine, L-α,β-diaminopropionic acid, L-β-lysine, capreomycidine (IV) and alanine[8] (ratio 2:1:1:1:1) but no glycine. The conversion of the guanidine moiety of viomycin to capreomycidine by hydrogenolysis has previously been reported.[3,9] Alanine, as it is not derived from any of the amino acids present in viomycin, must have been formed by reduction of the chromophoric unit. This, combined with the results of the oxidation experiments (2) and (3), first reported by Jones[12]

and confirmed by us, leads to the partial structure (III).

Fig. 1

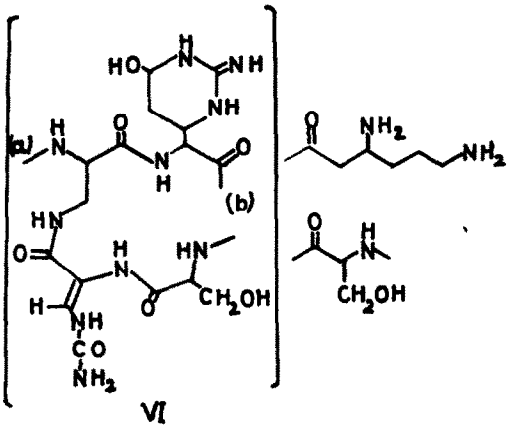


(1) (i) H_2/Pt, (ii) 6N HCl, (2) $KMnO_4$ see reference 12, (3) (i) I_2, (ii) $PhNHNH_2$, (iii) H^+ see reference 12, (4) 0.1N HCl.

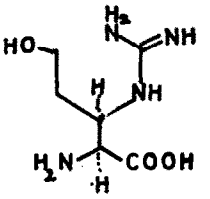
The chromophore (III) is compatible with the observed spectral (n.m.r. and u.v.) properties of viomycin, and syntheses of models of this novel system will be reported later.

End group analysis[3,7,13] and pk_a determinations[7] on viomycin reveals that there is no free carboxylic acid group, indicative of a cyclic peptide, and that only the amino groups of the β-lysine unit are free. Mild hydrolysis (0.1N HCl, 4 hr.) releases one equivalent of urea and affords a reactive compound,[14] possessing a free carboxylic acid group of a serine unit. We propose that this compound contains the unit (V), or a tautomeric equivalent, and that it is the further hydrolytic breakdown of this unit which gives rise to ammonia and carbon dioxide as well as traces of glycine. Further controlled acid hydrolysis of the above compound afforded a peptide,[15] not isolated, from which no amino acids had been liberated. End group analysis of this peptide showed the free amino groups of β-lysine, the β-amino group of αβ-diamino-propionic acid and a free serine carboxyl group. As no amino acids had been liberated from the molecule, the unit (V) must be attached to the β-amino group

of αβ-diamino-propionic acid. Summation of the above observations together with previously reported work[3] leads to the partial structure (VI) for viomycin.



VI



VII

The amino acid sequence analysis of viomycin is complicated by the presence of the reactive chromophoric and guanidine units in the molecule, which is evident in the number of conflicting sequences proposed for viomycin. Of the two possible structures derivable from (VI), on the grounds of degradative studies at present in progress, we favour the β-lysyl unit at position (a) and the seryl unit completing the cyclic peptide at position (b).

Thus viomycin and capreomycin[16] belong to a small group of cyclic peptides including for example ostreogrycin,[17] griseoviridin[18] and telomycin[19] containing a dehydro- or a modified dehydro-amino acid.

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8. Isolation of the alanine by chromatography on Dowex-50 showed it to be optically active (α_D^{24} -4.7°, C 0.3 in H_2O), due to stereospecific hydrogenation.

9. Japanese workers have recently claimed[10] to have isolated epi-capreomycidine by hydrolysis of a dihydro derivative obtained by sodium borohydride reduction of viomycin. The spectral and chromatographic properties of epi-capreomycidine, recently synthesised by us[11] are not consistent with those given by the Japanese workers. We suggest that their analytical, spectral and chemical data are more in accord with structure (VII).

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14. This product has been previously[7] referred to as desureaviomycin but we prefer to reserve this term for the compound obtained from viomycin by loss of urea only and no concomitant hydrolysis of peptide linkages.

15. Similar large peptides, but containing chromophoric groups presumably derived from the active unit (V), have been obtained by other workers.[13]

16. Similar conclusions have been reached on the nature of the chromophore of capreomycin and this work will be reported shortly.

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