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Synthesis of a Model relating to the Chromophores of Capreomycin and Viomycin

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In a recent communication[1] we presented considerable evidence to suggest that the unit (I) is responsible for the ultraviolet absorption spectra of the tuberculostatic antibiotics, viomycin and capreomycin. This combined with our evidence concerning the guanidine unit and the peptide sequence led us to propose a partial structure for viomycin[2].

The lability of both the chromophore and the guanidine moiety in viomycin has presented considerable difficulties in interpreting degradative results. Earlier formulations of the chromophore combined both these units,[3,4] whereas two recent publications[5,6] have misinterpreted results relating to the guanidine unit and made no account of the chromophore.

The most convenient synthetic approach to models of the unit (I) appeared to be through the condensation of urea with an appropriately substituted penaldate. In this communication we describe the synthesis of the compound (III).

Ethyl benzyl penaldate (II) was prepared by formylation of ethyl phenacetate[7] and characterised as its benzoate, m.p. 153-154°, and benzylamine derivative, m.p. 105-106°. Acid catalysed condensation of (II) with urea at room temperature in 1,2-dimethoxyethane afforded in 46% yield a crystalline ureide, $C_{14}H_{17}N_3O_4$ which could be isolated in two forms. Crystallisation from methanol-water afforded the enamine form (III), m.p. 218-219°, mass spec. M^+ m/e 291; i.r.(KBr) 1705, 1690 and 1655 cm^{-1}. The n.m.r. and u.v. spectra (Table 1) confirmed structure (III) for this compound. Crystallisation from chloroform afforded the imine form (IV), m.p. 218-219°, mass spec. M^+, m/e 291, i.r. (KBr) 1739, 1698 and 1655 cm^{-1} which on dissolving in prototropic solvents, or on heating, converted to the enamine (III).

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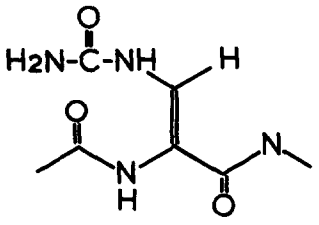
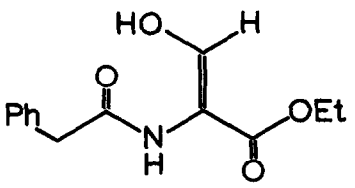


I



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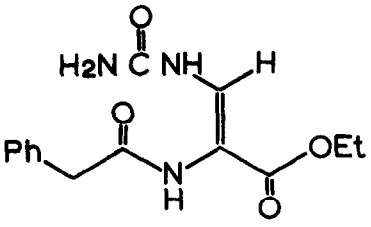
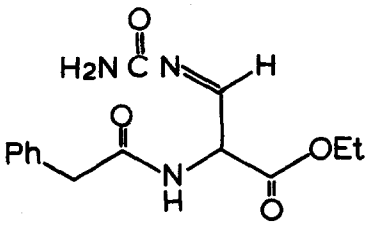


III



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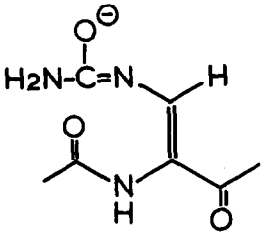

V

TABLE 1

	VIOMYCIN	CAPREOMYCIN 1B[8]	III
U.V. Spectra			
a) neutral/acid	267(24,000)	266(24,050)	266(22,100)
b) NaOH/H_2O	290(15,000)	290(15,000)	308(24,000)
N.M.R. Spectra			
(Singlet, 1H)	1.9(D_2O)	1.9(D_2O)	2.2(CD_3SOCD_3/D_2O)
pKa(H_2O)	12.6	-	12.6

A comparison of the spectral properties of (III) with those of viomycin and capreomycin (Table 1) completely substantiates our proposals concerning the chromophore of these antibiotics. The observed 'phenol' shift of the chromophores of the antibiotics and (III) on the addition of alkali is due to the formation of the resonance stabilised anions of the type (V). The pKa values associated with this ionisation in viomycin and compound (III) have been determined by the method of Parke and Davis[9] and are in good agreement (Table 1).

Catalytic reduction of (III) followed by acid hydrolysis gave alanine in good yield and oxidation with potassium permanganate yielded formylurea. Similar degradative results had been previously obtained[1] with viomycin and capreomycin.

A more detailed account of this work will be reported later.

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