Synthesis and Stereochemistry of Capreomycidine [α-(2-iminohexahydro-4-pyrimidyl)glycine]

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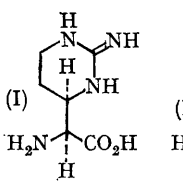
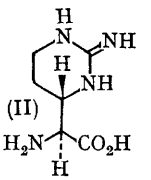
THE tuberculostatic peptide antibiotics of the capreomycin group, all afford, on acid hydrolysis, a new guanido-amino-acid[1] which has been termed capreomycidine. On the basis of its physical and spectral properties it has been tentatively assigned structure (I) or (II).[2] We report evidence which corroborates structure (I).

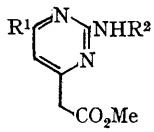
The racemic diastereoisomers (I) and (II) were synthesised as follows. Dimethyl acetonedicarboxylate readily condensed with guanidine to give the hydroxypyrimidine (III).[3] Chlorination of (III) with phosphoryl chloride afforded the chloro-compound (IV) (58%), m.p. 133·5—104·5°, which on hydrogenolysis gave (V). Treatment of the corresponding *N*-acetyl derivative (VI) with aqueous nitrous acid at pH 2·3 resulted in the formation of the oxime (VII) (85%), m.p. 229—231·5° (decomp.), λ_{max} 240 and 298 mμ (ε, 27,600 and 4570). Deacetylation of (VII) with saturated methanolic hydrogen chloride yielded (VIII), isolated as the hydrochloride, m.p. 190—192° (decomp.).

Hydrogenation (4 mol.) of (VIII) over palladium in acidic aqueous methanol, followed by acid hydrolysis, afforded a 1 : 1 mixture of the racemates (I) and (II), which were separated by fractional crystallisation of the picrates. Apart from physical properties involving optical activity, capreomycidine proved (chromatographic behaviour, n.m.r., and electrophoresis) to be identical with the racemate (I).

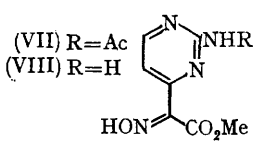
The relative and absolute chirality of capreomycidine from capreomycin has been conclusively established by a correlation with the closely related antibiotic viomycin. We have recently[4] presented evidence that viomycin contains the

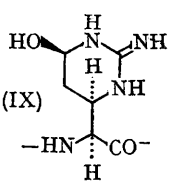


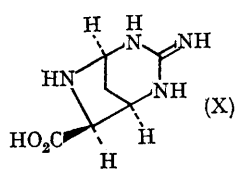




	R^1	R^2
(III)	OH	H
(IV)	Cl	H
(V)	H	H
(VI)	H	Ac







unit (IX). Acid hydrolysis results in the breakdown of this unit to give the bicyclic amino-acid viomycidine (X),[5] while preliminary hydrogenation of viomycin, followed by acid hydrolysis, results in the formation of capreomycidine (I), identical (i.r., n.m.r., t.l.c., and o.r.d.) with that

isolated from total hydrolysis of the capreomycin complex.

The synthesis of capreomycidine is a further conformation of the proposals regarding the structures of viomycin[4] and viomycidine.[5]

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[4] B. W. Bycroft, D. Cameron, L. R. Croft, A. W. Johnson, T. Webb, and P. Coggon, *Tetrahedron Letters*, 1968, 2925.
[5] G. Büchi and J. G. Raleigh, personal communication.