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THE STRUCTURE OF OSTREOGRYCIN A

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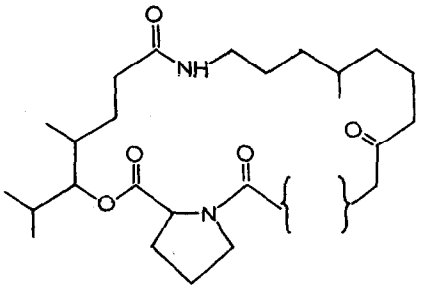
Ostreogrycin A is one of a group of synergistic antibiotics, produced by the soil organism Streptomyces ostreogriseus, described as the ostreogrycin complex and it has been shown to be identical with the substances described in the literature as staphylomycin M_1 and PA 114 A (1).

On the basis of analysis, and molecular weight determination by X-ray crystallographic and mass spectrometric methods, the antibiotic has the formula $C_{28}H_{35}N_3O_7$. It contains four double bonds readily saturated by hydrogenation with a palladium catalyst to give an amorphous material which we have designated "hydro A". The fact that "hydro A" is not homogeneous and that its formation proceeds with uptake of somewhat more than 4 moles hydrogen is in part explained by the presence of an allylic hydroxyl in ostreogrycin A which is partly hydrogenolysed in preparing "hydro A". Evidence for the partial structure (I) of the main hydroxyl-free component of "hydro A" has already been reported (2). The missing fragment

C_3HNO has now been identified as a simple oxazole ring on the following evidence. Hydrolysis of ostreogrycin A with 6N hydrochloric acid yields in addition to other products ca 1 mole ammonia with a trace ($<$ 0.05 mole) of glycine. Similar treatment of "hydro A" yields ca 1 mole ammonia, a trace of glycine and even smaller traces of serine and alanine [derived from trace amounts of more highly reduced contaminants (cf. III and IV) in "hydro A"], while the product of exhaustive hydrogenation of ostreogrycin A with a platinum catalyst ("perhydro A") gives under these conditions 1 mole DL-alanine with no trace of ammonia, glycine or serine. Moreover, when hydrolysis of "hydro A" with acid is carried out in presence of 2,4-dinitrophenylhydrazine, a substantial yield of glyoxal bis-2,4-dinitrophenylhydrazone is obtained. Such behaviour is characteristic of 2-substituted oxazole-4-carboxylic esters and amides as outlined in the sequence II $\rightarrow$ III $\rightarrow$ IV. The 5-H of the oxazole ring in the antibiotic (see II) reveals itself in the n.m.r. spectrum as a sharp singlet at δ = 7.85 p.p.m. ($CDCl_3$ solution) and is similarly located in the spectra of model oxazoles.



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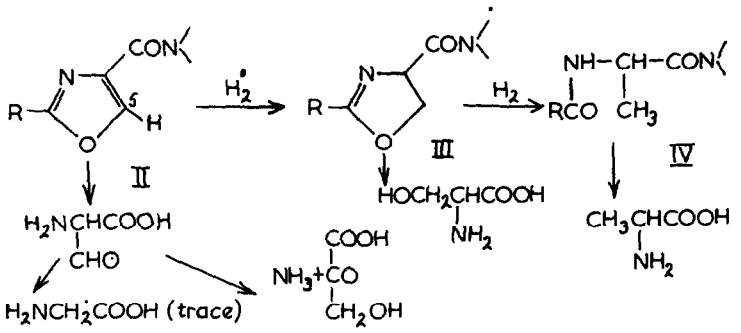
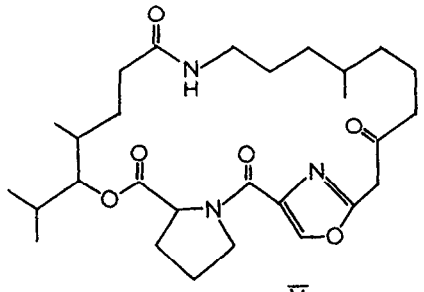


Taking into account also the known production of 1 mole CO_2 on acid hydrolysis, and of ca 1 mole acetic acid on alkaline hydrolysis of both ostreogrycin A and "hydro A", the partial formula (II) can now be expanded to the complete structure (V) for deoxy-octahydro-ostreogrycin A. The location of one ethylenic double bond in ostreogrycin A follows from the isolation of 2,4-dimethylpent-2-en-1-al on ozonolysis; a second must be in the pyrrolidine ring of (V) and the remaining two located in a conjugated system giving rise to methylglyoxal on ozonolysis. The position of these three linkages was fixed by n.m.r. spectroscopic double resonance studies on the one hand and by chemical degradation on the other. When ostreogrycin A was ozonised and the product worked up oxidatively, substantial amounts of β-alanine and glycine (not aspartic acid as earlier reported (2)) were obtained. The location of the allylic hydroxyl in the antibiotic adjacent to the conjugated system yielding methylglyoxal on ozonisation was determined by n.m.r. spectroscopy, high resolution mass spectrometry, and by degradative studies on "perhydro A". The conclusion that (VI) represents the molecular structure of ostreogrycin A not only explains all results of chemical degradation and mass spectrometric studies, but is in accord with every detail of the proton

magnetic resonance spectrum of the antibiotic which has been completely analyzed by double resonance techniques at 100 Mc.



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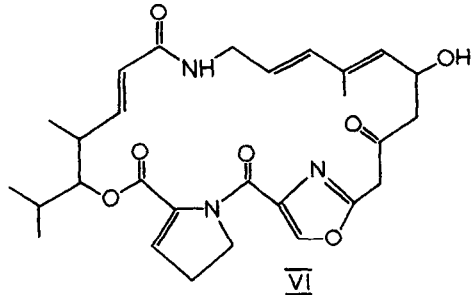

VI

Cstreogrycin A thus belongs to the very small group of natural products containing an oxazole nucleus. As far as we are aware it is the first antibiotic embodying this system, although griseoviridin (3) contains a system of three carbons, nitrogen and an oxygen which could yield an oxazole ring by simple cyclisation.

Full details of the work leading to the establishment of structure (VI) will published elsewhere.

References

S. Ball, B. Boothroyd, K.A. Lees, A.H. Raper and E. Lester Smith, Biochem. J., 68, 248 (1958)

Lord Todd, Ind. Chim. Belge, 12, 1433, (1962)

M.C. Fallona, P. de Mayo, T.C. McMorris, T. Money and A. Stoessl, Can. J. Chem., 42, 371, (1964)