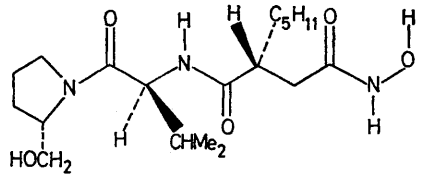
Total Synthesis of the Antibiotic, Actinonin

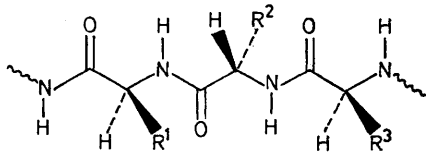
By NICHOLAS H. ANDERSON, W. DAVID OLLIS,* JOHN E. THORPE, and A. DAVID WARD
(*Department of Chemistry, The University, Sheffield* S3 7HF)

Summary A regioselective and stereoselective synthesis of the antibiotic, actinonin (**1**), is described.

THE antibiotic, actinonin (**1**),[1] produced by *Streptomyces roseopallidus* is of interest in several respects. It is the first natural product to be identified (a) as a hydroxamic

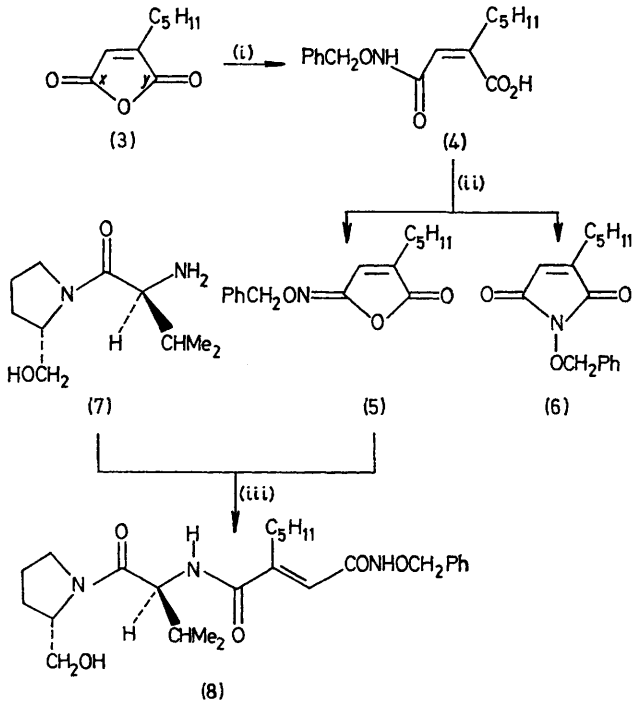


(1) Actinonin



(2)

acid[2] and (b) a derivative of L-prolinol. Furthermore, although actinonin contains a residue derived from D-(+)-pentylsuccinic acid,[3] the absolute configuration (**1**) of actinonin[1] is such that the topological[4] arrangement of its pentyl, isopropyl, CO, and NH groups shows a noteworthy isosteric correspondence with a polypeptide (**2**) containing only L-amino acid residues. This topological correspond-



SCHEME

Reagents and conditions: (i) $PhCH_2ONH_2$ in anhydrous ether at 0°; (ii) *NN'*-dicyclohexylcarbodi-imide in ethyl acetate at 0° followed by thick layer chromatography (silica–benzene); (iii) ethyl acetate at room temperature. Abbreviations (i—iii) are also employed in the text.

ence (*cf.* **1** and **2**) could be relevant in structure—activity correlation.[5,6] The synthesis of actinonin (**1**) is now reported.

The reaction of pentylmaleic anhydride (**3**)[7] with nucleophiles was expected to be regioselective by steric control (see **3**; reaction preferred at x rather than y). Reaction (i) of pentylmaleic anhydride (**3**) and *O*-benzylhydroxylamine[8] gave *one* product identified as the maleamic acid (**4**); its ozonolysis, reduction of the intermediate ozonide, and treatment with diazomethane yielded methyl 2-oxoheptanoate, characterised as its 2,4-dinitrophenylhydrazone. In contrast with earlier beliefs,[9] dehydration (ii) of the maleamic acid (**4**) yielded the isomaleimide (**5**; λ_{max} 285 nm; ν_{max} 1795, 1640 cm^{-1}) as the *major* product and the maleimide (**6**; λ_{max} 216 nm, ν_{max} 1730, 1625 cm^{-1}) as the *minor* product.

The reaction of the isomaleimide (**5**) with nucleophiles was expected to be regioselective (see **5**; reaction preferred at C=O rather than C=N).[10] The maleimide (**5**) and L-valyl-L-prolinol (**7**)[11] yielded (iii) the fumaryl bisamide (**8**)† which by catalytic hydrogenation and hydrogenolysis (palladised charcoal catalyst in ethanol–pyridine[12]) gave actinonin (**1**).

(*Received*, 31*st December* 1973; *Com.* 1755.)

† The fumaryl configuration (**8**) is proposed on the basis of model reactions between the maleimide (**5**) and other primary amines.

[1] J. J. Gordon, B. K. Kelly, and G. A. Miller, *Nature*, **1962**, **195**, 701; A. J. East, W. D. Ollis, and I. O. Sutherland in 'Chemistry of Microbial Products,' Institute of Applied Microbiology Symposium No. 6, University of Tokyo, **1964**, p. 204.

[2] J. B. Bapat, D. St. C. Black, and R. F. C. Brown, *Adv. Heterocyclic Chem.*, **1969**, **10**, 199; H. Maehr, *Pure Appl. Chem.*, **1971**, **28**, 603.

[3] A. Fredga, *Arkiv Kemi*, **1953**, **6**, 277.

[4] R. O. Studer, 'Progress in Medicinal Chemistry,' Butterworths, London, **1967**, Vol. 5, p. 1; M. M. Shemyakin, Yu. A. Ovchinnikov, and V. T. Ivanov, *Angew. Chem. Internat. Edn.*, **1969**, **8**, 492; J. S. Davies in 'Amino-acids, Peptides, and Proteins,' ed., G. T. Young (Specialist Periodical Reports), The Chemical Society, London, **1969**, Vol. 1, p. 211; **1970**, Vol. 2, p. 192; **1971**, Vol. 3, 276; V. T. Ivanov and Yu. A. Ovchinnikov, 'Conformational Analysis,' ed. G. Chiurdoglu, Academic Press, New York, **1971**, p. 111.

[5] G. Hartmann, W. Behr, K.-A. Beissner, K. Honikel, and A. Sippel, *Angew. Chem. Internat. Edn.*, **1968**, **7**, 693; R. Bentley, 'Molecular Asymmetry in Biology,' Academic Press, New York, **1969**, Vol. 1, 239; J. Schmidt-Thomé, *Angew. Chem. Internat. Edn.*, **1971**, **10**, 817; C. Toniolo and A. Signor, *Experientia*, **1972**, **28**, 753.

[6] M. M. Attwood, *J. Gen. Microbiol.*, **1969**, **55**, 209.

[7] Pentylfumaric acid was prepared by the general method of W. R. Vaughan and K. S. Anderson, *J. Amer. Chem. Soc.*, **1955**, **77**, 6702; *J. Org. Chem.*, **1956**, **21**, 673. Dehydration (P_4O_{10}; 180°; 1 h) gave the anhydride (**3**).

[8] O. Janny, *Ber.*, **1883**, **16**, 174; R. Behrend and K. Leuchs, *Annalen*, **1890**, **257**, 207.

[9] D. E. Ames and T. F. Grey, *J. Chem. Soc.*, **1955**, 631. In this report the anhydro-derivative of *N*-benzyloxy-maleamic acid was incorrectly formulated as a symmetrical maleimide. It is, in fact, the isomaleimide (λ_{max} 288 nm, ν_{max} 1795, 1640 cm^{-1}).

[10] W. R. Roderick and P. L. Bhatia, *J. Org. Chem.*, **1963**, **28**, 2018; R. Paul and A. S. Kende, *J. Amer. Chem. Soc.*, **1964**, **86**, 4162; C. K. Sauers and R. J. Cotter, U.S. 3,133,070 (*Chem. Abs.*, **1964**, **61**, 7026); E. Hedaya, R. L. Hinman, and S. Theodoropulos, *J. Org. Chem.*, **1966**, **31**, 1317.

[11] L-Valyl-L-prolinol (**7**) was synthesised by standard methods (M. Bodanzksy and V. de Vigneaud, *J. Amer. Chem. Soc.*, **1959**, **81**, 5688).

[12] M. Masaki, J. Ohtake, M. Sugigama, and M. Ohta, *Bull. Chem. Soc. Japan*, **1965**, **38**, 1802.