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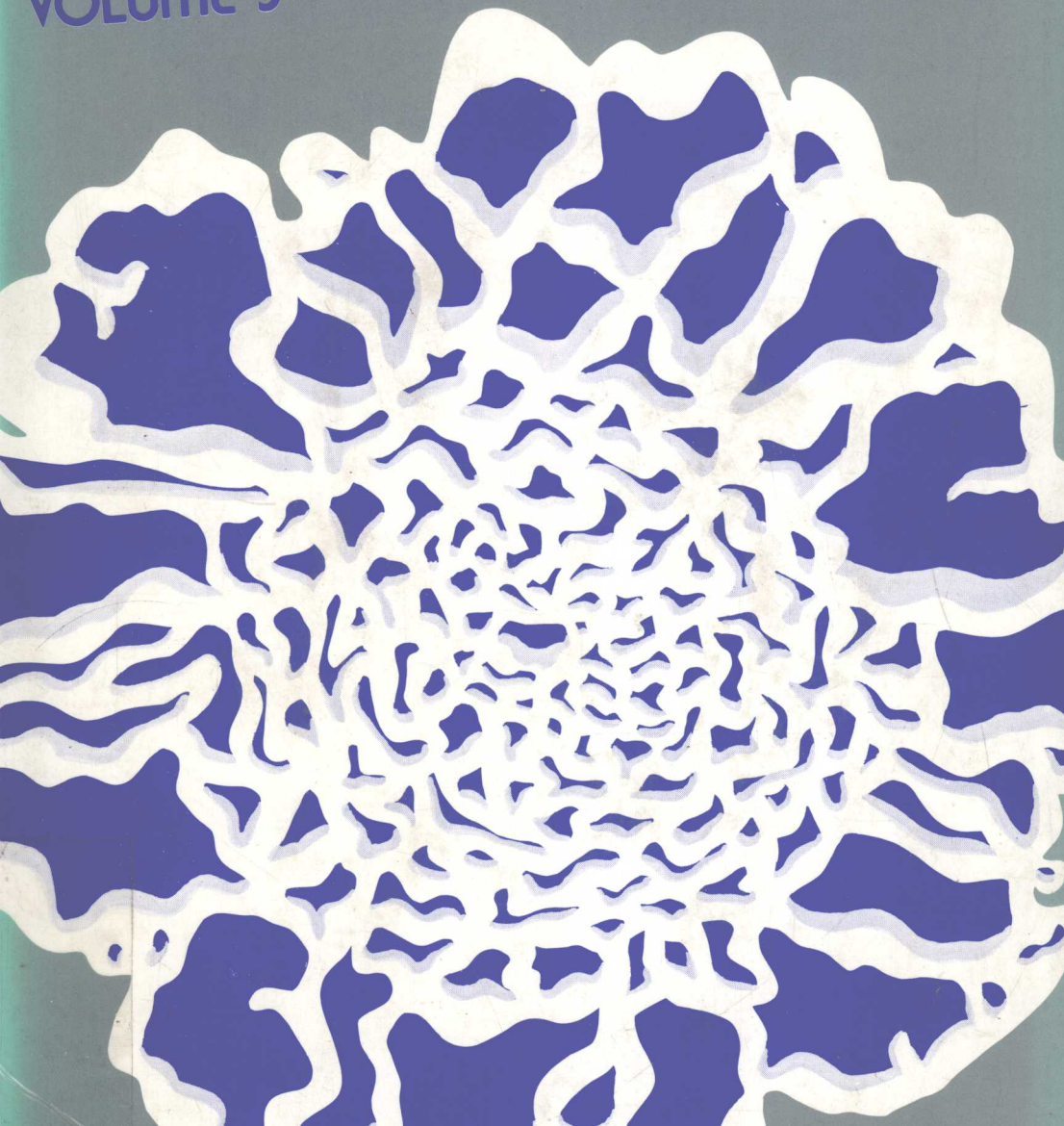
TOPICS IN ANTIBIOTIC CHEMISTRY

edited by Peter Sammes

VOLUME 5



TOPICS IN ANTIBIOTIC CHEMISTRY
Vol. 5

TOPICS IN ANTIBIOTIC CHEMISTRY

Series Editor:
P. G. SAMMES, Head of Department of Organic Chemistry,
University of Leeds

The object of this international series is to keep all interested workers informed on the advances of our knowledge concerning the role of antibiotics in nature, and on the mechanisms by which they act against pathogenic organisms. Future volumes have been planned and will appear regularly.

Volume 1 **The Aminoglycosides** – D. A. Cox, K. Richardson and B. C. Ross, Pfizer Central Research, Sandwich, Kent.

The Ansamycins – M. Brufani, University of Siena, Italy.

Volume 2 **Antibiotics from Marine Organisms** – D. J. Faulkner, Scripps Institution of Oceanography, University of California, San Diego.

Oligosaccharide Antibiotics – A. K. Ganguly, Schering Corporation, Bloomfield, New Jersey.

Daunomycin and Related Antibiotics – F. Arcamone, Farmitalia-Ricerca Chemica, Milan.

Interactions of Daunomycin and Related Antibiotics with Biological Receptors – S. Neidle, Department of Biophysics, King's College, University of London.

Volume 3 **Mechanisms of Action of Nalidixic Acids and its Congeners** – G. C. Crumplin, J. M. Midgley and J. T. Smith, London University School of Pharmacy.

New β-Lactam Antibiotics – R. D. G. Cooper, The Lilly Research Laboratories, Eli Lilly Company, Indianapolis, Indiana.

Volume 4 **The Chemistry and Antimicrobial Activity of New Synthetic β-Lactam Antibiotics** – Frederic A. Jung, William R. Pilgrim, J. Philip Poyser and Patrice J. Siret, I.C.I. Pharma S.A., Reims, France.

Volume 5 **Antibiotics and Peptidoglycan Metabolism** – J. M. Ghuysen, Faculté de Médicine, Institute de Botanique, Universitié de Liège.

The Vancomycin and Ristocetin Group of Antibiotics – D. H. Williams, V. Rajanada, M. P. Williamson and G. Bojesen, University Chemical Laboratory, Cambridge.

Properties and Action of Kirromycin (Mocimycin) and Related Antibiotics – A. Parmeggiani and G. Sander, Laboratoire de Biochemie, École Polytechnique, Palaiseau Cedex.

The Actinomycins – A. B. Mauger, Research Foundation of the Washington Hospital Center, Washington, D. C.

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Table of Contents

Editor's Preface

The target of previous volumes of the series, 'Topics in Antibiotic Chemistry', has been to keep all interested workers and students informed on the advances being made in our knowledge on the role antibiotics play in nature and on the mechanisms by which they act against various microorganisms. This target remains the prime objective of Volume 5.

As the title of the series implies, emphasis is given to the chemical nature of such interactions, although due account is taken of related factors, such as the function of pharmaco-kinetics and on the mechanisms of resistance.

Contributions to 'Topics in Antibiotic Chemistry' are only sought from experts in the various fields, and a further important requirement is that these experts must be actively engaged in research in the topic covered by their articles. This precedent was set in Volume 1 and has been rigorously followed in all subsequent volumes.

This current issue of the series includes four topics. The first, by Professor J.-M. Ghuysen, of the University of Liege, Belgium, is devoted to consideration of the consequences of antibiotic action on bacterial cell wall formation, specifically the peptidoglycan components, and also reviews current knowledge on the carboxypeptidases and transpeptidases involved in peptidoglycan metabolism.

Nature has provided many novel and complex structures and one must include in these the vancomycin and ristocetin group of antibiotics. In the second topic Dr. Dudley Williams and his colleagues, from the University of Cambridge, U.K., describe their work at characterising these agents and their investigations on their properties as chelating agents which mask the terminal D-alanyl-D-alanine part of bacterial peptidoglycan strands.

In the third review, Professor Parmeggiani and Dr G. Sander correlate the recent work on the mode of action of kirromycin and related antibiotics, a family which includes the commercial antibiotic, aurodox. These antibiotics interfere with the catalysts promoting elongation of peptide chains at ribosomal sites.

The final review is of the actinomycins, the classical DNA intercalating agents; although they are rather toxic compounds and used only against a few

specific diseases, these agents have an important role in helping to unravel the intricacies of bacterial cell biology and this review presents a current picture of knowledge in the area. Dr Tony Mauger, working at the Research Foundation, Washington Hospital Center, U.S.A., also describes the structure-activity relationships so far found in these agents, which now number more than a hundred.

As editor of 'Topics in Antibiotic Chemistry' it is gratifying to learn that the series is becoming more widely known and accepted as a standard item in chemical, biochemical and medical libraries. I wish to thank all those who have made constructive remarks about the previous volumes and to extend an invitation for helpful and critical comments on the present volume. Suggestions for future articles will be very welcome and will receive serious consideration. As before, it is not our intention to restrict articles to purely chemical aspects of the subject, but to also include associated areas of interest, such as modern methods for assaying, screening, and isolation of this very important group of drugs. Volume 6 of the series is already being planned and further volumes are under discussion.

The production of this volumes depends a great deal on many people, in particular the authors, who bear the brunt of my editorial foibles and who constantly, but thankfully, surprise me by their prompt preparation and correction of manuscripts and proofs. The continued assistance of the growing family at Ellis Horwood Ltd, our publishers, is particularly important. May I, once again, acknowledge with thanks their help and encouragement.

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July 1980

Part A

Antibiotics and Peptidoglycan Metabolism

by

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PART A

CONTENTS

1 INTRODUCTION

The wall peptidoglycan, the main supporting exostructure of the bacterial cell, has as its essential function, to keep the bacteria alive, under ordinary hypotonic environmental conditions. The wall peptidoglycan is both indispensable and unique to the prokaryotes so that antibiotics that act as inhibitors of peptidoglycan synthesis (cell wall inhibitors) have no corresponding targets in the eukaryotes, which explains their high selective toxicity. The cell wall inhibitors have another property not shared by many other antibiotics. Not only do they inhibit cellular growth, but they induce killing and lysis of the great majority of sensitive bacteria, which explains their high efficacy as antibacterial agents. This article is composed of three parts. Chapter 2 deals with the organization and assembly of the peptidoglycan and the other polymers which, altogether, form the bacterial cell wall. Chapter 3 describes (i) the susceptible points of attack along the peptidoglycan biosynthesis pathway; (ii) the modes of action of the main known cell wall inhibitors at each point of attack; (iii) the mechanisms through which these antibiotics exert their irreversible effects, i.e. bacterial death and lysis; and (iv) the mechanisms through which bacteria protect themselves against these toxic effects. Finally, in Chapters 4–7, an attempt has been made to present a comprehensive view of the mode of action of the most important cell wall inhibitors, the β-lactam antibiotics.

2 ASSEMBLY OF BACTERIAL CELL WALLS

2.1 Primary Structure of the Peptidoglycans

A complete bibliography on this topic can be found in [1-6]. The peptidoglycan is a network of high tensile strength which encloses the bacterial cell. It consists of linear glycan strands that are cross-linked by branched peptide chains. The glycan moiety consists of alternate pyranoside residues of N-acetylglucosamine and N-acetylmuramic acid, linked together by β, 1-4 linkages (Figure 2.1). It is a chitin-like structure in which each alternative N-acetylglucosamine residue contains a D-lactyl group ether linked to C(3). This structure is remarkably well conserved. The only variations encountered are the replacement of N-acetylmuramic acid by N-glycolylmuramic acid in *Nocardia* and *Mycobacteria* and the occurrence of small amounts of mannomuramic acid, along with the glucose derivative in a few bacteria.

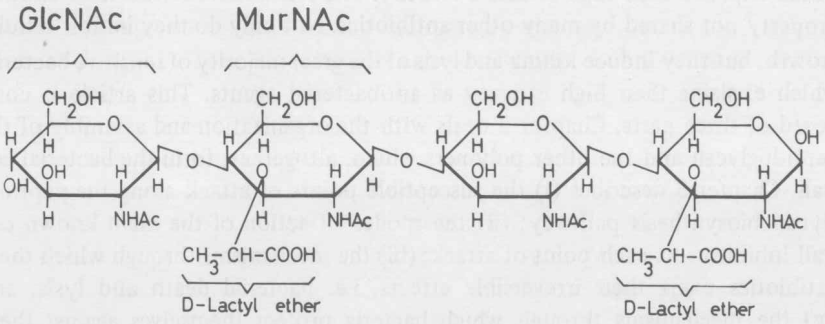

Figure 2.1 A portion of a glycan strand. In the peptidoglycan network, the COOH of the D-lactyl groups are substituted by tetrapeptides L-Ala-D-Glu-L-R_3-D-Ala where R_3 is a variable amino acid residue.

The glycan strands have short L-Ala-D-Glu-L-R_3-D-Ala tetrapeptide units linked to their muramyl carboxyl groups. The peptide linkages are α except the bond between D-glutamic acid and the L-R_3 residue, which is in a γ linkage. This structure is also well conserved. In a few cases, L-serine or glycine occur at the N-terminus instead of L-alanine so that, except for the occasional appearance of glycine at this position, the backbone of the tetrapeptides always exhibits an alternating LDLD sequence. The residue at the third position (the L-R_3 residue), however, is susceptible to wide variations. It may be a diamino acid (L-ornithine, L-lysine, LL or *meso*-diaminopimelic acid), a neutral amino acid (L-alanine, L-homoserine) or a dicarboxylic amino acid (L-glutamic acid). Variations may also occur at the D-glutamic acid unit, where the carboxyl group can be either free, amidated, substituted by a C-terminal glycine or a glycine amide.

Peptide units substituting adjacent glycan strands are covalently linked together. The interpeptide bridges always extend between the C-terminal D-alanine