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TOPICS IN ANTIBIOTIC CHEMISTRY

VOLUME 3

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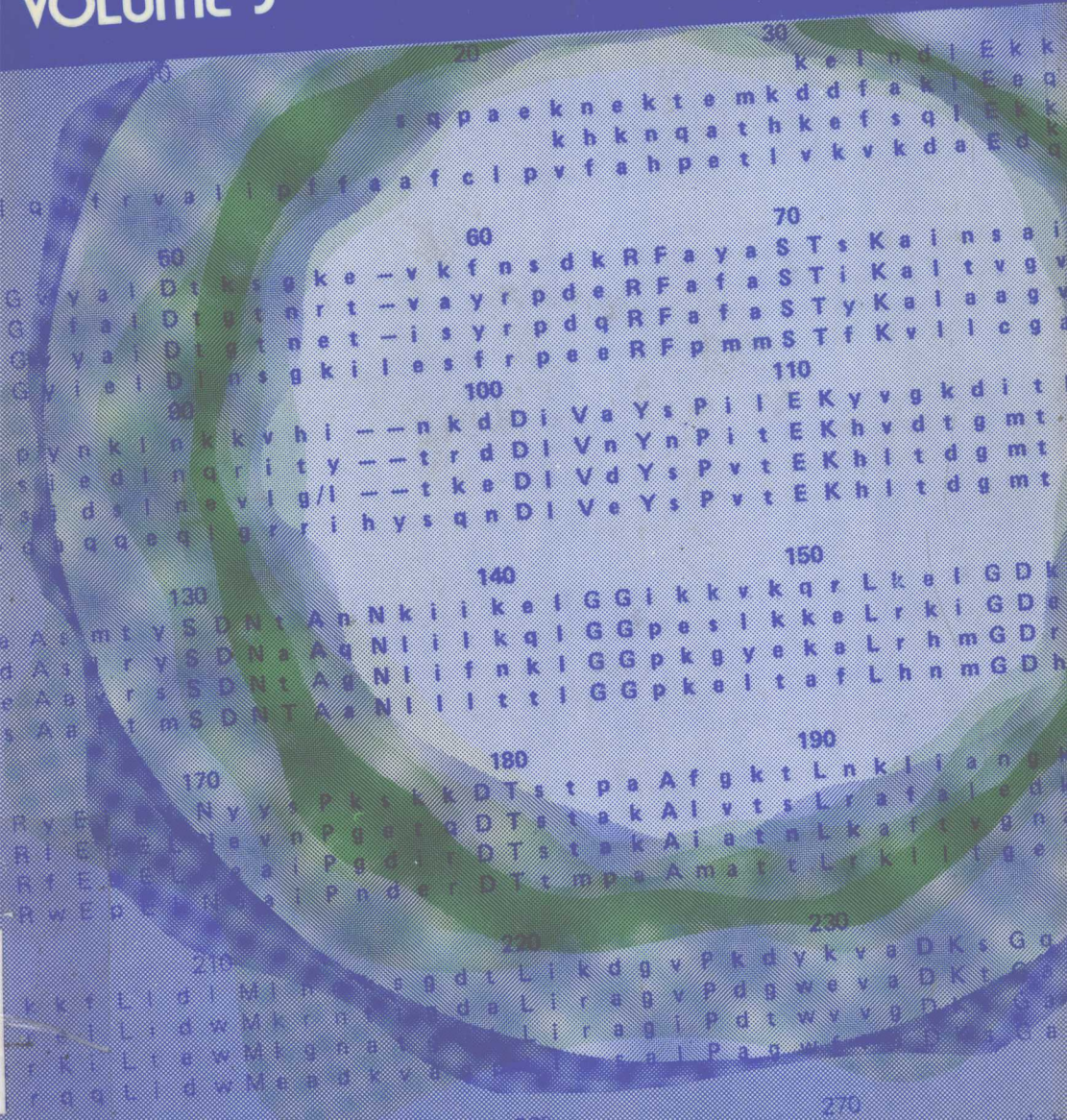

TOPICS IN ANTIBIOTIC CHEMISTRY

Volume 3

Mechanisms of Action of Nalidixic Acid and its Congeners
New β-Lactam Antibiotics

TOPICS IN ANTIBIOTIC CHEMISTRY

Series Editor:

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

The object of this continuing 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.

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Volume 3 **MECHANISMS OF ACTION OF NALIDIXIC ACID AND ITS CONGENERS, NEW β-LACTAM ANTIBIOTICS**

Mechanisms of Action of Nalidixic Acid and Its Cogeners – G. C. Crumplin, J. M. Midgley, 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.

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Editor's Preface

This continuing series on antibiotic chemistry will keep all interested workers fully informed on the advances being made on the role antibiotics play in nature and on the mechanisms by which they act against pathogenic organisms. The emphasis is on the chemical nature of such interactions, although account is taken of related factors such as the function of pharmaco-kinetics and on inbuilt resistance mechanisms. Antibiotics not only serve an important function in helping to fight disease, but they also serve as useful tools in unravelling the mysteries of nature, especially the precise chemical details by which living matter survives and regenerates.

Contributions to *Topics in Antibiotic Chemistry* are sought only from experts who are actively engaged in research in the fields covered by their articles. This precedent was set in Volume 1 and has subsequently been rigorously followed. Although the intention is to try to cover several topics in each volume, each reflecting different aspects of the subject, the sheer amount of effort being devoted to research in the area of β-lactam antibiotics has meant that, in this present volume, only two topics could be included.

In Part A Professor John Smith and his colleagues, from the School of Pharmacy, at the Square, London, have written a critical article on current knowledge on the mechanisms of action of nalidixic acid and its congeners. The nalidixic acid types of antibiotics are unusual amongst prescribed antibiotics in that they are totally synthetic compounds; nalidixic acid was itself discovered as a side product during the synthesis of the antimalarial compound chloroquine. This article reveals the complex nature of the problems associated with solving the interactions of relatively simple molecules, such as nalidixic acid, with complex biopolymers.

In recent years experts on the penicillin and cephalosporin group of antibiotics have been greatly excited by the discovered of several novel, natural products containing the β-lactam function. Hitherto no review of these compounds has been made. This volume provides a comprehensive survey of these compounds which include clavulanic acid, the thienamycins, olivanic acids and

nocardicins, and the review emphasises their structure-activity relationships as well as chemical routes aimed at their synthesis and details on their chemical properties.

It is gratifying to learn of the growing interest in this series of volumes. As editor of *Topics in Antibiotic Chemistry* I would welcome constructive comments and criticisms. Any suggestions for future articles, will be very welcome and will all receive serious consideration. As before, it is not our intention to restrict the scope of articles to purely chemical aspects of the subject but to also include associated areas of interest, such as modern methods for screening, isolation and production of this very large and important group of drugs.

The production of these volumes depends a great deal on a large number of people. May I especially acknowledge the co-operation received from the contributors to the volume and the staff at Ellis Horwood Ltd., our publishers.

P. G. Sammes,
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Leeds LS2 9JT

July 1979

Table of Contents

Part A

Mechanisms of Action of Nalidixic Acid and its Congeners

by

GEOFFREY C. CRUMPLIN, JOHN M. MIDGLEY, and JOHN T. SMITH

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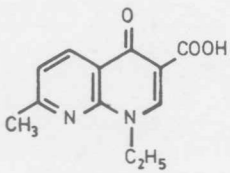
UNIVERSITY OF LONDON, LONDON, ENGLAND

PART A

CONTENTS

1 INTRODUCTION

Nalidixic acid (**1**), a synthetic antibacterial agent first synthesized by Lesher *et al.* [1], has been widely used for the treatment of urinary-tract infections for 15 years. At the time of its introduction nalidixic acid was a completely new structural type of chemotherapeutic agent. Many congeners of nalidixic acid have since been synthesized despite the fact that the mechanism of action of this type of compound has been, and still remains, poorly understood. Many workers have investigated the activity of nalidixic acid upon susceptible bacteria in the hope of resolving its mechanism of action. The extent of the resultant literature is a testimony to the surprising complexities associated with the activity of this structurally simple type of compound.



NALIDIXIC ACID

(**1**)

Nalidixic acid (1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid) was synthesized [1] after the discovery that the corresponding 7-chloroquinoline (7-chloro-1,4-dihydro-1-ethyl-4-oxoquinoline-3-carboxylic acid), obtained from the mother liquors during the purification of chloroquine, possessed antibacterial activity. Nalidixic acid is a heat-stable, weak organic acid which is relatively insoluble in water but soluble in aqueous bases (e.g. NaOH) and polar organic solvents. It is a crystalline solid of molecular formula $C_{12}H_{12}N_2O_3$ (MW 232.3). In aqueous solutions nalidixic acid decomposes on exposure to ultraviolet radiation, and several bacterially inactive photo-products are formed [2].

Nalidixic acid is particularly active against Gram-negative bacteria *in vitro* and *in vivo* [3] (Table 1.1) and has proved useful in the clinical management of

urinary tract infections caused by *Eschericia coli,* Proteus, and Klebsiella species [4, 5, 6]. It has also been found to be well tolerated by humans, and excreted at therapeutic levels in patients with impaired renal function [7, 8]. Because of its specific activity against Gram-negative bacteria, nalidixic acid has also proved beneficial in the treatment of enteric infections, particularly dysentery caused by *Shigella sonnei* [9]. Although it is relatively easy to isolate nalidixic acid-resistant bacteria *in vitro* [10, 11], surveys of the resistance of clinically isolated uropathogens have showed that the incidence of nalidixic acid-resistant isolates has remained surprisingly low despite extensive clinical use [12, 13].

Table 1.1

Representative minimal inhibitory concentrations (MICs) for nalidixic acid. MICs were measured using single-cell inocula on nutrient agar plates (Data from Microbiology Section Laboratory, The School of Pharmacy, University of London)

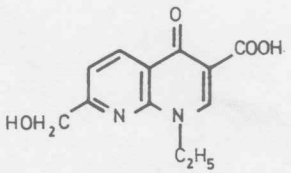
Test organism	*No. of strains*	*Range of MICs (μg/ml)*
E. coli	8	1 – 10.0
Klebsiella aerogenes	2	2 – 5.0
Proteus mirabilis	1	3.0
Shigella sonnei	1	1.5
Salmonella typhimurium	2	2.5 – 4.0
Pseudomonas aeruginosa	3	20 – 750
Staphylococcus aureus	4	20 – 750
Streptococcus faecalis	2	80 – 500
Diplococcus pneumoniae	1	350
Bacillus subtilis	2	5 – 10

2 CONGENERS OF NALIDIXIC ACID

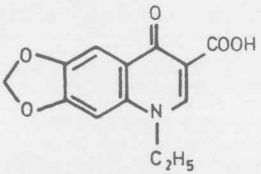
As a result of the therapeutic and commercial success of nalidixic acid there has been an extensive search for derivatives possessing either a broader spectrum of antibacterial activity, or improved pharmacological properties. Many hundreds of compounds have been synthesized and screened, and their chemistry has been recently reviewed by Albrecht [14]. However, very few compounds have found clinical use: only nine compounds have become available for either clinical or *in vitro* investigation. These compounds are:

Nalidixic acid (**1**) [1]
hydroxynalidixic acid (**2**) [15]
oxolinic acid (**3**) [16]
piromidic acid (**4**) [17]
cinoxacin (**5**) [18]
flumequine (R802) (**6**) [19]
pipemidic acid (**7**) [20, 21]
tioxic acid (**8**) [22]
a thieno[2,3-b]pyridine analogue (**9**) [23]

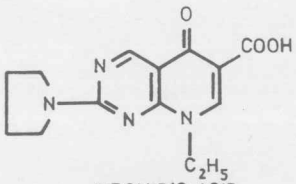
The mechanism of action of several of these compounds upon susceptible bacteria has been studied, and the results suggest that they all exhibit a common mechanism of action [24]. However, nalidixic acid has been by far the most extensively investigated compound of the class, and hence this chapter will be largely devoted to the study of its mode of action.



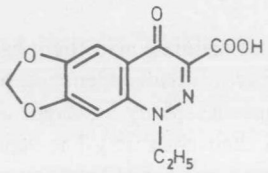
HYDROXYNALIDIXIC ACID
(**2**)



OXOLINIC ACID
(**3**)

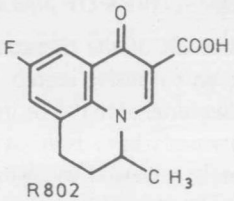


PIROMIDIC ACID
(**4**)



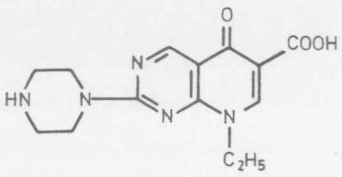
CINOXACIN

(5)



R802

(6)



PIPEMIDIC ACID

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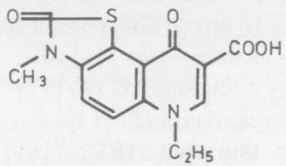
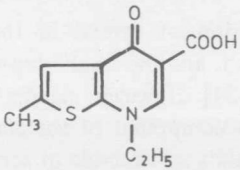


TIOXIC ACID

(8)



THIENO [2,3-b] PYRIDINE ANALOGUE

(9)