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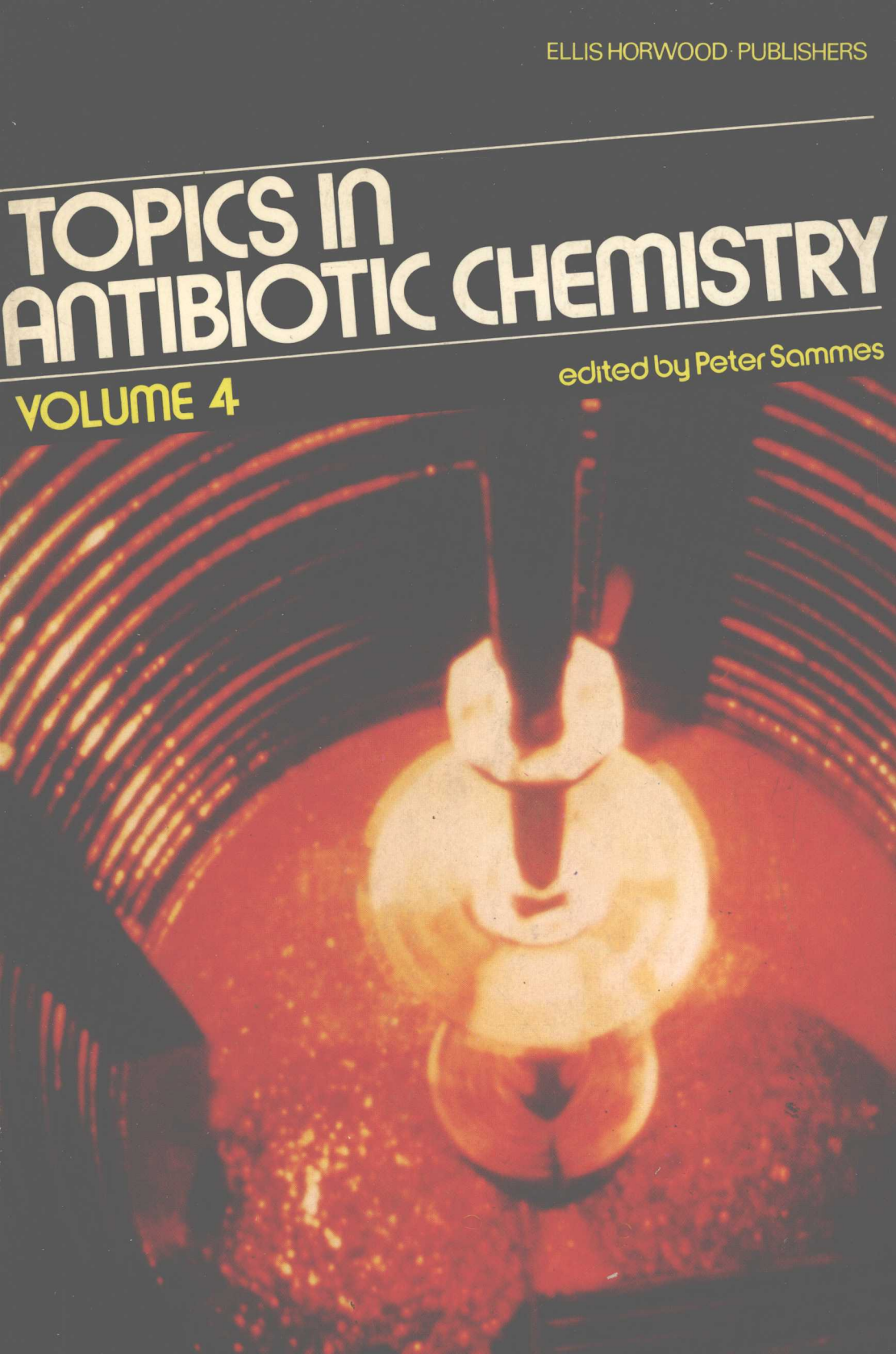
TOPICS IN ANTIBIOTIC CHEMISTRY

VOLUME 4

edited by Peter Sammes



TOPICS IN ANTIBIOTIC CHEMISTRY

Vol. 4

The Chemistry and Antimicrobial Activity of New Synthetic 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 continuation 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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The Ansamycins – M. Brufani, University of Siena, Italy.

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

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Mechanisms of Action of Nalidixic Acid and Its Congeners – 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.

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.

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Preface

In Volume 4 of this series the target set in the earlier volumes has again been followed, namely 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.

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 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.

As an exception to our general policy to try to cover several topics in each volume, this issue contains only one article, covering recent work on the total synthesis of penicillin and cephalosporin types of antibiotics and on the biological activity of such systems. No apologies are offered for this specialisation. The β-lactam group of antibiotics, which includes the penicillin and cephalosporin families, are the most important of all the antibiotics in general therapeutic use, and their annual production is in the order of kilo-tons. Within the last decade great advances have been made in the technology of their total chemical synthesis. This change has permitted the preparation of a large number of variations of the naturally occurring skeleton based on the penam and cephem systems. Furthermore, this methodology has come about at the same time as the discovery of a large number of new β-lactam structural types such as clavulanic acid, thienamycin, and the olivanic acids. The latter group of compounds were reviewed by Dr Robin Cooper in Volume 3 of this series. In the present volume Drs Jung, Pilgrim, Poyser, and Siret of ICI Pharma S.A., Reims, France, have surveyed modern synthetic approaches to a wide range of variants in the β-lactam field. These chemical approaches are set into context with details of the biological activity of these new analogues wherever they have been reported.

As a consequence, general trends and possible new approaches can be discerned to the problem of designing new β-lactam antibiotics with resistance to enzymic attack and with novel, desirable biological profiles.

As editor of *Topics in Antibiotic Chemistry* I have been greatly encouraged by the interest and demand generated by previous volumes. I wish to thank all those who have made constructive remarks about the series and to extend an invitation for constructive 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. Further volumes of the series are already planned and in preparation.

The production of these volumes depends a great deal on many people. The willingness of contributors to collaborate in the prompt preparation of manuscripts has greatly eased my task. The continued assistance of the staff at Ellis Horwood Ltd, our publishers, is particularly important. May I acknowledge with thanks their help and encouragement.

August 1979

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1

Introduction

The penicillins, as the first successful family of antibiotics, occupy a privileged position in antibacterial chemotherapy. Together with the closely-related cephalosporins, they continue as first-line drugs in the treatment of bacterial infections. Today β-lactams account for almost half of all medically prescribed antibiotics.

The relatively low toxicity of β-lactam agents makes it highly desirable to extend their therapeutic range to Gram-negative species especially *Pseudomonas* strains, where the existing useful drugs are, for the most part, ones which have a rather low therapeutic ratio.

The success of this class of compound, however, has not been total. Resistant strains have come to occupy the ecological niches previously dominated by penicillin- or cephalosporin-susceptible strains. Sensitivity patterns to available antibacterials are changing, at times quite suddenly, owing to the emergence of new resistant strains and to the transfer of resistance factors, especially among Gram-negative bacteria.

β-lactam antibiotics are among the safest of the major drugs, but their use in human medicine has not been without problems. Immune-related side effects to penicillins occur in about 3% of the population although, fortunately, anaphylaxis occurs in only a very small fraction of these cases. The introduction of the cephalosporins has improved this situation somewhat, but about one in ten penicillin-sensitive patients is still at risk. Finally, with the exception of a few agents of limited antibacterial properties, good oral activity remains an elusive goal.

The patent activity in this domain – more than 150 different research laboratories filed patent applications between 1975 and 1978 – attests to the worldwide effort to ameliorate the current drugs. The international research effort has evolved in three different areas:

- chemical modification of natural products (e.g. penicillins, cephalosporins, cephamycins);
- screening of microbial metabolites for new antibacterial activity;
- preparation of new β-lactam-containing compounds by total synthesis.

Very large numbers of side-chain modified penicillins and cephalosporins have been reported, and it is this approach which has provided all of the β-lactams now used in medicine, including the most recent introductions (mecillinam, cefamandole, cefuroxime, cefoxitin, the ureidopenicillins, cefachlor, and cefotaxime).

New natural, biologically interesting β-lactam-containing ring systems, few in number but remarkable in their diversity and activity, have been discovered by modern screening methods and have revolutionised accepted structure-activity concepts (for example, the nocardicins, thienamycin, olivanic acids) and have even introduced new prospects for the treatment of infections due to resistant organisms (clavulanic acid). These compounds, described in Part B, Volume 3 of this series, have also served to stimulate new efforts to modify the earlier β-lactam antibiotics, just as the cephalosporins and cephamycins did in their time, and to create a greater interest in the synthesis of new ring systems.

The limited objective of the present volume is to describe, in both chemical and microbiological terms, the new synthetic modifications of penicillins and cephalosporins that have appeared from 1974 to the end of 1978. Earlier work is only included here as support material or for purposes of comparison, but has been well covered in other reviews dealing with the chemistry of β-lactams [1-10], structure-activity relationships in penicillins and cephalosporins [11-13], and the mode of action of β-lactam antibiotics [14-16]. The contents of this volume are arranged as follows:

- total synthesis of the natural skeletons and direct variations thereon;
- new systems obtained by modification of the natural β-lactam antibiotics;
- modifications to the natural penicillin and cephalosporin systems.

2

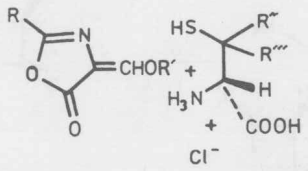
Total Synthesis of Penicillins and Cephalosporins

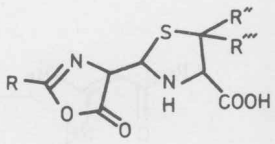
2.1 NATURAL SKELETON

The present section deals firstly with the synthesis of the parent systems and secondly with analogues which show some antimicrobial properties (or which might reasonably have been expected to do so). Incomplete total syntheses or those leading to inactive molecules are only included when important chemical advances have been made. Surprisingly, only three of the total syntheses so far reported are stereospecific [17].

The first attempts at total synthesis of penicillins were initiated very shortly after its isolation and before its structure had even been clearly elucidated [18]. Early efforts were directed towards the erroneous thiazolidine-oxazolone (**1**), as well as towards the correct structure (**2**) [19, 20]. Only traces of bioactive material were obtained.

SCHEME 2.1





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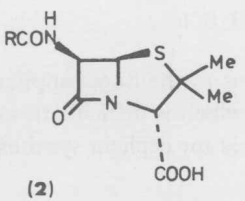

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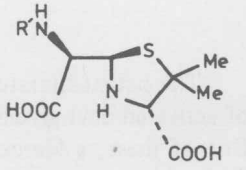
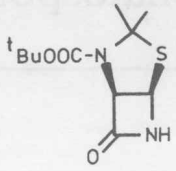


(3)

The first clearly successful synthesis, accomplished in 1957 by Sheehan and Henery-Logan [21–23] was achieved by carbodiimide cyclisation of a 5(R), 6(R)-penicilloate (3). Woodward and his colleagues reported their elegant synthesis of cephalosporin C in 1966 [24]. The versatile key compound (4), derived from L-cysteine, has since been obtained from penicillin [25, 26]. These classical approaches have been fully discussed elsewhere [27, 28].

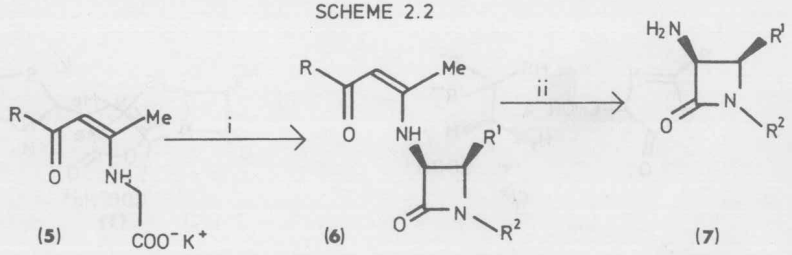


(4)

2.1.1 Total synthesis of penicillins

A route to penicillin construction very different from that of Sheehan has been based on the imine annulation reaction, the mechanism, scope and variations of which have been reviewed [10, 29]. Azidoacetyl chloride is the usual reagent, the azido group being the precursor of the side-chain nitrogen atom. Use of phthalimidoacetyl chloride has in the past posed deprotection problems, although new methods have since appeared [30, 39]. It has normally been supposed that activated acylamino acid derivatives are prohibited by azlactone formation. Illustrative of tactics which have been employed to avoid this is the use of the glycine-β-dicarbonyl condensation product (5), which, when reacted with an imine in the presence of phosphorus oxychloride and triethylamine [31], gives (6) and thus α-amino-β-lactam (7) (Scheme 2.2).

SCHEME 2.2



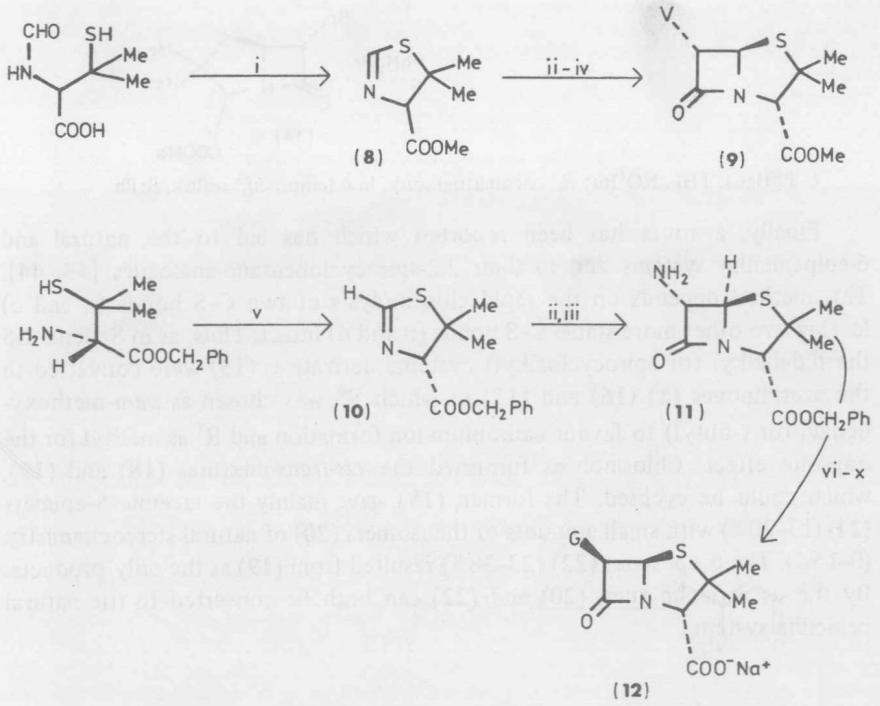
(5) (6) (7)

i, $R^1CH{=}NR^2$, $POCl_3$, NEt_3; *ii*, EtOH, HCl.

The patent literature contains two relevant claims to the direct application of activated acyl glycines [10, 32, 33], the value of which is difficult to assess. One of these, a Merck patent [33] covering a process for cephem synthesis, is discussed in Section 2.1.3.

Using the reaction which they have developed and studied, Bose and his co-workers have thus prepared (±)-6-epipenicillin V methyl ester (**9**) from racemic thiazoline (**8**), although in this case the β-lactam-forming reaction went in very low yield [34] (Scheme 2.3). In order to complete the synthesis, the stereochemistry at C-6 required inversion. Monocyclic β-lactams, generally, and some bicyclic systems, withstand nucleophilic displacement at this position, whereas other systems require an equilibration technique [29, 36, 37, 38]. The Merck group has developed [40] an effective deprotonation-protonation sequence on a 6α-Schiff base, and a 2:1 (kinetic) ratio of 6-epimers is obtained which favours the 6β-isomer. Using the optically active benzyl ester (**10**), azidoacetyl chloride added with 98% stereospecificity to give the *trans*-6α-epimer (**11**). Application of the epimerisation method afforded sodium penicillin G (**12**).

SCHEME 2.3

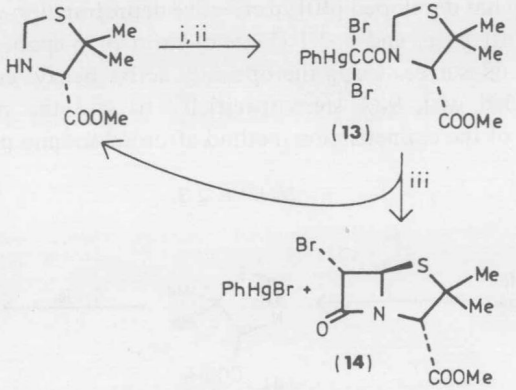


i, BF_3, MeOH; *ii*, N_3CH_2COCl, NEt_3, CH_2Cl_2, reflux; *iii*, H_2, benzene, PtO_2; *iv*, $PhOCH_2COCl$, NEt_3; *v*, HCSOEt, NEt_3; *vi*, p-$NO_2C_6H_4CHO$; *vii*, PhLi, DMF; AcOH, H_2O; separation; *viii*, DNPH, pTsOH; *ix*, $PhCH_2COCl$, pyr; *x*, 3 atm. H_2, 10% Pd/C, $NaHCO_3$, H_2O, MeOH.

5α-Phenylpenicillin V has been made [41] by a similar approach, a discussion being given in Section 2.1.4.3.

An interesting synthesis of the penam system has been reported [42] involving an organomercury derived carbene. Thermolysis of the intermediate mercurial (**13**) gave, after purification a 10% yield of pure (+)-methyl 6α-bromopenicillanate (**14**) (Scheme 2.4).

SCHEME 2.4



i, PhHgCl, THF, KO^{t}Bu; *ii*, chromatography, low temp.; *iii*, reflux, BrPh.

Finally, a route has been reported which has led to the natural and 6-epipenicillin systems and to their 2,2-spirocyclopentano-analogues [43, 44]. This method depends on the rapid chlorinolysis of two C–S bonds (a and c) leaving two other more stable C–S bonds (b and d) intact. Thus, as in Scheme 2.5 the β,β-dialkyl (or spirocycloalkyl) cysteine derivatives (**15**) were converted to the azetidinones (±) (**16**) and (**17**) in which R^4 was chosen as *para*-methoxybenzyl (or t-butyl) to favour carbonium ion formation and R^5 as methyl for the opposite effect. Chlorinolysis furnished the *cis-trans*-mixtures (**18**) and (**19**), which could be cyclised. The former, (**18**), gave mainly the racemic 5-epimers (**21**) (13–70%) with small amounts of the isomers (**20**) of natural stereochemistry (0–16%). The 6-epi series (**22**) (23–38%) resulted from (**19**) as the only products. By the usual techniques, (**20**) and (**22**) can both be converted to the natural penicillin system.