SYNTHETIC APPROACHES TO AROMATIC ANTITUMOR AGENTS AND ANTIBIOTICS

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DEGREE DATE: 1986

8703779

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Iowa State University PH.D. 1986

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Synthetic approaches to aromatic antitumor agents and antibiotics

by

John Allen Walling

A Dissertation Submitted to the
Graduate Faculty in Partial Fulfillment of the
Requirements for the Degree of
DOCTOR OF PHILOSOPHY

Department: Chemistry
Major: Organic Chemistry

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Iowa State University
Ames, Iowa

1986

DEDICATION

This dissertation is dedicated to my late grandfathers, Mr. Melvin Campbell and Mr. Julias "Al" Walling. Although neither of these men had the opportunity for higher education, their outstanding wisdom and qualities have and will continue to play an important role in my life. My great love and respect for them will never be forgotten.

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GENERAL INTRODUCTION

When a synthesis of a complex natural product or class of natural products is planned, many considerations are brought to the fore. Aside from the desire to accomplish an esthetically pleasing synthesis, the reactions used must proceed in high yield, and guarantee a high degree of regio- and stereoselectivity. If the reactions employed or discovered are operationally convenient, then another synthetic goal has been achieved. It was the purpose of this research to discover and apply novel synthetic strategies to aromatic antitumor antibiotics. Part I describes a facile entry to the carbon framework of olivin. Part II describes an efficient and convenient preparation of the aromatic subunit of alkavinone. Finally, Part III details the total synthesis of two important members of the pyranonaphthoquinone class of antibiotics.

Explanation of Thesis Format

This thesis is written so that each section can be regarded as a separate article in publishable form. Therefore, the numbering of the figures, schemes, tables, and references is independent in each division.

PART I: A SYNTHETIC APPROACH TO OLIVIN

INTRODUCTION

Olivin and chromomycinone are structural subunits of a growing class of potent antitumor antibiotics collectively known as the aureolic acids. At the time this work was initiated, no total synthesis of these interesting natural products had been reported. This manuscript will detail the results of a program directed toward the total synthesis of olivin in optically active form.

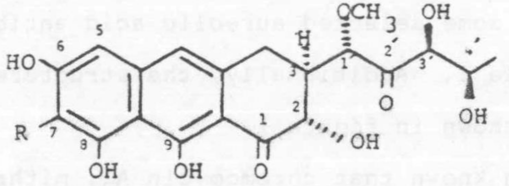
HISTORICAL

The first member of the aureolic acid class of antitumor antibiotics was isolated at the Abbott Laboratories in 1953 from an unknown Streptomyces species (1). Microbiological testing indicated activity against Gram(+)bacteria *in vitro*. Its high toxicity precluded its use as a potential antibacterial agent (lb). The compound was named aureolic acid due to its acidic properties. Aureolic acid was later discovered as LA-7017 by workers at Lepetit Laboratories (lc), and as mithramycin by workers at Pfizer Laboratories (ld). It was not until 1968 that LA-7017 and mithramycin were correlated with aureolic acid (le).

Since the initial isolation of members of the aureolic acid class in 1953, two other subclasses of aureolic acid antibiotics have been isolated and microbiologically characterized. The chromomycins were isolated from Streptomyces griseusis by Shibata et al. in 1960 (2). Later, the discovery and isolation of the olivomycins as NSC A-649 was accomplished by workers at the Bristol Laboratories. The antibiotic was found to be active against Gram(+)bacteria, and several animal tumors including the Ridgway osteogenic sarcoma, the Harding-Passey melanoma in mice, and the Walker carcinosarcoma in rats (3).

Many of the aureolic acid antibiotics have now evolved into clinically useful drugs for the treatment of human cancers. Mithramycin (aureolic acid) has been approved for use in the treatment of testicular cancers (4). The medicinal and biochemical aspects of this class of interesting drugs have been the subject of several reviews (5-10). The most important aspects of structure will be summarized here and, along with more recent information, the studies relating to the mode of DNA binding, and syntheses of the polysaccharide and aglycone subunits.

The structures of the three subclasses of aureolic acid antibiotics; the aureolic acids, the chromomycins, and the olivomycins, are based in part upon two aglycones, olivin (11) (1a) and chromomycinone (12) (1b).



1a R= H: olivin
1b R= CH_3: chromomycinone

The aureolic acids and the chromomycins have in common the aglycone chromomycinone, while the olivomycins contain the tetrahydroanthracene subunit known as olivin. The structures of the two aglycones are nearly identical except for the methyl group at position 7.

The above aglycones are linked at both the phenolic 6- and hydroxylic 2-positions by dideoxypyranose sugar residues. The C-6 position is most often linked with a disaccharide residue, while a trisaccharide is the common substituent at the C-2 position. The structure of one member of each subclass of aureolic acids has recently been revised. Thiem and Meyer have used a combination of detailed high field ^{13}C and ^{1}H NMR analyses to arrive at the nature of the interglycosidic linkages of chromomycin A_3 (13) and olivomycin A (14). Their initial studies of the interglycosidic linkages of mithramycin were conclusive at all but one linkage (14). Fortunately, a combination of synthetic and spectroscopic techniques led to the assignment of the previously unknown linkage (15).

The complete structure of olivomycin A ($\underset{\sim}{2}$) is shown below. The compositions of some selected aureolic acid antibiotics are provided in Table 1. Additionally, the structures of the dideoxy sugars are shown in figure 1.

It has long been known that chromomycin A_3, mithramycin, and olivomycin A complex with double-stranded DNA (16). Each inhibits DNA-dependent RNA synthesis by complexing with DNA. Unique to this class of antibiotics is the fact that Mg(II) or another divalent metal cation is necessary for complexation to occur (17). Furthermore, intercalation of the aglycone moieties with the purine and pyrimidine bases of DNA is not the important binding interaction (18). This is surprising in

Table 1. Compositions of some selected aureolic acid antibiotics

Compound	Aglycone	Sugars[a]
mithramycin	chromomycinone	oliose, olivose, olivose, olivose, D-mycarose
olivomycin A	olivin	acetyloliose, divomose, olivose, olivose, 4-isobutyrylolivomycose
olivomycin B	olivin	acetyloliose, olivomose, olivose, divose, 4-acetylolivomycose
olivomycin C	olivin	oliose, olivomose, olivose, olivose, 4-isobutyrylolivomycose
olivomycin D[b]	olivin	acetyloliose, olivomose, olivose, olivose
chromomycin A_3	chromomycinone	acetyloliose, olivomose, olivose, olivose, 4-isobutyrylolivomycose

[a] Named in the order A, B, C, D, E as shown in structure **2** for olivomycin A.

[b] Olivomycin D contains only four dideoxy sugars.

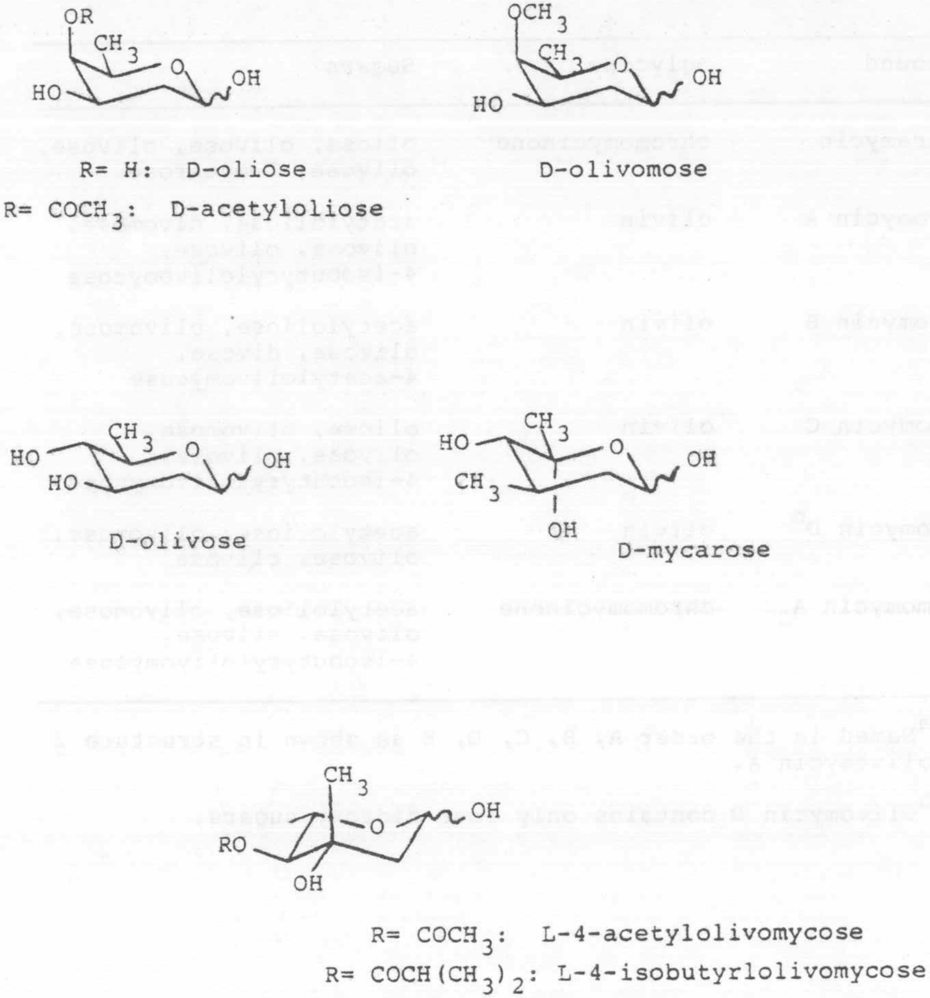


Figure 1. Structures of the dideoxy sugars commonly found in the aureolic acid group