

CHEMISTRY, BIOCHEMISTRY, AND PHARMACOLOGY OF VITAMIN B₆
AND OTHER TOPICS

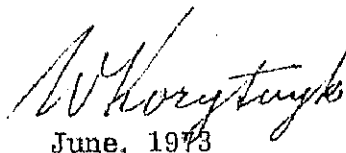
W. Korytnyk, Ph.D.

A thesis
presented for the degree of
Doctor of Science
in the
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ARRANGEMENT OF THE THESIS

The thesis consists of the following parts:

- A. Preface stating the genesis of the research projects, the nature of collaboration, and acknowledgments.
- B. Categorization and Significance of Research. This provides the reader with a guide to different aspects of research covered in the submitted publications, which are referred to by numbers.
- C. List of Publications. The list includes all publications in chronological order and each publication is numbered. Publications which are submitted are checked on the list (✓).
- D. Publications. The submitted publications include mainly papers, but some reviews and abstracts have also been included, the subject matter of which have not been covered adequately by papers. Papers resulting from the two years of post-doctoral studies have not been included. The number on the upper right hand corner refers to the number given in the List of Publications.



June, 1973

Buffalo, New York, U.S.A.

A. Preface

The majority of papers and some reviews comprising this thesis are dealing with various aspects of vitamin B₆. These studies commenced in 1960 with my appointment as a Senior Cancer Research Scientist at Roswell Park Memorial Institute in Buffalo, N.Y. At that time there was considerable interest in the development of more selective and potent antagonists of this vitamin as a rational approach to the chemotherapy of cancer and possibly other diseases. While keeping in mind this goal, it became clear to me at the beginning of that project that a prerequisite for a successful program in this area was a complete mastery of the chemistry of this vitamin in terms of chemical methodology as well as chemical reactions and interconversions that were pertinent to the projected synthesis of metabolites and antimetabolites. Thus the basic chemistry research on this vitamin went hand-in-hand with the synthetic projects. Collaborative studies with my biological colleagues on the mode of action of the antagonist have also been carried out. To a great measure all these studies were inspired and aided by my previous experiences in natural product chemistry, particularly in the carbohydrate chemistry, as well as by the encouragement received from Dr. Charles A. Nichol, then the Director of the Department of Experimental Therapeutics at Roswell Park Memorial Institute (till 1968). At a later date it has become desirable to add biochemical aspects to the problem, so to understand the mode of actions of the antagonists in molecular terms. These studies were aided by experience gained in the enzymology in the laboratory of Dr. Esmond E. Snell in the Biochemistry Department of the University of California at Berkeley, where I have spent six months in 1967-1968. On returning to Buffalo I have initiated enzymological investigations which have primarily contributed to our deeper understanding of the mode of action of the new antagonists synthesized.

A few papers unrelated to the "Chemistry and Biology of Vitamin B₆" series of papers have been submitted here. Thus, the two papers, one the lipid constituents of beans (17) and the other on the biosynthesis of stachyose and raffinose (11), are the result of my stay at the U.S. Department of Agriculture laboratory during 1959-1960. More recently, we have undertaken studies in guanyldihydrazones, which show some antileukemic activity, and the first short paper in this series is also included.

In the course of my studies I had the good fortune to be associated with a number of able collaborators on different levels: graduate technicians, graduate students, post-doctoral fellows, and established scientists within and outside Roswell Park. While in many cases their contribution was substantial, it is not possible to detail in each case the different turns the collaboration taken and to pinpoint their particular contribution. Nevertheless, in each case the problem has been presented by me to the particular investigator, and was followed up by constant discussion and consultations. The writing of the final paper was always the result of joint efforts. A list of collaborators is provided at the end of this section.

In developing the subject I have been deeply influenced by my early experiences in the various areas of the natural product chemistry at the Department of Chemistry, University of Adelaide such as carbohydrate and flavan chemistry, to which I was personally contributing, as well as by active research at the time of my stay during the 1950's on carcinogenic substances, nucleic acids, synthetic chemistry, conformational analysis, etc. This gave me a rounded outlook on science and was of great value in my scientific career. Of particular importance was the role played by Professor G. M. Badger in inspiring and guiding me in my early career. His trust in my ability to develop a carbohydrate research project for my Ph.D. degree with Dr. J. A. Mills has given me confidence in undertaking research in new, unfamiliar areas. Also, Prof. Badger has been instrumental in guiding me in my post-doctoral career, which led to some important joint contributions with Professors J. W. Clark-Lewis at the University of Adelaide and Herbert C. Brown at Purdue University.