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CHEMISTRY AND BIOLOGY OF PTERIDINES AND FOLATES

Edited by

June E. Ayling
M. Gopal Nair
Charles M. Baugh

University of South Alabama
Mobile, Alabama

SPRINGER SCIENCE+BUSINESS MEDIA, LLC

Library of Congress Cataloging in Publication Data

Chemistry and biology of pteridines and folates / edited by June E. Ayling, M. Gopal Nair, Charles M. Baugh.

p. cm.—(Advances in experimental medicine and biology; v. 338)

"Proceedings of the Tenth International Symposium on Chemistry and Biology of Pteridines, held March 21–26, 1993, in Orange Beach, Alabama"—T.p. verso.

Includes bibliographical references and indexes.

ISBN 978-1-4613-6287-6 ISBN 978-1-4615-2960-6 (eBook)

DOI 10.1007/978-1-4615-2960-6

1. Pteridines—Congresses. 2. Folic acid—Congresses. 3. Prosthetic groups (Enzymes)—Congresses. I. Ayling, June E. II. Nair, M. Gopal. III. Baugh, Charles M. IV. International Symposium on Chemistry and Biology of Pteridines (10th: 1993: Orange Beach, Ala.) V. Series.

QP801.P69C47 1993 93-29401

599'.019'25—dc20 CIP

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ISBN 978-1-4613-6287-6

Originally published by Plenum Press, New York in 1993

PREFACE

The pteridines in their multitude of forms fulfill many roles in nature ranging from pigments to cofactors for numerous redox and one-carbon transfer reactions. This extraordinary diversity of function is unified by the unique chemistry of the pteridine heterocycle. The International Symposium on the Chemistry and Biology of Pteridines and Folates is a forum for presenting recent and exciting advances in this expanding field. In bringing together various disciplines, a synergy of ideas results that has often stimulated fresh approaches to major problems. The Tenth International Symposium held at Orange Beach, Alabama, March 21 - 23, 1993, proved no exception by providing new insights into folate enzymology, tetrahydrobiopterin and molybdopterin biosynthesis and function, enzyme synthesis and regulation, along with novel synthetic strategies for producing compounds that will expedite further study. The many outstanding scientific contributions found in the following chapters, which represent the work presented at the Symposium, are a reflection of the significant advances made since the Ninth International Symposium held in Zurich in 1989.

Since the 7th International Symposium in St. Andrews, Scotland, a tradition has evolved of honoring scientists who have made outstanding contributions to pteridine research with a Gowland Hopkins medal and lectureship. Sir Frederick Gowland Hopkins initiated the first investigation of what later proved to be pteridines in his studies of the yellow and white colors of butterflies. The selection of Edward Taylor and Wolfgang Pfleiderer for the 1993 Hopkins award seems especially appropriate in view of the impending 100th anniversary of the first synthesis of a pteridine (lumazine 6,7-dicarboxylic acid) by Kühling in 1894. Almost every chemist in the field, as well as many others, have greatly benefited from the careful and insightful work of these two scientists. Their many contributions are summarized on the following pages by Peter Beardsley, a former Ph.D. student of Edward Taylor, and Max Viscontini, still a very active pteridine chemist himself.

We would like to acknowledge members of the Advisory Committee who were of great assistance in various aspects of planning the Symposium. We would also like to thank the sponsors, listed on the Acknowledgments page, who made the meeting possible. The breadth of the support we have received from both governmental and corporate sponsors is an indication of the continuing recognition of the major role that pteridines play in biology and medicine. The efforts of members of the finance committee in helping to obtain this support are also greatly appreciated. Special thanks to Dusti Steelman and Judi Naylor for so cheerfully helping with the mailings, the preparation of the program and abstract book and with the registration before and during the meeting. Finally, we would like to acknowledge the invaluable involvement of Steven Bailey.

We were pleased to host this meeting in Alabama where significant and continuous contributions have been made to this field over the past 30 years. We look forward to the 11th International Symposium which will be organized by Wolfgang Pfleiderer and Hartmut Rokos and held in Germany.

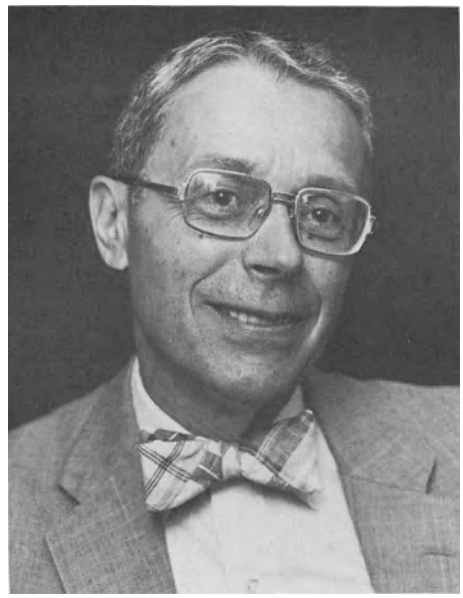
June Ayling
Gopal Nair
Charles Baugh

College of Medicine
University of South Alabama

Mobile, April 1993

GOWLAND HOPKINS LECTURESHIP

EDWARD C. TAYLOR



The choice of Ted Taylor as one of the two Gowland Hopkins Lecturers for this International Symposium could not be more appropriate. His contributions to the field of pteridine chemistry and biochemistry over a career spanning more than 45 years are equalled only by those of Wolfgang Pfleiderer, the co-recipient of this honor. No one else even comes close!

While his work in general is so broad-based to perhaps defy specific characterization, yet through it all run the traits of exceptional cleverness, imagination and "elegant simplicity". He has a knack not only for designing and implementing novel synthetic approaches, but also for noticing the unexpected result and exploiting it in many variations to synthetic advantage. Taylor is famous for making the complex seem simple. His work is replete with examples of the synthesis of complex heterocyclic and other compounds in a short series of steps, many of which involve clever sequences of condensation, ring cleavage and rearrangement reactions, often occurring "in one pot".

Taylor's contributions to pteridine chemistry include a series of more than 125 papers on pteridines, aza- and deaza-pteridines, numerous patents, and the classic volume *Pteridine Chemistry*, co-edited with Pfleiderer. These describe work which ranges from the basic chemistry of these ring systems, through development of synthetic methodology, to applications in the synthesis of natural products and the development of novel folate antimetabolites. The classic "Taylor Synthesis" involves elaboration of a pyrazine intermediate and allows unequivocal synthesis of the biologically important 6-substituted pteridines. He has applied this approach to the synthesis of natural pteridines including xanthopterin, folic acid, *L-erythro*-biopterin, neopterin, urothione, and Form A of the molybdenum cofactor - only a partial list.

Probably the most striking achievement recently has been the synthesis of a wide variety of deaza analogs of tetrahydrofolate. This work began with the synthesis nearly ten years ago of 5,10-dideazatetrahydrofolate (DDATHF, Lometrexol). This compound was shortly found to be a potent inhibitor of de novo purine biosynthesis. Broad spectrum antitumor activity was then found in pre-clinical models, and Lometrexol is now undergoing clinical trials with encouraging early results. The initial discovery of DDATHF has had a major impact on subsequent antifolate drug development. Not only was a new class of structures opened to further investigation, but added impetus was provided to the search for other novel inhibitors of previously unexplored enzymatic targets for antifolate attack. The result has been a major rekindling of interest in antifolate drug development, an area in which Taylor himself has been a major participant. This work has been full of new synthetic chemistry and biochemical surprises, and forms the basis for this Gowland Hopkins Lecture.

Many whose relationship to Taylor is through a common interest in pteridines may not realize that, despite the magnitude of his achievements in our field, this represents only a portion of the overall scope of his work. He has also made major contributions to basic chemistry and synthetic methodology in purines, pyrimidines, triazines and diazetidinones. In fact, he has contributed very significantly to our knowledge of virtually all heterocyclic systems. His contributions extend much further than heterocyclic chemistry and include elegant total syntheses of Chinchona alkaloids. His well known one step synthesis of tetrahydrocannabinol is a particularly illustrative example of his clever and imaginative approach to synthetic design. Finally, Taylor has made numerous major contributions to the whole field of synthetic organic chemistry. While there are many examples, particularly outstanding has been his pioneering and extensive work in the use of thallium reagents in organic syntheses. A long and highly productive collaboration between Taylor and Prof. Alexander McKillop has led to the development of extraordinarily versatile thallium reagents and reactions which have wide application in virtually every area of synthetic organic chemistry.

Taylor's role as a teacher and mentor may be almost as important as his own work. Those who hear his lectures and seminars are treated not only to exciting chemistry, but to presentations of extraordinary organization and clarity. To students and others who work with him, he transmits not only some of his profound understanding of how molecules work and how to assemble them but, perhaps more importantly, a considerable measure of his boundless enthusiasm and perpetual optimism. For Ted, it's never that a good idea "doesn't work", it's just that it "hasn't worked yet". Those who come to know him soon realize that these same qualities of vigor, enthusiasm and optimism apply to his whole approach to life. Those who have known him over the years realize that these are not diminishing, rather they are on a continuing upswing. We, therefore, look forward to a great deal more in the way of exciting new developments and contributions to pteridines and to chemistry in general.

G. Peter Beardsley
Yale University School of Medicine

GOWLAND HOPKINS LECTURESHIP

WOLFGANG PFLEIDERER

The year 1955 was a milestone in pteridine chemistry. After four years of intense, exciting work, we had just published in Helvetica Chimica Acta three articles together with P. Karrer and E. Hadorn, in which we described the isolation of new compounds from the small fly *Drosophila melanogaster*, two of which had a deep sky blue (in German "Himmel Blau", H B) fluorescence and were therefore baptized HB_1 and HB_2 in our laboratory slang. We found out very quickly that HB_1 corresponded to pterin, while the structure of HB_2 gave us a lot of trouble. Experienced chemists like those of Stokstad's team would have immediately identified HB_2 as L-biopterin. My lack of experience in pterin chemistry plunged me into an abyss of doubt, because I trusted blindly the elemental analyses, which, I must admit, in case of pterins, were far from being as accurate as they are today. To end a long story, our work remained more or less unnoticed - what were we looking for in these small flies, everybody wondered - especially because some weeks later Stokstad published the isolation of a growth factor, starting from a thousand liters of human urine, which he called L-biopterin, and determined its structure. Our work remained more or less overlooked, except in the eyes of a young chemist who recognized rapidly the importance of the research which was going on in our laboratory. In the beginning of 1956, a handsome looking man of good appearance, tall, with a determined face, missing the left arm, entered my office. A war-wounded man, I thought as I looked at him. I had in front of me Wolfgang Pfleiderer, not the Professor Pfleiderer we know today, but a young man. At that time he was 29 years old and well resolved to make his way in life.

"Professor Viscontini, I am a chemist at the University of Stuttgart, where in 1952 I gained my Ph.D. under the supervision of Professor Bredereck. My dissertation was devoted to the chemical and physicochemical properties of some purine derivatives. Now

I am writing my Habilitation about lumazines. Unfortunately, the topic does not really fill my supervisor with enthusiasm. As a consequence I am obliged to work by myself without people with whom I can discuss results, problems or difficulties. Recently I read your papers on pteridines isolated from *Drosophila melanogaster* and I was greatly impressed by the results you published on the research carried out on this fly. I have, therefore, ventured to come to Zurich in order to make contact with a person who shares my scientific interest. I would like to know, if I am correct or mistaken in involving myself so strongly in the field of pteridine chemistry". Here was finally somebody with whom I was in perfect communication! I felt that my work attracted him. I did my best to convince him how right he was, taking the way of hard research where results do not manifest themselves in kilograms of publications, but brings out the author's originality. I emphasized, that in my opinion, pteridines might play a great role in nature, that he had to go on in the direction he chose and that he would find later the benefit of it. In a short time we became close friends, with a very similar scientific philosophy. We separated, promising to meet again and to discuss as often as possible the results of our research. Some months later, in 1957 Pfleiderer gained his Habilitation and his appointment as Dozent at the University of Stuttgart. In 1958 he spent one year as Research Associate at the University of Princeton with Professor Edward Taylor.

In the meantime we went on with the isolation of three orange pigments, drosopterin, isodrosopterin, and neodrosopterin from *Drosophila*. In 1959 we published the first hypothetical structures that we proposed for these pigments. After one year of absence Pfleiderer did not hesitate to come to Zurich. "Sir, your structures are wrong. The UV and the VIS spectra do not match the proposed formulae". I understood perfectly his point of view, and suddenly it came to me: I felt isolated with my research, my results were not especially well appreciated, I was short of money and coworkers and now I had in front of me a promising young chemist, who, as I sensed, had a mind to get involved with the field of natural pterins. My decision was immediate: "Listen, Herr Pfleiderer, in my opinion, from the pteridines we just isolated there are two classes of compounds that seem important, the drosopterins and the L-biopterin. Both are difficult to study, but both will bring recognition to the chemist who elucidates their properties. I have confidence in you, devote yourself to the chemistry of drosopterins and I, for my part, will work on the chemistry of the L-biopterin".

From that day on I stopped working with drosopterin. In 1962 Professor Pfleiderer formulated his first ideas on their structure. I could have as easily proposed to Pfleiderer the study of L-biopterin and chosen the drosopterin for myself. Why did I choose L-biopterin? Don't ask me, I have no idea myself. Anyway, we never regretted our oral agreement, neither he nor me. We have remained close friends and loyal to our agreement. As it turned out, destiny and my choice made Professor Pfleiderer the oracle for drosopterins while I became the expert for tetrahydrobiopterins. Nevertheless, it is quite certain, that without my encouragement Professor Pfleiderer would have become famous, because of his personality. Some hundreds of communications and seven books published between 1953 and 1992 about pteridines and their derivatives bear witness to the wideness of the research he carried out, and the importance of the results he obtained. Let us cite succinctly: tautomeric structures of pteridines, photochemistry, electrochemistry, and most especially the chemistry of natural pteridines: structure of eugleniapterin, partial synthesis of tetrahydromethanopterin and, to my opinion the most important and the most admirable of all his works the structure and the synthesis of the drosopterin pigments.

Good luck for the future, dear Wolfgang!

Max Viscontini
University of Zürich

ACKNOWLEDGMENTS

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