THE PYRIMIDINES

D. J. Brown
The Australian National University
Canberra

WITH AN ESSAY BY

S. F. Mason
The University, Exeter, England

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This is the sixteenth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

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A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER, *Consulting Editor*

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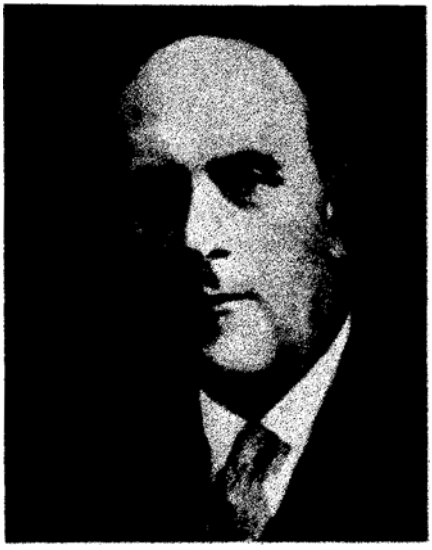
Library of Congress Catalog Card Number 61–9039

To the Memory of

TREAT BALDWIN JOHNSON



Treat B. Johnson

The Chemistry of Heterocyclic Compounds

The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocyclic compounds.

A field of such importance and intrinsic difficulty should be made as readily accessible as possible, and the lack of a modern detailed and comprehensive presentation of heterocyclic chemistry is therefore keenly felt. It is the intention of the present series to fill this gap by expert presentations of the various branches of heterocyclic chemistry. The subdivisions have been designed to cover the field in its entirety by monographs which reflect the importance and the interrelations of the various compounds, and accommodate the specific interests of the authors.

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ARNOLD WEISSBERGER

Preface

This book is intended as a critical review of pyrimidine chemistry with emphasis on practical rather than theoretical aspects. The literature from the earliest times to 1960 is used to furnish examples illustrating syntheses, physical properties, and reactions, but no attempt is made to include all relevant data. The tables interspersed with the text serve to multiply and diversify these examples, but are likewise not intended as complete catalogues. In general, if a simple example suffices to make a point, examples involving more highly substituted pyrimidines are omitted. The more biological aspects of pyrimidine chemistry, such as the nucleic acids or the structural requirements for activity in barbiturates, are treated quite briefly, in particular as adequate reviews by workers in such fields exist.

The tables grouped in the Appendix give ready access to the literature and melting points of known simple pyrimidines. All such compounds described up to the end of 1957 are included, and they are supplemented by a selection of important or interesting members described thereafter until mid-1960.

The world-wide appeal of pyrimidine chemistry may be judged by the following approximate analysis of the origins of the twenty two hundred references used in the book:

United States of America	36.5%
Germany (East and West)	22.7%
British Commonwealth	19.4%
Japan	8.0%
France and Switzerland	3.0%
Italy and Spain	2.6%
Russia	2.2%
Netherlands and Belgium	1.5%
Eastern Europe	1.3%
China	1.3%
Austria	1.1%
Scandinavia and Others	0.4%

It will be realised that the present-day output of pyrimidine papers is very different to the above, which covers the last 140 years. The United States

remains the centre of gravity, but the output of Japan, China, and Eastern Europe has risen considerably and mainly at the expense of Germany.

Many kind people have helped me enormously during the years of writing. My friend and former colleague, Dr. S. F. Mason, wrote a learned essay on pyrimidine spectra for Chapter XIII, a task which would have been quite beyond me. Professor Adrien Albert carefully read the entire text, and made numerous helpful suggestions from his wide knowledge and experience in heterocyclic work. Dr. J. P. English and Dr. J. H. Clark of American Cyanamid Company, loaned me a fine card index covering the earlier pyrimidine literature. Dr. S. Matsuura helped me with Japanese papers. Dr. J. F. W. McOmie sent me much unpublished material, and Dr. H. Mautner, Dr. H. B. Vickery, Dr. J. Staněk, Dr. D. I. Magrath, Dr. R. F. Evans, Dr. E. Spinner, and Dr. N. W. Jacobsen helped in other ways. The National Academy of Sciences (Dr. H. L. Dryden) kindly gave me Johnson's photograph. Mr. J. Harper, Mr. B. T. England, and Mrs. D. McLeod assisted nobly with the references and in other ways. Miss P. L. Baetons typed most of the manuscript and among the others who helped in various ways are Miss M. Bell, Mrs. H. Edmonston, who drew the curves, Mrs. S. M. Schenk, Mr. H. Satrapa, Mr. F. V. Robinson, Mrs. E. M. Lee, and Miss S. Green. Professor F. Bergel, F. R. S., generously provided facilities for me at the Chester Beatty Institute, London, at the proof stage. To these, to the unnamed others, and in particular to my wife for her help and remarkable patience, I offer my gratitude and thanks.

The Australian National University, Canberra D. J. Brown

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CHAPTER I

Introduction to the Pyrimidines

1. History

In 1818 Gaspare Brugnatelli[1,2] isolated the first pyrimidine derivative, alloxan, by oxidation of uric acid with nitric acid. A few years later his experiments were put on a sound basis and extended to other derivatives by Wöhler and Liebig in their outstanding paper: Untersuchungen über die Natur der Harnsäure.[3] In 1848 Frankland and Kolbe[4] carried out the first primary synthesis of a pyrimidine by the action of metallic potassium on propionitrile. It later proved[5] to be 4-amino-2,6-diethyl-5-methylpyrimidine (I). The next landmark in pyrimidine chemistry was the synthesis by Grimaux,[6–8] in 1878 of barbituric acid from malonic acid and urea. This was the first example of what has become the principal pyrimidine synthesis. But it was not until 1884 that Pinner[9] made his first pyrimidine derivative. The following year[10] he recognized pyrimidine as an hexagonal brother of benzene, pyridine, and triazine, and he named the new ring system with the words: "Die neue von der Grundsubstanz, $C_4H_4N_2$, sich herleitende Verbindungsklasse möchte ich als Pyrimidin bezeichnen". Three years later an attempt was made by Widmann[11] to systematize the nomenclature of nitrogen heterocycles, and "miazine" was suggested in place of pyrimidine. Although this name did enjoy a limited vogue, by 1905 von Meyer[12] was able to say, "Die von O. Widmann statt Pyrimidin vorgeschlagene Bezeichnung *Miazin* hat, so viele Vorzüge sie bietet, keinen Eingang gefunden". The parent compound (II) was first isolated by Gabriel and Colman[13] in 1899.

The beginnings of pyrimidine chemistry have been reviewed very

appropriately by T. B. Johnson,[14*] who, during forty years of work in the pyrimidine field, nobly and almost alone bridged the gap between two great periods of pyrimidine history. The first of these embraced the classical contributions of Robert Behrend,[15] Siegmund Gabriel,[16,17] Emil Fischer,[18] Wilhelm Traube[19] and Ernst von Meyer,[20] and was stimulated to some extent by the isolation of thymine, uracil, and cytosine from biological material, and by the advent of the barbiturates. The second period was even more biologically based. It arose from vitamin B_1 in the late thirties, and was amply nourished thereafter by resurgence of interest in the nucleic acid field, by the discovery of sulphadiazine, by the immensely useful anti-thyrotoxicotic activity of the alkyl thiouracils, and by the searches for more effective antimalarials (*e.g.* "Daraprim"), oral diuretics (*e.g.* "Amisometradine"), and other drugs. Further, the new interest in folic acid and the simple pteridines as well as the renewed interest in purines, greatly stimulated research in the chemistry of their pyrimidine intermediates. To forecast the future trends would indeed be bold.

The recent discovery by Professor M. Calvin[22,23] that the soluble fraction from a meteorite contained a nitrogeneous heterocycle, which from spectra might well be cytosine, is fascinating. The observation has already been confirmed in other meteorites,[24] and if the presence of cytosine (or other nucleic acid constituents) can be conclusively proven, the finding must rank as one of the most significant in history.

The best review of the older literature of pyrimidines (to 1920) is in the text-book of Meyer and Jacobson.[25] Similar types of review have been written by Johnson and Harn[26] (1933) and by Johnson[27] (1938). More concise reviews have appeared from Lythgoe[28] in 1949, from Kenner[29] in 1950, from Brown[30] and Wiley[31] in 1953, and from Bendich[32] in 1955. The fullest treatment to date has come from Kenner and Todd[33] in 1957, covering the literature to several years before publication. An excellent sixty-page review of pyrimidines has been written by Ramage and Landquist,[34] and the best idea of the place of pyrimidines in heterocyclic chemistry can be gained from Albert.[35]

* Treat Baldwin Johnson was born in Bethany, Connecticut, in 1875. In 1898 he published from Yale his first paper with Henry L. Wheeler from whom he acquired an interest in pyrimidines. He finally contributed about 180 papers on this subject alone, and an equal number on related topics. Despite the occasional error in his voluminous writings, this "kindly, simple-mannered man" exerted a profound influence on the course of pyrimidine chemistry.[21] The dedication of this book is a small tribute to a great chemist and teacher.