FUSED PYRIMIDINES

Edited by

D. J. Brown

Part I

QUINAZOLINES

W. L. F. Armarego

Department of Medical Chemistry,
The John Curtin School of Medical Research,
The Australian National University, Canberra

With collaboration in part by
GEORGE H. HITCHINGS and GERTRUDE B. ELION
Wellcome Research Laboratories, Tuckahoe, N.Y.

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Part I: QUINAZOLINES

This is the twenty-fourth volume (Part I) in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

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A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER, *Editor*

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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.

ARNOLD WEISSBERGER

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Foreword to The Fused Pyrimidines

Originally it was intended to present all the fused pyrimidine systems in one volume of this series. Resurgence of interest in purines and quinazolines, the development of pteridine chemistry, and the wide exploration of a great many new fused systems embracing the pyrimidine ring, have made the task impossible.

The fused pyrimidines will now be covered in four parts, of which Dr. Armarego's *Quinazolines* is the first. Others, dealing with *Purines*, *Pteridines*, and *Miscellaneous Fused Pyrimidines* respectively, are in active preparation. Eventually, this bracket of volumes will bring to the series the expertise of six enthusiastic authors with wide and diverse experience in the field.

It is a privilege to assist Dr. Weissberger and the authors in organizing this project and in maintaining a measure of uniformity and balance in its parts.

D. J. Brown

The Australian National University
Canberra, Australia

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Preface

The presence of the benzene ring in quinazoline modifies the chemistry of the pyrimidine ring in a number of ways. The modifications are so diverse that a description of the chemistry of quinazolines merits a separate monograph. Quinazolines were originally prepared for academic interest, and a considerable variety were made because many synthetic approaches were possible. In the last two decades several naturally occurring quinazolines were discovered, and many quinazolines were synthesized for biological testing. The antimalarial activity of the alkaloid febrifugine, for example, led to the preparation of a large number of different quinazoline derivatives. The neurotoxic activity of the recently discovered tetrodotoxin, a perhydroiminoquinazoline, will undoubtedly stimulate research in this previously unknown class of quinazolines.

This monograph is intended as a critical review of quinazoline chemistry as well as a compilation of the melting points of quinazolines. Condensed quinazolines are excluded, with the exception of the thiazoloquinazolines (thiopegenes) because the chemistry of these is closely related to that of the thioquinazolines. The literature is covered completely from the preparation of the first quinazoline in 1869 to the middle of 1965, and incompletely until mid-1966.

I am grateful to the many people who helped me during the months of writing. Drs. G. H. Hitchings and G. B. Elion loaned me a preliminary account of the chemistry of quinazolines based essentially on synthetic methods. Dr. D. J. Brown has unselfishly guided and inspired me, particularly through the most difficult sections, and to him I owe a great debt of gratitude. Professor Adrien Albert carefully read several chapters and made constructive criticisms. The following were of considerable help in discussions, in making available to me information prior to publication, and in allowing me to reproduce some of their published data: Professors R. D. Brown, A. R. Katritzky, K. S. Narang, Drs. G. B. Barlin, T. J. Batterham, M. E. C. Biffin, J. W. Bunting, Gordon Catterall, M. L. Heffernan, D. D. Perrin, N. K. Ralhan, J. I. C. Smith, and Mr. H. Yamamoto. My wife (who is also an organic

chemist) assisted in making the tables, compiling the index, and in reading the whole manuscript. Finally, grateful thanks are due to Miss P. Cope who carried out the tedious task of typing the manuscript and to Mrs. D. McLeod for library facilities.

W. L. F. ARMAREGO

The Australian National University, Canberra
June 1966

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CHAPTER I

Introduction

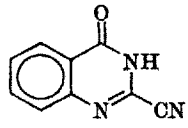
1. History

In 1869 Griess[1] prepared the first quinazoline derivative, 2-cyano-3,4-dihydro-4-oxoquinazoline, by the reaction of cyanogen with anthranilic acid. Griess apparently recognized the bicyclic nature of the product, which he called bicyanoamidobenzoyl and used this name until 1885[2] when the structure **1** was known with some certainty.

Weddige[3,4] carried out systematic quinazoline syntheses following the observation that the formyl and acetyl derivatives of anthranilamide lost water on heating. He correctly interpreted this as a cyclization reaction and was the first to realize the possibility of tautomerism in the oxoquinazolines. The preparation of the parent quinazoline came many years later when Bischler and Lang[5] obtained it by decarboxylation of the 2-carboxy derivative. A more satisfactory synthesis of quinazoline was subsequently devised by Gabriel[6] who studied its properties and those of its derivatives in greater detail. A large number and variety of quinazolines were synthesized in an intensive research programme by Bogert and his collaborators at Columbia University, U.S.A. The earlier part of this research was reviewed in 1910.[7] The published papers on quinazoline chemistry grew steadily until about 1939 when the annual output until about 1945 was constant. After the second world war the number of papers rose rapidly for a few years, then was steady until about 1959, and has been increasing rapidly since then.

The discovery in 1956,[8] that quinazoline exists mainly as a hydrated molecule in aqueous acid and the confirmation of the structure of the hydrated cation in 1961,[9] has thrown much light on the understanding of the properties and reactions of quinazolines. A knowledge of the effects of substituents on the hydration pattern in substituted quinazolines is very useful in devising new experiments and in understanding already known properties. The chemistry of quinazolines was

reviewed by Williamson[10] in 1957, then by Landquist[11] in 1959, and was brought up to date by Armarego[12] in 1963.



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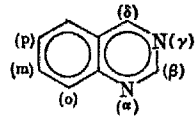

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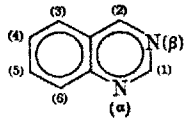

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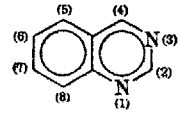

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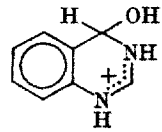

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2. Nomenclature

Quinazoline has also been called phenmiazine, benzyleneamidine, benzo-1,3-diazine, 5,6-benzopyrimidine, and 1,3-diazanaphthalene. The term phenmiazine was used by Widman[13] and later by Bischler,[5] and the positions in the pyrimidine ring were designated by α, β, γ, and δ (**2**). A second system of numbering is shown in **3**. The name quinazoline (German: chinazoline), which is now universally adopted, was first proposed by Weddige[3] because he observed that his compounds were isomeric with the then known cinnoline and quinoxaline. It probably arose from the fact that it was an aza derivative of quinoline, hence quinazoline. The numbering shown in **4** was suggested by Paal and Busch[14] and is the one in current use.[15] The above names and numbering must be remembered particularly when reading through the earlier literature.

The nomenclature used in this volume is essentially, though not entirely, in accordance with the *Handbook for Chemical Society Authors*[16] published by the Chemical Society of London in 1960. The nomenclature rules used are known as the I.U.P.A.C. 1957 rules. The substitutive naming system is adopted because in this way it is much easier to find a particular compound from the index and the tables; e.g.