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# THE NAPHTHYRIDINES

**D. J. Brown**

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Canberra



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# **THE NAPHTHYRIDINES**

*This Is the Sixty-Third Volume in the Series*

**THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS**

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**THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS**

A SERIES OF MONOGRAPHS

**EDWARD C. TAYLOR and PETER WIPF**, *Editors*

**ARNOLD WEISSBERGER**, *Founding Editor*

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*To the memory of  
Marian Wozniak, a prolific contributor  
to naphthyridine research*

## The Chemistry of Heterocyclic Compounds

### Introduction to the Series

The chemistry of heterocyclic compounds is one of the most complex and intriguing branches of organic chemistry, of equal interest for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocycles.

*The Chemistry of Heterocyclic Compounds* has been published since 1950 under the initial editorship of Arnold Weissberger, and later, until his death in 1984, under the joint editorship of Arnold Weissberger and Edward C. Taylor. In 1997, Peter Wipf joined Prof. Taylor as editor. This series attempts to make the extraordinarily complex and diverse field of heterocyclic chemistry as organized and readily accessible as possible. Each volume has traditionally dealt with syntheses, reactions, properties, structure, physical chemistry, and utility of compounds belonging to a specific ring system or class (e.g., pyridines, thiophenes, pyrimidines, three-membered ring systems). This series has become the basic reference collection for information on heterocyclic compounds.

Many broader aspects of heterocyclic chemistry are recognized as disciplines of general significance that impinge on almost all aspects of modern organic chemistry, medicinal chemistry, and biochemistry, and for this reason we initiated about 1971 a parallel series entitled *General Heterocyclic Chemistry*, which treated such topics as nuclear magnetic resonance, mass spectra, and photochemistry of heterocyclic compounds, the utility of heterocycles in organic synthesis, and the synthesis of heterocycles by means of 1,3-dipolar cycloaddition reactions. These volumes were intended to be of interest to all organic, medicinal, and biochemically oriented chemists, as well as to those whose particular concern is heterocyclic chemistry. It has, however, become increasingly clear that the above distinction between the two series was unnecessary and somewhat confusing, and we have therefore elected to discontinue *General Heterocyclic Chemistry* and to publish all forthcoming volumes in this general area in *The Chemistry of Heterocyclic Compounds* series.

Dr. Des J. Brown is again to be applauded and profoundly thanked for still another fine contribution to the literature of heterocyclic chemistry. This volume on *The Naphthyridines* is the first book devoted in its entirety to the six pyridopyridine ring systems, and it covers the last 80 years of the literature until 2007. It must be noted with admiration that many of the books in this series that have come to be regarded as classics in heterocyclic chemistry (*The Pyrimidines*, *The Pyrimidines*

*Supplement I, The Pyrimidines Supplement II, Pteridines, Quinazolines Supplement I, The Quinoxalines Supplement II, The Pyrazines Supplement I, and Cinnolines and Phthalazines) are also from the pen of Dr. Brown.*

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PETER WIPF



## Preface

This is the first book devoted entirely to the chemistry of the six naphthyridine systems.

Because of structural uncertainties and confusing nomenclature, much of the early literature is, frankly, of little more than historical interest. However, after 1930, when most authors adopted the present *Chemical Abstracts* naming (see “Note on Nomenclature” that follows), a reliable body of literature gradually accumulated on all six systems, albeit at very different rates. For example, data on the 1,8-naphthyridines greatly outnumbered those on the other systems, probably as a result of the discovery of significant antimicrobial properties associated with nalidixic acid as well as the intrinsic suitability of the 1,8-system for metal complexation.

In this book, the respective volumes of reported data have led to treatment of the first four of the other naphthyridines in seven chapters each, whereas each-naphthyridine system is covered in a single rather long chapter. The appendix tables aim to list all simple naphthyridines, along with an indication of their physical properties, that have been reported before 2006.

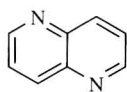
I am greatly indebted to the Dean of the Research School of Chemistry, Professor Denis Evans, for the provision of postretirement facilities within the School; to the Librarian, Joan Smith, for her kindly assistance in all library matters; and to my wife, Jan, for her patient encouragement and practical help during the years of writing.

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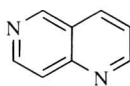
DES J. BROWN

## Note on Chemical Nomenclature

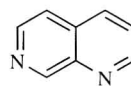
The six possible pyridopyridine systems have been known almost universally since circa 1930 as 1,5- (1), 1,6- (2), 1,7- (3), 1,8- (4), 2,6- (5), and 2,7-naphthyridine (6). However, the occasional use of an appropriate pyridopyridine or diazanaphthalene may still be found in some publications. Historically, the word “naphthyridin(e)” was coined by Arnold Reissert in 1893 specifically for the 1,8-naphthyridine system (4) and was so used for some years, especially in the German literature. Other terms, such as “isonaphthyridine” [for 1,5-naphthyridine (1)], “benzodiazines” (very misleading), “pyridinopyridines”, “2,5-naphthyridine” [for 1,6-naphthyridine (2)], and “copyrin(e)”<sup>13,40</sup> or copurine<sup>39</sup> [for 2,7-naphthyridine (6)] have appeared in the literature.



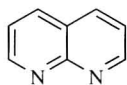
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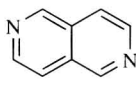
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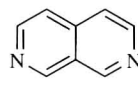
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(4)



(5)



(6)

In this book, all such systems are designated as the appropriate naphthyridines; other ring systems are also named and numbered according to recommendations of the Chemical Abstracts Service [*Ring Systems Handbook* (eds. anonymous, American Chemical Society, Columbus, Ohio, 1998 edition and supplements)]; and general chemical nomenclature follows current IUPAC rules [*Nomenclature of Organic Chemistry, Sections A–E, H* (J. Rigaudy and S. P. Klesney, eds., Pergamon, Oxford, 1979)], with one important exception: in order to keep “naphthyridine” as the principal part of each name, those groups that would normally qualify as principal suffixes but are not attached directly to the nucleus are rendered as prefixes. Thus, 3-carboxymethyl-1,5-naphthyridin-2(1*H*)-one would be used instead of 2-(2-oxo-1,2-dihydro-1,5-naphthyridin-3-yl)acetic acid; secondary, tertiary, or quaternary amino groups are also rendered as prefixes.

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