CONDENSED PYRAZINES

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JANSSEN PHARMACEUTICAL LTD.

AN INTERSCIENCE ® PUBLICATION

JOHN WILEY & SONS
NEW YORK · CHICHESTER · BRISBANE · TORONTO

An Interscience ® Publication

Library of Congress Cataloging in Publication Data:

Cheeseman, G. W. H., 1927–
Condensed pyrazines.

(The Chemistry of heterocyclic compounds; v. 35)
"An Interscience publication."
Includes indexes.
1. Pyridazine. 2. Quinoxaline. 3. Condensation products (Chemistry). I. Cookson, Ronald Frederick, 1943– joint author. II. Title

QD401.C493 547'.593 78—17533
ISBN 0-471-38204-3

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

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This is the Thirty-Fifth Volume in the Series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER and EDWARD C. TAYLOR

Editors

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.

In order to continue to make heterocyclic chemistry as readily accessible as possible new editions are planned for those areas where the respective volumes in the first edition have become obsolete by overwhelming progress. If, however, the changes are not too great so that the first editions can be brought up-to-date by supplementary volumes, supplements to the respective volumes will be published in the first edition.

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Preface

This book provides an account of the preparation, properties, and uses of the more important bicyclic and tricyclic ring systems incorporating the pyrazine ring. Twenty of the chapters survey the developments in quinoxaline chemistry since the publication of the Simpson monograph on condensed pyridazines and pyrazines in 1953. Continuity has been ensured by some small overlap with the previous monograph, and to facilitate cross-referencing the same basic organization of subject material has been retained.

The remaining 20 chapters incorporate reviews on selected 5,6–, 6,6–, 5,6,6–, and 6,6,6–ring systems. These reviews give comprehensive coverage to such important ring systems as the pyrrolopyrazines and the pyridopyrazines. The tricyclic heterocycles chosen for inclusion are those in which the third ring is fused to the pyrazine ring of a quinoxaline. Space limitations have dictated this somewhat arbitrary choice of material. Also excluded from this monograph is a discussion of the chemistry of pteridines, because a future volume in this series will be devoted to them, and of phenazines, because a monograph on them has already been published.

The chapters are organized for easy reference and incorporate tables by which information on specific compounds can be readily traced. Table entries on individual compounds are listed in order of their molecular formula. We suggest that a molecular formula check is the surest way of ascertaining if a particular compound is listed in the tabulation. Also, a molecular formula provides a convenient search term for locating specific information in *Chemical Abstracts*. It is clearly impossible to include the entries for polyfunctional compounds in each appropriate table so that in the case, for example, of a chloroamino compound the tabulation of both chloro- and amino compounds must be consulted.

The literature has been covered to the end of 1975, but additional material from papers published in 1976 and 1977 has been included. It is hoped that this book will help to stimulate further research as well as prove a useful source of reference for chemists with widely differing interests.

London
September 1977

G. W. H. Cheeseman
R. F. Cookson

Acknowledgments

We are grateful for help and encouragment from a variety of sources. Professor W. Pfleiderer provided hospitality for one of us at the University of Konstanz, where the initial planning of the book was done. Much of the research and writing was carried out in the libraries of the Chemical Society (London) and the Nicholas Research Institute, and we appreciated the facilities so readily made available to us. We should like to thank Aspro-Nicholas Ltd. and, more recently, Janssen Pharmaceutical Ltd. for allowing one of their employees to act as coauthor of this work. We are particularly indebted to colleagues at Queen Elizabeth College for their helpful comments. Special mention should also be made of C. W. Bird, D. J. Brown, and R. T. Parfitt, all of whom provided much appreciated advice and encouragement.

Above all, we should like to thank our wives, Ann and Mildred, for their help and support at every stage in the production of this book. We are most grateful that somehow they found time to undertake the arduous task of typing the manuscript.

London
September 1977

G. W. H. C.
R. F. C.

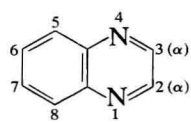
Contents

CHAPTER I

General Introduction to Quinoxaline Chemistry

I. Nomenclature

The approved numbering for the quinoxaline ring system is shown in structure **1**; positions 2 and 3 are sometimes designated α-positions. An alternative name for quinoxaline occasionally to be found in the literature is 1,4-diazanaphthalene.



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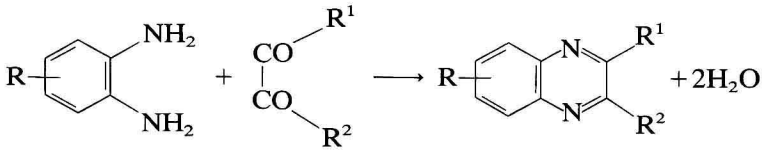
II. Synthesis

The vast majority of quinoxalines are of synthetic origin, and with very few exceptions the synthetic method used is to condense an *o*-disubstituted benzene with a two-carbon synthon. Thus condensation of

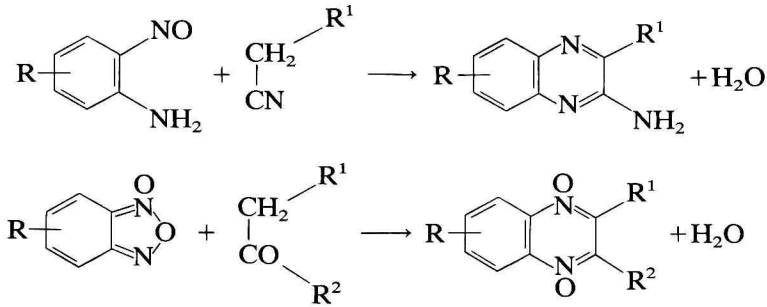
o-phenylenediamines with α-dicarbonyl compounds results in quinoxaline formation as shown in Scheme 1. By suitable choice of the α-dicarbonyl component, alkyl- and arylquinoxalines, quinoxalinones, and



Scheme 1

quinoxalinecarboxylic acids have been prepared (Chapters XIV, XV, V, and IX, respectively). Other two-carbon synthons that have been reacted with *o*-phenylenediamines to form quinoxalines include α-halogenocarbonyl compounds, α,β-dihalides, and acetylene 1,2-dicarboxylic acid esters.

Major variants on this method are the use of *o*-nitrosoaminobenzenes (Chapter IX) and benzofuroxans (Chapter IV) as substrates for reaction with a two-carbon component as illustrated in Scheme 2. The *o*-nitrosoaminobenzene-based synthesis has the advantage that it leads to products



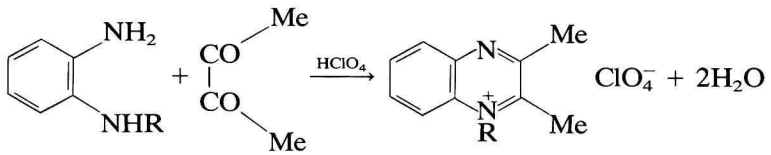
Scheme 2

of unambiguous structure, which is not the case where unsymmetric *o*-phenylenediamines or benzofuroxans are used. The synthesis of quinoxaline di-*N*-oxides from benzofuroxans is known as the Beirut reaction and has been exploited extensively in recent years.

III. Reactions of Quinoxalines with Electrophilic Reagents on Ring Nitrogen

Quinoxaline (1,4-diazanaphthalene) has a pK_a value of 0.6, and it is therefore less basic than either cinnoline (1,2-diazanaphthalene),

quinazoline (1,3-diazanaphthalene), or phthalazine (2,3-diazanaphthalene) (Chapter II). Quinoxaline is reported to have a second pK_a of −5.52, and it is therefore only significantly diprotonated in a strongly acidic medium. Quinoxaline and its simple derivatives are readily converted into both mono- and di-*N*-oxides by oxidation with peracids (Chapter IV). As mentioned above, di-*N*-oxides are available from primary synthesis from benzofuroxans. Quinoxalines form monoquaternary salts when treated with the common quaternizing agents such as methyl sulfate and methyl *p*-toluenesulfonate (Chapter XVII). The quaternary salts of 2-alkylquinoxalines are unstable and on oxidation are converted into complex colored products (Chapter XVII). Quinoxaline quaternary salts have also been prepared by primary synthesis from *N*-substituted *o*-phenylenediamines and α-dicarbonyl compounds (Scheme 3) (Chapter XVII).



Scheme 3

IV. Substitution Behavior of Quinoxaline Derivatives on Carbon

Quinoxaline itself and many of its simple derivatives do not readily undergo substitution on carbon when treated with electrophilic reagents; however, under forcing conditions the parent base is nitrated to give 5,6-dinitroquinoxaline as the major product (Chapter II). The benzene ring of quinoxalin-2-ones is activated to electrophilic substitution and nitration, and halogenation occurs smoothly in the 7-position when the reactions are carried out in acetic acid solution (Chapter V). The quinoxalinium cation is however susceptible to substitution at C-2 by a whole range of radical reagents. For example, acyl radicals (RCO·), generated under oxidizing conditions from aldehydes, react with quinoxaline to give 2-quinoxalinyl ketones (Chapter VIII). 2-Alkyl-, carboxamido-, and ethoxycarbonylquinoxalines have also been prepared by radical substitution (Chapter II). Homolytic δ-aminoalkylation of the quinoxalinium cation also occurs at the 2-position, but at high acidity, when a significant amount of diprotonated base is present, both 2- and 6-substitution occurs (Chapter II).

V. Addition Reactions of Quinoxalines

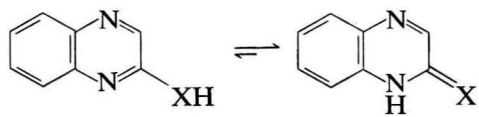
1,2-Dihydro-, 1,4-dihydro-, 1,2,3,4-tetrahydro-, and decahydroquinoxalines are known (Chapter XVIII). Thus reduction of quinoxaline with lithium aluminum hydride yields 1,2,3,4-tetrahydroquinoxaline (Chapter II). Quinoxaline also adds two molecular proportions of Grignard reagent to give a 2,3-disubstituted 1,2,3,4-tetrahydroquinoxaline (Chapter II). It also undergoes cycloaddition reactions with reagents such as diphenylcyclopropenone to form 1:1 molecular adducts (Chapter II).

VI. Reactions of Substituted Quinoxalines

2-Alkylquinoxalines show enhanced reactivity in terms of their ability to undergo condensation reactions with aldehydes and their ability to undergo Michael additions (Chapter XIV). Similarly 2-halogenoquinoxalines have been found to participate in a wide range of nucleophilic substitution reactions with oxygen, sulfur, nitrogen, and carbon nucleophiles. Chlorine in the 2-position is also readily removed by catalytic hydrogenation (Chapter X). Quinoxaline 2-carboxylic acids are very readily decarboxylated which renders their purification difficult but in some cases increases their utility as intermediates in other quinoxaline preparations; for example 2-chloroquinoxaline can be readily prepared from 3-chloroquinoxaline-2-carboxylic acid (Chapter X).

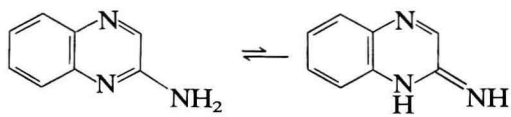
VII. Tautomerism of Quinoxaline Derivatives

2-Hydroxy- and 2-mercaptoquinoxalines exist in the quinoxalin-2-one (Chapter V) and quinoxaline-2-thione forms (Chapter VI), whereas 2-aminoquinoxaline exists as such rather than as an imine (Chapter XI) (Scheme 4).

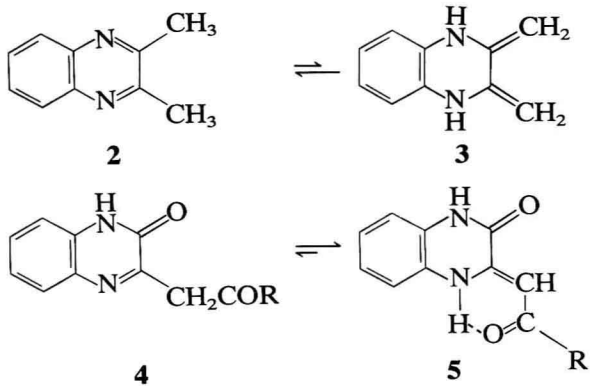


(X = O or S)

Scheme 4



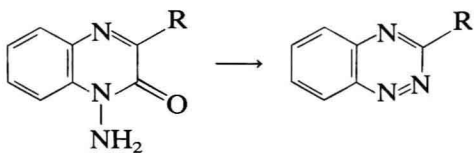
2,3-Dihydroxy- and 2,3-dimercaptoquinoxaline similarly exist in 2,3-dione (Chapter V) and 2,3-dithione forms (Chapter VI), respectively. Literature statements that 2,3-dimethylquinoxaline (**2**) reacts in the tautomeric diene form (**3**) are incorrect (Chapter XIV), although in the case of the acyl derivatives (**4**) enamine forms (**5**) are preferred (Scheme 5) (Chapter V).



Scheme 5

VIII. Reactions of Quinoxalines Involving Ring Change

Relatively few reactions of quinoxaline derivatives occur with change of ring size. Isolated examples are noted in the following text. For example, ring contraction to benzimidazole derivatives occurs when 2,3-diphenylquinoxaline (Chapter XV) or 2-halogenoquinoxalines (Chapter X) are treated with potassium amide in liquid ammonia and quinoxalin-2-one is treated with hydrazine (Chapter V). It is also found that oxidation of 1-aminoquinoxalin-2-ones with lead tetraacetate give benzo-1,2,4-triazines (Scheme 6) (Chapter V).

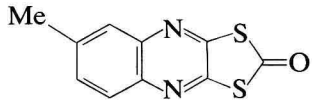


Scheme 6

IX. Biological Properties of Quinoxaline Derivatives

The main search for biologically active quinoxalines has centered around the preparation of quinoxaline *N*-oxides. 3-Substituted 2-methylquinoxaline 1,4-dioxides with high antibacterial activity have been prepared (Chapter IV). Quinoxaline 2-sulfonamide has had sustained use as a coccidiostat for poultry (Chapter XI). A series of naturally occurring quinoxaline antibiotics, the quinomycins and triostins, are known, but their therapeutic index is low (Chapter IX).

5,6,7,8-Tetrachloroquinoxaline (Chlorquinox) is the active compound in various fungicidal formulations (Chapter III) and Morestan (**6**) is used as an insecticide (Chapter VI).



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X. Major Sources of Reference

The early literature on quinoxaline chemistry can be conveniently located either via Beilstein's *Handbuch der organischen Chemie* or in Meyer-Jacobson's *Lehrbuch der organischen Chemie.* The period 1917–1948 is covered by the previous monograph in this series by Simpson,[1] and it is the aim of the present volume to cover the quinoxaline literature in the period 1949–1975 and in addition to refer to major papers appearing in 1976. In an attempt to preserve continuity, quinoxaline chemistry is discussed as far as possible under the same chapter headings as used in Simpson's monograph. Much detailed information on quinoxalines has appeared in several review articles.[2–5]

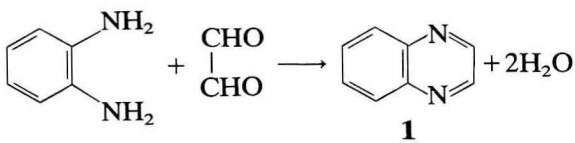
1. J. C. E. Simpson, "Condensed Pyridazine and Pyrazine Rings," Interscience, New York, 1953.
2. Y. T. Pratt, "Heterocyclic compounds," Vol. 6, R. C. Elderfield, Ed., Wiley, New York, 1956, Chap. 10.
3. G. R. Ramage and J. K. Landquist, "Chemistry of Carbon Compounds," Vol. IVB, Elsevier, Amsterdam, 1959, Chap. 15.
4. G. W. H. Cheeseman, "Advances in Heterocyclic Chemistry," Vol. 2, A. R. Katritzky, Ed., Academic Press, New York, 1963, p. 203.
5. G. W. H. Cheeseman and E. S. G. Werstiuk, "Advances in Heterocyclic Chemistry," Vol. 22, A. J. Boulton and A. R. Katritzky, Eds., Academic Press, New York, 1978, p. 367.

CHAPTER II

Quinoxaline—The Parent Heterocycle

I. Methods of Preparation

Quinoxaline (**1**) has been prepared in 85–90% yield by reaction of *o*-phenylenediamine with glyoxal sodium bisulfite.[1] It has also been prepared in excellent yield from the diamine by treatment with 30% aqueous glyoxal in the presence of sodium carbonate (Scheme 1).[2]



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Scheme 1

II. Properties

1. Physical Properties

Quinoxaline is conveniently purified by distillation, and a fraction of b.p. 108–111°/12 mm has a m.p. of 29–30°.[1] Quinoxaline forms a 2:1 molecular complex with phloroglucinol of m.p. 131–132°.[3] The pK_a of