CONDENSED PYRAZINES

G. W. H. Cheeseman

DEPARTMENT OF CHEMISTRY, QUEEN ELIZABETH COLLEGE
UNIVERSITY OF LONDON

R. F. Cookson

JANSSEN PHARMACEUTICAL LTD.

AN INTERSCIENCE ® PUBLICATION

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

This Page Intentionally Left Blank

CONDENSED PYRAZINES

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

CONDENSED PYRAZINES

G. W. H. Cheeseman

DEPARTMENT OF CHEMISTRY, QUEEN ELIZABETH COLLEGE
UNIVERSITY OF LONDON

R. F. Cookson

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

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.

ARNOLD WEISSBERGER

Research Laboratories
Eastman Kodak Company
Rochester, New York

EDWARD C. TAYLOR

Princeton University
Princeton, New Jersey

This Page Intentionally Left Blank

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

This Page Intentionally Left Blank

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 G. W. H. C.
September 1977 R. F. C.

This Page Intentionally Left Blank

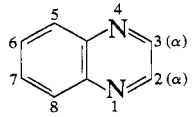
Contents

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.

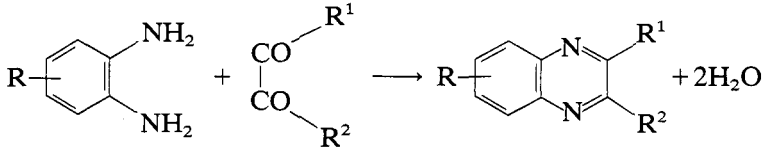


1

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

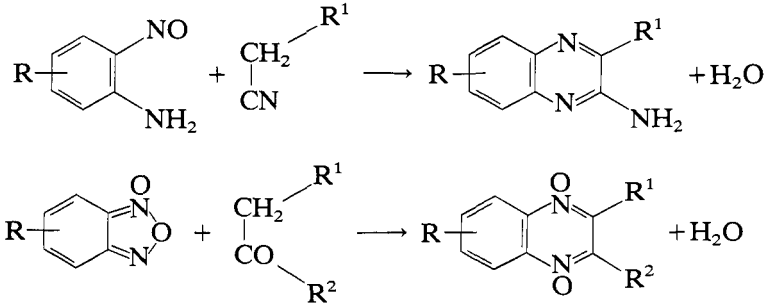
o-phenylenediamines with α-dicarbonyl compounds results in quinoxaline formation as shown in Scheme 1. By suitable choice of the α-dicarbonyl component, alkyl- and arylquinoxalines, quinoxalinones, and



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



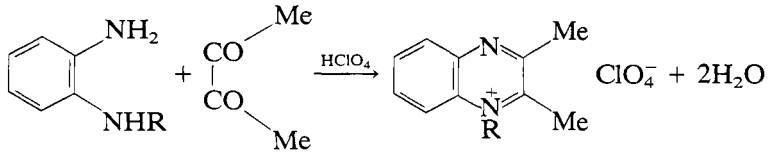
Scheme 2

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

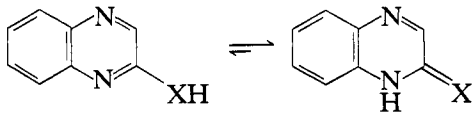
1,2-Dihydro-, 1,4-dihydro-, 1,2,3,4-tetrahydro-, and decahydroquinoxalines are known (Chapter XVIII). Thus reduction of quinoxaline with lithium aluminum hydride yields 1,2,3,4-tetrahydroquinoxaline (Chapter II). Quinoxaline also adds two molecular proportions of Grignard reagent to give a 2,3-disubstituted 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).

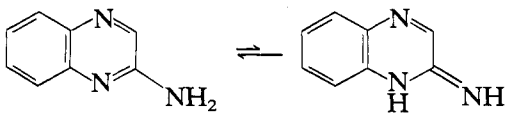
VII. Tautomerism of Quinoxaline Derivatives

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).

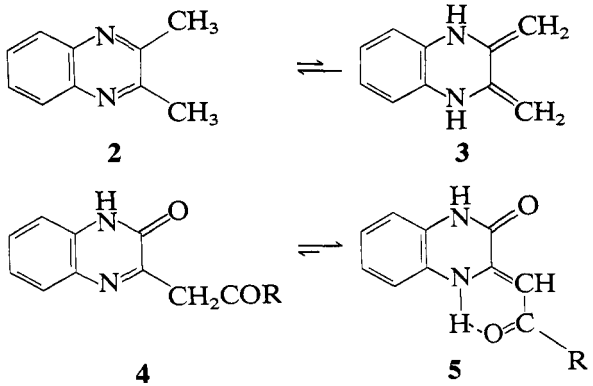


(X = O or S)

Scheme 4



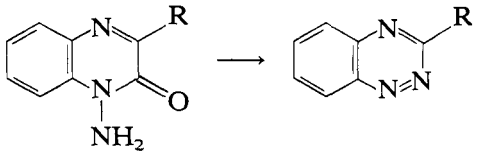
2,3-Dihydroxy- and 2,3-dimercaptoquinoxaline similarly exist in 2,3-dione (Chapter V) and 2,3-dithione forms (Chapter VI), respectively. Literature statements that 2,3-dimethylquinoxaline (**2**) reacts in the tautomeric diene form (**3**) are incorrect (Chapter XIV), although in the case of the acyl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

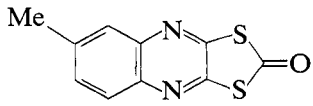


Scheme 6

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).



6

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]

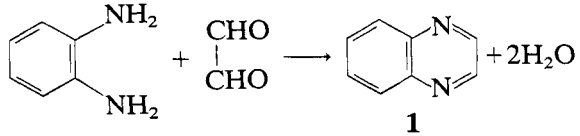
1. J. C. E. Simpson, "Condensed Pyridazine and Pyrazine Rings," Interscience, New York, 1953.
2. Y. T. Pratt, "Heterocyclic compounds," Vol. 6, R. C. Elderfield, Ed., Wiley, New York, 1956, Chap. 10.
3. G. R. Ramage and J. K. Landquist, "Chemistry of Carbon Compounds," Vol. IVB, Elsevier, Amsterdam, 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]



1

Scheme 1

II. Properties

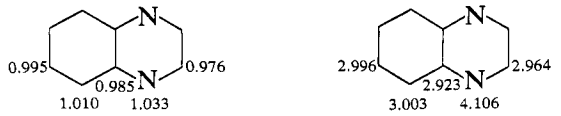
1. Physical Properties

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

quinoxaline in water at 20° is 0.56; it is therefore a considerably weaker base than the isomeric diazanaphthalenes, namely, cinnoline (pK_a 2.42), phthalazine (pK_a 3.47), and quinazoline (pK_a 1.95).[4] Quinoxaline has a second pK_a of −5.52.[72] The effect of substitution of Cl, OMe, SMe, $CONH_2$, and CO_2Et in the 2-position is base weakening. These substituents are less base weakening in the quinoxaline series than in the pyridine or in the quinoline series, probably because protonation occurs at N-4. 2-Substituents such as Me, NHCOMe, NH_2, NHMe, and NMe_2 are base strengthening and direct protonation to N-1. These substituents cause a greater enhancement of basic strength than in the pyridine or quinoline series. For example, 2-aminoquinoxaline has a pK_a of 3.96 (3.40 pK_a units greater than the parent base) whereas the pK_a values of 2-aminopyridine and pyridine differ by only 1.63 pK_a units.[5] 5-Amino-, 6-amino-, 5-hydroxy and 6-hydroxyquinoxalines are stronger bases than quinoxaline itself, and 5-aminoquinoxaline is exceptional in undergoing protonation at the amino group rather than at a ring nitrogen atom.[6] The basic center in 5-hydroxyquinoxaline is N-1. Reaction of 5-hydroxyquinoxaline with methyl iodide gives a methiodide which must be the 1-methiodide because of its ability to form a strongly bound nickel complex.[7] Quinoxaline has a dipole moment of 0.51 D in benzene,[8] whereas quinoline has a dipole moment of 2.18 D.

The first and second ionization potentials of quinoxaline measured by photon electron spectroscopy are 8.99 and 10.72 eV, respectively.[9] Since the highest-occupied π orbital and nonbonding orbitals of quinoxaline are very close in energy, it is not known unambiguously from which orbital the first electron is lost.[10] The heat of atomization of quinoxaline has been calculated by a self-consistent field molecular orbital treatment to be 79.739 eV, and similar calculations have been carried out out on related diazanaphthalenes.[11] Several molecular orbital calculations of the π-electron density in quinoxaline have been made. These calculations indicate that the highest electron density at ring carbon is at positions 5 and 8, the next at positions 6 and 7, and the lowest at positions 2 and 3; the related σ-charge densities have also been calculated (Fig. 1).[12] Various attempts have been made to correlate chemical reactivity and chemical shift data with calculated π-electron densities, but no very clear correlations have emerged.[13]

The infrared spectrum of quinoxaline, nine of its 2-substituted, five of its 5-substituted, and eight of its 6-substituted derivatives have been measured in chloroform.[14,15] Eight ring-stretching bands are found in the region 1620–1350 cm^{-1} at frequencies close to those observed in substituted quinolines. The positions of these bands are not very sensitive to substituent change, but the intensities are much more variable. Thus the



π-Electron densities σ-Electron densities

Figure 1

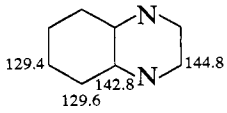
intensity of the band near 1600 cm^{-1} rises as the substituents change from electron acceptors to electron donors. β-CH Bending modes give rise to absorption in the region 1300–1050 cm^{-1}, ring breathing modes to absorption near to 1000 cm^{-1}, and out-of-plane γ-CH bending modes to absorption in the region below 1000 cm^{-1}.

The ultraviolet absorption spectrum of quinoxaline in cyclohexane shows bands with vibrational fine structure at 340 ($\log \varepsilon$ 2.84), 312 ($\log \varepsilon$ 3.81), and 232 nm ($\log \varepsilon$ 4.51) which are attributed to n–π^* and π–π^* transitions.[16] In ethanol the vibrational fine structure disappears and the less intense n–π^* band appears as a shoulder on the long-wave π–π^* band.[17] However in methanol[18] and in water[19] the n–π^* band is obscured by the more intense π–π^* band. The weak n–π^* bands in the ultraviolet spectra of 6-chloro- and 6-bromoquinoxaline[20] and certain 2-substituted quinoxalines also show shifts to shorter wavelengths on change from a nonpolar to polar solvent, whereas the π–π^* bands are not greatly affected by change of solvent. Substitution in the 2-position of the quinoxaline nucleus produces bathochromic shifts in the π–π^* bands. This increases in the order $Me < Cl < OMe < SMe < NMe_2$.[21,22] The phosphorescence spectra of quinoxaline and other diazanaphthalenes have been examined, the diazanaphthalenes showing the same π–π^* phosphorescence band as naphthalene.[23]

The ^1H NMR spectrum of quinoxaline has been measured in acetone,[24] carbon tetrachloride,[24] dimethyl sulfoxide,[25] dichloromethane,[26] and trifluoroacetic acid.[26] The signal for H2 and H3 in carbon tetrachloride appears as a low-field singlet, and the aromatic ring protons appear as an $AA'BB'$ system. The low-field half of the $AA'BB'$ multiplet is assigned to the 5- and 8-protons and the high-field half, to protons 6 and 7. Some broadening of the signals from protons 6 and 7 is attributed to long-range coupling with protons 2 and 3. The computed chemical shifts for protons 2 and 3, 5 and 8, and 6 and 7 are 8.73, 8.06, and 7.67 δ, respectively. In the more polar solvent acetone, there is a general small low-field shift. Coupling constant values are J_{56} 8.4 Hz, J_{57} 1.4 Hz, J_{58} 0.6 Hz, and J_{67} 6.9 Hz. Analysis of the ^1H NMR spectra of a number of 2-, 5-, and 6-monosubstituted quinoxalines show the following coupling

constant variations: J_{23} 1.7–1.9 Hz, J_{67} 5.0–8.3 Hz, J_{78} 8.4–10.3 Hz, J_{57} 1.4–2.7 Hz, J_{68} 0.7–2.9 Hz, and J_{58} 0.3–0.8 Hz.[25]

The ^{13}C NMR spectrum of the parent heterocycle in deuterochloroform shows resonances at δ 144.8, 142.8, 129.6, and 129.4 assigned to carbons 2 and 3, 4a and 8a, 5 and 8, and 6 and 7, respectively (Fig. 2).[12,27] The ^{14}N chemical shifts have been measured for a series of aromatic



^{13}C Chemical shifts

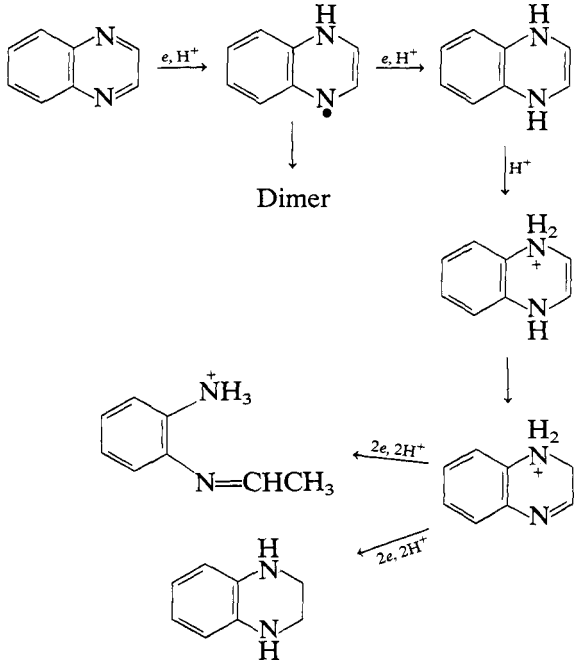
Figure 2

heterocycles including quinoxaline, for which the ^{14}N resonance is at $+46 \pm 3$ ppm from nitromethane and the peak half-height width is 950 ± 50 Hz. The ^{14}N chemical shifts have been found to depend almost linearly on the π-electron density at nitrogen, as calculated by the Pariser–Parr–Pople method.[28]

The mass spectrum of quinoxaline shows fragment ions resulting from the loss of one and two molecules of hydrogen cyanide. Where structurally possible, loss of hydrogen cyanide from the molecular ion is found to be the major fragmentation process for many nitrogen heteroaromatic compounds.[29] Similarly in the case of 2-alkyl- and 2-arylquinoxalines, $(M—HCN)^+$ and $(M—RCN)^+$ ions are observed. A notable feature of the spectrum of 2-methyl-3-phenylquinoxaline is the formation of an intense $(M\text{-}1)^+$ ion.[30,31]

The polarographic reduction of quinoxaline and its derivatives has been studied by a number of workers.[32–38] Half-wave electrode potentials are pH dependent; and over the pH range of 1 to 10, $E_{\frac{1}{2}}$ has been reported to vary from -0.254 to -0.863 V.[32] The half-wave electrode potential in anhydrous dimethylformamide is -1.09 V for quinoxaline, -1.06 V for cinnoline, -1.41 V for phthalazine, and -1.22 V for quinazoline. The benzodiazines are more easily reduced than the corresponding diazines, thus pyrazine has a half-wave electrode potential of -1.57 V. Pyridine with a half-wave potential of -2.15 V is still more difficult to reduce. The reversible reduction potential of quinoxaline as determined by cyclic voltammetry is -1.097 V.[33] The observed energy differences between azine and radical anion are well correlated with the results of CNDO and SCF π-electron calculations.

Detailed study of the electrochemical reduction of quinoxaline in aqueous media has revealed that 1,2,3,4-tetrahydroquinoxaline is formed via a sequence involving 1,4-dihydroquinoxaline and acid-catalyzed rearrangement of the 1,4-dihydro derivative to 1,2-dihydroquinoxaline (Scheme 2).[34]



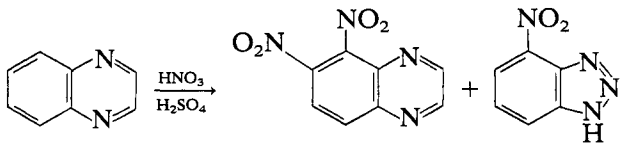
Scheme 2

2. Chemical Properties

Reduction of quinoxaline with sodium in THF at 20° yields a deep-purple solution from which 1,4-dihydroquinoxaline is isolated.[39] Reduction with either sodium in refluxing alcohol or lithium aluminum hydride in ether gives 1,2,3,4-tetrahydroquinoxaline.[39] Hydrogenation of quinoxaline over a 5% rhodium-on-alumina catalyst at 100° and 136 atm or over freshly prepared Raney nickel W-6 under similar conditions gives *meso*-(*cis*)-decahydroquinoxaline.[40] However hydrogenation of quinoxaline over a palladium-on-charcoal catalyst at 180° and 50 atm gives DL-(*trans*)-decahydroquinoxaline.[41]

Treatment of quinoxaline with one equivalent of peracetic acid in acetic acid yields quinoxaline 1-oxide, and with excess of peracetic acid quinoxaline 1,4-dioxide is formed.[42] Reaction of quinoxaline with 30% aqueous hydrogen peroxide in acetic acid, however, gives quinoxaline-2,3-dione as the main product.[43] Electrolytic oxidation of quinoxaline at a copper anode gives pyrazine-2,3-dicarboxylic acid in excellent yield.[44] The latter compound is also prepared in high yield by oxidation of quinoxaline with alkaline potassium permanganate[1]; a number of α-substituted quinoxalines have been similarly converted into substituted pyrazine-2,3-dicarboxylic acids.[45] On heating quinoxaline at 200° in the presence of a 5% palladium-on-carbon catalyst, 2,2′-biquinoxaline is formed.[46]

Quinoxaline itself is resistant to nitration with fuming nitric acid (*d* 1.52) and concentrated sulfuric acid at 100°,[47] but under prolonged treatment with nitric acid and oleum it has been converted into a mixture of 5-nitro- and 5,6-dinitroquinoxaline in 1.5 and 24% yield, respectively.[48,49] Later workers report* that nitration of quinoxaline gives a mixture of 5,6-dinitroquinoxaline and 4-nitrobenzotriazole (Scheme 3).[50]



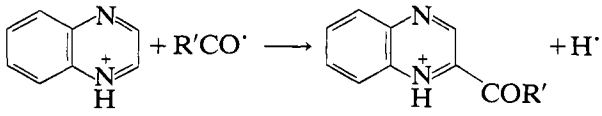
Scheme 3

A careful study of the phenylation of quinoxaline with benzoyl peroxide, various benzenediazonium salts, and *N*-nitrosoacetanilide showed that position 2 is the most reactive and that position 5 is more reactive than position 6.[51] With benzoyl peroxide in glacial acetic acid at 118°, the product formed contains 77% 2-phenylquinoxaline and 23% 5- and 6-phenylquinoxaline.[52] 2-Benzylquinoxaline is the only product isolated from the homolytic benzylation of quinoxaline with dibenzylmercury in acetic acid.[53] In a series of publications Italian workers have described the alkylation,[54] acylation,[55–57] α-oxyalkylation,[58] δ-aminoalkylation,[59] ethoxycarbonylation,[60] and amidation[61] of the quinoxalinium ion. For example, acylation of quinoxaline is achieved by the simultaneous addition of saturated solutions of ferrous sulfate and *t*-butyl hydroperoxide to a cooled (5–15°) mixture of aldehyde, quinoxaline, and 4*M* sulfuric acid.

* A possible route to 4-nitrobenzotriazole may be ring cleavage of the initially formed 5-nitroquinoxaline to 3-nitro-*o*-phenylenediamine and its subsequent ring closure to 4-nitrobenzotriazole by nitrous acid present in the nitrating medium.

Using a range of aliphatic and aromatic aldehydes the yields of 2-acylquinoxalines range from 45 to 73%. The reaction is formulated as shown in Scheme 4.

$$Fe^{2+} + ROOH \longrightarrow Fe^{3+} + OH^- + RO^{\cdot}$$
$$RO^{\cdot} + R'CHO \longrightarrow ROH + R'CO^{\cdot} \qquad (R = H \text{ or } t\text{-Bu})$$



Scheme 4

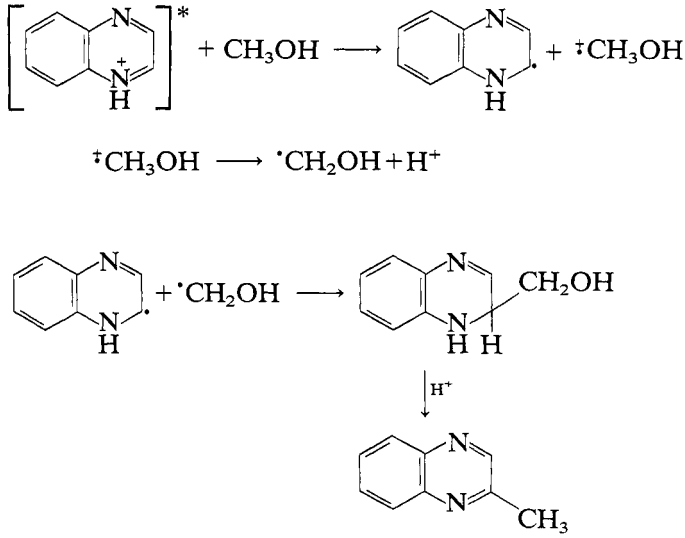
Ethers have been used as reagents for α-oxyalkylation,[58] and the addition product of ethyl pyruvate and hydrogen peroxide

$$[CH_3C(OH)(OOH)CO_2Et]^{52}$$

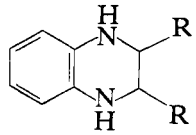
and formamide[61] are used as the source of $EtO_2C^{\cdot}$ and $NH_2CO^{\cdot}$ radicals, respectively. In all cases substitution occurs at the 2-position although in some instances 2,3-disubstituted products are obtained.[58] Treatment of quinoxaline with *N*-chlorodi-*n*-butylamine and ferrous sulfate in 50% sulfuric acid gives exclusive 2-substitution, but in concentrated acid a mixture of 2- and 6-(4-*n*-butylaminobutyl)quinoxaline is obtained. Abnormal substitution at position 6 is explained by postulating radical attack on the diprotonated species.[59]

Substitution of quinoxaline takes place at C-2 when it is irradiated in ether, methanol, or ethanol.[62,63] Irradiation of quinoxaline in acidified methanol furnishes 2-methylquinoxaline, and the reaction is suggested to go through a pathway involving electron transfer from the solvent to an excited state of the protonated quinoxaline (Scheme 5).[64] Irradiation of quinoxaline under aerobic conditions in acidic aqueous solution leads to the formation of 5-hydroxyquinoxaline.[65]

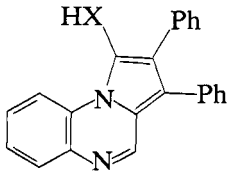
Quinoxaline readily reacts with Grignard reagents. Addition of two molecular proportions of allylmagnesium bromide[66] and of 3-(dimethylamino)propylmagnesium chloride,[67] and hydrolysis of the initial adducts, gives the tetrahydroquinoxalines **2** and **3**, respectively. The 1:1 adducts **4**, **5**, and **6** are obtained from the reaction of quinoxaline with diphenylcyclopropenone,[68] diphenylcyclopropenethione,[69] and methyl phenylhydrazonochloroacetate in the presence of triethylamine,[70] respectively. In the latter case the presumed intermediate is the dipolar species ($MeO_2C\overset{+}{C}{=}N{-}\bar{N}Ph$).



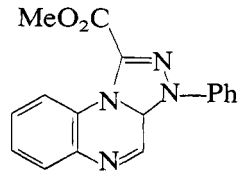
Scheme 5



2 R = $CH_2CH{=}CH_2$
3 R = $CH_2CH_2CH_2NMe_2$



4 X = O
5 X = S



6

Reaction of quinoxaline with ethyl iodide in boiling acetonitrile gives ethylquinoxalinium iodide in 76% yield, and treatment of the parent base with methyl *p*-toluenesulfonate at room temperature gives methylquinoxalinium *p*-toluenesulfonate in quantitative yield.[71] There are apparently no reports of the isolation of quinoxaline bisquaternary salts.

III. References

1. R. G. Jones and K. C. McLaughlin, *Org. Synth.*, **30,** 86 (1950).
2. A. Zmujdzin, Pol. Pat. 69,644; *Chem. Abstr.*, **81,** 77966z (1974).
3. P. E. Verkade and M. van Leeuwen, *Rec. Trav. Chim.*, **70,** 142 (1951).
4. A. Albert, "Physical Methods in Heterocyclic Chemistry," Vol. 1, A. R. Katritzky, Ed. Academic Press, New York, 1963, Chap. 1.
5. M. M. Kaganskii, G. G. Dvoryantseva, and A. S. Elina, *Chem. Heterocycl. Comp.*, 369 (1973).
6. A. R. Osborn, K. Schofield, and L. N. Short, *J. Chem. Soc.*, 4191 (1956).
7. A. Albert and A. Hampton, *J. Chem. Soc.*, 505 (1954).
8. H. Lumbroso and G. Palamidessi, *Bull. Soc. Chim. Fr.* 3150 (1965).
9. M. J. S. Dewar and S. D. Worley, *J. Chem. Phys.*, **51,** 263 (1969).
10. S. D. Worley, *Chem. Rev.*, **71,** 295 (1971).
11. M. J. S. Dewar and T. Morita, *J. Am. Chem. Soc.*, **91,** 796 (1969).
12. R. J. Pugmire, D. M. Grant, M. J. Robins, and R. K. Robins, *J. Am. Chem. Soc.*, **91,** 6381 (1969).
13. W. W. Paudler and T. J. Kress, "Topics in Heterocyclic Chemistry," R. N. Castle, Ed., Interscience, New York, 1969, p. 86.
14. H. H. Perkampus and A. Roders, *Z. Naturforsch.*, **15b,** 1 (1960).
15. G. W. H. Cheeseman, A. R. Katritzky, and B. J. Ridgewell, *J. Chem. Soc.*, 3764 (1963).
16. S. F. Mason, *Chem. Soc. (London) Spec. Publ.*, **No. 3,** 139 (1955).
17. G. M. Badger and J. S. Walker, *J. Chem. Soc.*, 122 (1956).
18. F. Bohlmann, *Chem. Ber.*, **84,** 860 (1951).
19. A. Albert, D. J. Brown, and G. W. H. Cheeseman, *J. Chem. Soc.*, 474 (1951).
20. R. C. Hirt, T. F. King, and J. C. Cavagnol, *J. Chem. Phys.*, **25,** 574 (1956).
21. G. W. H. Cheeseman, *J. Chem. Soc.*, 108 (1958).
22. H. H. Perkampus, *Z. Naturforsch.*, **17a,** 614 (1962).
23. R. Müller and F. Dörr, *Z. Electrochem.*, **63,** 1150 (1959); *Chem. Abstr.*, **54,** 5243 (1960).
24. P. J. Black and M. L. Heffernan, *Austr. J. Chem.*, **18,** 707 (1965).
25. P. J. Brignell, A. R. Katritzky, R. E. Reavill, G. W. H. Cheeseman, and A. A. Sarsfield, *J. Chem. Soc. B*, 1241 (1967).
26. D. J. Blears and S. S. Danyluk, *Tetrahedron*, **23,** 2927 (1967).
27. L. F. Johnson and W. C. Jankowski, "Carbon-13 N.M.R. Spectra," Wiley-Interscience, New York, 1972.
28. M. Witanowski, L. Stefaniak, H. Januszewski, and G. A. Webb, *Tetrahedron*, **27,** 3129 (1971).
29. A. Karjalainen and H. Krieger, *Soumen Kemistilehti B*, **43,** 273 (1970).
30. S. N. Bannore, J. L. Bose, K. G. Das, and V. N. Gogte, *Indian J. Chem.*, **7,** 654 (1969).
31. V. Kovacik, M. Fedoronko, and I. Jezo, *Org. Mass Spectrom.*, **7,** 449 (1973).
32. M. P. Streier and J. C. Cavagnol, *J. Am. Chem. Soc.*, **79,** 4331 (1957).
33. K. B. Wiberg and T. P. Lewis, *J. Am. Chem. Soc.*, **92,** 7154 (1970).
34. O. Fischer and Tran Hong Thuy, *Collect. Czech. Chem. Commun.*, **41,** 1853 (1976).
35. M. Fedoronko and I. Jezo, *Collect. Czech. Chem. Commun.*, **37,** 1781 (1972).
36. B. J. Tabner and J. R. Yandle, *J. Chem. Soc. A*, 381 (1968).
37. S. Millefiori, *J. Heterocycl. Chem.*, **7,** 145 (1970).
38. D. van der Meer and D. Feil, *Rec. Trav. Chim.*, **87,** 746 (1968).

39. J. Hamer and R. E. Holliday, *J. Org. Chem.*, **28,** 2488 (1963).
40. H. Smith-Broadbent, E. L. Allred, L. Pendleton, and C. W. Whittle, *J. Am. Chem. Soc.*, **82,** 189 (1960).
41. S. Maffei and S. Pietra, *Gazz. Chim. Ital.*, **88,** 556 (1958); *Chem. Abstr.*, **53,** 20060 (1959).
42. J. K. Landquist, *J. Chem. Soc.*, 2816 (1953).
43. M. Asai, *Yakugaku Zasshi*, **79,** 260 (1959); *Chem. Abstr.*, **53,** 13160 (1959).
44. T. Kimura, S. Yamada, K. Yoshizue, and T. Nagoka, *Yakugaku Zasshi*, **77,** 891 (1957); *Chem. Abstr.*, **52,** 1181 (1958).
45. H. I. X. Mager and W. Berends, *Rec. Trav. Chim.*, **78,** 5 (1959).
46. H. Smith-Broadbent and R. C. Anderson, *J. Org. Chem.*, **27,** 2679 (1962).
47. H. Otomasu and S. Nakajima, *Chem. Pharm. Bull.* (Tokyo), **6,** 566 (1958).
48. M. J. S. Dewar and P. M. Maitlis, *J. Chem. Soc.*, 2518 (1957).
49. F. H. Case and J. A. Brennan, *J. Am. Chem. Soc.*, **81,** 6297 (1959).
50. R. Nasielski-Hinkens and M. Benedek-Vamos, *J. Chem. Soc., Perkin I*, 1229 (1975).
51. C. M. Atkinson and C. J. Sharpe, *J. Chem. Soc.*, 3040 (1959).
52. H. J. M. Dou and B. M. Lynch, *Bull. Soc. Chim. Fr.*, 3815 (1966).
53. K. C. Bass and P. Nababsing, *Org Prepr. and Proc. Int.*, **3,** 45 (1971).
54. G. P. Gardini and F. Minisci, *Ann. Chim.* (Rome), **60,** 746 (1970); *Chem. Abstr.*, **74,** 87128x (1971).
55. T. Caronna, G. P. Gardini, and F. Minisci, *Chem. Commun.*, 201 (1969).
56. G. P. Gardini and F. Minisci, *J. Chem. Soc.* (C), 929 (1970).
57. G. P. Gardini, *Tetrahedron Lett.*, 4113 (1972).
58. W. Buratti, G. P. Gardini, F. Minisci, F. Bertini, R. Galli, and P. Perchinunno, *Tetrahedron*, **27,** 3655 (1971).
59. A. Citterio, M. Ghirardini, and F. Minisci, *Tetrahedron Lett.*, 203 (1976); T. Caronna, A. Citterio, M. Ghirardini, and F. Minisci, *J. Heterocycl. Chem.*, **13,** 955 (1976).
60. R. Bernardi, T. Caronna, R. Galli, F. Minisci, and M. Perchinunno, *Tetrahedron Lett.*, 645 (1973).
61. F. Minisci, R. Galli, and A. Quilico, *Ger. Offen.*, 2,056,433; *Chem. Abstr.*, **75,** 49055j (1971).
62. T. T. Chen, W. Dörscheln, H. Göth, M. Hesse, and H. Schmid, *Helv. Chim. Acta*, **51,** 632 (1968).
63. A. Castellano, J. P. Catteau, A. Lablache-Combier, B. Planckaert, and G. Allen, *Tetrahedron*, **28,** 3511 (1972).
64. S. Wake, Y. Takayama, Y. Otsuji, and E. Imoto, *Bull. Chem. Soc. Jap.*, **47,** 1257 (1974).
65. J. Verbeek, W. Berends and H. C. A. van Beek, *Rec. Trav. Chim.*, **95,** 285 (1976).
66. H. Gilman, J. Eisch, and T. Soddy, *J. Am. Chem. Soc.*, **79,** 1249 (1957).
67. A. Marrer, U. Salzmann, and F. Hofer, *Helv. Chim. Acta*, **54,** 2507 (1971).
68. J. W. Lown and K. Matsumoto, *Can. J. Chem.*, **49,** 1165 (1971).
69. J. W. Lown and K. Matsumoto, *Can. J. Chem.*, **49,** 3119 (1971).
70. P. D. Croce, *J. Heterocycl. Chem.*, **12,** 1133 (1975).
71. R. F. Smith, W. J. Rebel, and T. N. Beach, *J. Org. Chem.*, **24,** 205 (1959).
72. T. Caronna, A. Citterio, T. Crolla, and F. Minisci, *J. Chem. Soc. Perkin I*, 865 (1977).