QUINOXALINES
Supplement II

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QUINOXALINES

Supplement II

This is the sixty-first volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS
Dedicated to the Memory of
John Campbell Earl1
1890–1978

1J. C. Earl was born and died in Adelaide but spent the greater part of his working life in the Chair of Organic Chemistry at Sydney University. A man of great integrity, an exemplary chemist, and an inspiring teacher, he was, alas, often misunderstood by his colleagues. He is remembered especially for his discovery of the sydnones and (in collaboration with the late Wilson Baker) for their structural elucidation as mesionic 1,2,3-oxadiazoles.
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 several years ago 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. D. J. Brown is once again to be applauded and profoundly thanked for another fine contribution to the literature of heterocyclic chemistry. This volume on Quinoxalines brings the field up to the end of 2002 (with some 2003 citations) with a comprehensive compilation and discussion of the 23 years of quinoxaline chemistry that followed our latest volume on this subject by G. W. H. Cheeseman and R. F. Cookson. It should 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, and The Pyrazines, Supplement I), are also from the pen of Dr. D. J. Brown.

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Quinoxalines have been reviewed twice in this *Chemistry of Heterocyclic Compounds* series: first by J. C. E. Simpson as part of Volume 5 in 1953 and later in a supplementary way by G. W. H. Cheeseman and R. F. Cookson as part of Volume 35 in 1979. The present *Second Supplement* seeks to build on these excellent foundations by covering the quinoxaline literature from ~1976 to the end of 2002 and a little beyond. In doing so, it seemed wise to make certain changes in format to conform with the treatments of related diazines and benzodiazines in recent (as of 2003) volumes of the series. Thus all types of primary synthesis have been collected for the first time into a single chapter; quinoxalines, quinoxaline N-oxides, and hydroquinoxalines are no longer considered as separate systems; the content of each chapter has been expanded to embrace families rather than single types of derivative; and the scattered tables of quinoxaline derivatives have been replaced by a single user-friendly alphabetical table of clearly defined simple quinoxalines that aims to list *all* such quinoxalines reported to date (including those already listed in the tables of earlier reviews). In view of these and other necessary changes, the status of the present volume as a supplement has been maintained by many cross-references (e.g., *H* 235 or *E* 78) to pages of Simpson’s original review (*Hauptwerk*) or the Cheeseman and Cookson supplementary review (*Ergänzungs¬werk*), respectively.

The chemical nomenclature used in this supplement follows current IUPAC recommendations [*Nomenclature of Organic Chemistry, Sections A–E, H* (J. Rigaudi and S. P. Klesney, eds., Pergamon Press, Oxford, 1970)] with one important exception—in order to keep “quinoxaline” 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. For example, 1-carboxymethyl-2(1H)quinoxalinone is used instead of 2-(2-oxo-1,2-dihydroquinoxalin-1-yl)acetic acid. Secondary, tertiary, or quaternary amino substituents are also rendered as prefixes. Ring systems are named according to the *Chemical Abstracts* Service recommendations [*Ring Systems Handbook* (eds. anonymous, American Chemical Society, Columbus, Ohio, 1998 edition and supplements)]. In preparing this supplement, the patent literature has been largely ignored in the belief that useful factual information therein usually appears subsequently in the regular literature.

Throughout this book, an indication such as 0°C—70°C (within parenthesized reaction conditions) means that the reaction was commenced at the first temperature and completed at the second; in contrast, an indication such as 20–30°C means that the reaction was conducted somewhere within that range. Terms such as “recent literature” invariably refer to publications within the period 1975 to 2003.

I am greatly indebted to my good friend and coauthor of the first supplement, Dr. Gordon Cheeseman, for encouraging me to undertake this update on
quinoxalines; to the Dean of the Research School of Chemistry, Professor Denis Evans, for the provision of postretirement facilities within the School; to the branch librarian, Mrs. Joan Smith, for patient assistance in library matters; and to my wife, Jan, for her continual encouragement and practical help during indexing, proof-reading, and other such processes.

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CHAPTER 1

Primary Syntheses

The primary synthesis of quinoxalines may be accomplished by cyclization of benzene substrates already bearing appropriate substituents; by cyclocondensation of benzene substrates with acyclic synthons to provide one or more of the ring atoms required to complete the pyrazine ring; by analogous processing of preformed pyrazine substrates; or by rearrangement, ring expansion/contraction, degradation, or modification of appropriate derivatives of other heterocyclic systems. Partially or even fully reduced quinoxalines may often be made by somewhat similar procedures; such cases are usually illustrated toward the end of each subsection. Examples of any pre-1977 syntheses in each category may be found from the cross-references to Simpson’s volume\textsuperscript{1013} (e.g., \textit{H} 203) or to Cheeseman and Cookson’s volume\textsuperscript{1014} (e.g., \textit{E} 79) that appear on some section headings; some post-1977 material on primary syntheses has been reviewed less comprehensively elsewhere.\textsuperscript{1021–1030}

1.1. FROM A SINGLE BENZENE SUBSTRATE

Such syntheses are subdivided according to whether the N1,C8a, N1,C2, or C2,C3 bond is formed during the procedure to afford a quinoxaline.

1.1.1. By Formation of the N1,C8a Bond

Given the relatively unreactive nature of the carbon atoms in benzene, this synthesis appears unappealing. However, several such processes have been devised, as illustrated in the following examples. All deserve further development.

By Intramolecular Aminolysis of \textit{N}-(2-Aminoethyl)-\textit{o}-halogenoanilines

Note: The \textit{N}-substituent may be varied considerably; for example, the amino group may be part of a carbamoyl group.
N-(Benzy laminoacetyl)-2-bromo-4-chloro-N-methylaniline (1) gave 1-benzyl-4-methyl-2,3(1H,4H)-quinoxalinedion (3), probably by aerial oxidation of the dihydro intermediate (2) [Bu$_3$N, Ph$_3$P, Pd(OAc)$_3$, OP(NMe$_2$)$_3$, 110°C, CO or A (4 atm), 26 h: 68% or 38%, respectively; mechanism remains unclear].

\[
\begin{align*}
\text{Cl} & \quad \text{Br} & \quad \text{NHCH}_2\text{Ph} \\
\text{Me} & \quad \text{CO} & \quad \text{N} \\
\end{align*}
\]

\[
\begin{align*}
\text{(1)} & \quad \text{Me} & \quad \text{N} & \quad \text{O} \\
\text{CH}_2\text{Ph} & \quad \text{CH}_2\text{Ph} & \quad \text{N} & \quad \text{O} \\
\text{(2)} & \quad \text{(3)} & \quad [O] \\
\end{align*}
\]

N-(Carbamoylmethyl)-o-chloroaniline (4) gave 3,4-dihydro-2(1H)-quinoxalidnone (5) (‘‘base-catalyzed cyclization’’: >80%).

\[
\begin{align*}
\text{Cl} & \quad \text{CO} & \quad \text{NH}_2 \\
\text{H} & \quad \text{N} & \quad \text{H} & \quad \text{H} \\
\text{(4)} & \quad \text{(5)} & \quad \text{(6)} & \quad \text{(7)} & \quad \text{(8)} \\
\end{align*}
\]

Also other examples.

**By Thermolysis of N-(Phenylhydrazonoethylidene)anilines**

N-(Phenylhydrazonoethylidene)aniline (6, R = H) gave quinoxaline (8, R = H) via the intermediate radical (7) (vacuum-distilled through a tube at 600°C: 35%).

\[
\begin{align*}
\text{R} & \quad \text{N} & \quad \text{CH} & \quad \text{N} & \quad \text{H} \\
\text{R} & \quad \text{N} & \quad \text{NH} & \quad \text{H} & \quad \text{N} \\
\text{(6)} & \quad \text{(7)} & \quad \text{(8)} \\
\end{align*}
\]

N-(p-Tolylhydrazonoethylidene)-p-toluidine (6, R = Me) gave 6-methylquinoxaline (8, R = Me) (likewise: 36%) but the unsymmetric substrate, N-(phenylhydrazonoethylidene)-m-toluidine (9), gave a separable mixture of
6- (10) and 5-methylquinoxaline (11) (likewise: 15% and 23%, respectively).\(^{528}\)

\[
\includegraphics[width=0.8\textwidth]{image}
\]

Also other examples that include observations on mechanism.\(^{531–533}\)

**By Cyclization of \(\text{N-}(\text{Hydroxyiminoethylidene})\text{anilines}\)**

\(\text{N-}(2-\text{Hydroxyimino}-1,2\text{-diphenylethylidene})\text{aniline (13)}\) gave 2,3-diphenylquinoxaline (12) [neat \(\text{Ac}_2\text{O}, \text{reflux, }<24\text{ h}\) [monitored by thin-layer chromatography (tlc)]: 57%; via the isolable acetoxyimino intermediate by a radical mechanism\(^{1011}\) or 2,3-diphenylquinoxaline 1-oxide (14) [\(\text{Pb(OAc)}_4, \text{CH}_2\text{Cl}_2, 25^\circ\text{C, 1 h: 48%}\)]\(^{583}\) when unsymmetric aniline substrates were used, two isomers were formed in each case.\(^{583,1011}\)

\[
\includegraphics[width=0.8\textwidth]{image2}
\]

The somewhat analogous substrate, \(p\)-methoxy-\(\text{N-}(2\text{-nitroprop-1-enyl})\text{aniline (15)}\), afforded 6-methoxy-3-methylquinoxaline 4-oxide (16) (98% \(\text{H}_2\text{SO}_4: ?\%\))\(^{252}\)

\[
\includegraphics[width=0.8\textwidth]{image3}
\]

**By Cyclorearrangement of \(\text{N-}(\text{Alkoxycarbonylmethylene})-\text{N}^0\text{-phenylhydrazines}\)**

\(\text{N-}(\alpha\text{-Ethoxycarbonylbenzylidene})-\text{N}^0\text{-phenylhydrazine (17, } R = \text{H})\) gave 3-phenyl-2(1\(H\))-quinoxalinone (18, \( R = \text{H}\)) [neat polyphosphoric acid, 90\(^\circ\text{C} \rightarrow \sim 130^\circ\text{C}\)
(exothermic), \( \sim 5 \text{ min} \) (?): 20\%}; \( N-(\alpha\text{-ethoxycarbonyl})\text{-ethylenedene}-N',N'-\text{diphenyldiazine} (17, R = \text{Ph}) \) likewise gave 1,3-diphenyl-2(1H)-quinoxalinone (18, R = \text{Ph}) (polyphosphoric acid, 105\text{°C}, 30 min: 20\%); and several analogs were made similarly.\(^{539}\)

\[
\begin{align*}
\text{(17)} & \quad \begin{pmatrix}
\text{Ph} \\
\text{N} & \text{N} & \text{C} & \text{O} & \text{CO}_2 \text{Et}
\end{pmatrix} \\
\text{(18)} & \quad \begin{pmatrix}
\text{Ph} \\
\text{N} & \text{N} & \text{C} & \text{O}
\end{pmatrix}
\end{align*}
\]

1.1.2. By Formation of the N1,C2 Bond

This synthesis has proved quite useful. In practice, it involves the cyclization of derivatives of \( o-(\text{ethylamino})\text{aniline} \) or \( o-(\text{ethylamino})\text{nitrobenzene} \): available examples fit naturally into three broad categories outlined in the following subsections.

1.1.2.1. Cyclization of \( o-(\text{Ethylamino})\text{aniline} \) Derivatives

The cyclization of several types of these derivatives is illustrated in the following examples.

**From \( o-(\text{Alk-2-ynylamino})\text{anilines} \)**

3-Nitro-6-(prop-2-ynylamino)aniline (19, \( R = \text{H} \)) gave 2-methyl-7-nitroquinoxaline (20, \( R = \text{H} \))\((\text{MeCN})_4\text{CuBF}_4, \text{PhMe}, 85\text{°C}, 20 \text{ h}: 75\%; \text{aerial oxidation?})\]; 2,6-dimethyl-7-nitroquinoxaline (20, \( R = \text{Me} \)) was made similarly (78\%).\(^{640}\)

\[
\begin{align*}
\text{(19)} & \quad \begin{pmatrix}
\text{H} & \text{O}_2\text{N} & \text{NH}_2 & \text{CH}_2 & \text{C} & \text{CH} \\
\text{N} & & & & & \\
\end{pmatrix} \\
\text{(20)} & \quad \begin{pmatrix}
\text{Me} & \text{O}_2\text{N} & \text{N} & \text{Me} & & \\
\text{N} & & & & & \\
\end{pmatrix}
\end{align*}
\]

**From \( o-(\text{2-Halogenoethylamino})\text{anilines or the Like} \)**

4-Bromo-6-(2-chloroethylamino)-1,3-benzenediamine (21) gave 7-bromo-1,2,3,4-tetrahydro-6-quinoxalinamine (22) (\( \text{Na}_2\text{CO}_3, \text{Me}_2\text{NCHO}, \text{reflux, 1 h: 85\%})\).\(^{39}\)
From a Single Benzene Substrate

N\textsubscript{2}N-Dibenzyl-2-(ethoxycarbonylmethyl)amino-4-(trifluoromethyl)aniline (27) underwent reductive debenzylation and spontaneous cyclization to 6-trifluoromethyl-3,4-dihydro-2(1\textit{H})-quinoxalinone (28) \[\text{Pd(OH)}\textsubscript{2}/\text{C}, \text{EtOH}, \text{H}_2 (3 \text{ atm}), 3 \text{ days}: 97\%\].
N-Benzyl-3-chloro-6-(ethoxalylamino)aniline (29) gave 1-benzyl-7-chloro-2, 3(1\(H\),4\(H\))-quinoxalinedione (30) (EtONa/EtOH or HCl/EtOH, 20°C, ? h: >95%).

Also other examples.\(^{998,1066,1104}\)

From \(o\)-[(Cyanomethyl)amino]aniline Analogs

1-(\(\alpha\)-Cyanomethyl)amino)-2-methylaminocyclohexene (32), made in situ by transamination of the 2-morpholino analog (31), cyclized spontaneously to a reduced bicyclic product formulated confidently as methyl 3-amino-4-methyl-4,6,7,8-tetrahydro-2-quinoxalinecarboxylate (33) [MeNH\(_2\), MeOH (?), 20°C, ? h: 84\%];\(^{50,655}\) the 4-(2-methoxyethyl) (90%) and other analogs were made similarly.\(^{50,655}\) (See also Section 1.2.1.)

1.1.2.2. Direct Cyclization of \(o\)-(Ethylamino)nitrobenzene Derivatives \((E\ 33)\)

Such direct cyclizations usually occur in basic media to afford quinoxaline \(N\)-oxides. For success, C2 in the ethyl group needs to be a carbonyl entity or to be suitably activated. The following examples illustrate this valuable route to such \(N\)-oxides (and thence to quinoxalines; see Section 4.6.2.1).

From \(o\)-[(Alkoxycarbonylmethyl)amino]nitrobenzenes

\(o\)-(\(N\)-Ethoxycarbonylmethyl-\(N\)-methylamino)nitrobenzene (34) gave 1-hydroxy-4-methyl-2,3(1\(H\),4\(H\))-quinoxalinedione (35) (EtONa, EtOH, <5°C, 15 h:...
44%); analogs were made similarly (or in the presence of other bases) in mediocre yield.\textsuperscript{542,556,648,677}

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{chemical_structure.png}
\end{figure}

**From o-Acetamidonitrobenzene**

1-(2-Cyanoacetamido)-4-methyl-2-nitrobenzene (36) gave 7-methyl-3-oxo-3,4-dihydro-2-quinoxalinecarbonitrile 1-oxide (37) (NaOH, pyridine-H\textsubscript{2}O, 20°C, 30 min: ? %).\textsuperscript{98}

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{chemical_structure.png}
\end{figure}

In contrast, o-(2-cyano-N-methylacetamido)nitrobenzene (38) gave 1-hydroxy-4-methyl-2,3(1\textsubscript{H},4\textsubscript{H})-quinoxalinedione (40), presumably by hydrolysis of the intermediate carbonitrile (39) (NaOH, H\textsubscript{2}O, reflux, 30 min: 53%; or EtONa, EtOH, reflux, 30 min, aqueous workup: 69%).\textsuperscript{542}

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{chemical_structure.png}
\end{figure}

1-(Acetoacetylamino)-4-chloro-2-nitrobenzene (41) gave 6-chloro-2(1\textsubscript{H})-quinoxalinone 4-oxide (42) (KOH, H\textsubscript{2}O, 60°C, 20 min: 86%);\textsuperscript{391,413} analogs likewise.\textsuperscript{391,413}

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{chemical_structure.png}
\end{figure}

Also other examples.\textsuperscript{742}
From \(o\)-(Ethylideneamino)nitrobenzenes

\(o\)-(1-Dimethylamino-2-phenylethylideneamino)nitrobenzene (43) gave 2-dimethylamino-3-phenylquinoxaline 4-oxide (44) (EtONa, EtOH, 20°C, 30 min: 65%); several analogs similarly.\(^{579}\)

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{NMe}_2 & \quad \text{PhCH}_2\text{Ph} \\
\text{CNMe}_2 & \quad \text{N} \\
\text{NO}_2 & \quad \text{H}_2\text{O}
\end{align*}
\]

\((43)\)

\[
\begin{align*}
\text{N} & \quad \text{NMe}_2 \\
\text{Ph} & \quad \text{O}
\end{align*}
\]

\((44)\)

\(o\)-(5,5-Dimethyl-3-oxocyclohex-1-en-1-yl)nitrobenzene (45) gave 2-(3-carboxy-2,2-dimethylpropyl)quinoxaline 4-oxide (46), probably via ring fission of a tricyclic intermediate (NaOH, Bu'OH, reflux, 1 h: 92%); several analogs similarly.\(^{568}\)

\[
\begin{align*}
\text{H} & \quad \text{N} \\
\text{NO}_2 & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{O} & \quad \text{N} \\
\text{CN} & \quad \text{CH}_2\text{CMe}_2\text{CH}_2\text{CO}_2\text{H}
\end{align*}
\]

\((45)\)

\[
\begin{align*}
\text{N} & \quad \text{O}
\end{align*}
\]

\((46)\)

Also somewhat less practical examples.\(^{528,820}\)

1.1.2.3. Reductive Cyclization of \(o\)-(Ethylamino)nitrobenzene Derivatives

Catalytic hydrogenation or chemical reduction with concomitant cyclization has been used to convert several types of such nitro substrates into a variety of quinoxalines. The following examples, classified according to type of substrate, illustrate the possibilities available.

From \(o\)-[(Acylmethyl(amin)nitrobenzenes and the Like

1-(\(N\)-Acetyl-\(N\)-phenethylamino)-3,5-dimethoxy-2-nitrobenzene (47) gave 1-acetyl-5,7-dimethoxy-3-phenyl-1,2-dihydroquinoxaline (48) (Na\(_2\)S\(_2\)O\(_4\), H\(_2\)O–MeOH, reflux, 30 min: 65%);\(^{486}\) by a similar procedure, 1,3-dimethoxy-4-
nitro-5-phenyloxalylaminobenzene (49) gave 5,7-dimethoxy-3-phenyl-2(1H)-quinoxalinone (50) (72%).

\[
\begin{align*}
\text{MeO} & \quad \text{Ac} & \quad \text{MeO} \\
\text{O} & \quad \text{N} & \quad \text{OMe} \\
\text{H} & \quad \text{CH}_2 & \quad \text{N}(\text{CO}=\text{O})\text{Ph} \\
\text{NO}_2 & & \\
\text{MeO} & \quad \text{Ac} & \quad \text{MeO} \\
\text{N} & \quad \text{N}\text{Ac} & \quad \text{OMe} & \quad \text{MeO} \\
\text{Ph} & & & \text{H}
\end{align*}
\]

(47) \rightarrow (48)

1-(N-Phenacyl-N-tosylamino)-4-methyl-2-nitrobenzene (51) gave 6-methyl-3-phenylquinoxaline (52) (SnCl\(_2\), HCl–AcOH, 60\(^\circ\)C, 90 min: 54%; aromatization by aerial oxidation during workup?).

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{N} & \quad \text{Ts} \\
\text{CH}_2 & \quad \text{N}(\text{CO}=\text{O})\text{Ph} \\
\text{NO}_2 & & \\
\text{Me} & \quad \text{Me} \\
\text{N} & \quad \text{Ph} \\
\text{N} & \quad \text{Ph}
\end{align*}
\]

(51) \rightarrow (52)

From o-(3-Ethoxycarbonylallylamino)nitrobenzenes or the Like

o-(3-Ethoxycarbonylallylamino)nitrobenzene (53) gave 2-ethoxycarbonylmethyl-1,2,3,4-tetrahydroquinoxaline (54) (Fe, AcOH, N\(_2\), reflux, 30 min: 89%); also a homolog likewise.

\[
\begin{align*}
\text{H} & \quad \text{CH}_2 & \quad \text{CH}=\text{CHCO}_2\text{Et} \\
\text{N} & \quad \text{N} & \quad \text{H} \\
\text{NO}_2 & & \text{CH}=\text{CHCO}_2\text{Et} \\
\text{Fe}, \text{AcOH} & & \\
\text{H} & \quad \text{CH}_2\text{CO}_2\text{Et} \\
\text{N} & \quad \text{N} \\
\text{CH}_2\text{CO}_2\text{Et} & & \text{H}
\end{align*}
\]

(53) \rightarrow (54)
O-(3-Ethoxycarbonylacrylamido)nitrobenzene (55) gave 3-ethoxycarbonylmethyl-3,4-dihydro-2(1H)-quinoxalinone (56) [Raney Ni, H₂ (3 atm), MeOH, 20°C, 2 h: 78%]; also analogs.⁴²⁸

Also other examples.³¹⁹

**From o-[(Carboxymethyl)amino]nitrobenzenes**

1-Acetyl-4-[(α-carboxybenzylamino)-3-nitrobenzene (57, R = Ac) gave 7-acetyl-3-phenyl-3,4-dihydro-2(1H)-quinoxalinone (58, R = Ac) [Pd/C, H₂ (3 atm), EtOH, 20°C, 30 min: 64%];⁸⁸⁵ 7-fluoromethyl-3-phenyl-3,4-dihydro-2(1H)-quinoxalinone (58, R = CF₃) was made similarly from substrate (57, R = CF₃) [Pd/C, H₂ (1 atm), EtOH, 18°C, 1 h: 57%].⁸⁴⁰

**From o-[(Alkoxycarbonylmethyl)amino]nitrobenzenes or the Like**

o-[(Ethoxycarbonylmethyl)amino]nitrobenzene (59, R = H) gave 3,4-dihydro-2(1H)-quinoxalinone (60, R = H) [Pd/C, H₂ (3 atm), MeOH, 20°C, 90 min: 88%];⁷²⁴ 1-[(Ethoxycarbonylmethyl)amino]-2-methyl-6-nitrobenzene (59, R = Me) gave 5-methyl-3,4-dihydro-2(1H)-quinoxalinone (60, R = Me) [Pd/C, H₂ (3 atm), EtOH, 20°C, 3.5 h: 93%; note that the product is incorrectly named in the original paper].¹⁰⁴²
1-Chloro-3-[(1-ethoxycarbonyl-1-methylethyl)amino]-4-nitrobenzene (61) gave 6-chloro-3,3-dimethyl-3,4-dihydro-2(1H)-quinoxalinone (62) (TiCl₃, AcONa, H₂O–MeOH, 20°C, 2.5 h: >95%).

In contrast, o-(N-ethoxalyl-N-propylamino)nitrobenzene (63) gave 1-hydroxy-4-propyl-2,3(1H,4H)-quinoxalinedione (65), perhaps via the partly reduced substrate (64) [Pd/C, H₂ (3 atm), Me₂NCHO, 3 h: 85%]; likewise, 1-(ethoxalylamino)-3-fluoro-6-nitrobenzene (66) gave 6-fluoro-1-hydroxy-2,3(1H,4H)-quinoxalinedione (67) (Zn, NH₄Cl, H₂O–Me₂NCHO, <35°C, 57%) and the 4-hydroxy isomer was made in even better yield using hydrogenation over Ir/C.

Also many other examples, including some solid-phase syntheses.

From o-[(Carbamoylmethyl)amino]nitrobenzene Derivatives

Note: Several complicated but interesting examples of this cyclization have been reported; all involve loss of a substituted-amino portion of the carbamoyl grouping.

o-{1-Carboxymethyl-2-[N-(carboxymethyl)carbamoyl]ethylamino}nitrobenzene (68) gave 3-carboxymethyl-3,4-dihydro-2(1H)-quinoxalinone (69) (Pd/C, H₂, H₂O–EtOH, 20°C: 17%), confirmed in structure by oxidative decarboxylation
during sublimation at 180°C to afford 3-methyl-2(1H)-quinoxalinone in 50% yield.\textsuperscript{81}

\[
\begin{align*}
\text{C}_8\text{H}_{17}\text{O} & \quad \text{N} \quad \text{CO} \\
\text{C}_8\text{H}_{17}\text{O} & \quad \text{N} \quad \text{C(=O)NHCH}_2\text{CO}_2\text{H} \\
\text{NO}_2 & \\
\text{NO}_2 & \quad \text{OC}_8\text{H}_{17} \\
\text{OC}_8\text{H}_{17} & \\
\text{Pd}/\text{C}, \text{H}_2 & \\
\text{Pd}/\text{C}, \text{H}_2 & \\
\end{align*}
\]

\text{(68)}

\[
\begin{align*}
\text{Pd}/\text{C}, \text{H}_2 & \\
\text{Pd}/\text{C}, \text{H}_2 & \\
\end{align*}
\]

\text{(69)}

\[
\begin{align*}
\text{C}_8\text{H}_{17}\text{O} & \quad \text{N} \\
\text{C}_8\text{H}_{17}\text{O} & \quad \text{N} \quad \text{C(=O)NHCH}_2\text{CO}_2\text{H} \\
\text{NO}_2 & \\
\text{OC}_8\text{H}_{17} & \\
\text{OC}_8\text{H}_{17} & \\
\text{Pd}/\text{C}, \text{H}_2 & \\
\text{Pd}/\text{C}, \text{H}_2 & \\
\end{align*}
\]

\text{(70)}

\[
\begin{align*}
\text{C}_8\text{H}_{17}\text{O} & \quad \text{N} \\
\text{C}_8\text{H}_{17}\text{O} & \quad \text{N} \quad \text{C(=O)NHCH}_2\text{CO}_2\text{H} \\
\text{NO}_2 & \\
\text{OC}_8\text{H}_{17} & \\
\text{OC}_8\text{H}_{17} & \\
\text{Pd}/\text{C}, \text{H}_2 & \\
\text{Pd}/\text{C}, \text{H}_2 & \\
\end{align*}
\]

\text{(71)}

\[
\begin{align*}
\text{N},\text{N}'-\text{Bis}(2\text{-nitro-4,5-dioctyloxyphenyl})\text{oxamide} \text{ (70)} & \text{ gave } 6,7\text{-dioctyloxy-}
\end{align*}
\]

2,3(1\text{H},4\text{H})\text{-quinoxalinedione} \text{ (71)} \text{ [Pd/C, } \text{H}_2 \text{ ("medium pressure"), CHCl}_3–
\]

\[
\text{MeOH, 20°C, 12 h: 27%).} \text{27}
\]

\[
\begin{align*}
\text{C}_8\text{H}_{17}\text{O} & \quad \text{N} \quad \text{CO} \\
\text{C}_8\text{H}_{17}\text{O} & \quad \text{N} \quad \text{C(=O)NHCH}_2\text{CO}_2\text{H} \\
\text{NO}_2 & \\
\text{OC}_8\text{H}_{17} & \\
\text{OC}_8\text{H}_{17} & \\
\text{Pd}/\text{C}, \text{H}_2 & \\
\text{Pd}/\text{C}, \text{H}_2 & \\
\end{align*}
\]

\text{(70)}

\[
\begin{align*}
\text{C}_8\text{H}_{17}\text{O} & \quad \text{N} \\
\text{C}_8\text{H}_{17}\text{O} & \quad \text{N} \quad \text{C(=O)NHCH}_2\text{CO}_2\text{H} \\
\text{NO}_2 & \\
\text{OC}_8\text{H}_{17} & \\
\text{OC}_8\text{H}_{17} & \\
\text{Pd}/\text{C}, \text{H}_2 & \\
\text{Pd}/\text{C}, \text{H}_2 & \\
\end{align*}
\]

\text{(71)}

\[
\text{Also other examples.} \text{739}
\]

1.1.3. By Formation of the C2,C3 Bond

The only recent (as of 2003) use of such bond formation involves two carbon atoms that are activated by double bonds or as isocyanides. The following examples illustrate the present limited scope of this type of synthesis.

1,2-Bis(benzylideneamino)cyclohexane \text{ (72)} gave 2,3-diphenyldecahydroquinoxaline \text{ (73)} \text{ (Pb cathode, C anode, Et}_4\text{NOTs, MsOH, Me}_2\text{NCHO: 59%); analogs likewise.} \text{118}

\[
\begin{align*}
\text{N} \quad \text{C(=O)NHCH}_2\text{Ph} & \\
\text{N} \quad \text{C(=O)NHCH}_2\text{Ph} & \\
\text{electro[H]} & \\
\text{electro[H]} & \\
\text{(72)} & \\
\text{(73)} & \\
\end{align*}
\]

\[
\begin{align*}
\text{o-Bis[(2,2-diethoxycarbonylvinyl)amino]benzene} \text{ (74)} & \text{ gave 2,3-bis(diethoxycar}
\end{align*}
\]

bonylmethyl)-1,2,3,4-tetrahydroquinoxaline \text{ (75)} \text{ (Hg cathode, Pt anode,}