RECENT PROGRESS IN THE QUINOXALINE CHEMISTRY: UTILITY OF 3-ALKOXY-CARBONYLMETHYLENE-2-OXO-1,2,3,4-TETRAHYDROQUINOXALINES AS STARTING MATERIALS

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Abstract — 3-Alkoxy carbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxalines have been converted into various quinoxaline derivatives via versatile intermediates by the facile synthetic methods. This review describes these synthetic routes, including the mechanistic considerations and the spectroscopic properties.

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I. INTRODUCTION  

According to some reviews,1,2,3 various quinoxaline derivatives have been prepared  
mainly by the following methods; (i) condensation of aromatic o-diamines and a-di-  
carbonyl compounds, (ii) intramolecular cyclization of N-substituted aromatic o-  
diamines, (iii) ring transformations of benzodiazepines, (iv) quinoxaline N-oxides  
from benzofurazan 1-oxides and o-quinone dioxines. By means of the above method  
(i), early in 1960s, the reaction of o-phenylenediamines with acetylenedicarboxyl-  
ates was reported to give 3-alkoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquino-  
xalines 1a,b by Iwanami.4 Thereafter, tautomeric behaviors of 1a,b and related  
compounds 1c,d, and 2 have been studied by NMR and UV spectroscopies, that is,  
there are tautomeric equilibria in the enaminocarbonyl moiety of 15,6 and 27  
(Scheme 1). The principle for the chemical modifications and transformations of  
1a,b principally based on the above tautomeric nature. In 1972, Chapman8 reported  

\[
\begin{align*} 
1a & : R=\text{OMe} \\
1b & : R=\text{OEt} \\
1c & : R=\text{Me} \\
1d & : R=\text{COOEt} \\
2 & 
\end{align*}
\]  

\text{SCHEME 1}
the chemical conversion of 1 into the condensed and noncondensed quinoxaline derivatives. Recently, Danswan et al., Kawahara et al., and the authors have presented some synthetic routes of 1 into a variety of quinoxalines. However, the quinoxaline synthesis utilizing 1 as the starting materials has not been reviewed so far, so that the results published by the above researchers are summarized as follows.

II. SYNTHESIS AND SPECTRAL PROPERTIES OF STARTING MATERIALS AND RELATED COMPOUNDS

3-Alkoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxalines (1a, R=Me R'=R''=H; 1b, R'=Et R''=R''=H) are easily synthesized by the reaction of α-phenylenediamines with dimethyl and diethyl acetylenedicarboxylates in ethanol, in almost quantitative yields. α-Phenylenediamine also reacts with β,γ-acetylenic-α-ketoacid ester in the presence of aqueous base to afford 2-phenacyl-3-quinoxalinone 1e in 83% yield. The reaction of 2,5,6-triamino-4-oxo-3,4-dihydropyrimidine with diethyl oxaloacetate produced ethyl 2-(9-xanthoneryl)-acetate 2 (Scheme 2).

\[
\begin{align*}
1a: & R^1 = Me, R^2 = R^3 = H \\
1b: & R^1 = Et, R^2 = R^3 = H \\
1e: & R^1 = Me, R^2 = Me, R^3 = Me, Cl
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 2}
\end{align*}
\]
Compounds 1a-d5 and le12,13 exhibited the tautomeric equilibria, which depend on kinds of solvents5 and temperature of solutions14 (Scheme 3). The NMR spectra in DMSO-d6 manifested that two tautomers A and B (Scheme 3) coexisted in 1a,b, and the tautomer A was predominant in 1c,d, as shown in Table I. In addition, the NMR spectra in trifluoroacetic acid (TFA) clarified that 1a,b existed as the tautomer B, ld,e as the tautomer A. Thus, the equilibria of 1a,b are proved to incline to the tautomer B in acidic media. This tendency is applied to the reaction of methylenic carbon of 1a,b with electrophilic reagents.

![Scheme 3](image)

**Scheme 3** Equilibria of 1 in DMSO-d6 or TFA

<table>
<thead>
<tr>
<th>Compound</th>
<th>Tautomer</th>
<th>in DMSO-d6</th>
<th>in TFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>COOMe</td>
<td>H</td>
<td>A</td>
</tr>
<tr>
<td>1b</td>
<td>COOEt</td>
<td>H</td>
<td>A</td>
</tr>
<tr>
<td>1c</td>
<td>COMe</td>
<td>H</td>
<td>A</td>
</tr>
<tr>
<td>1d</td>
<td>COOEt</td>
<td>Me</td>
<td>A</td>
</tr>
</tbody>
</table>

**III. OXIDATION AND HALOGENATION OF STARTING MATERIALS**

1. **OXIDATION WITH m-CHLOROPERBENZOIC ACID AND HYDROGEN PEROXIDE/ACETIC ACID**

Compound 1 is susceptible to oxidation with m-chloroperbenzoic acid (MCPBA) and H2O2. The reaction of 1b with an excess of H2O2 in AcOH provided 2,3-dioxo-1,2,3,4-
tetrahydroquinoxaline 3 (60%), presumably via an intermediate I-1,\textsuperscript{15} while oxidation of 1a with MCPBA produced the methylene C-hydroxylated compound 4 (40%) and 3 (9%)\textsuperscript{16} (Scheme 4). Treatment of 4 with 10% NaOH furnished 3-hydroxymethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline 5 (70%). The reaction mechanism of 1a to 3 and 4 is shown in Scheme 5, including intermediates I-2, I-3, and I-4.

**Scheme 4**

![Reaction scheme showing the transformation of 1a to 3 and 4 with intermediates I-1, I-3, and I-4.]

**Scheme 5**

![Reaction scheme showing the transformation of 1a to 3 with intermediate I-2.]

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2. HALOGENATION

Although MCPBA and \( \text{H}_2\text{O}_2/\text{AcOH} \) acted as the oxidizing agent for \( \text{la,b} \), the reactions of \( \text{la} \) with \( \text{H}_2\text{O}_2/\text{HBr} \) and \( \text{H}_2\text{O}_2/\text{HCl} \) resulted in the formations of \( \text{N}^4 \)- and methylenic C-dihalogenated compounds \( \text{6a} \) (87%) and \( \text{6b} \) (70%)\(^1\) (Scheme 6). On the other hand, the reactions of \( \text{la} \) with \( \text{Br}_2/\text{H}_2\text{O}, \text{Cl}_2/\text{H}_2\text{O} \), and \( \text{N} \)-halogenosuccinimide (NBS, NCS) resulted in \( \text{N}^4 \)-halogenations to give compounds \( \text{7a,b} \) (95-99%). Compound \( \text{6b} \) was also obtained by the reaction of \( \text{4} \) with \( \text{H}_2\text{O}_2/\text{HCl} \) in 63% yield. \( \text{N}^4 \)-Debromination of \( \text{6a} \) was successful by treatment with \( \text{ZnI}_2 \) in AcOH/TFA, affording the monobromo compound \( \text{8} \) (41%). Further chlorination of \( \text{7b} \) with \( \text{H}_2\text{O}_2/\text{HCl} \) provided the tetrachlorinated compound \( \text{9} \) (27%), presumably via \( \text{6b} \) or trichlorinated intermediate \( \text{1-5} \). These reaction mechanisms were also proposed as follows.

\[ (a) \text{ mechanism from } \text{la} \text{ to } \text{7} \]

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Scheme 6

(b) mechanism from 1a to 6
VI. SYNTHESIS OF KEY INTERMEDIATES

1. ETHYL 2-(3,4-DIHYDRO-3-OXO-2-QUINOXALINYL)-2-HYDROXYIMINOACETATE

The reaction of 1b (23.2 g) with isopentyl nitrite (15 g) in trichloroacetic acid (3 g)/AcOH (500 ml) at room temperature resulted in methylenic C-hydroxyimination to produce ethyl 2-(3,4-dihydro-3-oxo-2-quinoxalinyl)-2-hydroxyiminoacetate (10a) [10a (syn) (9.5 g), 10a (anti) (14 g)] (Scheme 7).

![Scheme 7]

2. 3-HYDRAZINOCARBONYLMETHYLENE-2-OXO-1,2,3,4-TETRAHYDROQUINOXALINE

The reaction of 1a (10 g) with 10-fold molar excess of hydrazine hydrate (22.95 g) in EtOH (200 ml) under reflux easily provided 3-hydrazinocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline 11 (9.80 g, 98%).

![11]

3. 3-(N,N-DIMETHYLCARBAMOYL)FUR[2,3-b]QUINOXALINE HYDROCHLORIDE

The reaction of 1b (10 g) with POCI₃ (100 ml)/DMF (100 ml) under heating on a boil-
ing water bath furnished 3-(N,N-dimethylcarbamoyl)furo[2,3-b]quinoxaline hydrochloride 12 (9.93 g, 83%), whereas the methylenic C-formylated compound 13 was not obtained\textsuperscript{21} (Scheme 8).

Compound 12 is susceptible to attack with nucleophiles. For example, its heating in aqueous alcohol, aqueous AcOH, 10% NaOH, 10% HCl provided furo[2,3-b]quinoxaline-3-carboxylic acid 14, 3-methyl-2-oxo-1,2-dihydroquinoxaline 15,\textsuperscript{22} and 1. These results are represented in Scheme 9 and Table II.\textsuperscript{21b} Predominant hydrolysis of 12 into 14 in AcONa/AcOH and pyridine/AcOH may be due to a moisture in the reaction media.

The above three key intermediates 10, 11, and 12 have been the source materials leading to a plenty of novel quinoxaline derivatives, and the conversions of 10, 11, and 12 are described below.

Scheme 8
TABLE II. Conversion of 12 into Quinoxaline Derivatives

<table>
<thead>
<tr>
<th>Reaction Medium</th>
<th>Product (Yield %)</th>
<th>Reaction Medium</th>
<th>Product (Yield %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AcONa/AcOH</td>
<td>14 (86)</td>
<td>80% aq. AcOH</td>
<td>15 (17)</td>
</tr>
<tr>
<td>Pyridine/AcOH</td>
<td>14 (78)</td>
<td>EtONa/EtOH</td>
<td>1b (95)</td>
</tr>
<tr>
<td>10% NaOH</td>
<td>15 (95)</td>
<td>80% aq. EtOH</td>
<td>1b (80)</td>
</tr>
<tr>
<td>10% HCl</td>
<td>15 (60)</td>
<td>80% aq. MeOH</td>
<td>1a (40)</td>
</tr>
</tbody>
</table>

SCHEME 9
V. SYNTHESIS OF QUINOXALINES FROM KEY INTERMEDIATES

1. PREPARATION OF ISOXAZOLE, TRIAZOLE, AND IMIDAZOLE RING-CONDENSED QUINOXALINES

Ring closure of 10a to isoxazole ring could be accomplished for the syn and anti isomers by heating in polyphosphoric acid (PPA), giving the isoxazolo[4,5-b]quinoxaline 16 in good yields (Scheme 10). Treatment of 16 with 5% NaOH formed the nitrile 17 (99%), while prolonged base treatment of 16 afforded the amide 18.

The hydroxyimino compounds 10a,b were also applicable for the preparation of the 1,2-fused quinoxalines such as v-triazolo[1,5-a]quinoxalines and imidazo[1,5-a]-quinoxalines. Namely, catalytic reductions of 10a,b provided the amino compounds 19a and 19b, which were cyclized with isopentyl nitrite and 1,1'-carbonyldiimidazole to produce the v-triazolo[1,5-a]quinoxaline-3-carboxylate 20 and 1,4-dioxo-imidazo[1,5-a]quinoxaline-3-carboxylate 21, respectively (Scheme 11).

\[ \text{Scheme 10} \]
Although 19a could not be purified by recrystallization owing to decomposition, its structure was established by the spectral properties and an examination of its acetylation products (Scheme 12). The acetate 22 was obtained under cold condition, while its isomeric acetate 23 under hot condition. Moreover, heating of 22 isomerized to the stable 23, and this isomerization was also confirmed when the NMR spec-
Compound 19b was also converted into the C\textsuperscript{1}-substituted imidazo[1,5-a]quinoxalines (Scheme 13).\textsuperscript{9} Acylation of 19b furnished the N-acyl derivatives 24a (81%), 24b (66%), and 24c (66%), which cyclized into the corresponding C\textsuperscript{1}-substituted imidazo-[1,5-a]quinoxaline-3-carboxylic acids 25a (60%), 25b (52%), and 25c (47%) by heating in KOH solution. 1-Chloromethyl derivative 26 was obtained by the reaction of 19b with triethyl orthochloroacetate in 72% yield.

\begin{center}
\begin{tikzpicture}
  \node [below=0.5cm] at (0,0) {19b};
  \node [below=0.5cm] at (1.5,0) {24a R=Et};
  \node [below=0.5cm] at (3,0) {24b R=Ph};
  \node [below=0.5cm] at (4.5,0) {24c R=CH\textsubscript{2}Ph};
  \node [below=0.5cm] at (6,0) {aq. KOH/EtOH};
  \node [below=0.5cm] at (0,-1.5) {26};
  \node [below=0.5cm] at (1.5,-1.5) {25a R=Et};
  \node [below=0.5cm] at (3,-1.5) {25b R=Ph};
  \node [below=0.5cm] at (4.5,-1.5) {25c R=CH\textsubscript{2}Ph};
\end{tikzpicture}
\end{center}

Scheme 13

2,4-Dioxoimidazo[1,5-a]quinoxalines (type 21 in Scheme 11) were also obtained from the key intermediate 11 (Scheme 14).\textsuperscript{23} The reaction of 11 with an equimolar amount of HNO\textsubscript{2} gave the azide 27 (98%), whose refluxing in xylene and in Ac\textsubscript{2}O afforded the 1,4-dioxoimidazo[1,5-a]quinoxaline 28a (98%) and the N\textsuperscript{2}-acetyl derivative 28b (88%).
respectively. Acetylation of $28a$ with $\text{Ac}_2\text{O}$ provided $28b$ in 88% yield.

![Scheme 14](image)

2. PREPARATION OF HETEROCYCLEMETHYLENE- AND HETEROCYCLE-CONJUGATED QUINOXALINES

Hereupon, the syntheses of the azolylmethylene- and azole-conjugated quinoxalines are described, wherein the azoles are 1,3,4- and 1,2,4-oxadiazoles, 1,2,4-triazoles, and pyrazolones, which have been known to possess biological activities. The reactions of $11$ with orthoesters in $\text{EtOH}$ produced the hydrazones $29a,b$ (98%), whose refluxing in 1,8-diazabicyclo[5,4,0]-7-undecene (DBU)/$n$-BuOH resulted in the formations of the 1,3,4-oxadiazolylmethylenequinoxalines $30a,b$ (91%) (Scheme 15).

The structures of $30a,b$ were established by the spectral data and ascertained by the following reactions. That is, the reactions of $30a,b$ with NBS gave the N-brominated derivatives $31a$ (74%) and $31b$ (86%), and the reaction of $30a$ with MCPBA formed the methylenic C-hydroxylated compound $32$ (22%) (cf. section 111).

When $29a,b$ were refluxed in DMF, interesting results were obtained (Scheme 16). Compound $29a$ (R=H) cyclized to the pyrazolylquinoxaline $33a$ (86%), which would be promoted by the tautomerization from 1A to 1B type with DMF (cf. Scheme 3). On the contrary, $29b$ (R=Me) was transformed into $30b$ (60%), wherein the steric hindrance by methyl group would block the cyclization into the pyrazolone ring.

As described above, the selective cyclizations are found to depend on the kinds of solvents. In relation to the above results, $\text{CS}_2$ was employed as a one-carbon reagent in order to prepare the 30 and 33 types of compounds having the S-functional
groups. The reaction of 11 with CS₂ in DBU/n-BuOH afforded the 2-thioxo-1,3,4-oxa-
diazolymethylenequinoxaline 34 (83%), whose methylation with MeI/NaOH provided the
thiomethyl derivative 35 (80%)25 (Scheme 17).

On the other hand, the reaction of 11 with CS₂ in DMF provided the 3-oxo-5-thioxo-
pyrazolylidenequinoxaline 36 (72%), whose methylation furnished the S-methylated
compound 37 (91%). Refluxing of 36 and hydrazine hydrate in EtOH formed the hydra-
zinium salt 38 (92%)25 (Scheme 18).
Moreover, when isothiocyanates were incorporated into 11, 1,2,4-triazolylmethylenequinoxalines were obtained\textsuperscript{24} (Scheme 19). The reactions of 11 with isothiocyanates \((a, R=\text{allyl}; b, R=\text{Me})\) in dioxane gave the thiosemicarbazides 39\(a\) (94\%) and 39\(b\) (97\%), respectively, whose treatments with bases such as DBU and aq. NaOH afforded the 3-thioxo-1,2,4-triazolylmethylenequinoxalines 40\(a\) (86\%) and 40\(b\) (93\%), respectively. Compounds 40\(a,b\) were also obtained directly by the reactions of 11 with isothiocyanates in DBU/n-BuOH in 69\% and 82\% yields, respectively. Methylation of 40\(a\) with Mel/DBU provided the thiomethyl derivative 41 (76\%), whose further refluxing in MeI/DMF furnished the N-methyl derivative 42 (46\%). On the other hand, oxidation of 41 with MCPBA (2 eq.) formed the methylenic C-hydroxylated methylsulfinyl derivative 43 (18\%).\textsuperscript{24b}

The reaction of 40 with HNO\(_2\) gave the hydroxyimino compound 44 (66\%), whose heating in PPA afforded the 3-(1,2,4-triazolyl)isoxazolo[4,5-b]quinoxaline 45 (40\%).

The thiosemicarbazides 39 also cyclized to the 1,2,4-triazole ring with benzoyl chloride.\textsuperscript{26} Refluxing of 39\(a,b\) in benzoyl chloride/dioxane provided the S-benzoylated 1,2,4-triazoles 46\(a\) (32\%) and 46\(b\) (32\%), respectively (Scheme 20). When they
were prepared from 11 by one-pot reaction, the yields of 46a and 46b were 31% and 40%, respectively. Treatment of 46b with KOH furnished 40b, whose benzylation with benzoyl chloride in pyridine/dioxane formed the N-benzoylated derivative 47 (44%).

As depicted in Scheme 21, the reaction of 11 with an equimolar amount of HNO₂ led to the production of the imidazo[1,5-a]quinoxalines 28a,b. However, a 5-fold molar excess of HNO₂ converted 11 into 1,2,4-oxadiazolylquinoxaline 48 (60%) and the nitrile 17 (27%) (Scheme 21). A 2-fold molar amount of HNO₂ predominantly gave 48 (90%). Compound 48 was unambiguously synthesized from 17. Namely, addition of NH₂OH to 17 afforded the carboxamide oxime 49 (96%), whose reaction with ethyl chlorocarbonate provided 48 (79%). Furthermore, the reaction of the key intermediate 10 with hydrazine hydrate formed the hydrazide 50 (93%), whose reaction with
HNO₂ provided 48 (69%). Compound 48 was further derivatized, as shown in Scheme 22. Chlorination of 48 with POC₁₃/DMF formed the monochloride 51 (92%), whose re-
action with an excess of hydrazine hydrate gave the hydrazide \(52\) (99%). Refluxing of \(52\) in orthoesters/\(\text{BuOH}\) afforded the 5-triazolo[4,3-\(a\)]quinoxalines \(53a\) (98%) and \(53b\) (83%).

Moreover, the route of the nitrile \(17\) to the 2-amidinoquinoxaline \(54\) could be developed\(^2\) (Scheme 23). As displayed in Scheme 21, the nitrile \(17\) was converted into \(48\) via \(49\), and reductions of \(48\) and \(49\) with \(\text{Fe/HCl/AcOH}\) and \(\text{FeSO}_4/\text{HCl/AcOH}\) produced the Fe-complexes \(55\) (55-88%). Treatment of \(55\) with 10% \(\text{NaOH}\) furnished \(54\) (69-83%).

While the hydrazone \(29b\) was converted into 1,3,4-oxadiazolylmethylenequinoxaline \(30b\) (Scheme 15), \(29b\) could also be the starting material to the 4-amino-4\(H\)-1,2,4-triazolylmethylenequinoxaline \(55\) (Scheme 24).\(^3\) The reaction of \(29b\) with hydrazine hydrate/DBU in ethanol formed the requisite compound \(55\) (80%). The reactions of \(55\) with triethyl orthoformate and o-chlorobenzaldehyde in DMF gave the substituted 4-amino-4\(H\)-1,2,4-triazoles \(56a\) (84%) and \(56b\) (45%), respectively. However, \(56a\) did not cyclize into the pyrazolotriazole \(57\) (cf. Scheme 16). The reactions of \(55\) with an equimolar and 2-fold molar amount of \(\text{HNO}_2\) afforded the hydroxyimino derivative \(58\) (79%) and the deaminated hydroxyimino compound \(59\) (97%). The structure of \(59\) was assumed to be the 1\(H\)-1,2,4-triazole form.\(^3\) Refluxing of \(59\) in \(\text{POCl}_3\) formed the 3-(5-triazolyl)isoxazolo[4,5-\(b\)]quinoxaline \(60\) (88%). Moreover, the reactions of \(58\) with o- and p-chlorobenzaldehydes provided the 4-benzylideneamino-4\(H\)-1,2,4-triazoles \(61a\) (76%) and \(61b\) (41%), respectively, whose refluxing in \(\text{POCl}_3\) resulted in dehydrative cyclization to produce the isoxazolo[4,5-\(b\)]quinoxaline derivatives.
Scheme 24

62a (76%) and 62b (91%), respectively.
3. PREPARATION OF VARIOUS QUINOXALINES BY RING TRANSFORMATIONS

a. PYRAZOLYLQUINOXALINES AND PYRAZOL[3',4':3,4]PYRIDAZINO[5,6-b]QUINOXALINES

The reaction of 12 with 1,1-dimethylhydrazine afforded the hydrazide 63 (92%), while its reaction with hydrazine hydrate, methylhydrazine, and phenylhydrazine resulted in ring transformation to provide the pyrazolylquinoxalines 33a-c (85-96%)\(^2\) (Scheme 25). Chlorinations of 33b (R=Me) and 33c (R=Ph) with POCI\(_3\)/DMF formed the dichlorides 64b (90%) and 64c (50%), respectively. Refluxing of 64b and 64c in hydrazine hydrate produced the dihydropyrazolo[3',4':3,4]pyridazino[5,6-b]quinoxalines 65b (80%) and 65c (87%), respectively, which were easily oxidized with dibenzyl azodicarboxylate to furnish 2-methylpyrazolo[3',4':3,4]pyridazino[5,6-b]quinoxaline 66b (86%) and 2-phenylpyrazolo[3',4':3,4]pyridazino[5,6-b]quinoxaline 66c (80%), respectively.

![Scheme 25](image-url)
b. PYRIDO[1,2-a]PYRIMIDYLQUINOXALINE AND PYRIDAZINO[3,4-b]QUINOXALINES

The reaction of 12 with 2-aminopyridine (2-AP) effected ring transformation to form the pyrido[1,2-a]pyrimidylquinoxaline 67 (60%), whose reaction with POC13/DMF gave the chlorinated compound 68 (87%)\(^\text{32}\) (Scheme 26). The reaction of 68 with methylhydrazine in EtOH further resulted in ring transformation to afford 1-methyl-4-(1-methylhydrazinocarbonyl)-1,2-dihydropyridazino[3,4-b]quinoxaline 69 (78%), while the reactions of 68 with hydrazine hydrate in EtOH and in MeOH provided the 4-alkoxycarbonyl-1,2-dihydropyridazino[3,4-b]quinoxalines 70a (92%) and 70b (82%), respectively.

\[
\begin{array}{ccc}
\text{12} & \xrightarrow{\text{2-AP}} & \text{67} \\
\text{HCl} & & \text{POC13} & \xrightarrow{\text{NH}_2\text{NHR}} & \text{68} \\
\end{array}
\]

\[
\begin{array}{ccc}
\text{68} & \xrightarrow{\text{R=Me}} & \text{69} \\
\text{in R'OH} & & \\
\text{R=H} & & \text{70a R=E} \text{t} \text{, 70b R=Me} \\
\end{array}
\]

\text{Scheme 26}
c. QUINOXALINYL-1,5-BENZODIAZEPINES AND BENZIMIDAZOLYMETHYLENEQUINOXALINE

The reaction of 12 with o-phenylenediamine (o-PD) dihydrochloride effected ring transformation to produce the quinoxalinyl-1,5-benzodiazepine hydrochloride 71a or 71b (72%) (NH form), whose treatment with 10% NaOH produced the C_2^-H isomer 72 (91%)\(^3^3\) (Scheme 29). Further treatment of 72 with HCl/EtOH formed the hydrochloride of C_2^-H isomer 73 (98%). Refluxing of 71 in AcOH also induced the isomerization to give 75 (73%). On the other hand, the reactions of 12 with o-phenylenediamine and o-aminophenol resulted in only substitution to afford the 3-(N-arylcarbamoyl)furo[2,3-b]quinoxalines 74a (81%) and 74b (98%), respectively. However, refluxing of 74a in HCl/AcOH effected ring transformation to provide 71 (39%), and a prolonged refluxing produced 73 (65%). Treatments of 74a and 74b with 10% NaOH formed 15 (46% from 74a; 46% from 74b). In the reaction with the Vilsmeier reagent, 71 was converted into 12, while 72 and 73 into the N^1-formyl-C_2^-chlorinated compound 75 (26% from 72; 68% from 73). In addition, 74a and 74b were also transformed into 12 (22% from 74a; 72% from 74b). Acetylation of 72 in Ac_2O gave the N^1-acetylated compound 76 (50%) (Scheme 30).\(^3^3\)

Compound 71 was further transformed by refluxing in H_2O/AcOH, giving the benzimidazolymethylenequinoxaline 77 hydrochloride (87%), whose treatment with 10% NaOH afforded the free base 77 (93%)\(^3^4\) (Scheme 31). The reaction of 77 with HNO_2 provided the hydroxyimino compound 78 (91%), whose cyclization with POCl_3 produced the isoxazolo[4,5-b]quinoxaline 79 (96%). In addition, the reaction of 77 with MCPBA (2 eq.) furnished the ketone 80 (49%), whose reaction with o-phenylenediamine dihydrochloride followed by treatment with 10% NaOH gave the quinoxalino[2,3-b][1,5]-benzodiazepine 81 (27%).

d. SPIROQUINOXALINES AND PYRIDO[1,2-a]QUINOXALINES

The reactions of 12 with N-functional groups have been described above. In this section, the reaction of 12 with a carbanion is represented. The reaction of 12 with ethyl cyanoacetate in EtONa/EtOH resulted in ring transformation to produce the spiro[2-cyclobutene-1,2'(1H)-quinoxaline] 82 (86%)\(^3^5\) (Scheme 32).

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Scheme 29

Scheme 30
Scheme 31
(c) MCPBA

Scheme 31

Scheme 32
Refluxing of 82 in AcOH resulted in hydrolysis and decarboxylation to form an additional spiro[2-cyclobutene-1,2'(1H)-quinoxaline] 83 (93%), whose deuterized species 84 was confirmed on the NMR spectral measurement in D$_2$O/DMSO-d$_6$ (Scheme 33). On the other hand, refluxing of 82 in DMF and in pyridine/n-BuOH effected further ring transformation to give the pyrido[l,2-a]quinaxaline 85 (64%) and the pyridinium salt 86 (22%). The reactions of 82 with an excess of hydrazine hydrate and with the Vilsmeier reagent resulted in the formations of the hydrazide 11 (80%) and 12 (56%), respectively.
Kawahara et al.\textsuperscript{10} also reported the synthesis of the pyrido[1,2-\(a\)]quinoxaline ring system (Scheme 34). The reactions of 1a and 1f with dimethyl acetylenedicarboxylate afforded the aconitates 87a (56\%) and 87b (20\%), respectively, whose refluxing in dry DMSO provided the pyrido[1,2-\(a\)]quinoxaline-7,8-dicarboxylates 88a (64\%) and 88b (52\%), respectively.

![Chemical structures](image-url)

**Scheme 34**

e. QUINOXALINO[1',2':1,2]PYRIDO[4,3-b][1,5]BENZODIAZEPINE AND QUINOXALINYL-1,2-DIAZEPINE

The reaction of 82 with o-phenylenediamine dihydrochloride (1.5-fold) and hydrazine dihydrochloride (5-fold) in AcOH effected ring transformations to produce the quinoxalino[1',2':1,2]pyrido[4,3-b][1,5]benzodiazepine hydrochloride 89 (44\%) and quinoxaliny1-1,2-diazepine hydrochloride 90 (70\%), respectively, via intermediates\textsuperscript{35,36} shown in Scheme 35.
Scheme 35
VI. TAUTOMERIC BEHAVIORS OF 3-HETEROARYLMETHYLENE-2-OXO-1,2,3,4-TETRAHYDROQUINOLIN-XALINES

Some of 3-heteroarylmethylene-2-oxo-1,2,3,4-tetrahydroquinolines (prepared in the section V-2) exhibited the interesting tautomeric equilibria, which were confirmed by the NMR spectra in DMSO-d$_6$ and TFA.$^5,6,7$

Compounds 30a,b, 34, 35, 40a,b, and 46a,b exhibited the two tautomers A and B in DMSO-d$_6$ (Scheme 36).$^{37}$ The tautomer A is predominant in a low temperature, while the ratio of the tautomer B increased in a high temperature.$^{37}$ In TFA, 30a, 30b, and 35 represented the three tautomers C, D, and E (Scheme 37), while 34, 40a,b, and 46a,b showed only one species D (Scheme 38). On the other hand, the methylenic C-functionalized compounds 32 (Scheme 39) and 44 (Scheme 40) exhibited the two tautomers (C and E in 32; two of C, E, and G in 44), while 43 represented the one tautomer C or E (Scheme 41).

![Scheme 36 Equilibria in DMSO-d$_6$](image-url)
Scheme 37 Equilibria in TFA

Scheme 38 Equilibria in TFA
**Scheme 39** Equilibria of 32 in TFA

**Scheme 40** Equilibria of 44 in TFA

**Scheme 41** Protonated Species of 43 in TFA
REFERENCES AND FOOTNOTES

21. (a) Y. Kurasawa and A. Takada, Heterocycles, 1980, 14, 281; (b) Idem, Chem.

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