# Progress in the Chemistry of Quinoxaline *N*-Oxides and *N,N'*-Dioxides



Yoshihisa Kurasawa* and Atsushi Takada

School of Pharmaceutical Sciences, Kitasato University, Shirokane, Minato-ku, Tokyo 108, Japan

Ho Sik Kim

Department of Chemistry, Hyosung Women's University, Gyongsan 713-702, Korea

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This review describes the 1,3-dipolar cycloaddition reaction, deoxygenation, deoxygenative transformation, ring transformation and photochemical reaction of quinoxaline *N*-oxides and *N,N'*-dioxides.

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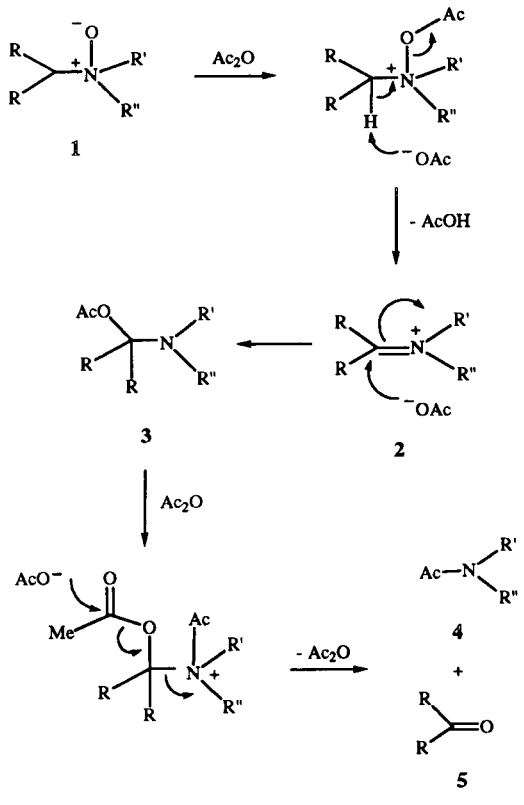
This review includes the following contents.



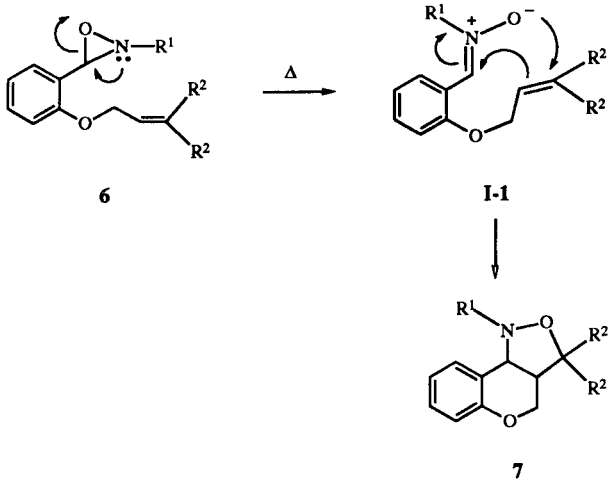
## A. Introduction.

The chemistry of organic *N*-oxide compounds has frequently presented interesting mechanistic pathways, which have appeared in some reviews and monographs [1-3]. For example, the reaction of the tertiary amine *N*-oxides **1** with acetic anhydride (or other acid anhydrides) resulted in deoxygenative acetoxylation to give the aminomethylene ester **3** *via* the iminium salt **2** (Scheme 1), and further reaction of the aminomethylene ester **3** with acetic anhydride afforded the acetamide derivative **4** and ketone or aldehyde **5** (Polonovski reaction) [1].

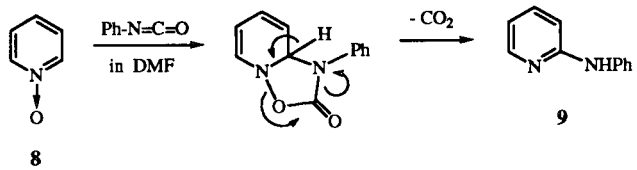
Scheme 1



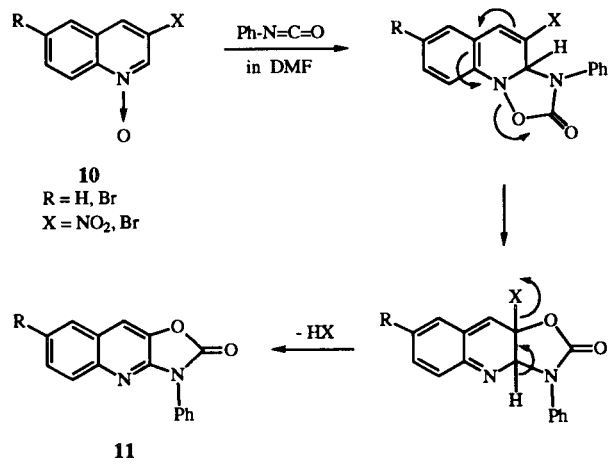
Scheme 2



Scheme 3



Scheme 4



Thermolysis of the *C*-aryloxaziridines **6** produced an intermediary nitrone **I-1**, whose intramolecular 1,3-dipolar cycloaddition reaction provided the isoxazolidine derivatives **7** (Scheme 2) [4]. The 1,3-dipolar cycloaddition reaction of pyridine 1-oxide **8** with phenyl isocyanate gave 2-anilinopyridine **9** (Scheme 3) [5], while the 1,3-dipolar cycloaddition reaction of the 3-nitro- or 3-bromoquinoline 1-oxides **10** with phenyl isocyanate afforded the oxazoloquinolines **11** (Scheme 4) [6]. Such interesting reactions as the above have also been reported in the chemistry of quinoxaline *N*-oxides or *N,N'*-dioxides. This review describes the chemistry of quinoxaline *N*-oxides

Chart 1

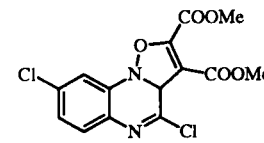
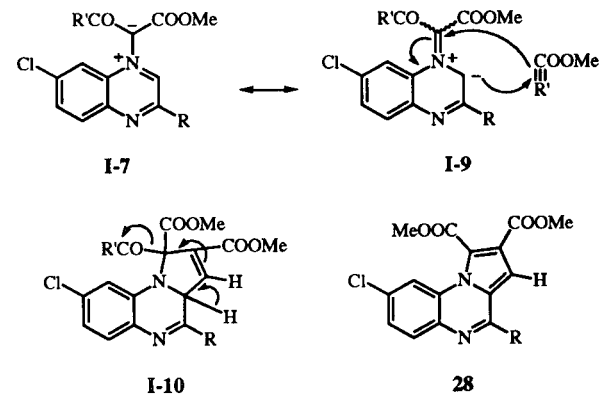
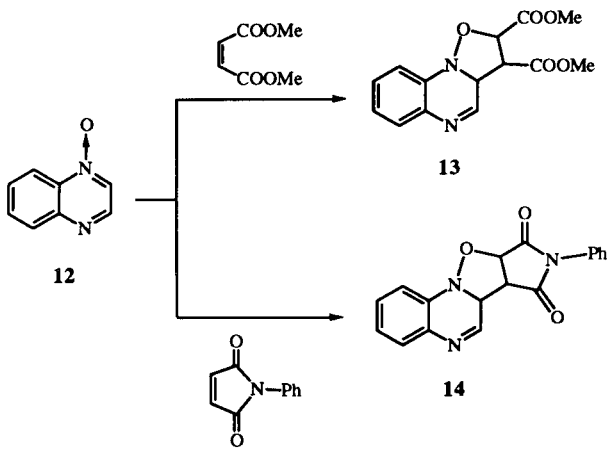


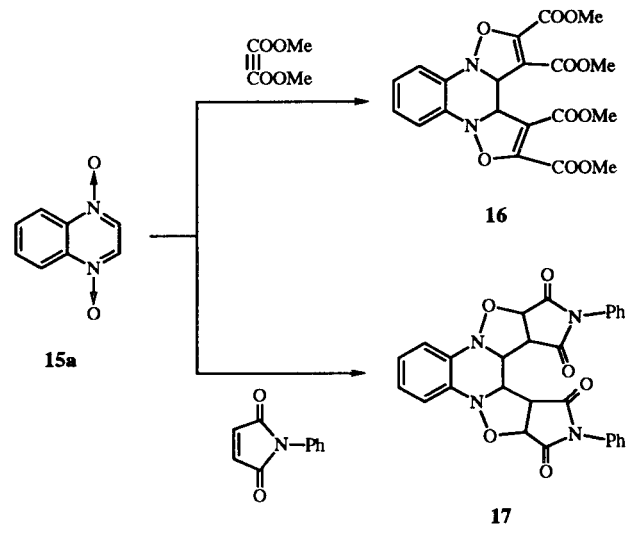
Chart 2



Scheme 5



Scheme 6



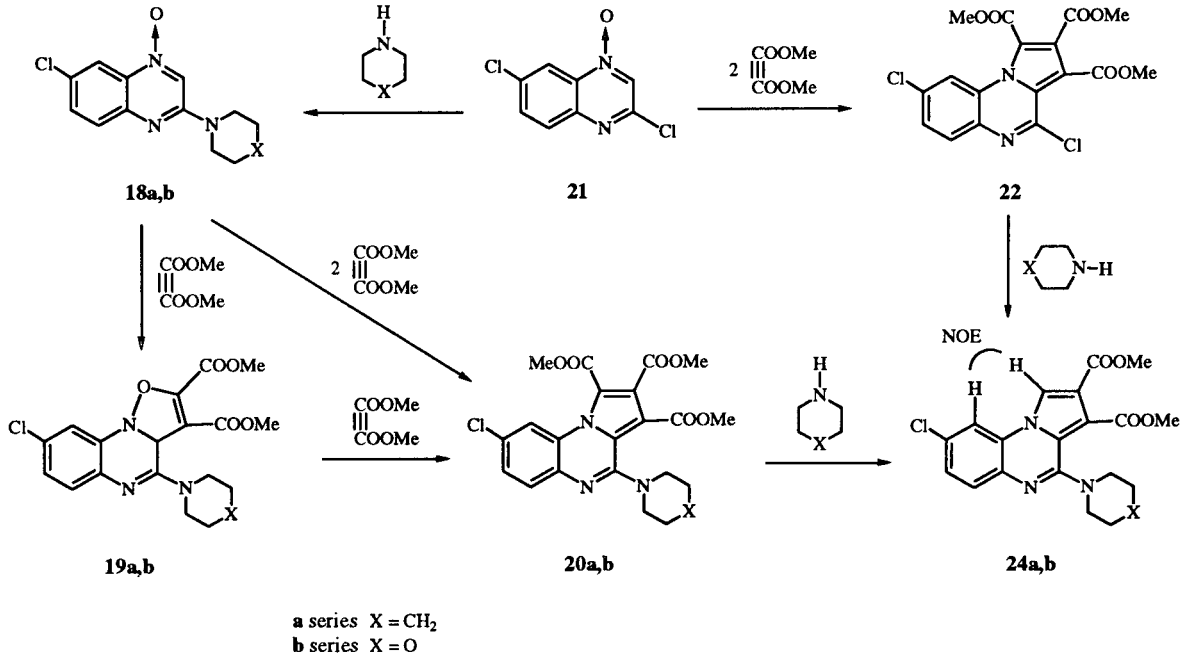
and *N,N'*-dioxides, which is divided into the following categories: (B) 1,3-dipolar cycloaddition reaction, (C) deoxygenation, (D) deoxygenative transformation, (E) ring transformation, (F) photochemical reaction.

B. 1,3-Dipolar Cycloaddition Reaction of Quinoxaline *N*-Oxides or *N,N'*-Dioxide.

B-a. Reaction of Quinoxaline *N*-Oxides or *N,N'*-Dioxide with Dimethyl Maleate, *N*-Phenylmaleimide, Dimethyl Acetylenedicarboxylate or Methyl Propiolate.

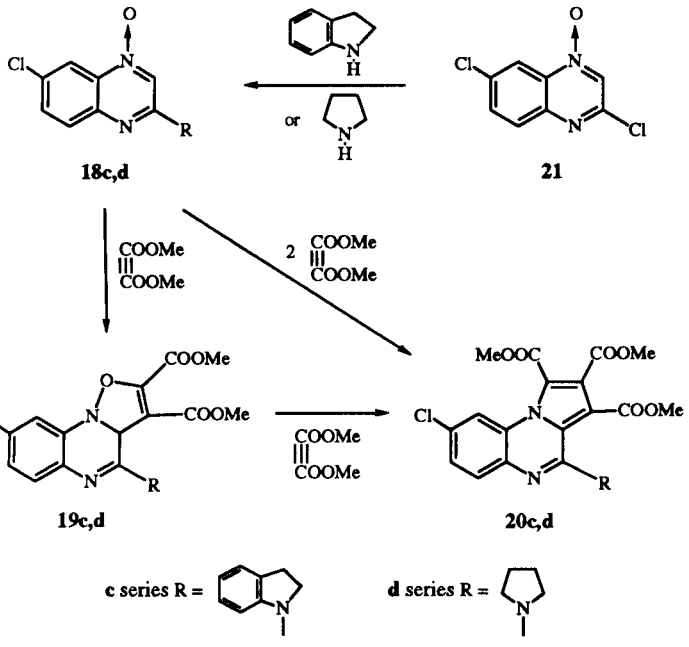
The reaction of quinoxaline 1-oxide **12** with dimethyl maleate or *N*-phenylmaleimide gave the isoxazolo[2,3-*a*]-quinoxaline derivative **13** or **14**, respectively (Scheme 5), while the reaction of quinoxaline 1,4-dioxide **15a** with dimethyl acetylenedicarboxylate or *N*-phenylmaleimide afforded the diisoxazolo[2,3-*a*:3',2'-*c*]quinoxaline derivative **16** or **17**, respectively (Scheme 6) [7]. On the other hand, the reaction of the 2-substituted 6-chloroquinoxaline 4-oxides **18a,b** with an equimolar amount of dimethyl acetylenedicarboxylate provided the isoxazolo-[2,3-*a*]quinoxalines **19a,b**, respectively, while the reaction of compounds **18a,b** with 2-fold molar amount of dimethyl acetylenedicarboxylate furnished the pyrrolo-[1,2-*a*]quinoxalines **20a,b**, respectively (Scheme 7) [8,9].

Scheme 7



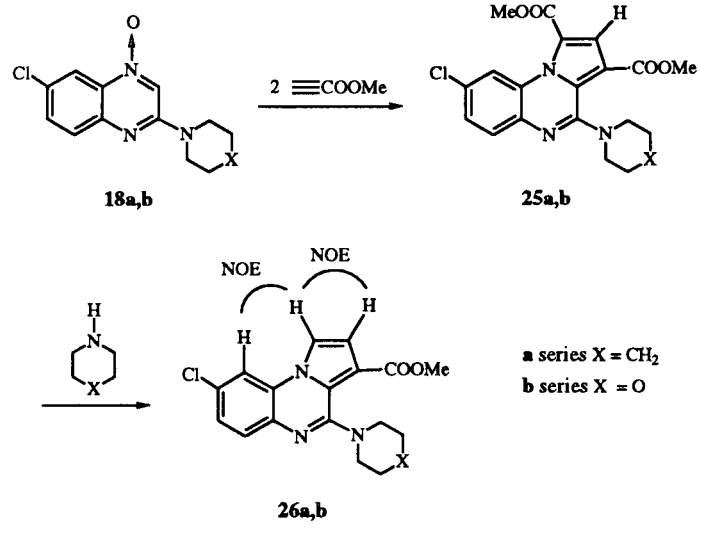
**a** series X = $CH_2$
**b** series X = O

Scheme 8

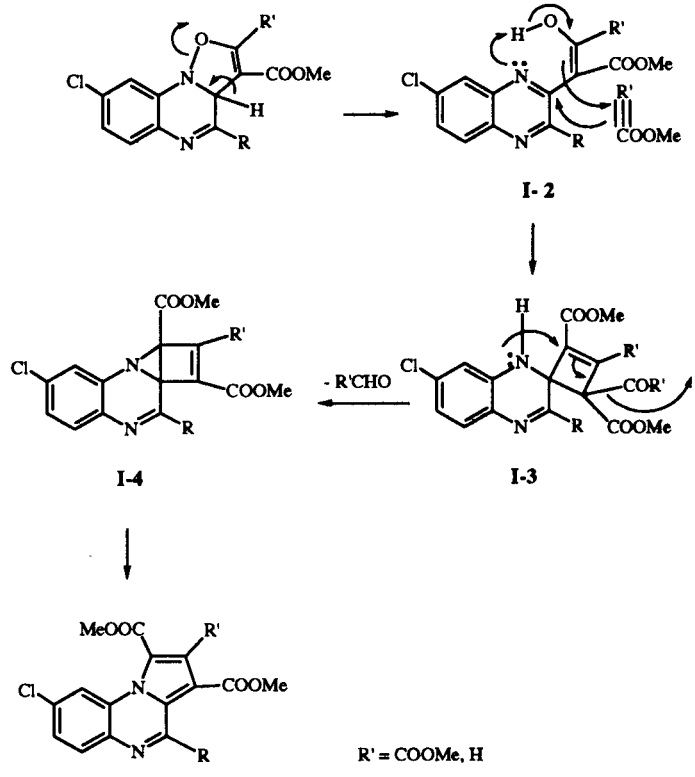



The reaction of the isoxazolo[2,3-*a*]quinoxalines **19a,b** with dimethyl acetylenedicarboxylate resulted in ring transformation to give the pyrrolo[1,2-*a*]quinoxalines **20a,b**, respectively. The reaction of 2,6-dichloroquinoxaline 4-oxide **21** with 2-fold molar amount of dimethyl acetylenedicarboxylate afforded the dichloropyrrolo-[1,2-*a*]quinoxaline **22**, although the dichloroisoxazolo-[2,3-*a*]quinoxaline **23** (Chart 1) could not be isolated [9]. The reaction of the pyrrolo[1,2-*a*]quinoxalines **20a,b** or **22** with secondary amines effected hydrolysis and decarboxylation to provide the pyrrolo[1,2-*a*]quinoxaline-2,3-

Scheme 9

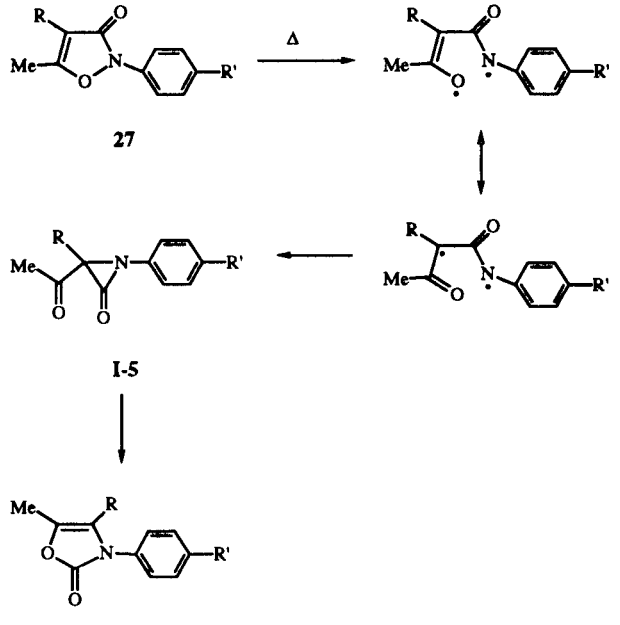



Scheme 10

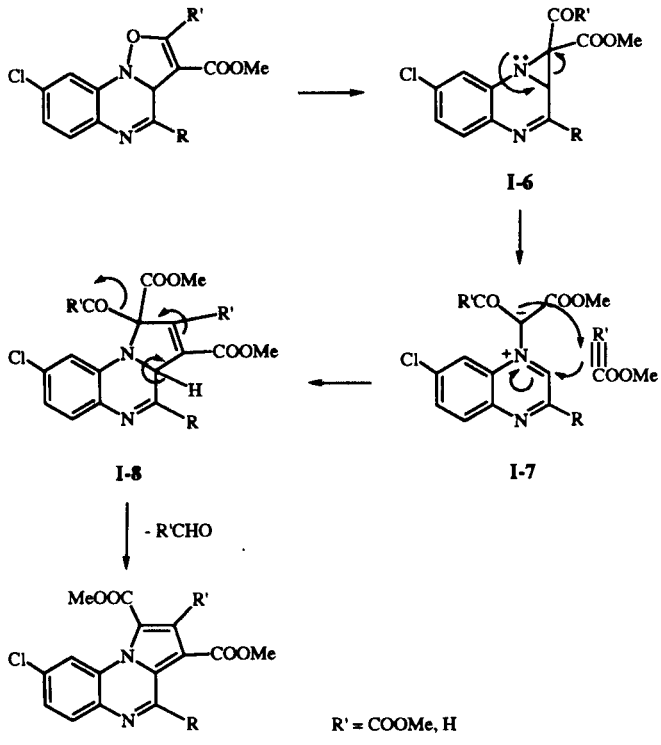



dicarboxylates **24a,b**, respectively. Thereafter, the reaction of the 2-substituted 6-chloroquinoxaline 4-oxides **18c,d** with dimethyl acetylenedicarboxylate was confirmed to give the isoxazolo[2,3-*a*]quinoxalines **19c,d** and

Scheme 11



Scheme 12




pyrrolo[1,2-*a*]quinoxalines **20c,d**, respectively (Scheme 8) [10]. Furthermore, the reaction of the 2-substituted 6-chloroquinoxaline 4-oxides **18a,b** with a 2-fold molar amount of methyl propiolate provided the pyrrolo[1,2-*a*]-quinoxaline-1,3-dicarboxylates **25a,b** (Scheme 9), but not the pyrrolo[1,2-*a*]quinoxaline-2,3-dicarboxylates **24a,b** (Scheme 7), and refluxing compounds **25a,b** in a secondary amine/*N*,*N*-dimethylformamide furnished the

Scheme 13

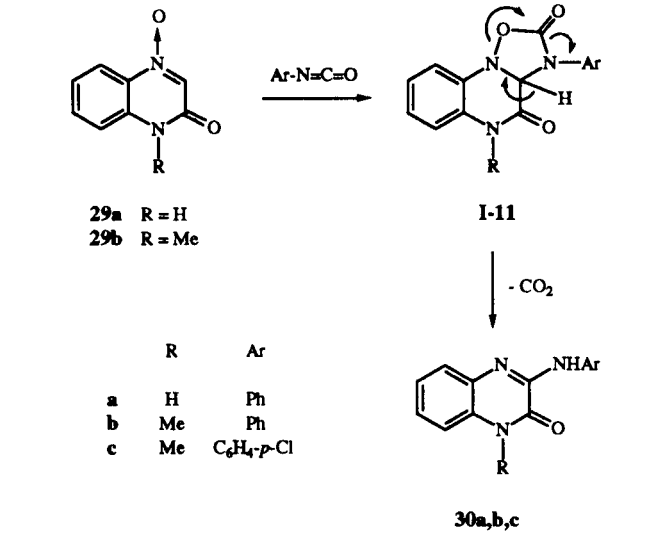
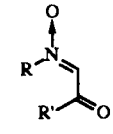


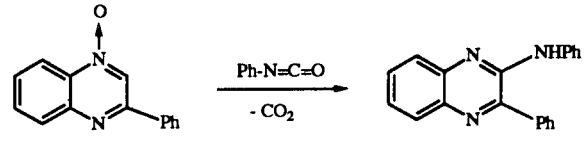

Chart 3



*C*-Acylnitrone

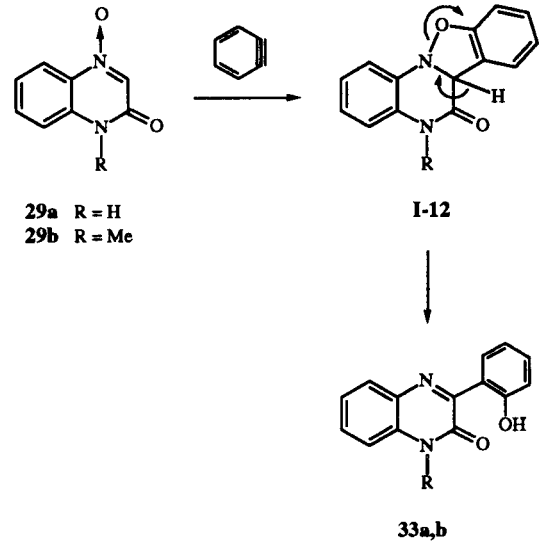
pyrrolo[1,2-*a*]quinoxaline-3-carboxylates **26a,b**, respectively [11]. These results enabled the assumption of the reaction mechanism for the ring transformation of the isoxazolo[2,3-*a*]quinoxalines into the pyrrolo[1,2-*a*]-quinoxalines. One of the reaction mechanisms includes

Scheme 14




the isoxazoline ring opening leading to the pyrrolo[1,2-*a*]-quinoxalines *via* intermediates **I-2** to **I-4** (Scheme 10) [11]. On the other hand, the thermal rearrangement of the isoxazolines **27** into an aziridine intermediate **I-5** has been well known (Scheme 11) [12], and hence the isoxa-

Scheme 15



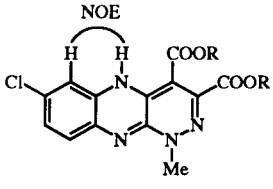

zolo[2,3-*a*]quinoxalines **19a-d** would also rearrange into an aziridine intermediate **I-6** (Scheme 12), whose ring opening provides a ylide intermediate **I-7** leading to the pyrrolo[1,2-*a*]quinoxalines *via* an intermediate **I-8** [11].

The reaction of a resonance isomer **I-9** (Chart 2) with methyl propiolate or dimethyl acetylenedicarboxylate was deniable, since the reaction of an intermediate **I-9** with methyl propiolate would produce the pyrrolo[1,2-*a*]quinoxaline-1,2-dicarboxylates **28** *via* an intermediate **I-10**.

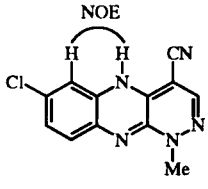
B-b. Reaction of *C*-Acylnitrone Type Quinoxaline *N*-Oxides with Isocyanates or Benzyne.

The *C*-acylnitrones (Chart 3) have been reported to show exceptionally fast rates in the 1,3-dipolar cycloaddition reaction [13-16]. The *C*-acylnitrone type of quinoxalin-2-one 4-oxides **29a,b** easily reacted with aryl isocyanates to give the 3-arylaminoquinoxalin-2-ones **30a** (99%), **30b** (53%), **30c** (56%), respectively, *via* an intermediate **I-11** (Scheme 13) [17]. In contrast, the reaction of compounds **18a,b** (section B-a) with phenyl isocyanate in dioxane resulted in recovery of the starting materials, and the reaction of 3-phenylquinoxaline 1-oxide **31a** with neat phenyl isocyanate afforded 2-anilino-3-phenylquinoxaline **32** in low yield (17%) (Scheme 14) [18]. The quinoxalin-2-one 4-oxides **29a,b** also reacted with benzyne to afford the 3-(*o*-hydroxyphenyl)quinoxalin-2-ones **33a,b**, respectively, *via* an intermediate **I-12** (Scheme 15) [17].

Chart 4




**36a** R = Me
**36b** R = Et




**37**

B-c. Reaction of 2-Hydrazinoquinoxaline *N*-Oxides with Acetylenedicarboxylates or 2-Chloroacrylonitrile.

As described in section B-a, the isoxazolo[2,3-*a*]quinoxalines **19a-d** were thermally transformed into an open chain intermediate **I-2** or aziridine intermediate **I-6**. Similarly, the reaction of 6-chloro-2-(1-methylhydrazino)-quinoxaline 4-oxide **34a** with acetylenedicarboxylates would give an open chain intermediate **I-14** or aziridine intermediate **I-15** *via* an isoxazolo[2,3-*a*]quinoxaline intermediate **I-13** (Scheme 16) [19,20]. Subsequent intramolecular dehydration of an intermediate **I-14** or **I-15** afforded the pyridazino[3,4-*b*]quinoxalines **35a,b**. The $C_2$-methylhydrazino group at a proximal position would accelerate a ring opening in an intermediate **I-13** or **I-15** and a dehydrative cyclization in an intermediate **I-14** or **I-15**, excluding the reaction with another acetylenedicarboxylate. The tautomeric structure of compounds **35a,b** was revised later as the 1,5-dihydropyridazino[3,4-*b*]-quinoxalines **36a,b** from the NOE spectral data (Chart 4) [21]. The 1,5-dihydropyridazino[3,4-*b*]quinoxaline **37** was also reported as an additional example [21]. These results are interesting, since the dihydropyridazine **38** or dihydrocinnolines **39** existed as the 1,4-dihydro form in a solution (Chart 5) [21].

Scheme 16

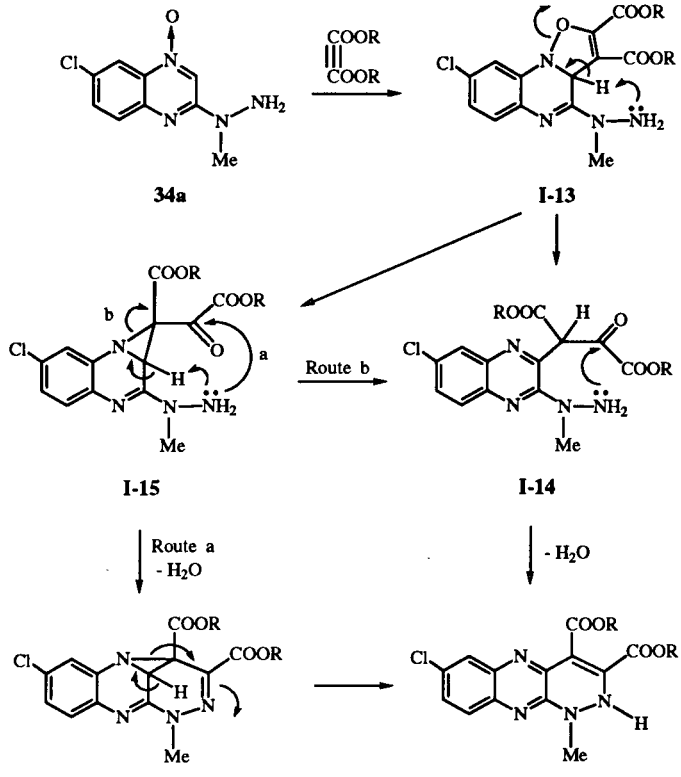
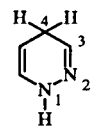
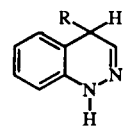



Chart 5

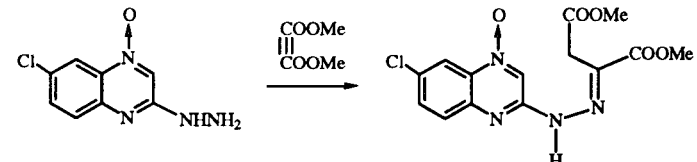



**38**




**39**

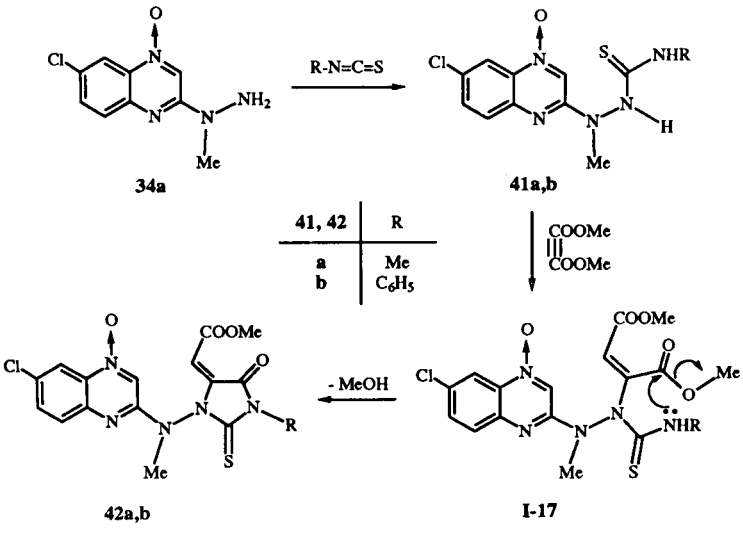
Scheme 17




**34b**

**40**

Scheme 18

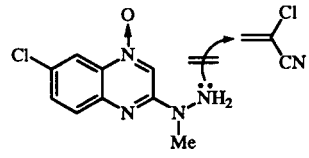



On the other hand, the reaction of 6-chloro-2-hydrazinoquinoxaline 4-oxide **34b** with dimethyl acetylenedicarboxylate furnished the hydrazone **40** (Scheme 17) [20]. The presence or absence of the methyl group in the $C_2$-hydrazino group produced a difference in the reactivity to acetylenedicarboxylates.

Further modification of the $C_2$-(1-methylhydrazino) group in compound **34a** did not prefer the 1,3-dipolar cycloaddition reaction. Namely, the reaction of compound **34a** with isothiocyanates afforded the 6-chloro-2-thiocarbamoylhydrazinoquinoxaline 4-oxides **41a,b**, whose reaction with dimethyl acetylenedicarboxylate provided the 6-chloro-2-(imidazolidin-1-yl)aminoquinoxalines **42a,b** *via* an intermediate **I-17** (Scheme 18) [22].

The reaction of compound **34a** with 2-chloroacrylonitrile resulted in the 1,3-dipolar cycloaddition reaction to give the pyrazolo[3,4-*b*]quinoxaline **43** presumably *via* intermediates **I-18** to **I-21** (Scheme 19) [20], while the reaction of compound **34b** with 2-chloroacrylonitrile recovered the starting material. The addition reaction shown in Chart 6 was unfavorable in the reaction of compound **34a** with 2-chloroacrylonitrile.

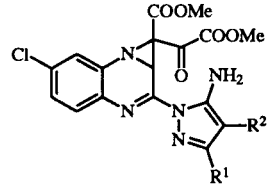
Chart 6



B-d. Reaction of 2-(5-Aminopyrazol-1-yl)quinoxaline 4-Oxides with Dimethyl Acetylenedicarboxylate.

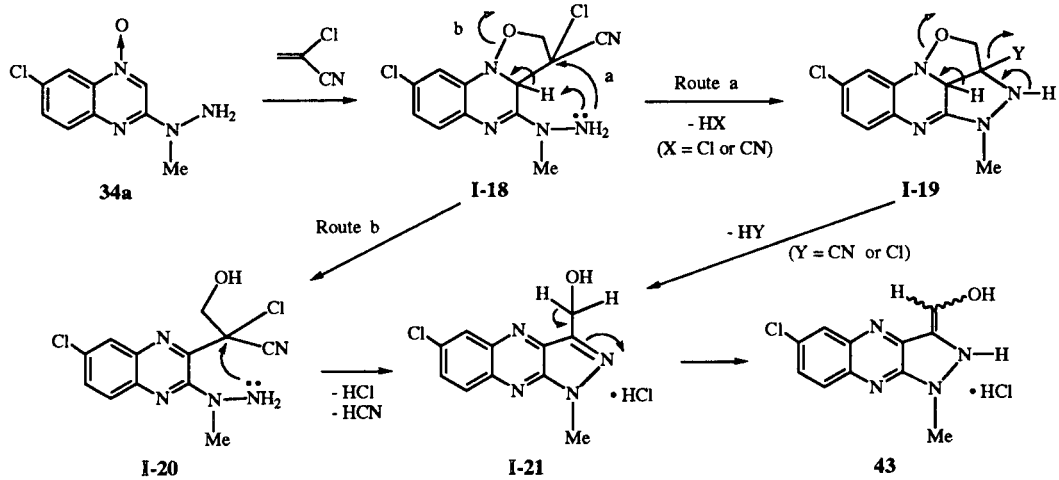
The reaction of compound **34b** with ethyl ethoxymethylenecyanoacetate or (1-ethoxyethylidene)malononitrile gave the 2-(5-aminopyrazol-1-yl)quinoxaline 4-oxides **44a,b**, respectively, whose reaction with dimethyl acetylenedicarboxylate afforded the pyrrolo[1,2-*a*]quinoxalines **45a,b**, respectively, presumably *via* intermediates **I-22** and **I-23** (Scheme 20) [23]. The nucleophilicity of the

Chart 7

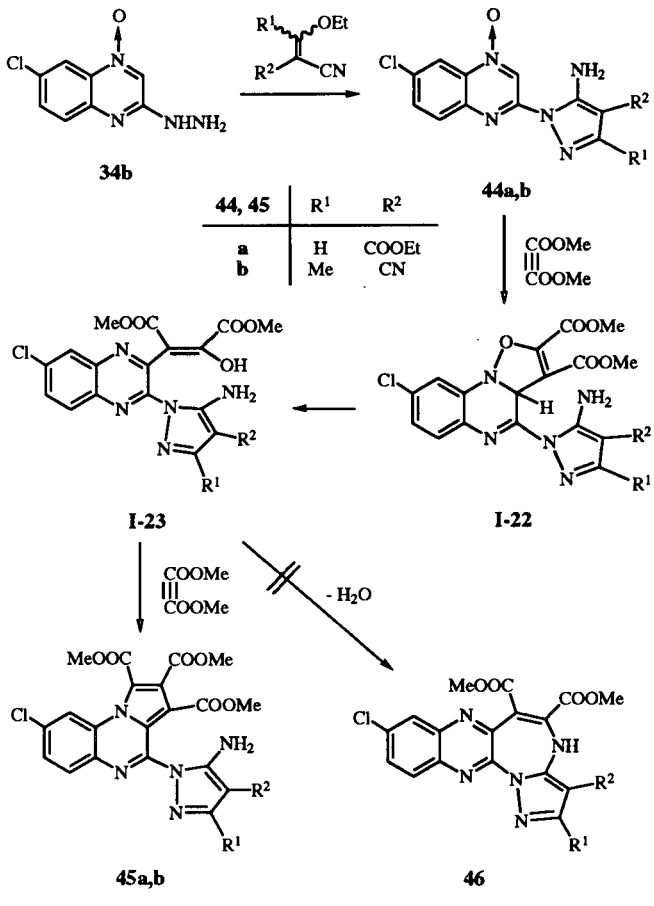


I-24

Scheme 19



Scheme 20




amino group in an intermediate **I-23** was not strong enough to result in an intramolecular dehydration in comparison with that of the methylhydrazino group in an intermediate **I-14** or **I-15** (section B-c), and hence compounds **46** were not produced. An intermediate **I-24** (Chart 7) would be also formed from an intermediate **I-22**.

B-e. Reaction of 2-(Benzylidenehydrazino)quinoxaline 4-Oxides with 2-Chloroacrylonitrile.

As shown in Scheme 19 (section B-c), compound **34a** was converted into the pyrazolo[3,4-*b*]quinoxaline **43** accompanied with an elimination of hydrogen chloride and hydrogen cyanide (Chart 8). In order to study further this type of reaction, compound **34a** was transformed into the 2-benzylidenehydrazinoquinoxaline 4-oxides **47a,b** (Scheme 21) [24,25]. The reaction of compounds **47a,b** with 2-chloroacrylonitrile gave the 5-cyano-4-hydroxy-1,2-diazepino[3,4-*b*]quinoxalines **48a,b** and/or **49a,b** presumably *via* intermediates **I-25** to **I-28**. Hereupon, the presence of the $C_2$-benzylidenehydrazino moiety in compounds **47a,b** enabled the cyclization into the 1,2-diazepine ring, while the $C_2$-(1-methylhydrazino) group of compound **34a** promoted the cyclization into the pyrazole

Chart 8

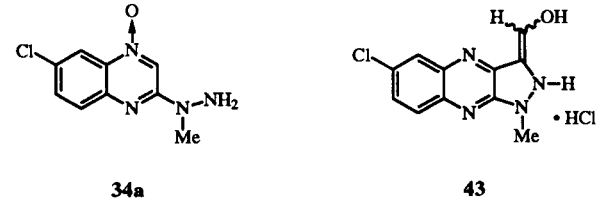
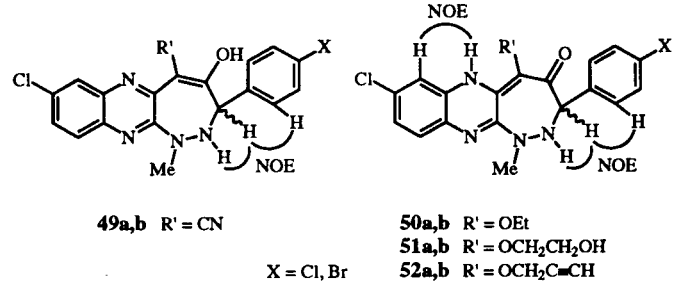
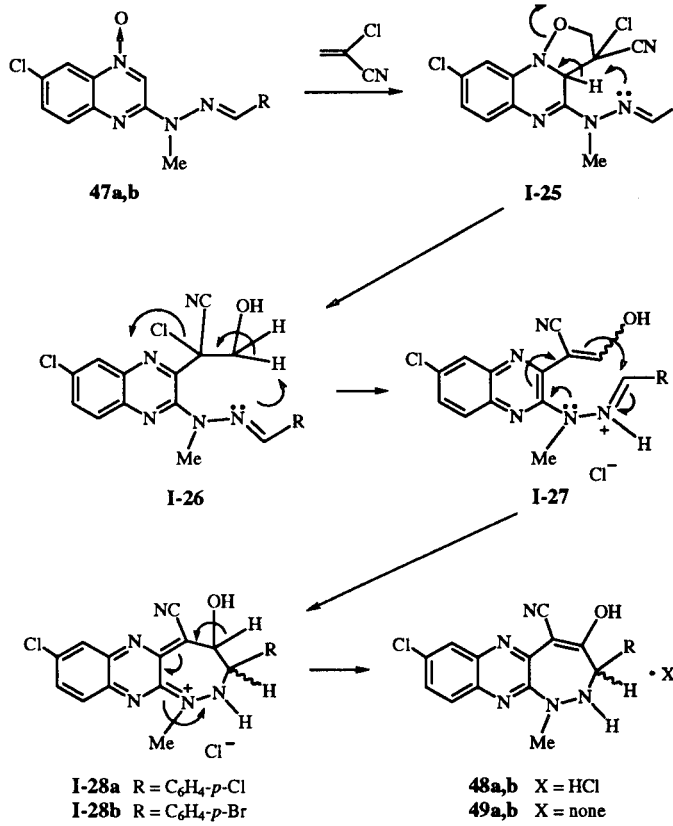



Chart 9

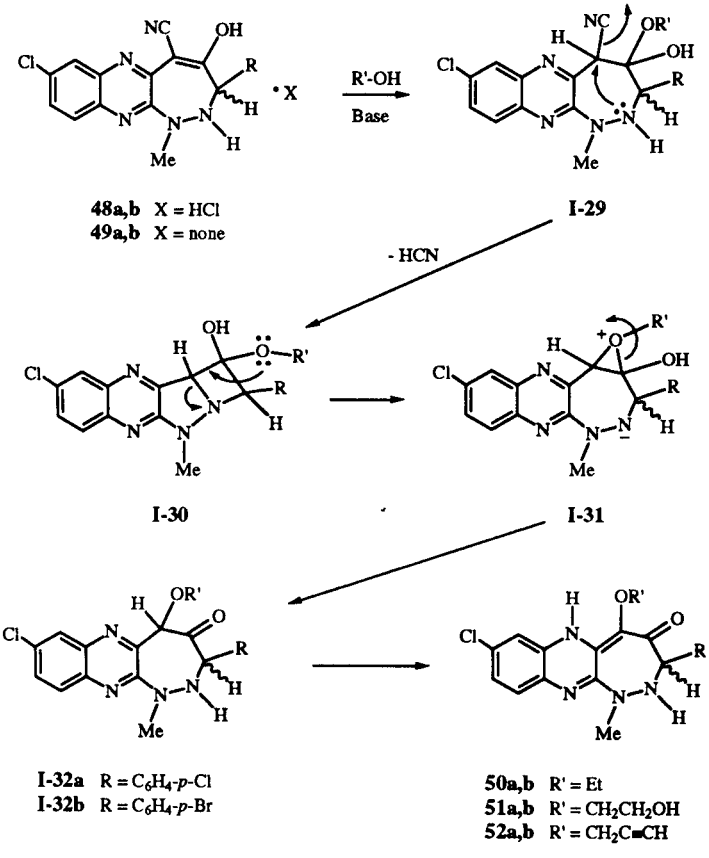



ring (Chart 8). Compounds **48a,b** or **49a,b** further underwent alcoholysis in the presence of a base to change into the 5-alkoxy-4-oxo-1,2-diazepino[3,4-*b*]quinoxalines **50-52** presumably *via* intermediates **I-29** to **I-32** (Scheme

Scheme 21



Scheme 22




**48a,b** X = HCl
**49a,b** X = none

**I-29**

**I-30**

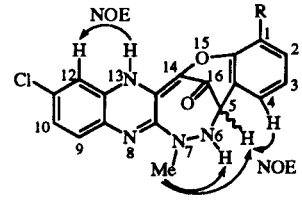
**I-31**

**I-32a** R = $C_6H_4$-*p*-Cl
**I-32b** R = $C_6H_4$-*p*-Br

**50a,b** R' = Et
**51a,b** R' = $CH_2CH_2OH$
**52a,b** R' = $CH_2C{\equiv}CH$

22). The 2,3-dihydro-4-hydroxy form of compounds **49** and the 2,3,4,6-tetrahydro-4-oxo form of compounds **50-52** were confirmed by NOE spectral data (Chart 9).

Chart 10

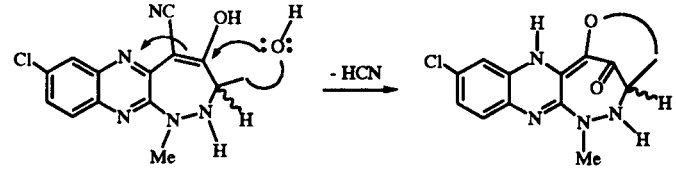



**55a,b**

B-f. Reaction of 2-(*o*-Hydroxybenzylidenehydrazino)-quinoxaline 4-Oxides with 2-Chloroacrylonitrile.

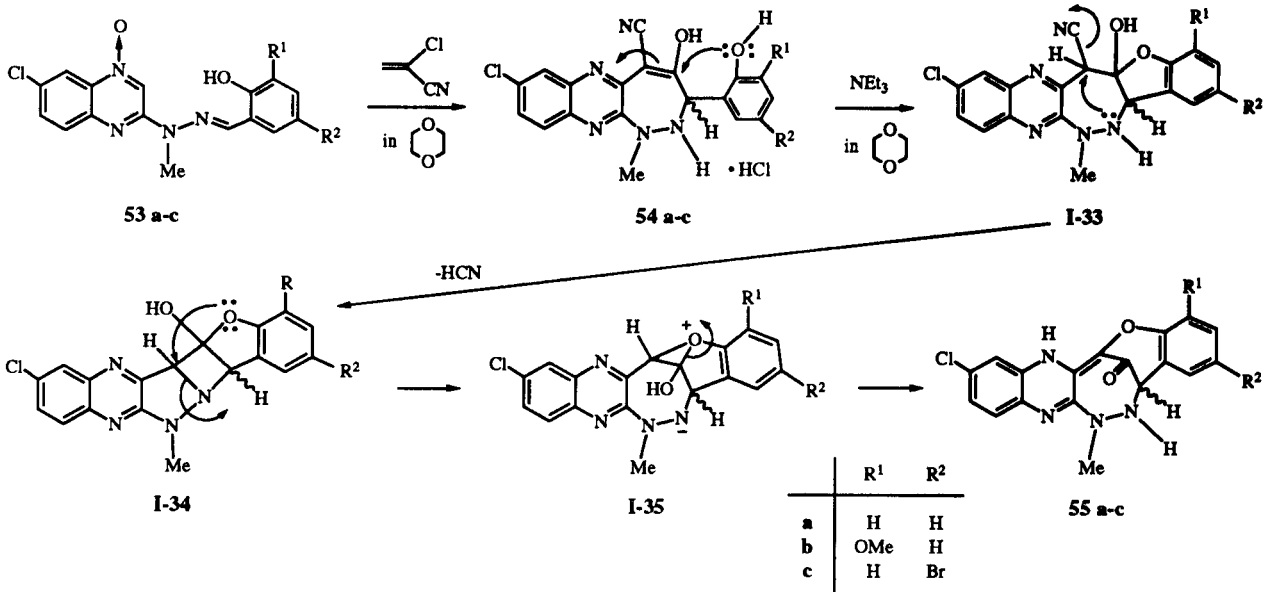
Since the 5-cyano-4-hydroxy-1,2-diazepino[3,4-*b*]quinoxalines **48a,b** or **49a,b** were found to undergo alcoholysis, the intramolecular alcoholysis was undertaken by a method shown in Scheme 23. The 2-(*o*-hydroxybenzylidenehydrazino)quinoxaline 4-oxides **53a-c** were synthesized as starting materials from compound **34a**. The reaction of compounds **53a-c** with 2-chloroacrylonitrile gave the 1,2-diazepino[3,4-*b*]quinoxalines **54a-c**, whose reflux-

Scheme 23




Intramolecular Alcoholysis

Scheme 24




**53 a-c**

**54 a-c**

**I-33**

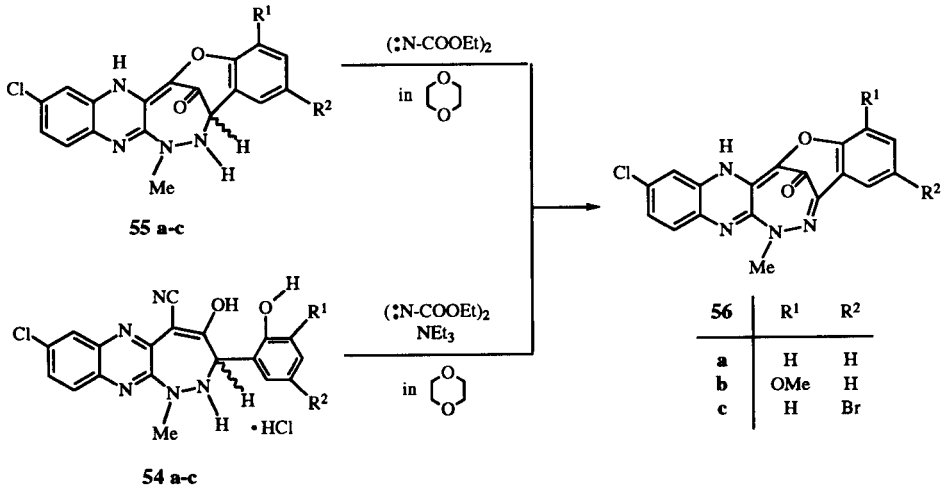
**I-34**

**I-35**

**55 a-c**

| | $R^1$ | $R^2$ |
|---|---|---|
| a | H | H |
| b | OMe | H |
| c | H | Br |

Scheme 25




ing in triethylamine/dioxane afforded the 5,6,7,13-tetrahydro-5,14-methano-16-oxo-1,5,6-benzoxadiazonino[3,4-*b*]-quinoxalines **55a-c**, respectively, presumably *via* intermediates **I-33** to **I-35** (Scheme 24) [26,27]. The oxidation of compounds **55a-c** or **54a-c** with diethyl azodicarboxylate produced the 7,13-dihydro-5,14-methano-16-oxo-1,5,6-benzoxadiazonino[3,4-*b*]quinoxalines **56a-c** (Scheme 25) [27]. The NOE spectral data supported the structure of compounds **55** (Chart 10).

B-g. Reaction of 2-(Heteroarylmethylenehydrazino)quinoxaline 4-Oxides with 2-Chloroacrylonitrile.

In order to synthesize a series of heteroaryl derivatives shown in Chart 11, the 2-(heteroarylmethylenehydrazino)-

Scheme 26

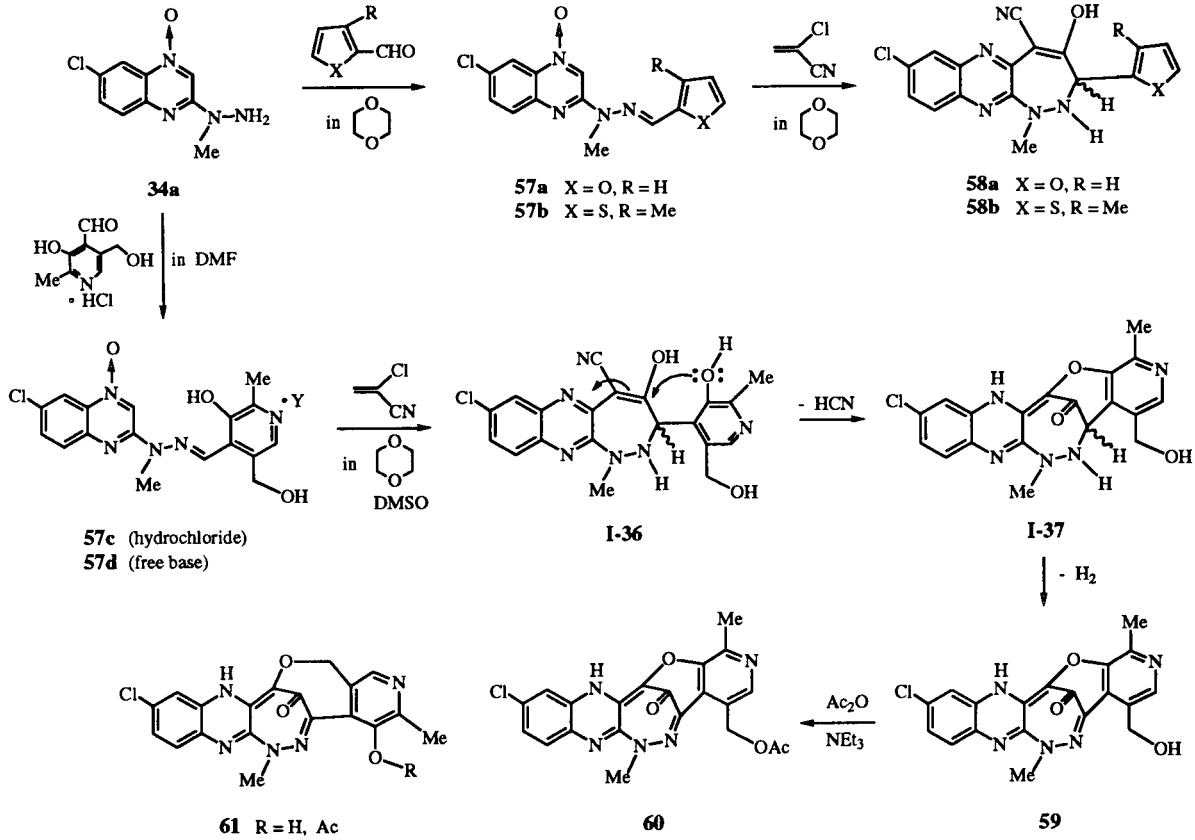
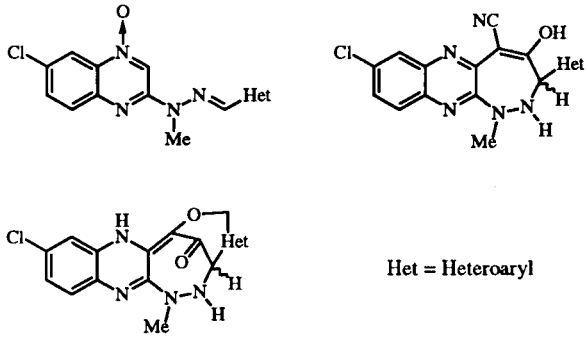


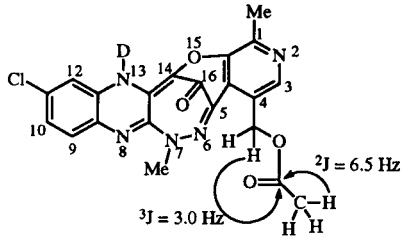
Chart 11



Het = Heteroaryl

quinoxaline 4-oxides **57a-d** were synthesized from compound **34a** (Scheme 26) [28]. The reaction of compounds **57a,b** with 2-chloroacrylonitrile gave the 1,2-diazepino-[3,4-*b*]quinoxalines **58a,b**, respectively, while the reaction of compound **57c** or **57d** with 2-chloroacrylonitrile afforded the 5,14-methano-16-oxopyrido[3'4':9,8][1,5,6]-oxadiazonino[3,4-*b*]quinoxaline **59** presumably *via* intermediates **I-36** and **I-37**. Acetylation of compound **59** produced the $C_4$-acetoxymethyl derivative **60**. The LSPD spectral data for compound **60** (Chart 12) excluded the $C_4$-acetoxy structure **61** (Scheme 26).

Chart 12

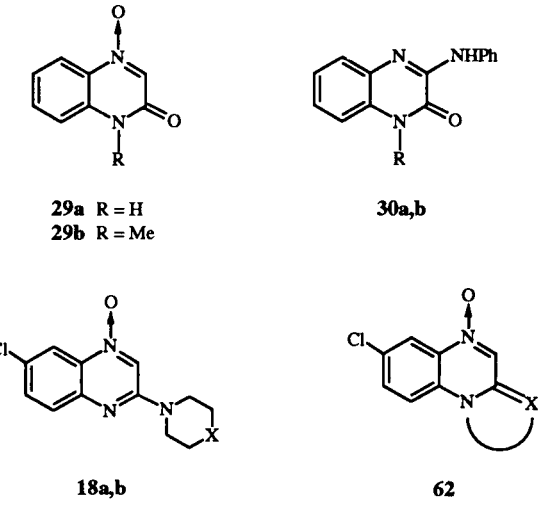


**60**
in Deuteriotrifluoroacetic Acid

B-h. Reaction of 1,2,4-Triazolo[4,3-*a*]quinoxaline 5-Oxide with Isothiocyanates.

As described in section B-b, the reaction of the lactam type of quinoxaline *N*-oxides **29a,b** with phenyl isocyanate resulted in the 1,3-dipolar cycloaddition reaction to give the 3-anilino derivatives **30a,b** (Chart 13), while the reaction of the 2-substituted 6-chloroquinoxaline 4-oxides **18a,b** with phenyl isocyanate recovered the starting materials. Accordingly, the aromatized ring system of compounds **18a,b** was changed into the dihydroquinoxaline ring system **62**, which was structurally analogous to the lactam type of quinoxaline *N*-oxides **29a,b**. The reaction of compound **34b** with triethyl orthoformate

Chart 13



**29a** R = H
**29b** R = Me

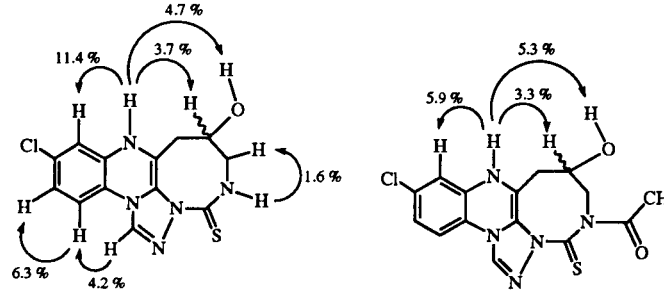
**30a,b**

**18a,b**

**62**

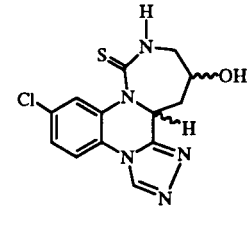
afforded 7-chloro-1,2,4-triazolo[4,3-*a*]quinoxaline 5-oxide **62**, whose reaction with phenyl isocyanate produced the 4-anilino derivative **63** *via* an intermediate **I-38** (Scheme 27) [29]. The reaction of compound **62** with phenyl isothiocyanate resulted in deoxygenation to provide 7-chloro-1,2,4-triazolo[4,3-*a*]quinoxaline **64**, while the reaction of compound **62** with allyl isothiocyanate effected the 1,3-dipolar cycloaddition reaction to give the isoxazolo[2,3-*a*][1,2,4]triazolo[3,4-*c*]quinoxalin-5-ylmethylisothiocyanate **65**, whose reductive ring transformation afforded the 1,2,4-triazolo[4,3,2-*o,p*][1,3]dia-

Chart 14



NOE Data for Compound **66**

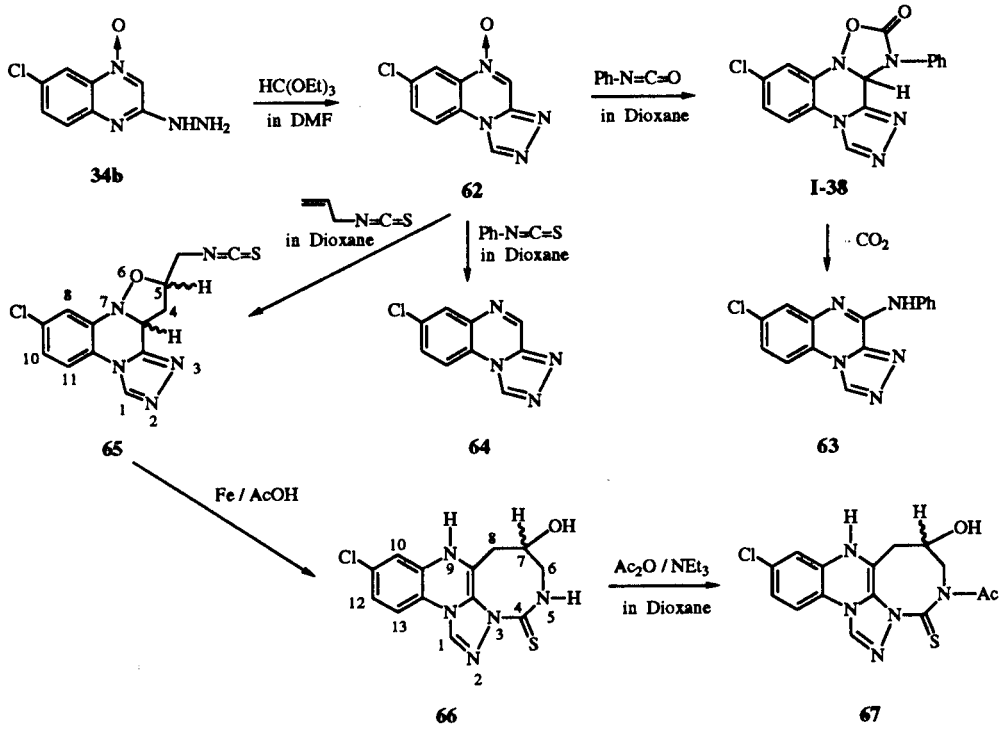
NOE Data for Compound **67**



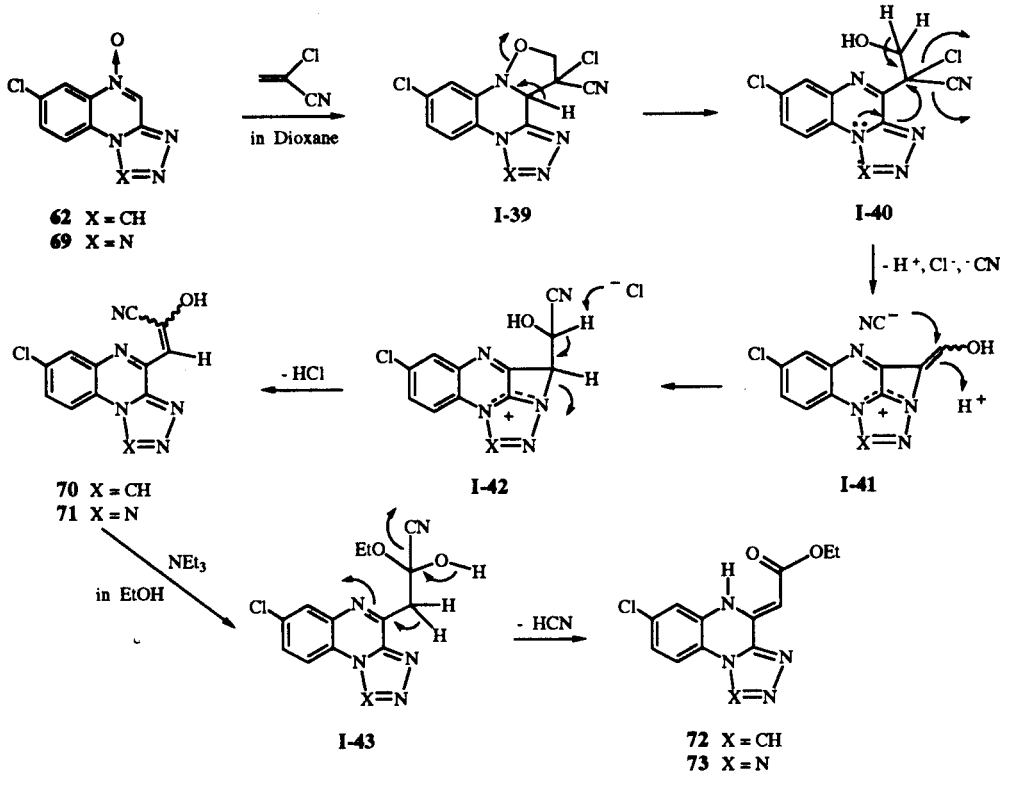
**68**

zocino[4,5-*b*]quinoxaline **66**. Acetylation of compound **66** produced the $N_5$-acetyl derivative **67**. The NOE spectral data for compounds **66** and **67** excluded the structure **68** (Chart 14).

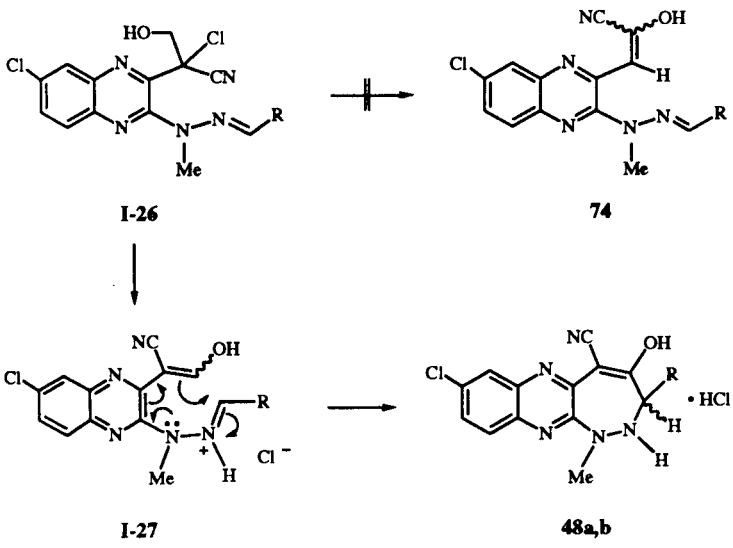
Scheme 27




Scheme 28



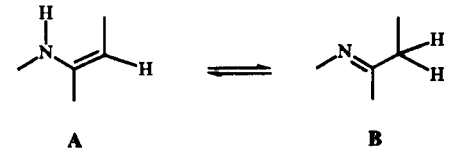
Scheme 29




B-i. Reaction of 1,2,4-Triazolo[4,3-*a*]quinoxaline 5-Oxide and Tetrazolo[1,5-*a*]quinoxaline 5-Oxide with 2-Chloroacrylonitrile.

The reaction of the 1,2,4-triazolo[4,3-*a*]quinoxaline 5-oxide **62** or tetrazolo[1,5-*a*]quinoxaline 5-oxide **69** with 2-chloroacrylonitrile gave the 4-(2-cyano-2-hydroxyvinyl)-1,2,4-triazolo[4,3-*a*]quinoxaline **70** or 4-(2-cyano-2-hydroxyvinyl)tetrazolo[1,5-*a*]quinoxaline **71**, respectively, presumably *via* intermediates **I-39** to **I-42** (Scheme 28) [30]. The structure of compounds **70** and **71** was ascertained by the LSPD and C-H NOE spectral data and further reactions, supporting that the cyano group migration took place presumably in the step of an intermediate **I-40** to **I-41**. Refluxing of compound **70** or **71** in triethylamine/ethanol resulted in alcoholysis to afford the 4-ethoxycarbonylmethylene-4,5-dihydro-1,2,4-triazolo[4,3-*a*]quinoxaline **72** or 4-ethoxycarbonylmethylene-4,5-dihydrotetrazolo[1,5-*a*]quinoxaline **73**, respectively, presumably *via* an intermediate **I-43**.

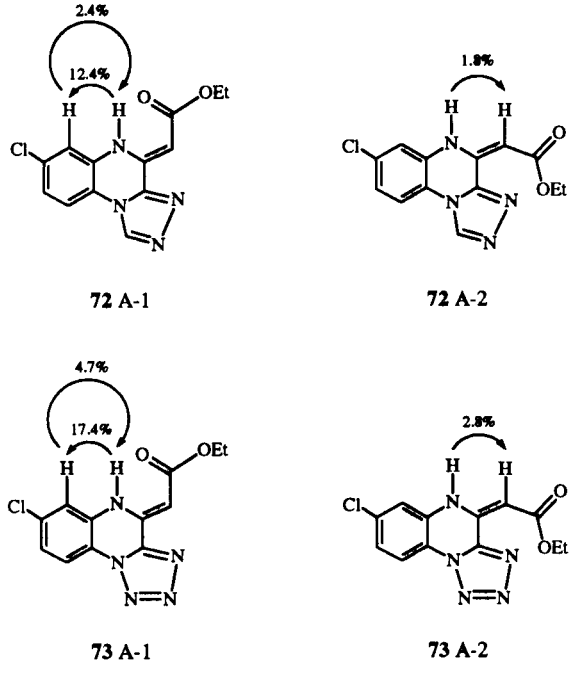
Scheme 30




An intermediate **I-26** shown in Scheme 21 (section B-e) was not changed into the $C_3$-(2-cyano-2-hydroxyvinyl) derivative **74** presumably due to a weak nucleophilicity of the $C_2$-hydrazone moiety (Scheme 29), but the 1,2-diazepino[3,4-*b*]quinoxalines **48a,b** were produced *via* an intermediate **I-27** accompanied with an elimination of hydrogen chloride.

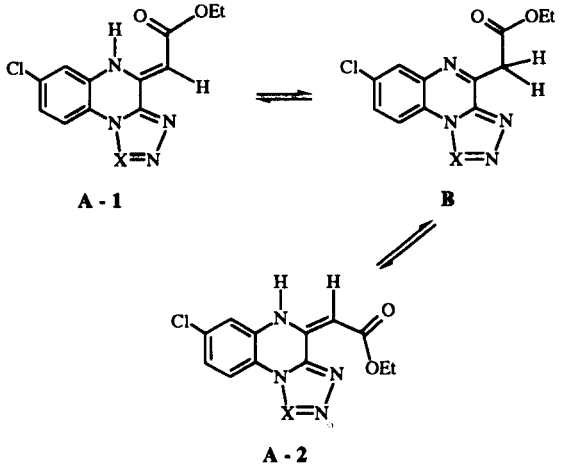
Compounds **72** and **73** showed the tautomeric equilibria between the enamine **A** and methylene imine **B** forms (Scheme 30) in dimethyl sulfoxide or trifluoroacetic acid media [31]. Moreover, compounds **72** and **73** were shown to exist as two geometrical isomers A-1 and A-2 (Chart 15), and hence the tautomeric equilibria were exhibited as shown in Schemes 31 and 32.

Chart 15



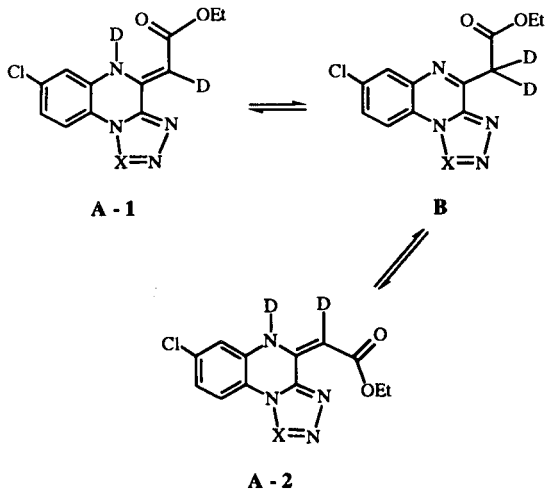

NOE Data for Compounds **72** and **73** in DMSO-$d_6$

Scheme 31



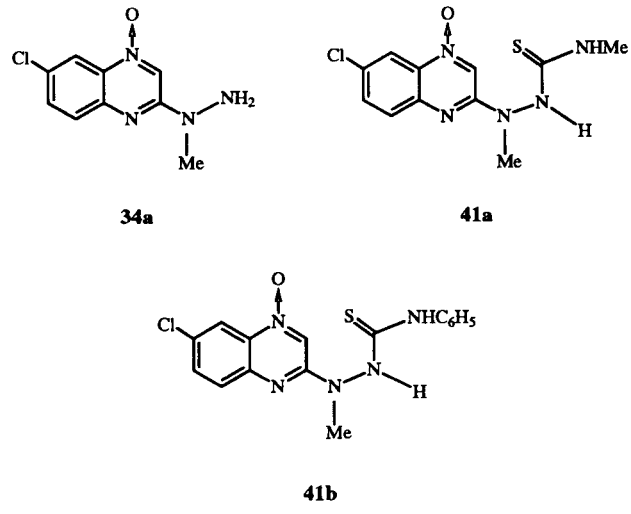

Tautomeric Equilibria of Compounds **72** and **73** in DMSO-$d_6$

Scheme 32



Tautomeric Equilibria of Compounds 72 and 73 in DMSO-$d_6$ / $D_2O$

Chart 16



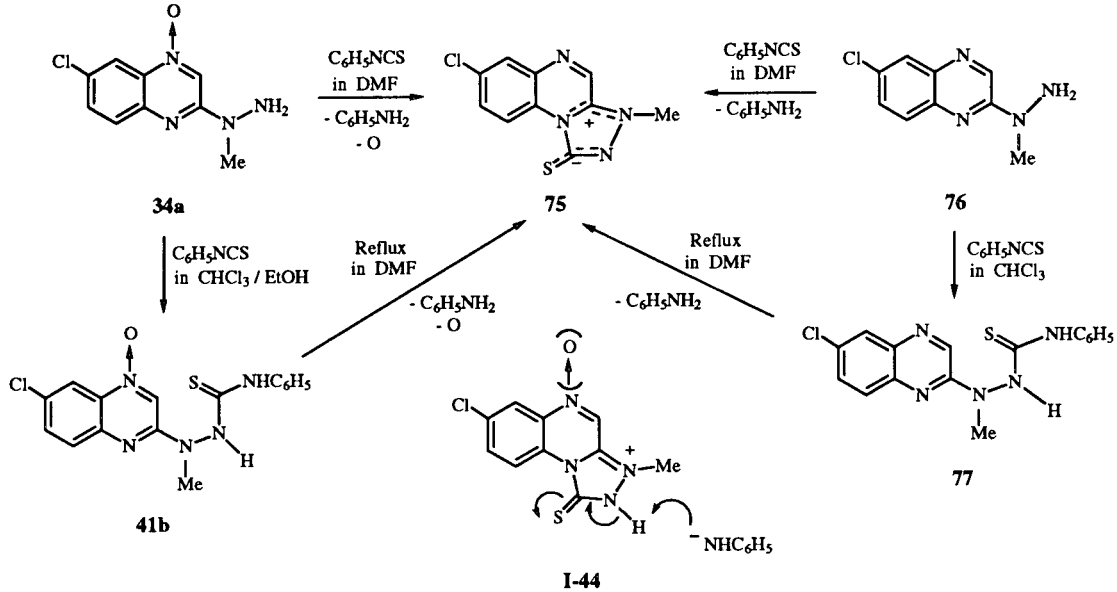
C. Deoxygenation of Quinoxaline *N*-Oxides and *N,N'*-Dioxides.

A monograph [32] describes the mechanism for the deoxygenation of heterocyclic *N*-oxides, which includes the reduction with complex hydrides such as lithium aluminum hydride (1), catalytic hydrogenation (2), deoxygenation with phosphorus compounds, sulphur compounds, amines, hydrogen halides, carbenes, or acyl compounds (3), electrolytic or polarographic reduction (4), thermal and oxidative reduction (5) and photochemical deoxygenation (6). This review describes several deoxygenations of quinoxaline *N*-oxides and *N,N'*-dioxides including some of the above categories (1)-(6).

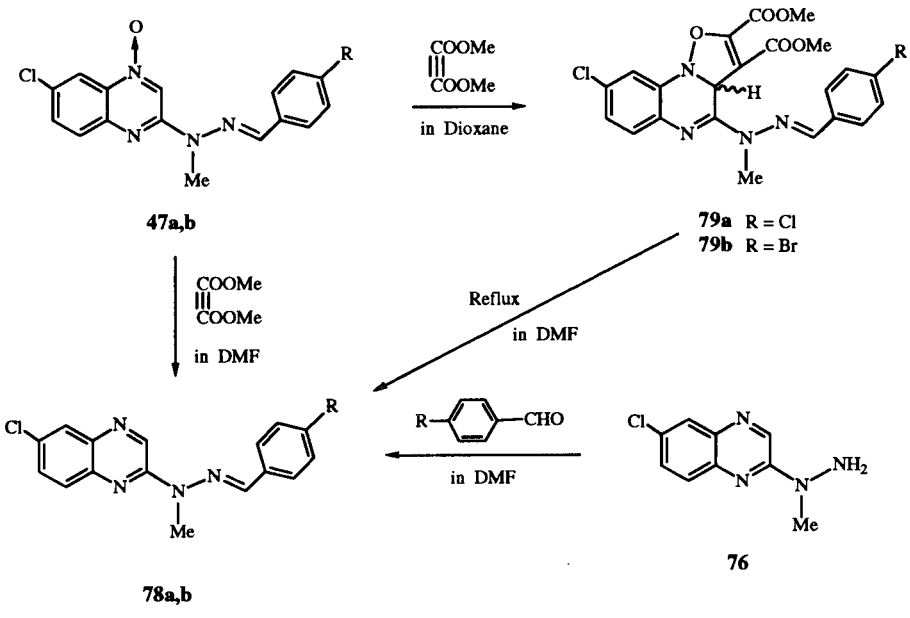
C-a. Deoxygenation with Phenyl Isothiocyanate.

Compound **34a** was converted into the thiosemicarbazide **41a** or **41b** (section B-c) (Chart 16). The methyl derivative **41a** was stable to heat, but the phenyl derivative **41b** was rather labile at a high temperature, changing into a red substance. Refluxing compound **41b** in *N,N*-dimethylformamide resulted in deoxygenative cyclization to afford the mesoionic triazolo[4,3-*a*]quinoxaline **75** (32%) presumably *via* an intermediate **I-44** (Scheme 33) [33]. The yield of compound **75** was improved to 49% or 77% in the presence of an equimolar amount of tri-

Scheme 33



Scheme 34

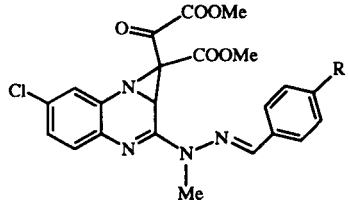



phenylphosphine or phenyl isothiocyanate, respectively. The reaction of compound **34a** with phenyl isothiocyanate (1.2-fold molar excess) directly provided compound **75** (55%). On the other hand, the reaction of compound **76** with an equimolar amount of phenyl isothiocyanate produced compound **75** (81%), and refluxing compound **77** in *N,N*-dimethylformamide furnished compound **75** (80%). From the comparison of the above yields for the mesoionic triazolo[4,3-*a*]quinoxaline **75**, phenyl isothiocyanate was suggested to participate the deoxygenation of the *N*-oxide **34a** or **41b**.

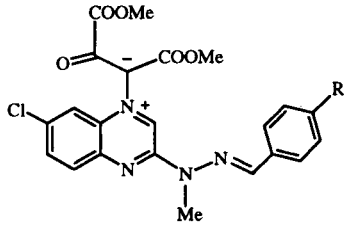
C-b. Deoxygenation *via* Isoxazolo[2,3-*a*]quinoxalines.

The reaction of the 2-(2-benzylidene-1-methylhydrazino)quinoxaline 4-oxide **47a** or **47b** with dimethyl acetylenedicarboxylate under reflux in *N,N*-dimethylformamide effected deoxygenation to give the 2-(2-benzylidene-1-methylhydrazino)quinoxaline **78a** or **78b**, respectively, while a similar reaction under reflux in dioxane precipitated the isoxazolo[2,3-*a*]quinoxaline **79a** or **79b**, respectively (Scheme 34) [34]. Further refluxing of compound **79a** or **79b** in *N,N*-dimethylformamide afforded compound **78a** or **78b**, respectively, whose structure was confirmed by an alternate synthesis from compound **76**. The above results suggested that the deoxygenation of compounds **47a,b** proceeded *via* the isoxazolo[2,3-*a*]-quinoxalines **79a,b**, azirinoquinoxalines **I-45** and then $N_4$-ylides **I-46** (Chart 17).

Chart 17

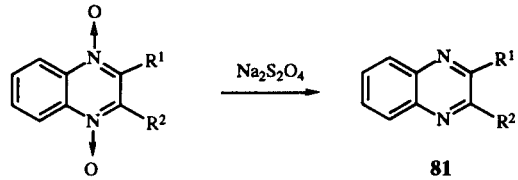


**I-45**



**I-46**

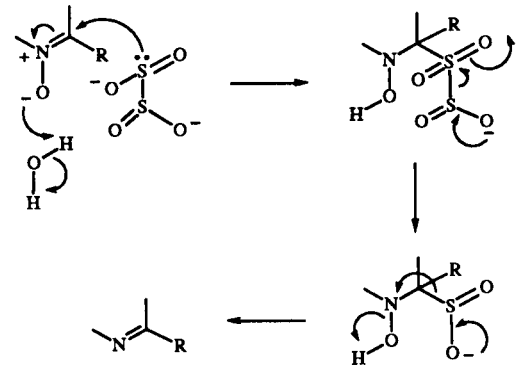
Scheme 35



**80** **81**

| | $R^1$ | $R^2$ |
|---|---|---|
| **a** | Me | Ph |
| **b** | Me | COMe |
| **c** | Me | COOEt |
| **d** | $CH_2Ph$ | Ph |
| **e** | Ph | COPh |

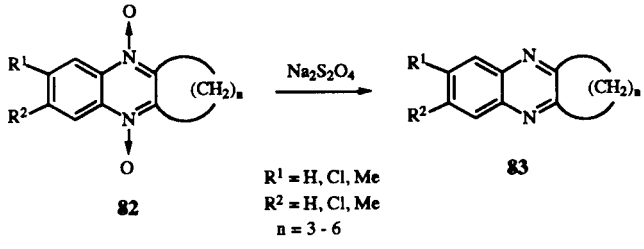
Scheme 36



C-c. Deoxygenation with Sodium Dithionite.

The reaction of the quinoxaline 1,4-dioxides **80a-e** with sodium dithionite resulted in deoxygenation to furnish the quinoxalines **81a-e**, respectively (Scheme 35) [35]. The mechanism is displayed in Scheme 36. Optimum yields were obtained with the 4:1 molar ratio of reductant:1,4-

Scheme 37



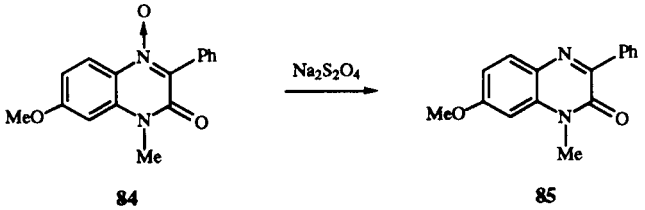

**82** **83**

dioxide. The condensed quinoxaline *N,N'*-dioxides **82** were also deoxygenated with sodium dithionite to give the condensed quinoxalines **83** (Scheme 37) [35]. The reaction of the quinoxalin-2-one 4-oxide **84** with sodium dithionite provided the quinoxalin-2-one **85** by a similar mechanism to the above (Scheme 38) [36].

C-d. Deoxygenation with Sodium Sulfite.

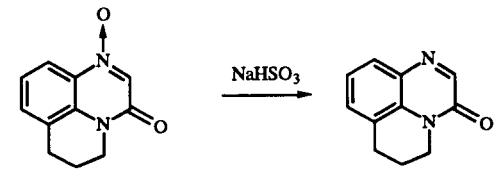
The reaction of the pyrido[3,2,1-*i,j*]quinoxalin-5-one 7-oxide **86** with sodium sulfite gave the pyrido[3,2,1-*i,j*]-quinoxalin-5-one **87** (Scheme 39) [37]. Similarly, the

Scheme 38




**84** **85**

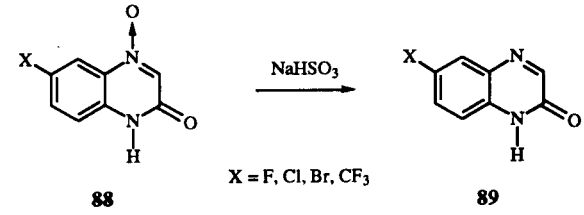
Scheme 39




**86** **87**

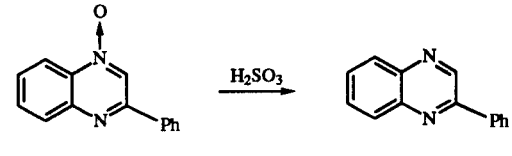
quinoxalin-2-one 4-oxides **88** were converted into the quinoxalin-2-ones **89** (Scheme 40) [38], and 3-phenylquinoxaline 1-oxide **31a** was transformed into 2-phenylquinoxaline **90** (Scheme 41) [18]. The deoxygenation mechanism is displayed in Scheme 42.

Scheme 40



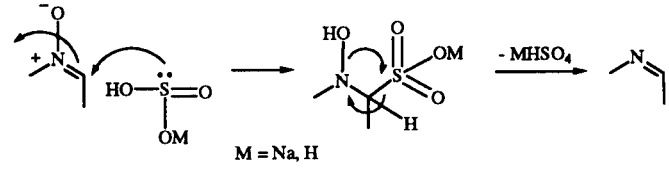

**88** **89**

Scheme 41




**31a** **90**

Scheme 42

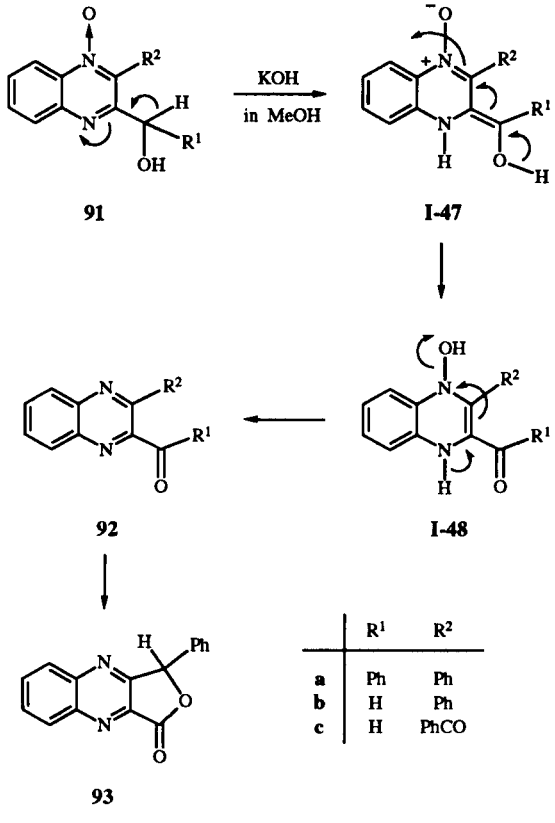



D. Deoxygenative Transformation of Quinoxaline *N*-Oxides and *N,N'*-Dioxides.

D-a. Dehydrative Deoxygenation with Alkali.

Treatment of the 2-phenylquinoxaline 1-oxides **91a,b** with hot methanolic potassium hydroxide effected dehydration to give the quinoxalines **92a,b**, respectively, *via* intermediates **I-47** and **I-48**, while a similar reaction of 2-benzoylquinoxaline 1-oxide **91c** provided the lactone **93** (Scheme 43) [35]. Compound **92c** was also converted into the lactone **93** under similar reac-

Scheme 43

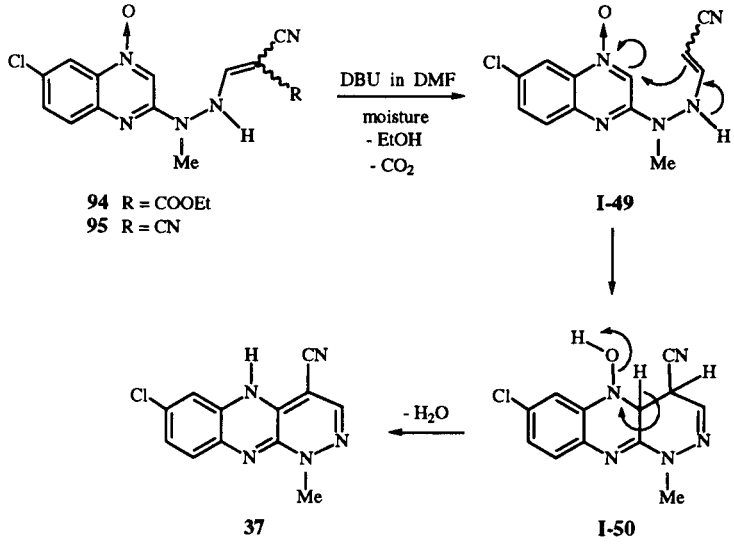



tion conditions to the above.

D-b. Deoxygenative Cyclization with Base.

Refluxing of the $C_2$-functionalized quinoxaline 4-oxide **94** and 1,8-diazabicyclo[5.4.0]-7-undecene in *N,N*-dimethylformamide gave the 1,5-dihydropyridazino[3,4-*b*]-

Scheme 44

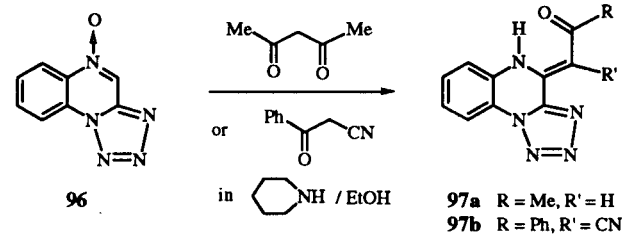



quinoxaline **37** presumably *via* intermediates **I-49** and **I-50** [21] (Scheme 44). Compound **95** was not cyclized into the pyridazino[3,4-*b*]quinoxaline ring.

D-c. Alkylative Deoxygenation with Active Methylene Compounds.

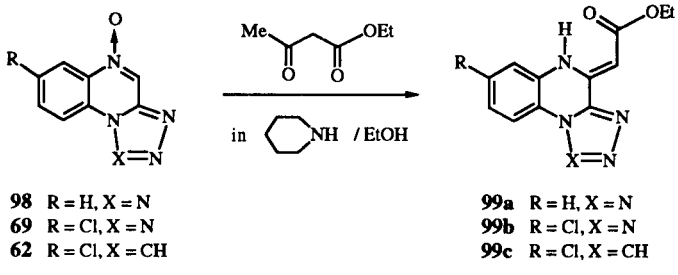
The reaction of tetrazolo[1,5-*a*]quinoxaline 5-oxide **96** with acetylacetone or benzoylacetonitrile gave the side-chained 4,5-dihydrotetrazolo[1,5-*a*]quinoxalines **97a** or **97b**, respectively (Scheme 45) [39], while the reaction of

Scheme 45

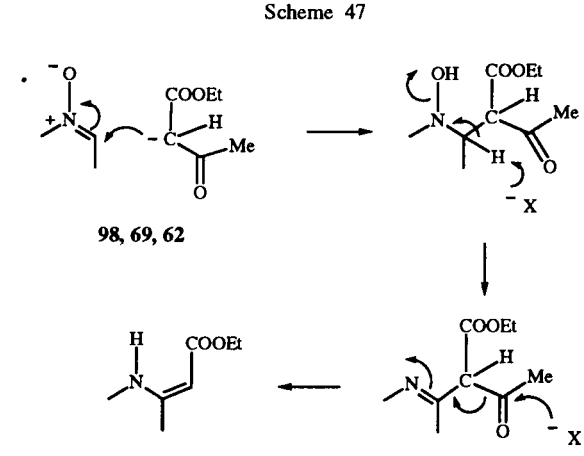



compounds **98**, **69** or **62** with ethyl acetoacetate afforded the side-chained compounds **99a** [39], **99b** [40,41] or **99c** [40,41], respectively (Scheme 46). The reaction mechanism is displayed in Scheme 47. On the other hand, the reaction of compound **96** with 3-methyl- or 3-ethylpentane-2,4-dione furnished the 3,4-dihydroazirino[1,2-*a*]-

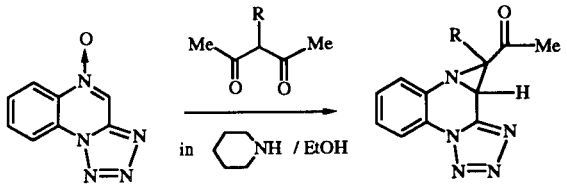
Scheme 46




Scheme 47



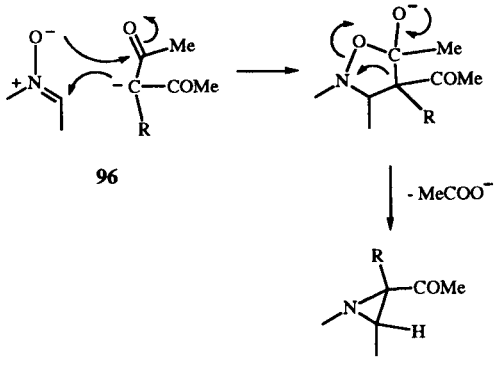
Scheme 48



96 100a R = Me; 100b R = Et

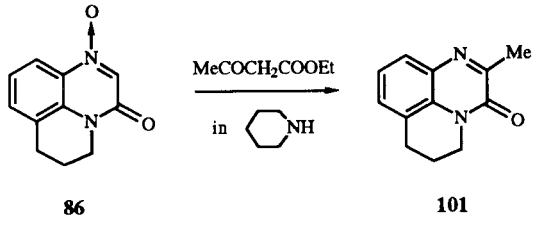
tetrazolo[5,1-*c*]quinoxaline **100a** or **100b** (Scheme 48), respectively, *via* the cycloaddition and then ring contraction as shown in Scheme 49 [39]. The reaction of the pyridoquinoxaline 7-oxide **86** and quinoxalin-2-one 4-oxides **88** with ethyl acetoacetate resulted in deoxygenative α-methylation to give compounds **101** [37] and **102** [42],

Scheme 49



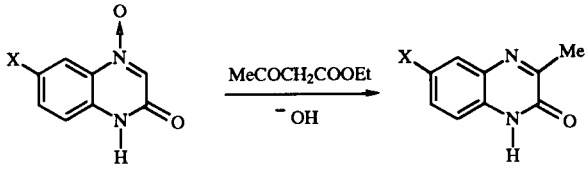
96 100

Scheme 50



86 101

Scheme 51



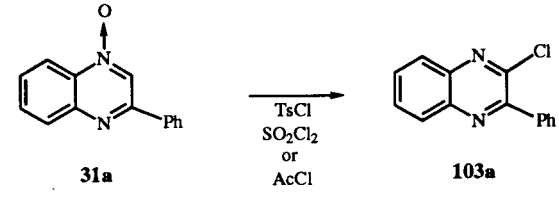
88 X = F, Cl, Br, $CF_3$ 102

respectively (Schemes 50 and 51).

D-d. Chlorinative or Acetoxylative Deoxygenation with Arylsulfonyl Chlorides, Sulfuryl Chloride, Acetyl Chloride, Phosphoryl Chloride, Benzoyl Chloride, Acetic Anhydride or Hydrochloric Acid.

The reaction of 3-phenylquinoxaline 1-oxide **31a** with tosyl chloride, sulfuryl chloride [18] or acetyl chloride [43] resulted in α-chlorinative deoxygenation to give 2-chloro-3-phenylquinoxaline **103a** (Scheme 52), while the reaction of quinoxaline 1-oxide **12** with tosyl chloride,

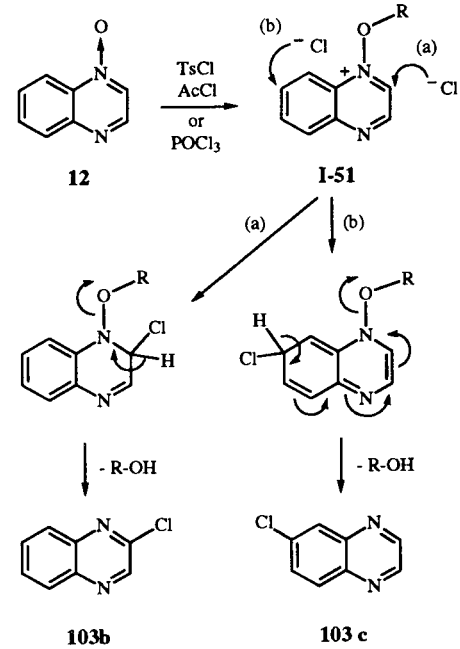
Scheme 52



31a 103a

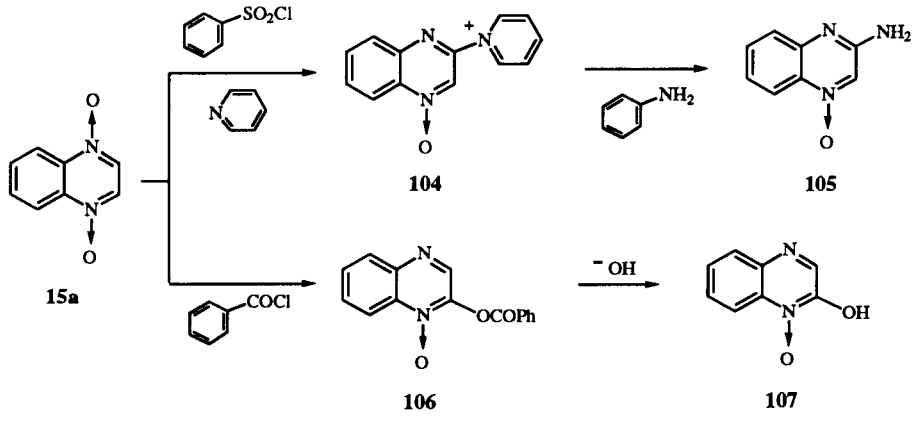
acetyl chloride or phosphoryl chloride produced 2-chloroquinoxaline **103b** and 6-chloroquinoxaline **103c** *via* an intermediate **I-51** (Scheme 53) [44]. The reaction of quinoxaline 1,4-dioxide **15a** with benzenesulfonyl chloride/pyridine afforded the pyridinium sulfonate **104**, whose reaction with aniline provided 3-aminoquinoxaline 1-oxide **105** [45] (Scheme 54). However, the reaction of compound **15a** with benzoyl chloride effected β-benzoxylation to furnish 2-benzoxyquinoxaline 1-oxide **106**, which was converted into 2-hydroxyquinoxaline 1-oxide

Scheme 53



12 I-51 103b 103 c

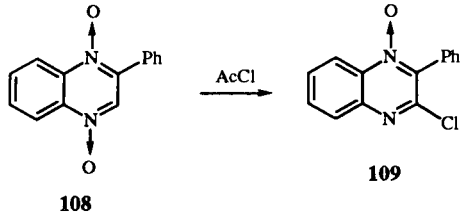
Scheme 54



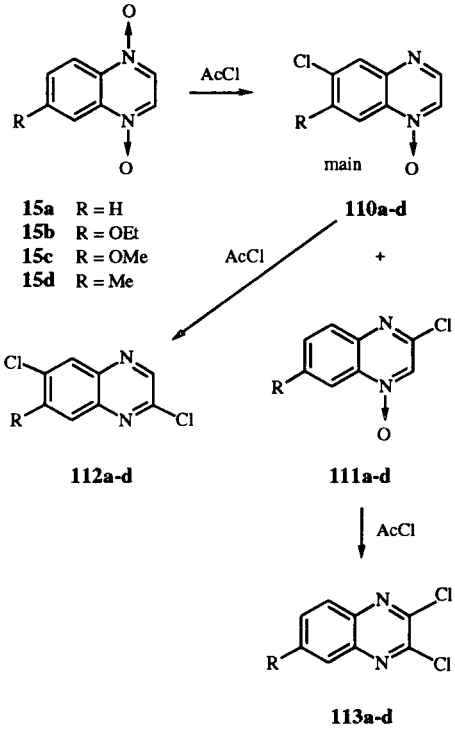

**107**. The mechanism for the production of compound **106** is not explained in the original paper [45]. Similarly, the reaction of 2-phenylquinoxaline 1,4-dioxide **108** with acetyl chloride also resulted in α-chlorination to give compound **109** [43] (Scheme 55). On the other hand, the reaction of 6-substituted compounds **15a-d** with acetyl chloride afforded the 6-chloroquinoxaline 1-oxides **110a-d** together with α-chlorinated compounds **111a-d** [46] (Scheme 56). Further reaction of compounds **110a-d** or **111a-d** with acetyl chloride effected α-chlorination to provide compounds **112a-d** or **113a-d**, respectively. The mechanism for the $C_6$-chlorination is shown in Scheme 57. The presence of the electron-donating group R promotes the $N_1$-*O*-acetylation to produce an intermediate **I-52**, which is transformed into compounds **110a-d** *via* intermediates **I-53** and **I-54**.

However, the reaction of 6-substituted compounds **15a-d** with acetic anhydride furnished the 6-substituted 1-acetoxyquinoxalin-2-ones **114a-d** (Scheme 58), while the reaction of 6-chloroquinoxaline 1,4-dioxide **15e** with

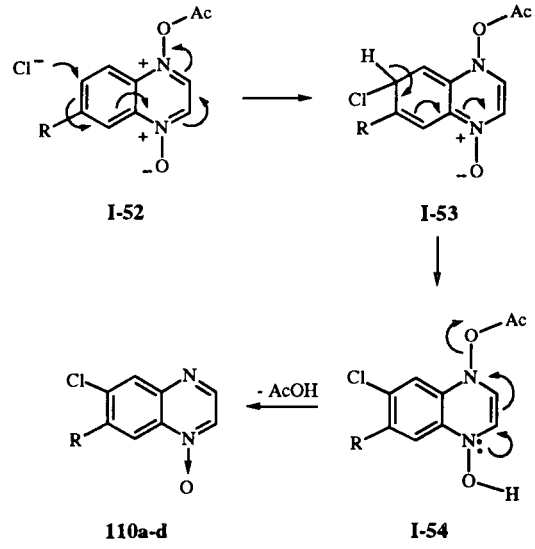
Scheme 55



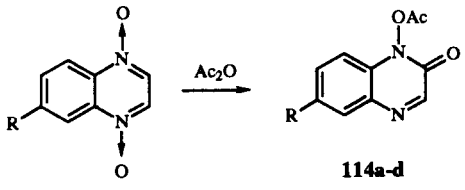

Scheme 56




Scheme 57



Scheme 58

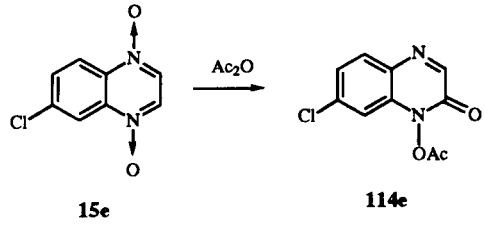


15a-d 114a-d

R = H, OEt, OMe, Me

acetic anhydride gave the 1-acetoxy-7-chloroquinoxalin-2-one **114e** (Scheme 59) [47]. The presence of the electron-donating group R resulted in $N_1$-*O*-acetylation to

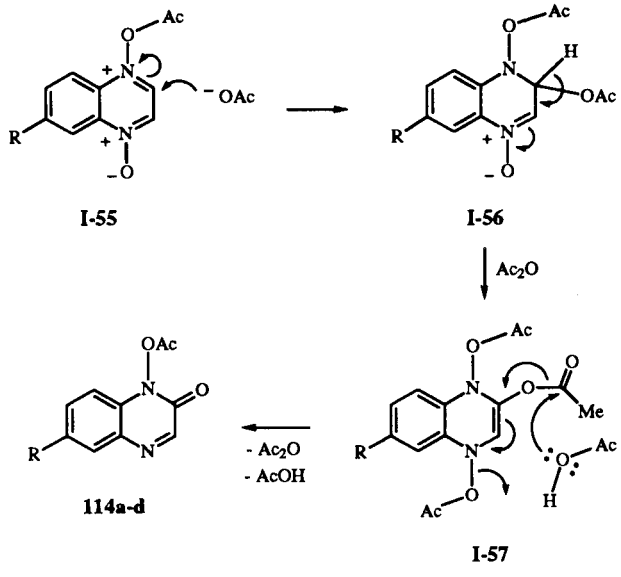
Scheme 59



15e 114e

provide an intermediate **I-55** (Scheme 60), and the subsequent $C_2$-acetoxylation led to the formation of compounds

Scheme 60

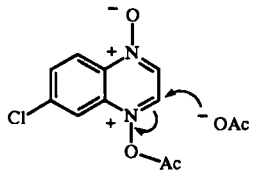


I-55 I-56 I-57 114a-d

**114a-d**. In contrast, the electron-withdrawing $C_6$-chlorine atom effected the $N_4$-*O*-acetylation to furnish an intermediate **I-58** (Chart 18), and then the $C_3$-acetoxylation led to the production of compound **114e**.

The reaction of 2,3-dimethylquinoxaline 1-oxide **115a**

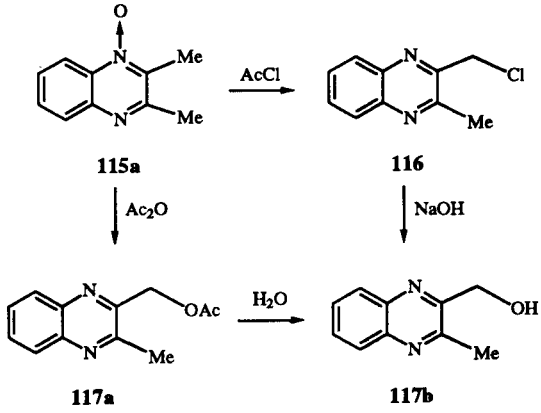
Chart 18



I-58

with acetyl chloride or acetic anhydride gave the 2-chloromethyl or 2-acetoxymethyl derivative **116** or **117a**, respectively [43] (Scheme 61). Hydrolysis of compound **116** or **117a** afforded the 2-hydroxymethyl derivative

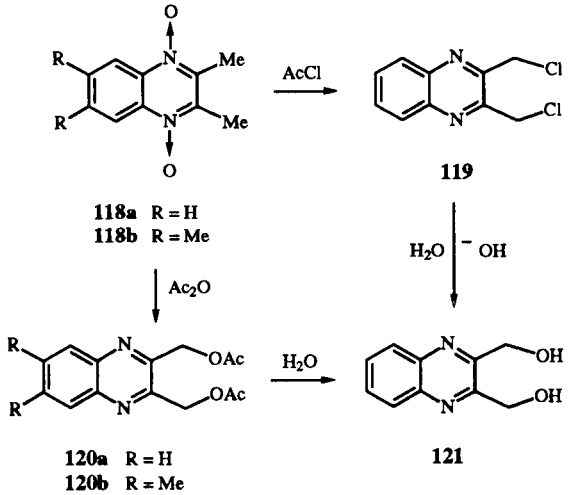
Scheme 61



115a 116 117a 117b

**117b**. The reaction of 2,3-dimethylquinoxaline 1,4-dioxide **118a** with acetyl chloride or acetic anhydride provided the 2,3-bischloromethyl or 2,3-bisacetoxymethyl derivative **119** or **120a**, respectively [43] (Scheme 62). The

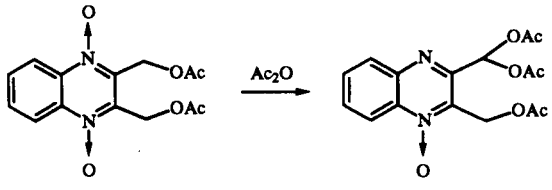
Scheme 62



118a R = H
118b R = Me
119
120a R = H
120b R = Me
121

reaction of 2,3,6,7-tetramethylquinoxaline 1,4-dioxide **118b** with acetic anhydride also gave the 2,3-bisacetoxymethyl derivative **120b** [48]. Hydrolysis of compounds **119** or **120a** furnished the 2,3-bishydroxymethyl derivative **121**. Moreover, the reaction of 2,3-bisacetoxymethylquinoxaline 1,4-dioxide **122** with acetic anhydride produced 2-acetoxymethyl-3-diacetoxymethylquinoxaline 1-oxide **123** [49] (Scheme 63). The above α-methyl acetoxylation or chlorination would proceed *via* intermediates **I-59** and **I-60** (Scheme 64).

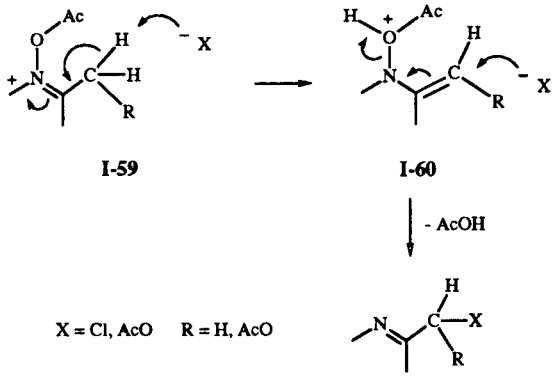
Scheme 63




**122** **123**

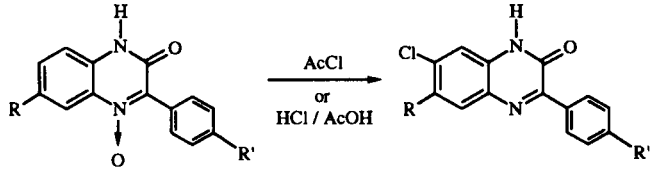
The reaction of 6-substituted 3-arylquinoxalin-2-one 4-oxides **124a-f** with acetyl chloride or hydrochloric acid/acetic acid resulted in $C_7$-chlorination to give compounds **125a-f**, respectively [50] (Scheme 65). This chlorination takes place *via* intermediates **I-61** to **I-63** (Scheme 66). Similarly, 3-ethoxy-2-methylquinoxaline 1-oxide **126** was converted into the 7-chloroquinoxalin-2-one derivative **127** [51,52] (Scheme 67). The reaction of the 1-methyl-3-phenylquinoxalin-2-one 4-oxides **128a** [36] and **128b** [53] with acetic anhydride effected $C_7$-acetoxylation to provide the 7-acetoxyquinoxalin-2-one derivatives **129a,b** (Scheme 68), respectively, by a similar mechanism to that shown in Scheme 66. On the other hand, the reaction of the 7-methylquinoxalin-2-one 4-oxides **130a-c** with acetic anhydride resulted in $C_7$-methyl acetoxylation to furnish the 7-acetoxymethylquinoxalin-2-

Scheme 64




**I-59** **I-60**

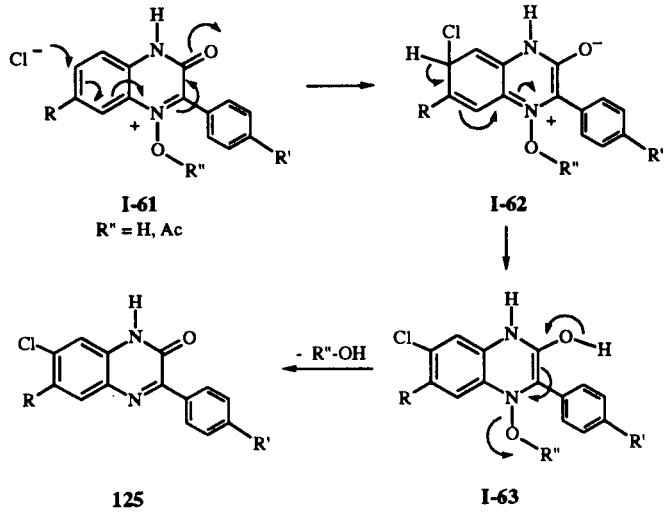
Scheme 65



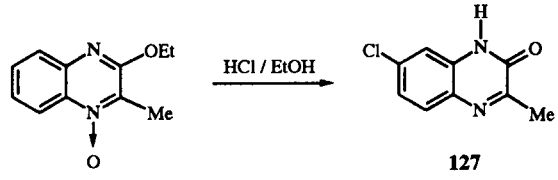

**124a-f** **125a-f**

| | R | R' |
|---|---|---|
| **a** | H | H |
| **b** | Cl | H |
| **c** | EtO | H |
| **d** | MeO | H |
| **e** | H | Cl |
| **f** | Cl | Cl |

Scheme 66

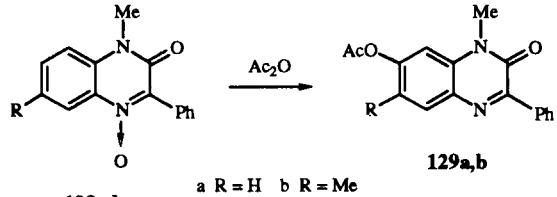



Scheme 67




**126** **127**

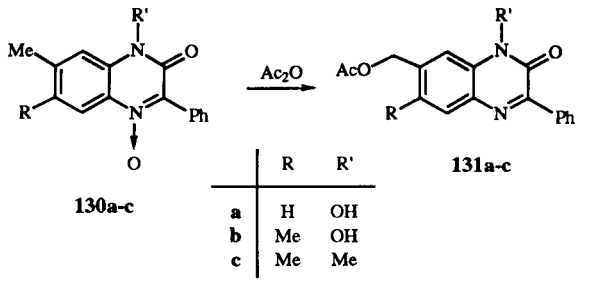
Scheme 68



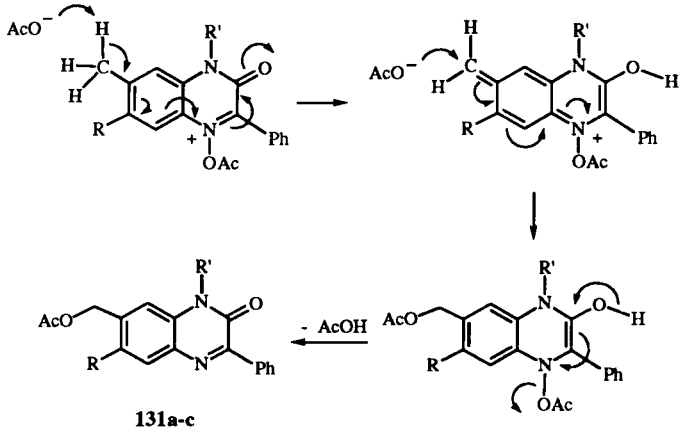

**128a,b** **129a,b**

a R = H b R = Me

Scheme 69




Scheme 70



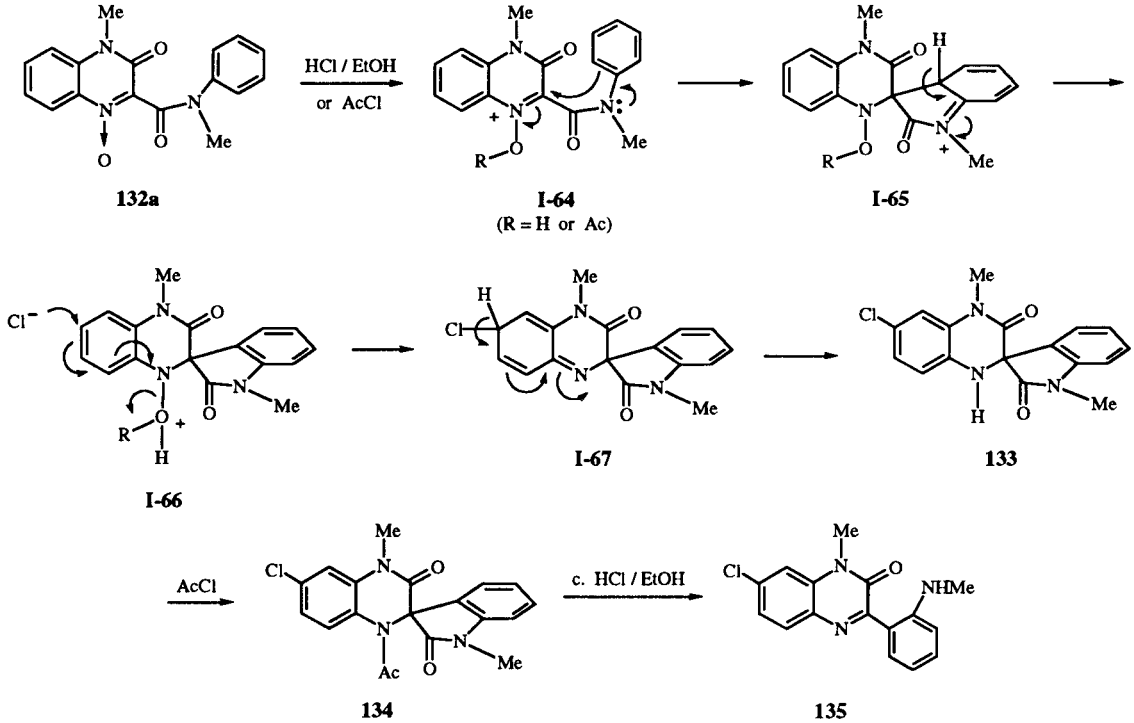

one derivatives **131a-c**, respectively [53] (Scheme 69). This acetoxylation mechanism is shown in Scheme 70.

When the *N*-methyl-*N*-phenylcarbamoyl group was present in the α-position of the *N*-oxide moiety, an interesting transformation was observed as shown in Scheme 71. The reaction of the 3-carbamoylquinoxalin-2-one 4-oxide **132a** in ethanolic hydrochloric acid produced the spiro[quinoxaline-indole] **133** *via* intermediates **I-64** to **I-67** [54], and a similar reaction of **132a** in acetyl chloride gave the acetyl derivative **134**. Treatment of compound **134** with concentrated hydrochloric acid/ethanol afforded the 7-chloro-3-arylquinoxalin-2-one derivative **135**. The reaction of compound **132a** in sulfuric acid directly afforded the 3-arylquinoxalin-2-one derivative **136a** *via* intermediates **I-66** and **I-68** [55,56] (Scheme 72). Similarly, the 3-carbamoylquinoxalin-2-one 1-oxides **132b-e** were transformed into the 3-arylquinoxalin-2-one derivatives **136b-e**, respectively [57] (Scheme 73).

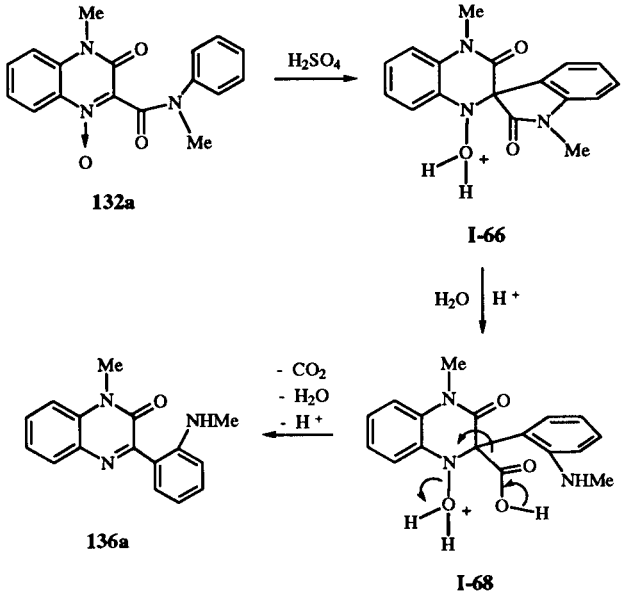
D-e. Deoxygenative Dimerization with Acetic Anhydride.

The reaction of quinoxaline 1-oxide **12** with acetic anhydride provided the 1-(quinoxalin-2-yl)quinoxalin-2-one **137** (4%) as a by-product together with quinoxaline (3%) and the quinoxalin-2-one (13%) [58] (Scheme 74). However, the reaction of the quinoxaline 5-oxide **69** or **62** with acetic anhydride predominantly gave the 5-(tetrazolo[1,5-*a*]quinoxalin-4-yl)tetrazolo[1,5-*a*]quinoxalin-4-one **138a** or 5-(1,2,4-triazolo[4,3-*a*]quinoxalin-4-yl)-

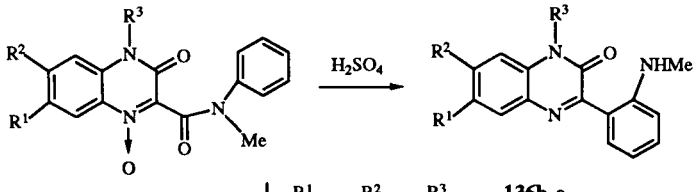
Scheme 71



Scheme 72




Scheme 73

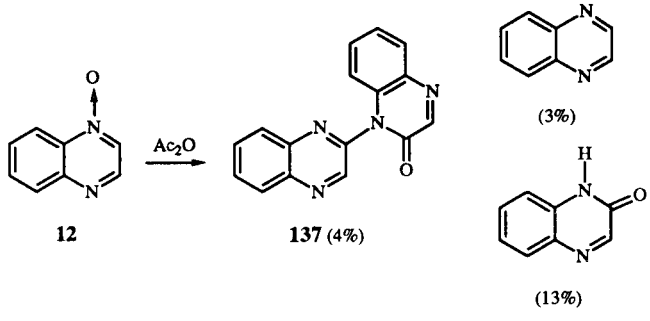



| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| b | Me | Me | Me |
| c | Me | Me | H |
| d | MeO | MeO | Me |
| e | MeO | MeO | H |

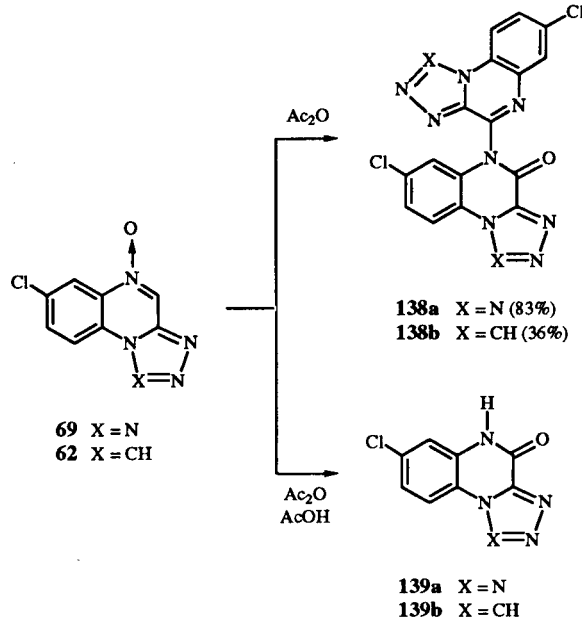
1,2,4-triazolo[4,3-*a*]quinoxalin-4-one **138b**, respectively [59] (Scheme 75). The reaction mechanism is shown in Scheme 76, which involves the dimerization step followed by the migration *via* an intermediate **I-69** [58,59].

A good yield of compound **138a** (83%) or **138b** (36%) was explained by the isomerization of compounds **69** and

Scheme 74




Scheme 75




**62** into a resonance isomer **I-70**, which was promoted by an electron-donating nature of $N_{10}$ atom (Chart 19) [59]. This resonance would strengthen the nucleophilic attack of an isomer **I-70** to an acetylated intermediate **I-71** in the dimerization step. In contrast, the reaction of compounds **69** or **62** in acetic anhydride/acetic acid afforded the tetrazolo[1,5-*a*]quinoxalin-4-one **139a** or the 1,2,4-triazolo-[4,3-*a*]quinoxalin-4-one **139b**, respectively (Scheme 75) [59]. Since the nucleophilicity of an intermediate **I-72** formed by the protonation of an isomer **I-70** is weaker than that of acetoxy anion, compounds **139a** or **139b** are preferably produced *via* intermediates **I-72**, **I-71**, **I-73** and **I-74**.

E. Ring Transformation of Quinoxaline *N*-Oxides and

Scheme 76

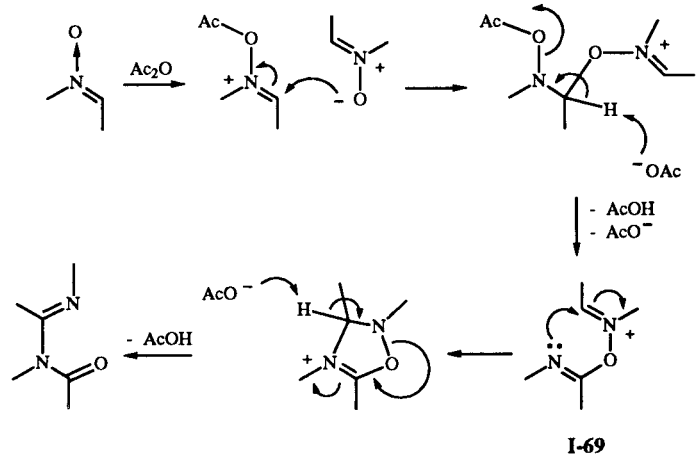
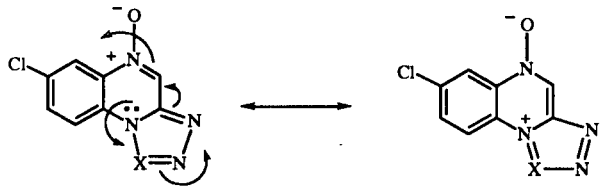
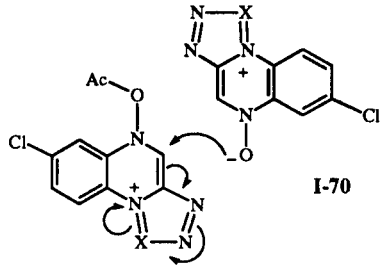


Chart 19

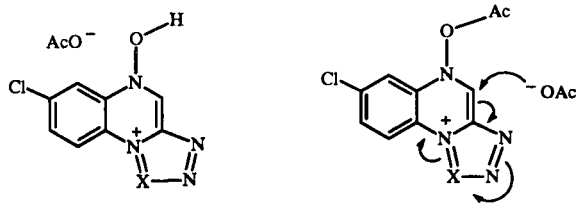


69, 62 I-70

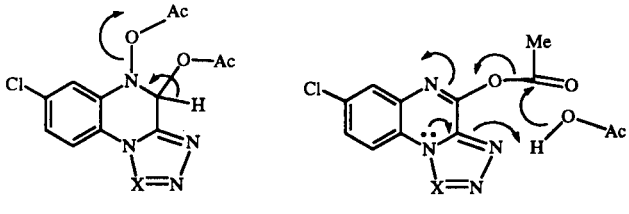


I-70

I-71



I-72 I-71



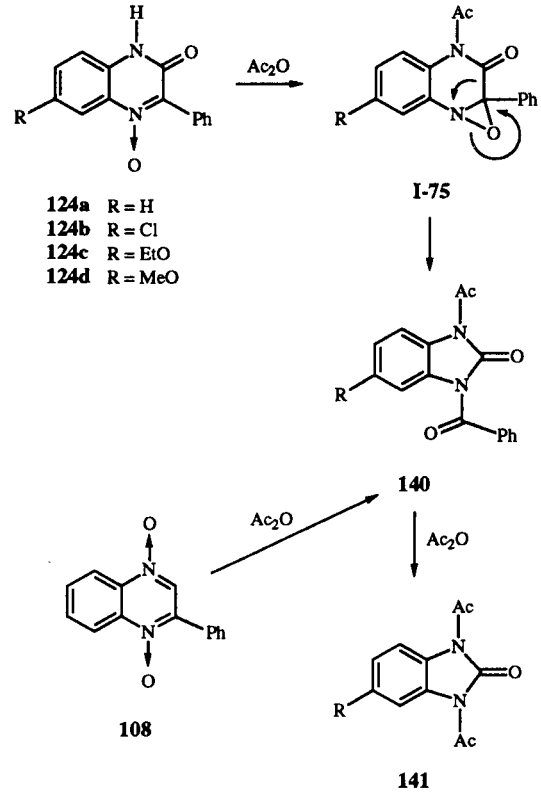
I-73 I-74

*N,N'*-Dioxides.

E-a. Thermal Ring Transformation of 3-Phenylquinoxalin-2-one 4-Oxides into Benzimidazolin-2-ones.

As shown in Scheme 68 (section D-d), refluxing 1-methyl-3-phenylquinoxalin-2-one 4-oxides **128a,b** in acetic anhydride resulted in $C_7$-acetoxylation, but the absence of the $N_1$-methyl group caused quite a different reaction. Namely, refluxing 3-phenylquinoxalin-2-one 4-oxides **124a,c,d** in acetic anhydride effected ring transformation to give the 1-acetyl-3-benzoylbenzimidazolin-2-ones **140a,c,d**, respectively, *via* an intermediate **I-75** [36] (Scheme 77). A similar reaction of compound **124b** afforded the 1,3-diacetylbenzimidazolin-2-one **141b**. Prolonged refluxing of compounds **124a,c,d** in acetic

Scheme 77



**124a** R = H
**124b** R = Cl
**124c** R = EtO
**124d** R = MeO

I-75

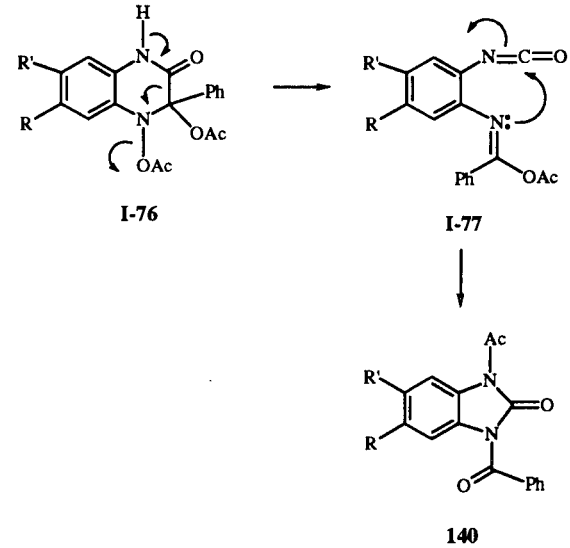
140

108

141

anhydride directly produced compounds **141a,c,d**, respectively. On the other hand, refluxing 2-phenylquinoxaline 1,4-dioxide **108** in acetic anhydride furnished compound **140a** *via* compound **124a** [60]. Concerning the reaction mechanism, intermediates **I-76** and **I-77** are also proposed as a Grob type of fragmentation [60] (Scheme 78).

Scheme 78



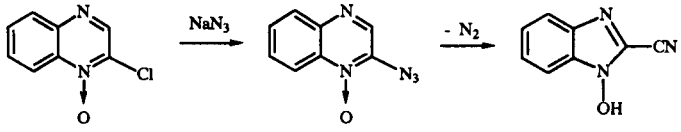
I-76 I-77

140

E-b. Thermal Ring Transformation of 2-Azidoquinoxaline 1-Oxide and 1,4-Dioxides into Benzimidazole, Benzimidazole 3-Oxide and 2,1,4-Benzoxadiazine 4-Oxide.

The reaction of 2-chloroquinoxaline 1-oxide **142** with sodium azide produced 2-azidoquinoxaline 1-oxide **143**, whose refluxing in benzene effected loss of nitrogen to give 2-cyano-1-hydroxy-1*H*-benzimidazole **144** [61] (Scheme 79). On the other hand, the reaction of 2-methylsulfonylquinoxaline 1,4-dioxide **145a** with sodium azide

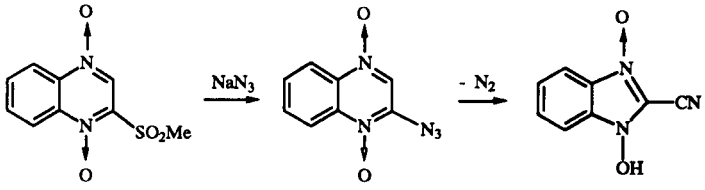
Scheme 79



**142** **143** **144**

produced 2-azidoquinoxaline 1,4-dioxide **146a**, whose refluxing in benzene afforded 2-cyano-1-hydroxy-1*H*-benzimidazole 3-oxide **147** [62] (Scheme 80). Compound

Scheme 80

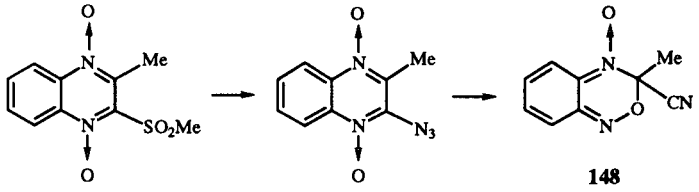


**145a** **146a** **147**

**146b** having the $C_3$-methyl group were transformed into 3-cyano-3-methyl-3*H*-2,1,4-benzoxadiazine 4-oxide **148** [62] (Scheme 81). The reaction mechanism is exhibited in Scheme 82.

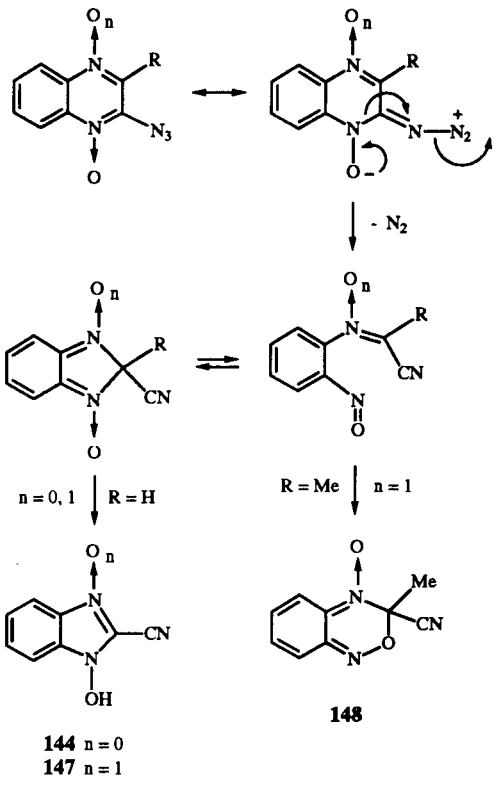
E-c. Ring Transformation of 3-Substituted Quinoxaline 1-Oxides into 2-Substituted Benzimidazole 3-Oxides.

Scheme 81



**145b** **146b** **148**

Scheme 82



**144** n = 0
**147** n = 1

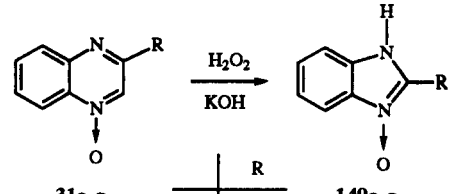
**148**

The reaction of the 3-substituted quinoxaline 1-oxides **31a-g** [18,63] with hydrogen peroxide/potassium hydroxide gave the 2-substituted benzimidazole 3-oxides **149a-g** (Scheme 83) *via* intermediates **I-78** to **I-80** (Scheme 84). An intermediate **I-81** (Chart 20) is also proposed in a monograph [64].

F. Photochemical Reaction of Quinoxaline *N*-Oxides and *N,N'*-Dioxides.

F-a. Photochemical Conversion of Quinoxaline 1,4-Dioxide into Quinoxalin-2-one 4-Oxide or 2-Chloroquinoxaline 1-Oxide.

Scheme 83



**31a-g** **149a-g**

| | R |
|---|---|
| **a** | Ph |
| **b** | Me |
| **c** | Et |
| **d** | *i*-Pr |
| **e** | *t*-Bu |
| **f** | OMe |
| **g** | OEt |

Scheme 84

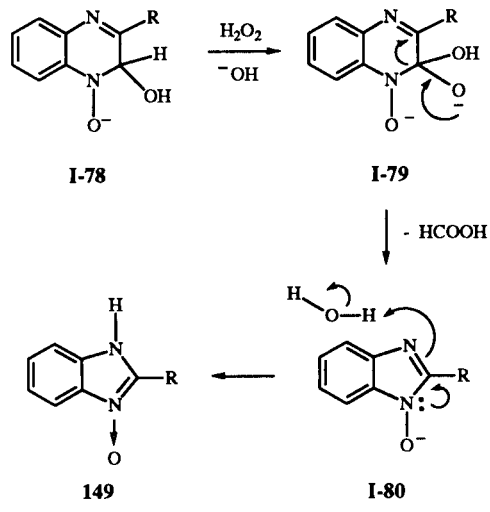
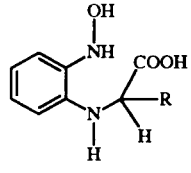
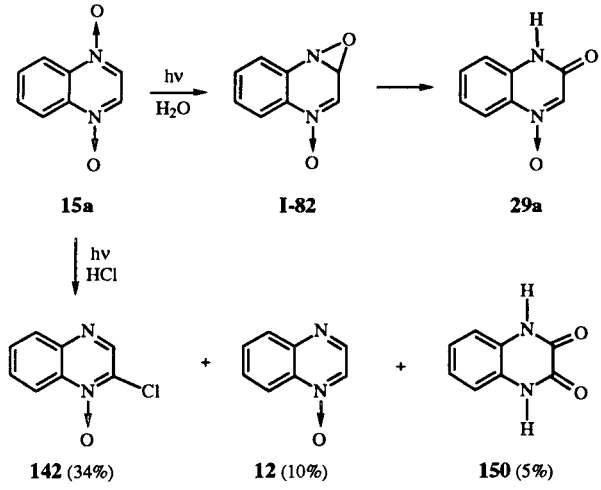


Chart 20

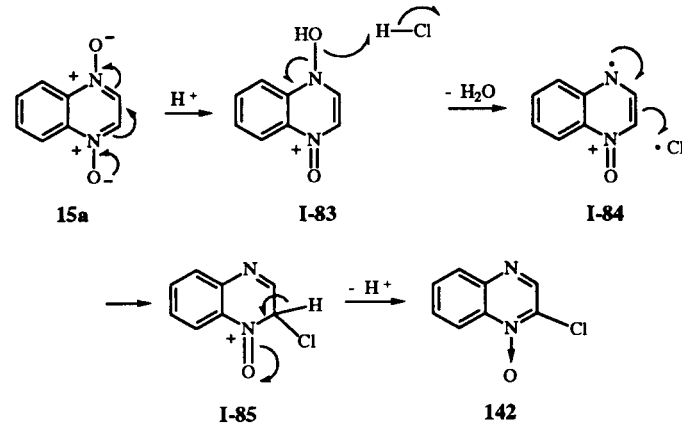


Irradiation of quinoxaline 1,4-dioxide **15a** in water afforded the quinoxalin-2-one 4-oxide **29a** *via* an oxaziridine intermediate **I-82** [65] (Scheme 85), while irradiation of compound **15a** in hydrochloric acid gave 2-chloroquinoxaline 1-oxide **142** as a major product *via* a radical cation intermediate **I-84** [66] (Scheme 86). Compounds **12** and **150** were also obtained in the latter reaction.

Scheme 85



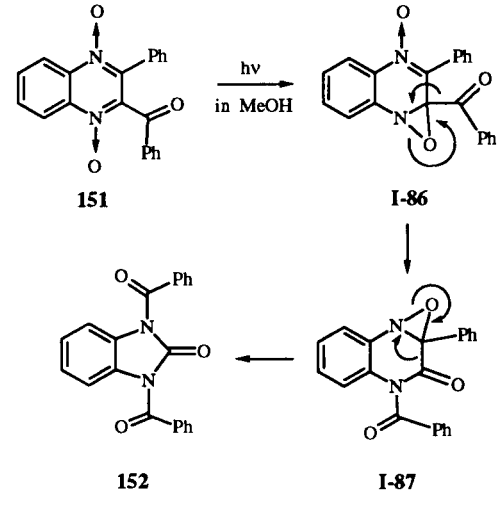
Scheme 86



F-b. Photochemical Ring Transformation of 2-Benzoyl-3-phenylquinoxaline 1,4-Dioxide into 1,3-Dibenzoylbenzimidazolin-2-one.

Irradiation of 2-benzoyl-3-phenylquinoxaline 1,4-dioxide **151** in methanol provided 1,3-dibenzoylbenzimidazolin-2-one **152** *via* oxaziridine intermediates **I-86** and **I-87** [67] (Scheme 87). Concerning the benzoyl group

Scheme 87



migration in the intermediate **I-86**, Haddadin recommended the mechanism *via* the thermal heterolytic N-O

Scheme 88

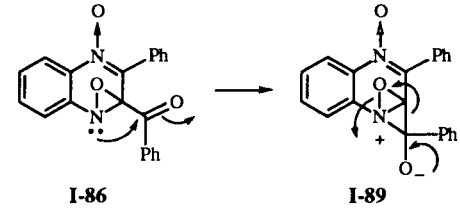
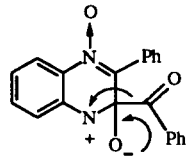


Chart 21



I-88

bond fission of intermediate **I-86** into intermediate **I-88** (Chart 21) rather than the mechanism *via* the formation of a strained intermediate **I-89** from intermediate **I-86** (Scheme 88).

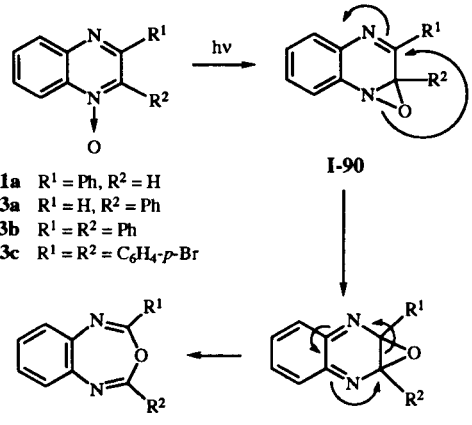
F-c. Photochemical Ring Transformation of Quinoxaline 1-Oxides into Benz[*d*][3,1,5]oxadiazepines.

Irradiation of the quinoxaline *N*-oxides **31a** and **153a,b** in benzene [68-70] and **153c** in acetone [71] produced the benz[*d*][3,1,5]oxadiazepines **154a,b,c** *via* intermediates **I-90** and **I-91** (Scheme 89). The X-ray study [71] determined the structure of the benz[*d*][3,1,5]oxadiazepine **154c**, and the nmr, ir and uv spectral data were described in detail in the original papers [69,71].

F-d. Photochemical Ring Transformation of Quinoxalin-2-ylcarbamate 1-Oxide into Benzimidazol-2-ylcarbamate.

Irradiation of the quinoxalin-2-ylcarbamate 1-oxide **155** in some solvents furnished the 1-formylbenzimidazol-2-ylcarbamate **156** *via* intermediates **I-92** and **I-93**, and the solvolysis of compound **156** gave the benzimidazol-2-ylcarbamate **157** [72] (Scheme 90). Under acidic condition, an intermediate **I-92** was converted into the ureidocarboxylate **158** *via* intermediate **I-94**. Compound **158** was transformed into the benzimidazolium salt **159** *via* an intermediate **I-95**. The presence of the $C_2$-nitrogen function in an intermediate **I-92** promotes the cleavage of the oxadiazepine ring, although the 2-phenyl- or 2,4-diarylbenz[*d*][3,1,5]oxadi-

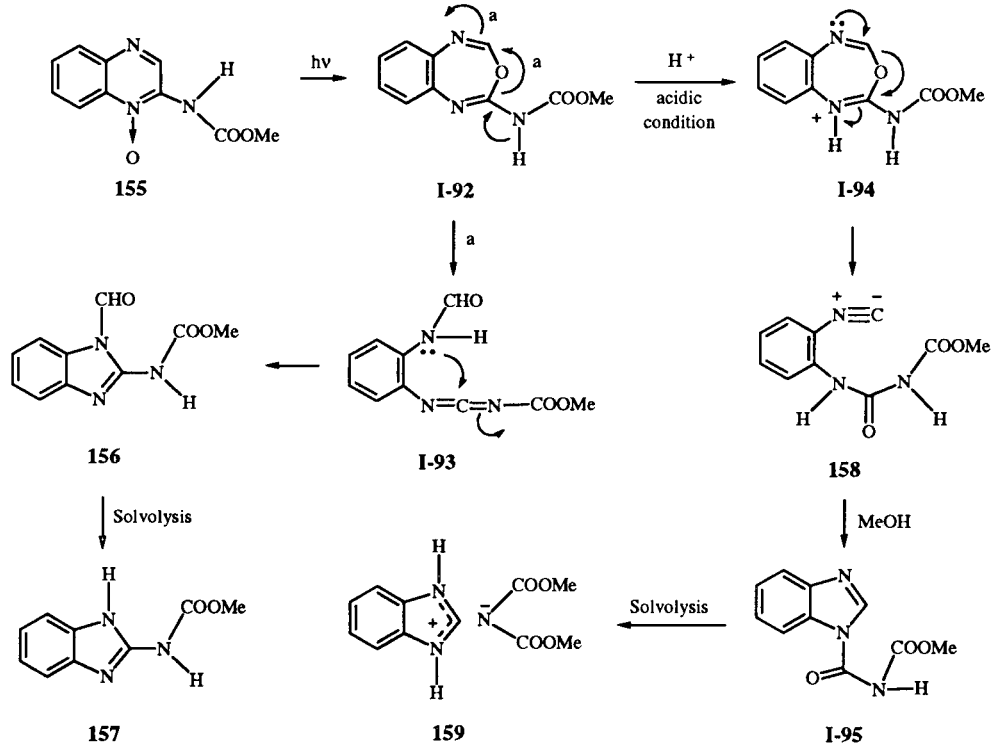
Scheme 89




**31a** $R^1 = Ph, R^2 = H$
**153a** $R^1 = H, R^2 = Ph$
**153b** $R^1 = R^2 = Ph$
**153c** $R^1 = R^2 = C_6H_4$-*p*-Br

**154a** $R^1 = Ph, R^2 = H$
**154b** $R^1 = R^2 = Ph$
**154c** $R^1 = R^2 = C_6H_4$-*p*-Br

Scheme 90

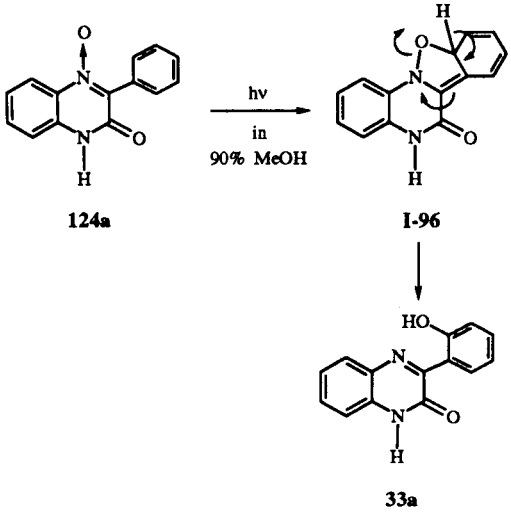


azepines **154a,b,c** (Section F-c) are isolated in good yields without oxadiazepine ring cleavage.

F-e. Photochemical Conversion of 3-Phenylquinoxalin-2-one 4-Oxide into 3-(*o*-Hydroxyphenyl)quinoxalin-2-one.

Sunlight irradiation of the quinoxalin-2-one 4-oxide **124a** in 90% methanol effected *O*-migration *via* intermediate **I-96** to give compound **33a** [73] (Scheme 91), while

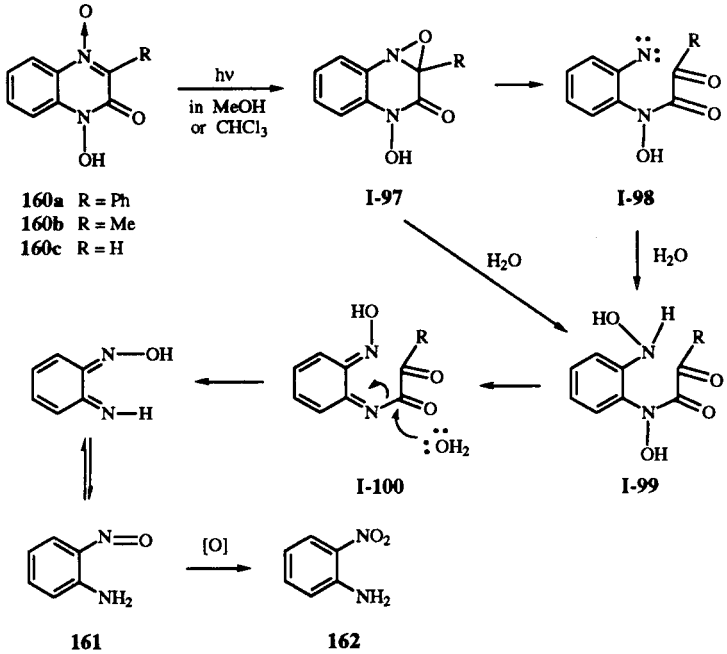
Scheme 91




**124a** **I-96** **33a**

photolysis of the 1-hydroxyquinoxalin-2-one 4-oxides **160a-c** in methanol or chloroform afforded *o*-nitrosoaniline **161** and *o*-nitroaniline **162** *via* intermediates **I-97** to **I-100** (Scheme 92). The presence of the $N_1$-hydroxyl group in compound **160a** favored a route to an oxaziridine intermediate **I-97**, but not to an isoxazoline intermediate such as **I-96**.

Scheme 92



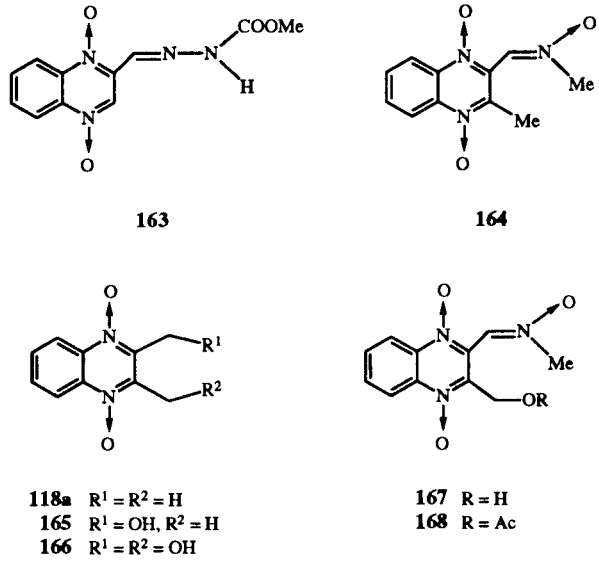

**160a** R = Ph
**160b** R = Me
**160c** R = H

**I-97** **I-98** **I-99** **I-100** **161** **162**

G. Biologically Active Quinoxaline Derivatives.

There have been many biologically active compounds in quinoxaline 1,4-dioxides **163-168** (Chart 22), which in general show antibacterial activity against Gram-positive and/or Gram-negative bacteria [74]. For example, Mecadox (Carbadox) **163** is the highly effective antibacterial and growth-promoting agent [75]. The methylnitrone **164** has exhibited exceptional activity against *Proteus mirabiris* and *Salmonella schottmeulleri* in experimental infections in mice [76], and 2,3-dimethylquinoxaline 1,4-dioxide **118a** has been one of the most effective agents against *Salmonella dublin* infection in mice; it is more active than aureomycin [77]. However, compound **118a** had little activity *in vitro*, and the metabolism of compound **118a** has been clarified to produce both 2-hydroxymethyl-3-methylquinoxaline 1,4-dioxide **165** and 2,3-bishydroxymethylquinoxaline 1,4-dioxide **166** as the *in vivo* active substances [78]. Thereafter, the methylnitrone analogues **167** and **168** were synthesized, and the activity of these compounds was of the same order as that of the methylnitrone **164** [79].

Chart 22



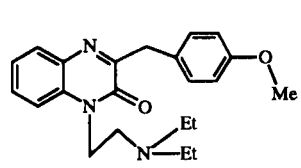
**163** **164**

**118a** $R^1 = R^2 = H$
**165** $R^1 = OH$, $R^2 = H$
**166** $R^1 = R^2 = OH$

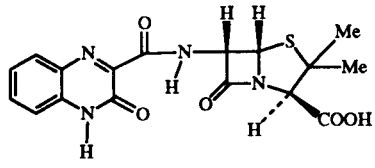
**167** R = H
**168** R = Ac

Besides the above quinoxaline 1,4-dioxides **163-168**, many biologically active quinoxaline derivatives have been reported in the journal and patent literature, which include Caroverine **169** [80] and Quinacilline **170** [81] as antibacterial agents, 6-chloro-2,3-bischloromethylquinox-

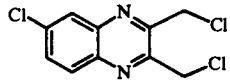
Chart 23



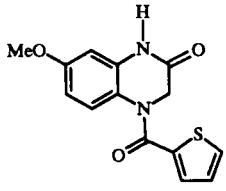
169



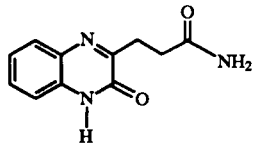
170



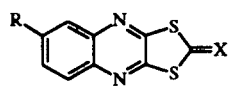
171



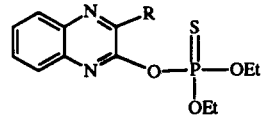
172



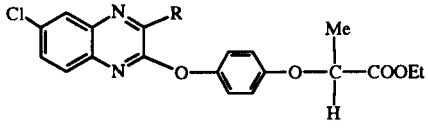
173



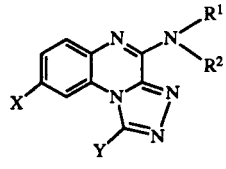
**174a** R = Me, X = O
**174b** R = H, X = S



**175a** R = H
**175b** R = OMe
**175c** R = OEt



176



177

aline **171** as a foliar fungicide [82,83], the quinoxalin-2-ones **172** [84] and **173** [85] as anti-inflammatory [84] and tranquilizing [85] agents, Morestan **174a** and Eradox **174b** as fungicidal and insecticidal agents [86], and Quinalphos **175a** [87] and its derivatives **175b,c** [88] as insecticidal and anthelmintic agents (Chart 23). In the early 1980's, Quizalofop-Et **176** has been developed as a potent and selective herbicide [89]. Recently, the 4-amino-1,2,4-triazolo[4,3-*a*]quinoxalines **177** have been synthesized as a novel class of potent adenosine receptor antagonists and potential rapid-onset antidepressants [90].

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