THE BEIRUT REACTION [1,2]

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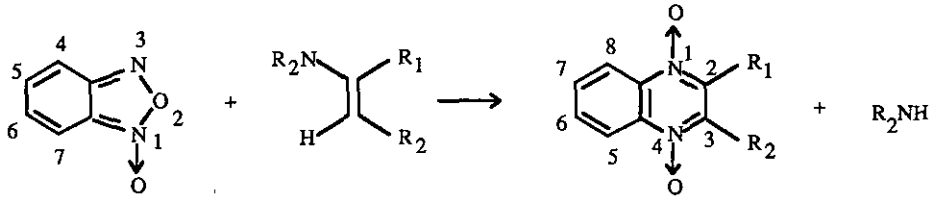
Abstract— Progress since 1976 in the chemistry of quinoxaline 1,4-dioxides, phenazine 9,10-dioxides and benzimidazole 1,3-dioxides is reviewed with special emphasis on the synthesis, *via* the Beirut reaction, of these products and their thermal and photochemical reactions.

1. Introduction

Prior to 1965, the general methods for the preparation of quinoxaline *N*- oxides, phenazine *N*-oxides and benzimidazole *N*- oxides followed two routes : (i) cyclization of a suitable precursor to give the *N*-oxide product or (ii) direct oxidation of the parent heterocyclic base.[3,4] These two approaches suffered from either the non-availability of the proper precursor or the formation of mixtures of products (mono and di-*N*- oxides) or extensive oxidation beyond the desired level.[5,6] The setting changed in 1965 when we reported[7] a simple efficient one-step synthesis for quinoxaline 1,4-dioxides (3) from the reaction of benzofurazan oxide (1) and enamines (2). The reaction of 1 with enolate anions was found also to yield 3, phenazine 9,10-dioxides or benzamidazol *N*-oxides.[8,9] Thereafter, the reaction was referred to in the chemical literature as the Beirut reaction[2] in honor of the city in which it was discovered.

We reviewed this reaction in 1976,[10] and later on a clear and concise account was reported as part of a review of benzofurazan oxide (benzofuroxan, 2,1,3-benzoxadiazole 1-oxide) chemistry.[11] The present review attempts to cover further developments in this exciting area of aromatic *N*-oxide chemistry.

Concomitant with the continuous interest in the basic aspects of the chemistry of this class of aromatic *N*-oxides is a sustained effort, especially by the pharmaceutical sector of chemical industry, which resulted in the synthesis of a large number of new derivatives of these compounds for the purpose of examining their antibacterial activity. Indeed, two quinoxaline 1,4-dioxide derivatives are currently marketed as animal feed additives (antibacterials and growth promotants) under the trade names of Carbadox (or Mecadox, 4) and Alaquindox (5).



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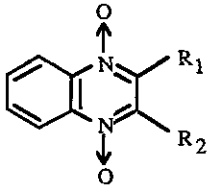


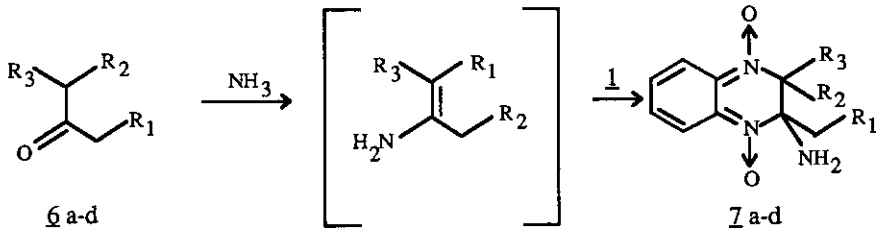
4. R_1= CH=NNHCOOCH$_3$, R_2=H
5. R_1= CONHCH$_2$CH$_2$OH , R_2=CH$_3$

2. a) Reactions with Enamines

Although the first report[7] of the Beirut reaction used simple enamines to react with benzofurazan oxide (1), it has been shown that the preparation of enamines is often unnecessary and quinoxaline 1,4-dioxides can be prepared from a solution of the appropriate ketone or aldehyde, benzofurazan oxide and ammonia[12] or a secondary amine.[13] It may well be that such reactions proceed through enamine intermediates formed *in situ*. An interesting recent example of where an enamine is formed *in situ* is demonstrated by the reaction of ammonia, benzofurazan oxide (1) and ketones (6a-d), to give the *o*-quinoid 2-amino-2,3-dihydro-2,3,3-trialkylquinoxaline 1,4-dioxides (7) in fair to good yields.[14] Additional examples that demonstrate the formation[14] of enamines *in situ* are provided by the formation of dihydroquinoxaline 1,4-oxide (8).

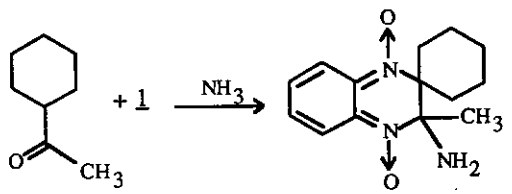
We have found that a warm acetonitrile solution of cyclohexanone or cyclopentanone or cyclobutanone or acetone reacts instantaneously with 1 upon the dropwise addition of a

secondary amine (pyrolidine or diethylamine) to give the corresponding quinoxaline 1,4-dioxide. Better yields are obtained if the reaction temperature is maintained slightly below the boiling point of the solvent. The products precipitate as pastes within minutes of reaction initiation which is manifested by the development of deep red coloration. The ease of these reactions is consistent with an *in situ* formed enamine intermediate.



6 a-d 7 a-d

	R1	R2	R3
a	H	CH_3	CH_3
b	H	CH_3	C_2H_5
c	$CH(CH_3)_2$	CH_3	CH_3
d	n-C_3H_7	CH_3	CH_3



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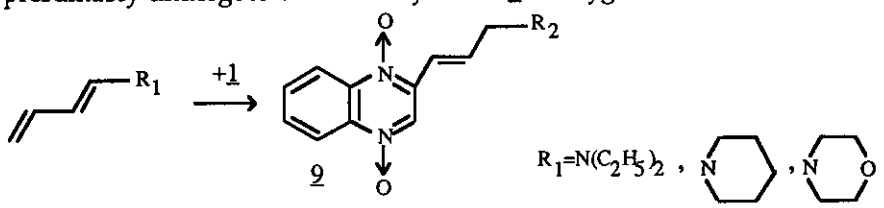
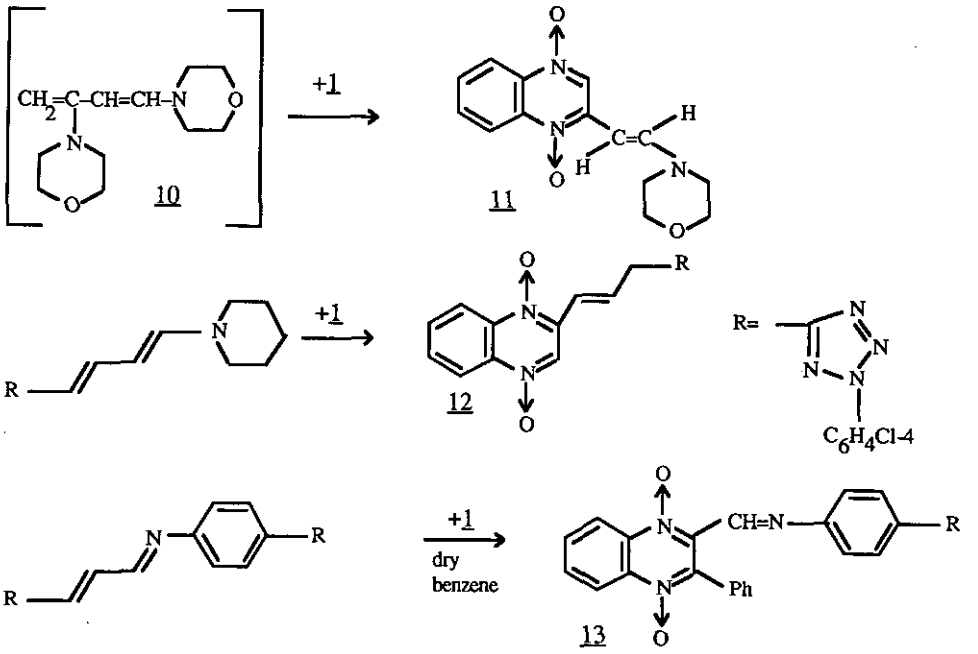
b) Reaction with Dienamines and 1-Aza-1,3-butadienes

A few reactions of dienamines and 1 have been reported.[15-17] In all these three examples, the bright red products (9,11,12) result from a reaction with the double bond holding an amino group. It should be pointed out that in the case of dienamine (10), its *in situ* formation provided the best explanation for the production of 11. 1-Aza-1,3-butadiene derivatives are reported[18,19] to react with benzofurazan oxide (1) *via* the carbon-carbon double bond to give quinoxaline 1,4-dioxide aldimines (13) in good yields. No mechanism is offered to explain the formation of the products (13), yet a simple ene addition to 1 leads to a dihydroquinoxaline 1,4-oxide which presumably undergoes oxidation by either 1 or oxygen to lead to 13.

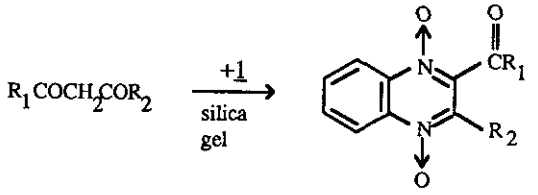


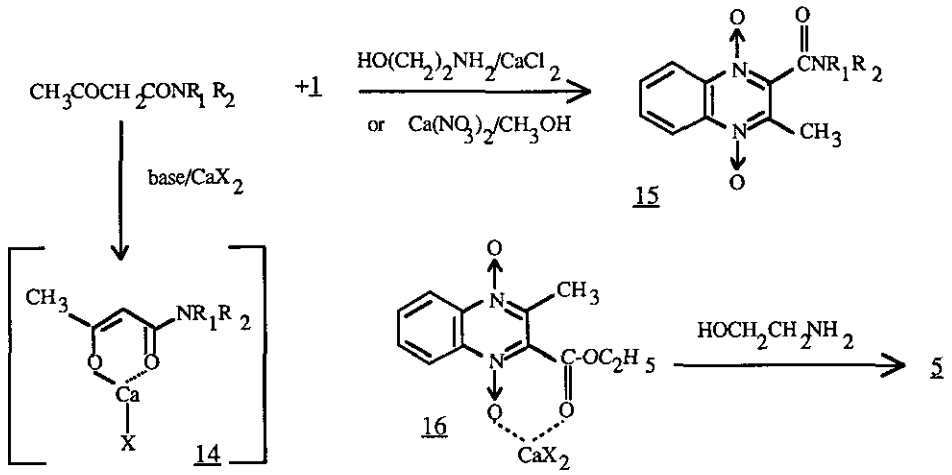
9 R_1=N(C_2H_5)$_2$,



c)Reaction with Enolates, Phenolates and α,β–Unsaturated Ketones

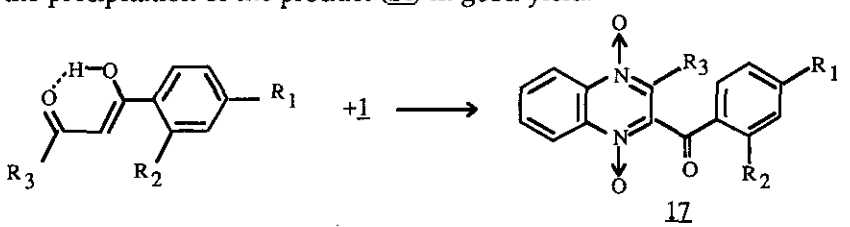
Although many examples of the reactions of enolate and phenolate anions were cited in previous reviews,[10,11] additional new aspects of these reactions include the use of silica gel as a catalyst in the preparation of a number of quinoxaline 1,4-dioxides in yields between 16- 90%.[19] Another interesting recent finding reports an improved and efficient method for the preparation of quinoxalinecarboxamide 1,4-dioxides (15) from 1 and acetoacetamides in the presence of calcium salts[20] in yields of 61-96%. It is suggested that calcium chelate (14) is an important intermediate in this reaction. It is noteworthy that Alaquindox (5) is obtained in 90% yield using ethanolamine/$Ca(NO_3)_2$. Furthermore, it is found that calcium salts enhance the reactivity of quinoxaline 1,4-dioxide 2- or 3-carboxylates. Thus, the reaction of 16 with ethanolamine in the presence of calcium chloride yields 5 in 75% yield which, without the use of $CaCl_2$, drops to 5%.

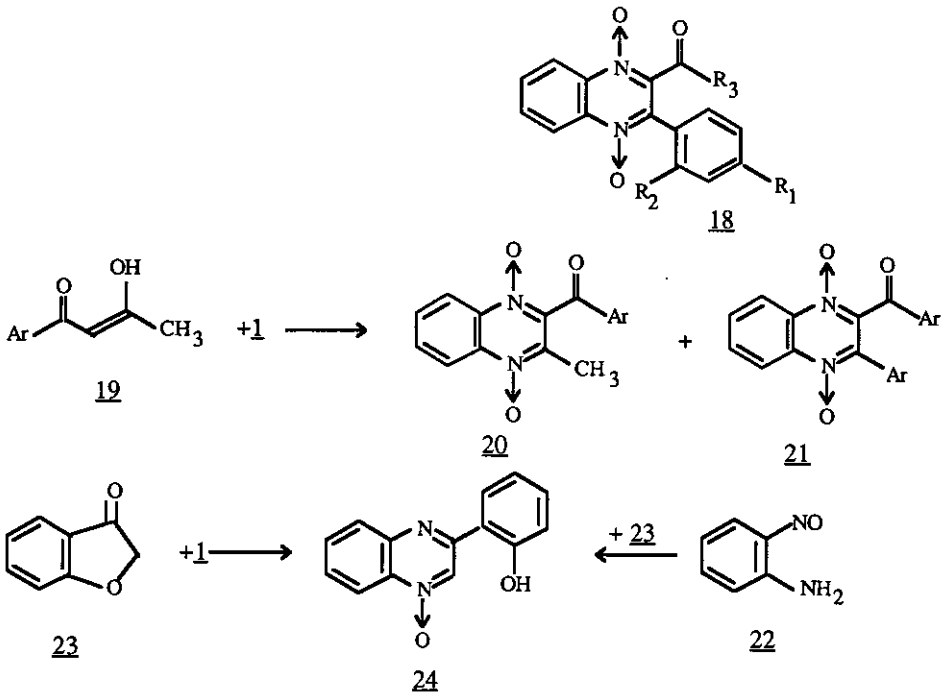




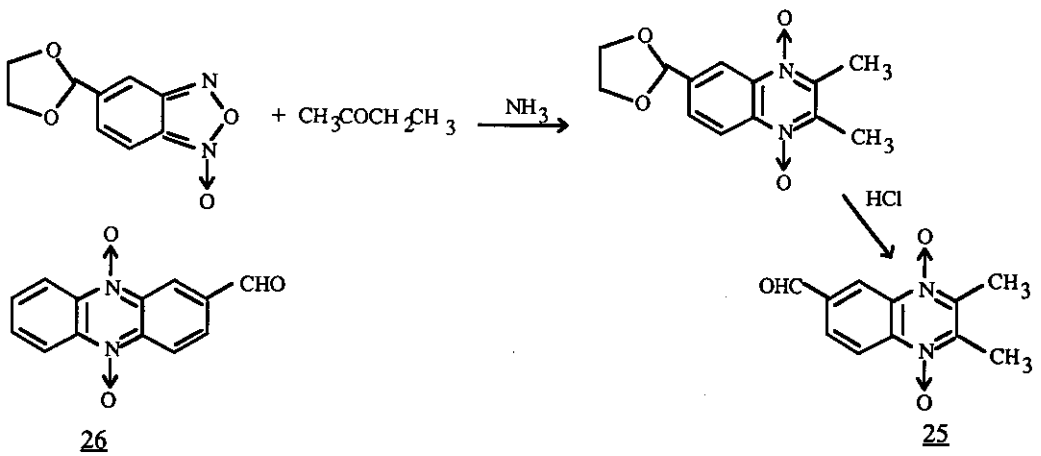
In an earlier study,[21] the reaction of unsymmetrical 1,3-diketones with 1 was investigated and it was found that the regiospecificity of cyclization was influenced by steric and polar factors in the diketone : for example, when R_3= CH_3, R_1= R_2= H, only 17 is formed whereas when R_3=*t*- C_4H_9, R_1=R_2=H, 18 is the only product. However, when R_1=NO_2 , R_2=H, R_3=CH_3 , C_2H_5 or iso-C_3H_7, 18 is the only product. In a closely related work,[22] it was found that the structure of the aryl group in 19 was of significance in determining the outcome of the reaction with 1. When Ar= 2-furyl or 2-pyridyl, quinoxaline 1,4-dioxide (20) and (21) (minor product) were isolated compared with only 20 if Ar= 2-naphthyl or 2-phenyl.

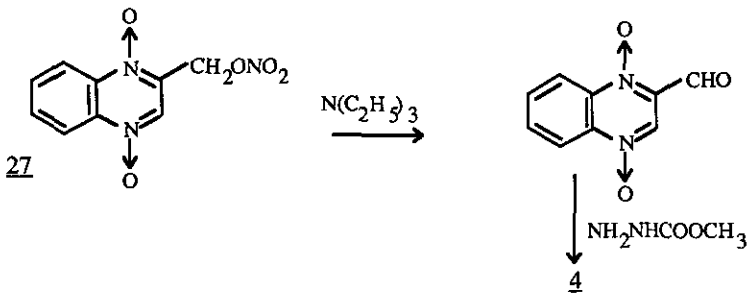
In a previously reported[23a] reaction of 1 with benzofuran-3(2*H*)-ones, *o*- nitrosoaniline (22) was postulated as an intermediate in this reaction. *o*- Nitrosoaniline (22), was prepared by us by two methods: the first method[23b] involved the reduction of *o*- quinonedioxime with the diethylamine, the second consisted[24] of oxidation of *o*- phenylenediamine with hydrogen peroxide. Indeed, when a methanolic solution of *o*- nitrosoaniline (22) and benzofuran-3(2*H*)-one (23) was treated with 5% methanolic potassium hydroxide, a vigorous reaction ensued with the precipitation of the product (24) in good yield.





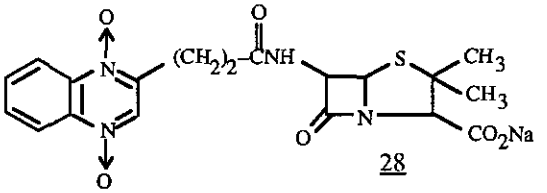
The commercially available quinoxaline 1,4-dioxide derivative, Carbadox (4), possesses a masked carboxaldehyde functionality at position 2. Introduction of this functionality at position 6 in quinoxaline dioxide (25) and at position 2 in phenazine 9,10-dioxide (26), was described[25,26] in two reports and a number of derivatives of 25 and 26 were prepared. In contrast with the previous approach, we prepared Carbadox (Mecadox, 4) by oxidative elimination of nitrous acid from nitrate ester (27).[27]

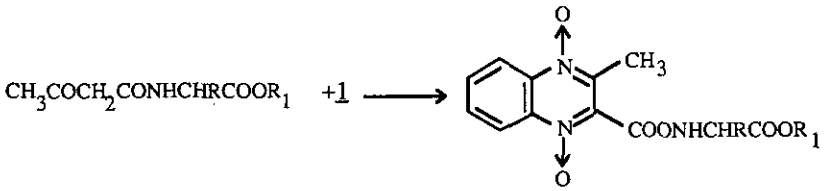




Elaboration of substituted quinoxaline 1,4-dioxides probably is best exemplified by adjoining a penicillin or a cephalosporin to a quinoxaline 1,4-dioxide (28). This was accomplished through a reaction between an acid chloride or mixed anhydride of a number of quinoxaline 1,4-dioxide, carboxylic acids with 6-aminopenicillinic acid or 7-aminodesacetoxycephalosporinic acid.[28] Another example is the introduction of an amino acid as the side chain.[29]

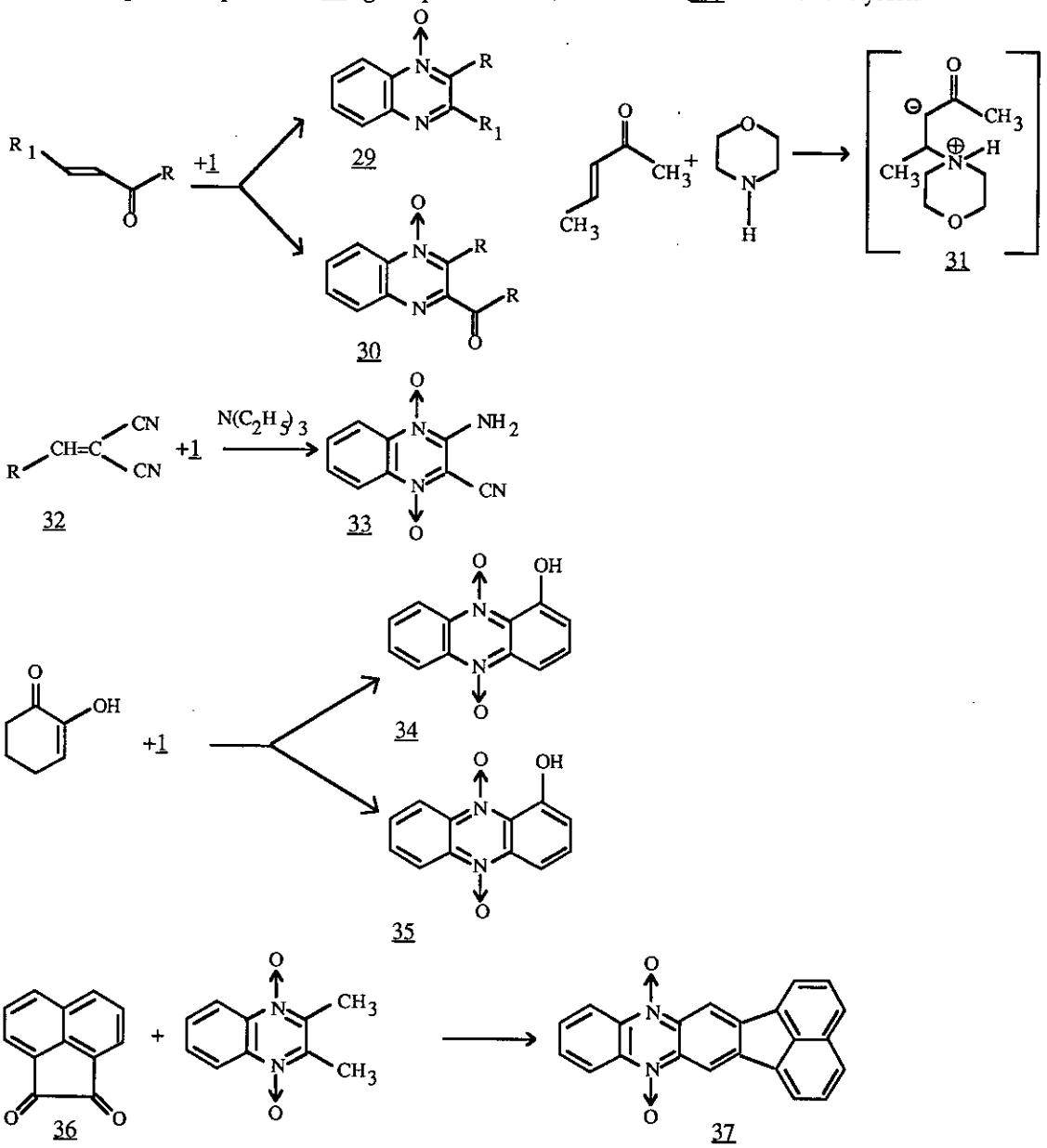
A curious report[30] describes a reaction of 1 with alkynes in the presence of triethylamine, diethylamine or butylamine to give quinoxaline 1,4-dioxide. In view of the fact that 1 reacts with diethylamine to give quinoxaline 1,4-dioxide among other products,[31] the role of alkynes in the previous reaction is suspect and requires clarification.





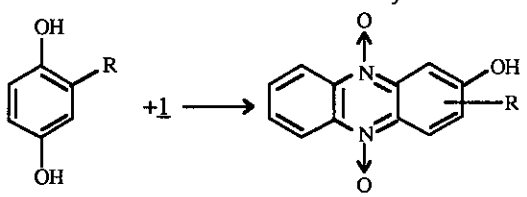
An interesting study[32] showed that 1 reacts with enones and amines to give quinoxaline monoxides. Secondary amines lead to product (29) whereas primary amines give quinoxaline monoxides (30). A mechanism which involves the intermediacy of 31 was postulated. While the reaction of 1 with enones has the advantage of giving specific quinoxaline monoxides, the yields are generally low (13-35%) and several enones have failed to give any isolable quinoxalines. Another closely related reaction was reported[33] where 1 reacted with arylidenemalononitriles (32) to give 33 via a Michael addition intermediate from the reaction of the amine with ene (32).The

utilization of benzofurazan oxide (1) in the preparation of phenazine monoxides and 9,10-dioxides was examined further. Cyclohexane-1,2-dione reacted with 1 to give a mixture of 34 and 35. On the other hand, the reaction of 2,3-dimethylquinoxaline 1,4-dioxide in methanolic KOH with acenaphthenequinone (36) gave phenazine 9,10-dioxide (37) in excellent yield.[34]

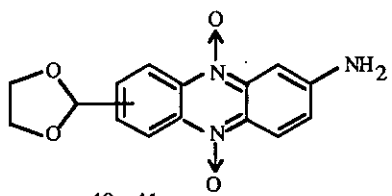


Moreover, the steric effect of monosubstituted (R=OCH_3, CH_3 ,Br, Cl, $COCH_3$, CN and CO_2H) hydroquinones on the substitution pattern and the product ratio of phenazine 9,10-dioxides to monoxides was studied. It is interesting to note that in the case of R=CO_2H, the product was 39 (R=H). Some of the products were identified after their reaction with diazomethane and subsequent reduction with H_2/Pd-C to the corresponding phenazines.[35] Another extension[36] of the reaction of 1 with phenolate anion was described through the reaction of 4-aminophenol with 5(6)-1,3-dioxolan-2-yl-benzofurazan oxide to give a mixture of 8-(1,3-dioxolan-2-yl)-2-aminophenazine 5,10-dioxide (40) and 7-(1,3-dioxolan-2-yl)-2-aminophenazine 5,10-dioxide (42) in a 2:1 ratio.

Reactions of 1 with carbanions from alkyl nitriles and nitroalkanes were reported[37-39] to give quinoxaline 1,4-dioxide (43) and benzimidazole *N*- oxides (44) and (45) respectively. It should be mentioned that an improved method for the preparation of 1-hydroxybenzimidazole 3-oxide (46) was described from the reaction of *o*- benzoquinone dioxime with aromatic and heteroaromatic substituted aldehydes in the presence of an excess of hydrochloric acid.[40]



38 39



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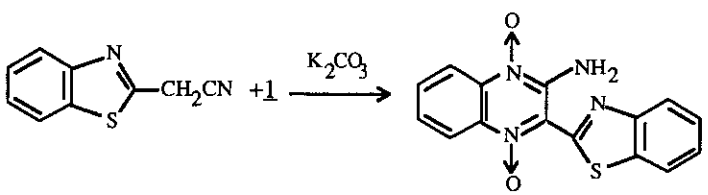
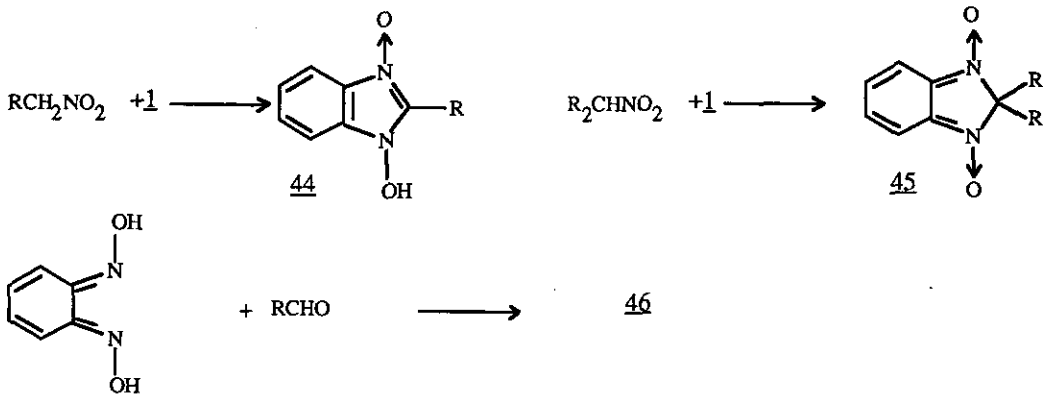


42 43

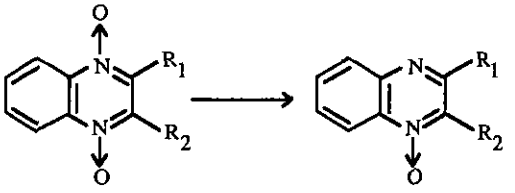


Reactions of quinoxaline 1,4-dioxides and other *N*-oxides

Most of the reactions of quinoxaline 1,4-dioxides involve the –C=N→O function directly (reduction and cycloaddition reactions) or ring substituents that are influenced by this functionality. The reactions described here are presented in a schematic form with minimal discussion to save space. It is noteworthy that most of the reactions in this section constitute an elaboration on the ring substituent(s) which lead(s) to the introduction of an additional heterocycle to the quinoxaline ring. Indeed, aziridino, furano, pyrrolo, pyrazolo, pyridino, diazino, triazolo, tetrazolo, diazepino, and diazoxepino rings were constructed.

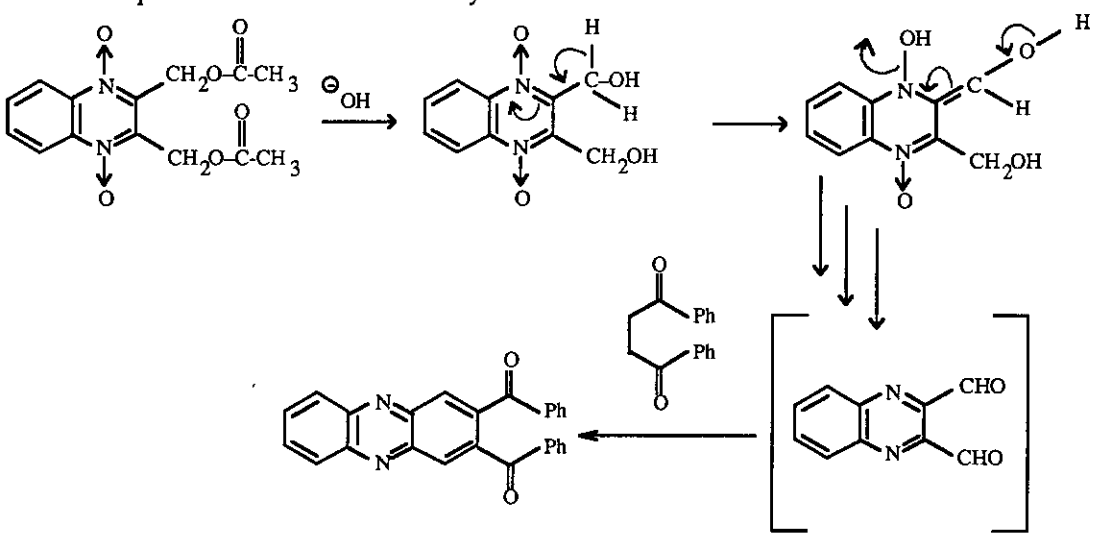
a) Reduction Reactions

Reduction of quinoxaline 1,4-dioxides to quinoxalines has been accomplished by a variety of recently introduced reducing agents most of which act under mild and simple conditions and give products in fair to good yields. These reducing agents are: $Cl_3SiSiCl_3$, $(CH_3)_3SiI$,$(CF_3CO)_2O$-NaI, and $TiCl_4$-Zn, $TiCl_4$/NaI;[41a,b] $NaHPO_3$-Pd/C; NaI-pyridine/SO_3, and P_2I_4;[42] $TiCl_4$ and Ti(o)[43](phenazine 9,10-dioxide to phenazine). Furthermore, some reducing agents ($(CH_3O)_3P$, L-ascorbic acid and PCl_3) were reported to be selective in converting a quinoxaline 1,4-dioxide into the corresponding mono *N*- oxide. However, selectivity appears to depend on the nature of substituents at positions 2 and/or 3.



Reagent	Product		Ref.
$(CH_3O)_3P$	R_1= COR, R_2 = CH_3		44
$(CH_3O)_3P$	R_1= CF_3 , R_2 = CH_3		44
$(CH_3O)_3P$	R_1= CH_3 , R_2 = CONHR	(R= $CHCH_3COOCH_3$)	45
L-Ascorbic acid	R_1= CH_3 , R_2 = R		46
PCl_3	R_1= H, R_2 = CONHR	(R= $CHCH_3COOCH_3$)	47
$Na_2S_2O_4$ - $MgSO_4$	R_1= CH_3 , R_2 = COR	(R= CH_3)	48

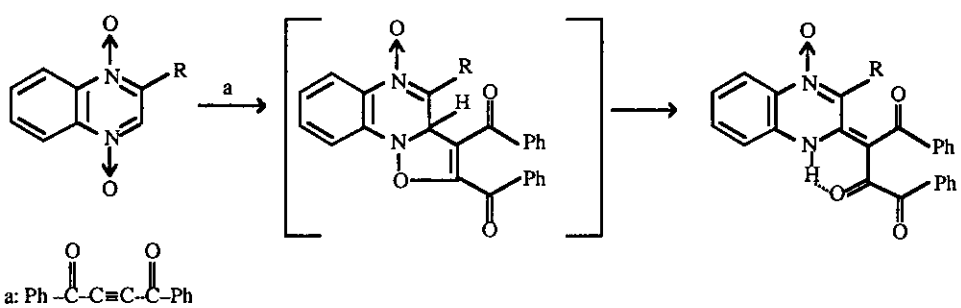
In this connection, a deoxygenation of quinoxaline di or mono *N*- oxides can be affected in an auto-oxidation reduction reaction. We have made use of this type of reaction to convert a carbinol at position 2 or 3 into an aldehyde or a ketone.[49]



Quinoxaline 1-oxides were reduced to quinoxalines by trimethylsilyl cyanide in the presence of base in tetrahydrofuran.[50] 2(1*H*)-Quinoxalinone 4-oxide can be reduced to 2(1*H*)-quinoxalinone by $NaBH_4$ or $NaHSO_3$ in 70-84% yield.[51]

b) Cycloaddition

Ref. 52



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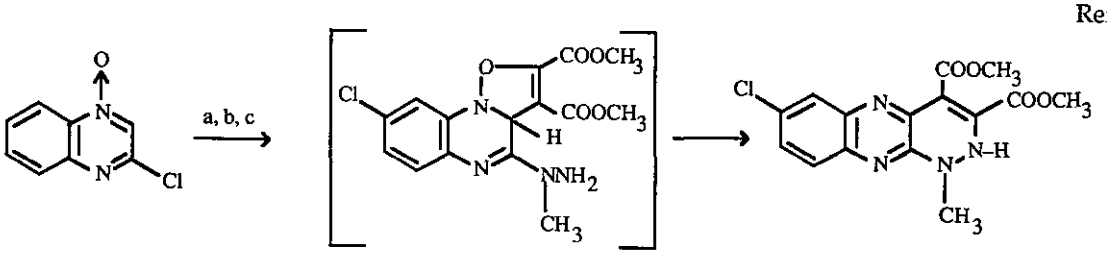
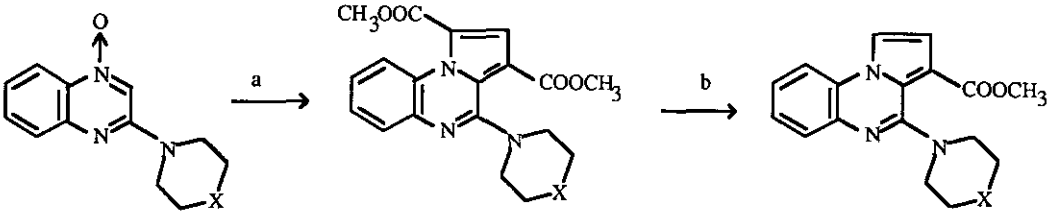


a: NH_2NHCH_3; b: $CH_3OOCC{\equiv}CCOOCH_3$(DMAD) ; c: H_2O

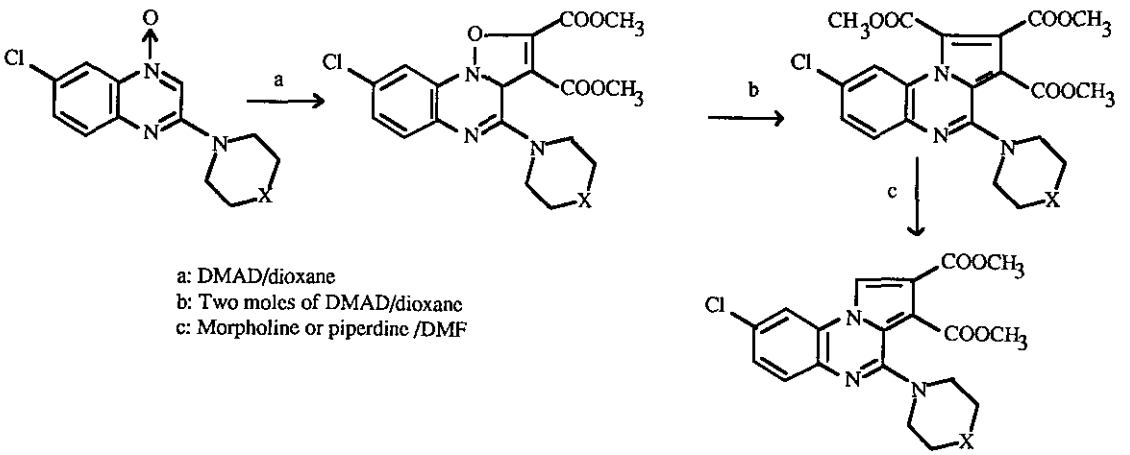
Ref. 54



X= CH_2
X= O

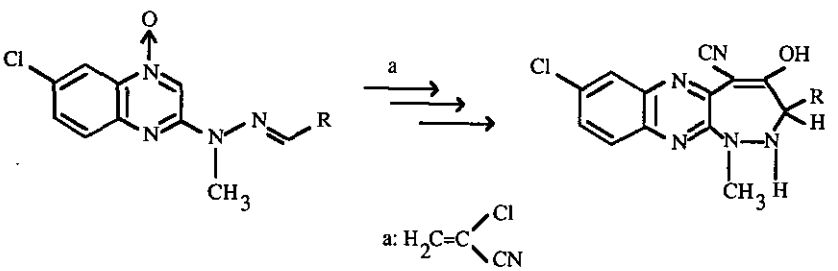
a: 2-fold molar amount of $HC{\equiv}CCOOCH_3$
b: piperdine or morpholine /DMF-H_2O

Ref. 55



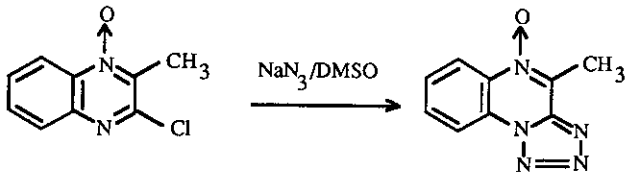
a: DMAD/dioxane
b: Two moles of DMAD/dioxane
c: Morpholine or piperdine /DMF

Ref. 56



a: $H_2C{=}C(Cl)(CN)$

Ref. 57



c) Reactions of Ring Substituents

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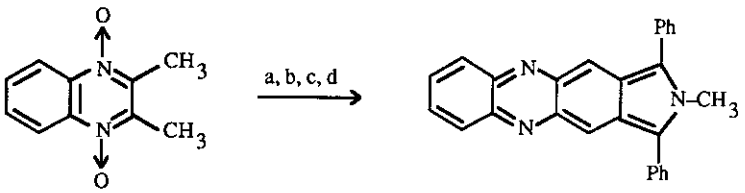
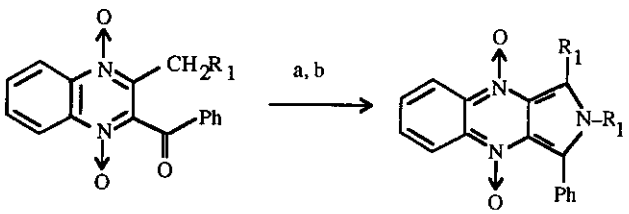


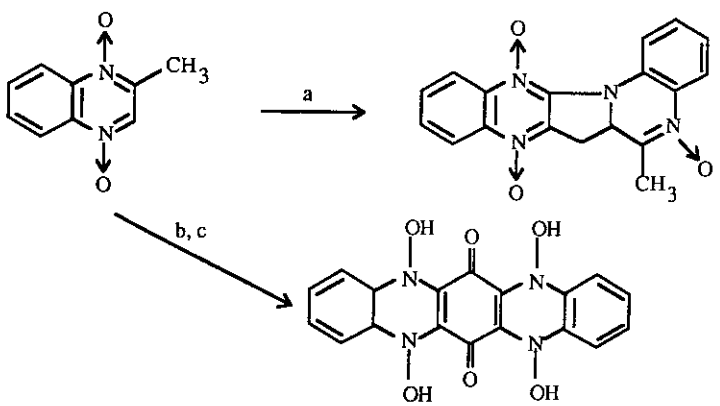
a: $Br_2/CH_3COOC_2H_5$; b: KOAc /DMSO; c: $PhCOCH_2CH_2COPh$; d: $CH_3NH_2/NaBH_4$

Ref. 59



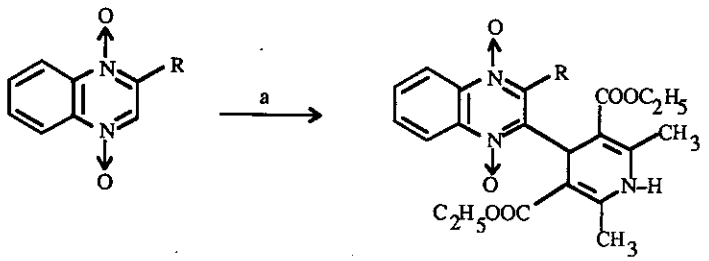
a: $Br_2/CH_3COOC_2H_5$; b: RNH_2

Ref. 60,61



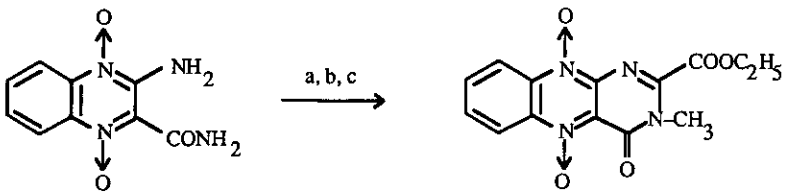
a: HX/oxidation; b: ^-OH; c: $K_2Cr_2O_7/H^+$

Ref. 62



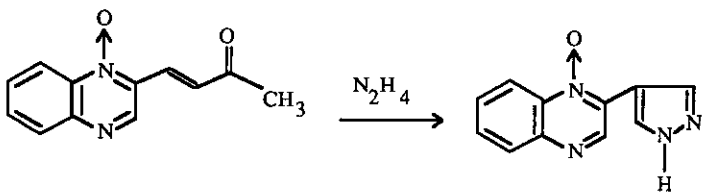
a: $CH_3COCH_2COOC_2H_5/NH_3$

Ref. 63

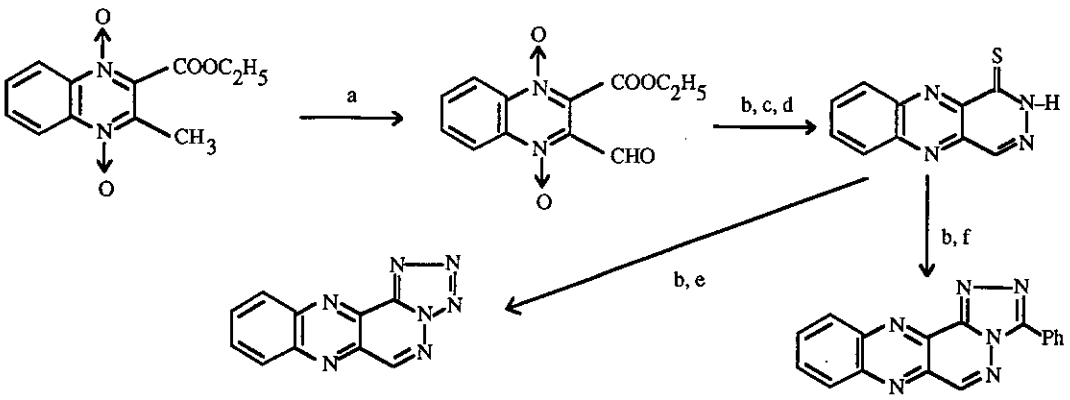


a: $Na_2S_2O_4$; b: $(C_2H_5OOC)_2$; c:CH_3I

Ref. 64

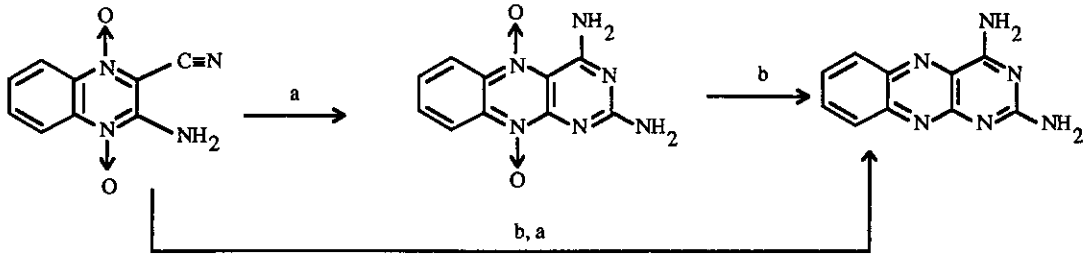


Ref. 65



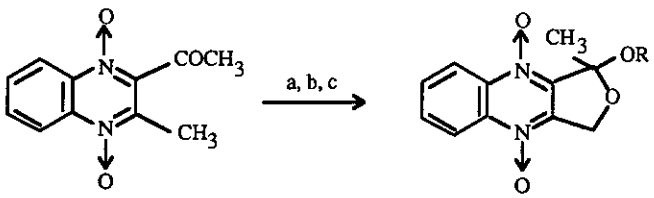
a, SeO_2; b: N_2H_4; c: $Na_2S_2O_4$; d: P_2S_5; e: $NaNO_2/H^+$; f: PhCOCl

Ref. 66



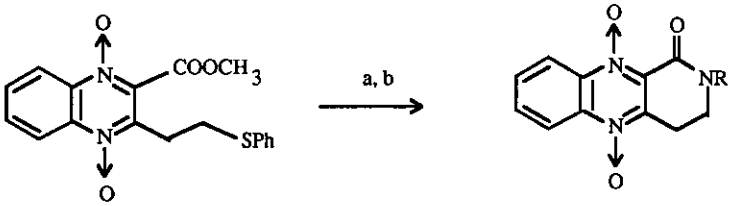
a: $NH_2C(=NH)NH_2$; b: $Na_2S_2O_4$

Ref. 67



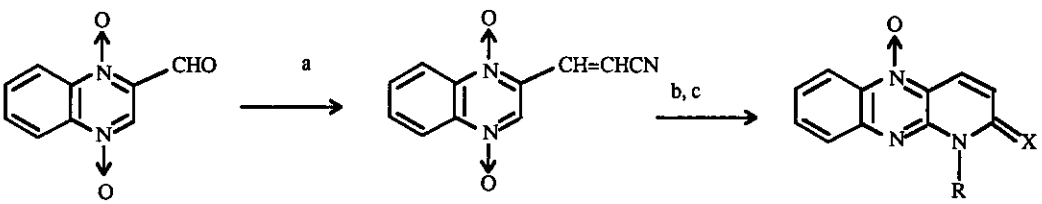
a: Br_2/CH_3OH; b: KOAc/KI/DMF; c: Conc. HCl or H_2O (R=H); d: HCl(g)/ROH (R=CH_3, C_2H_5, CH_2Ph)

Ref. 68



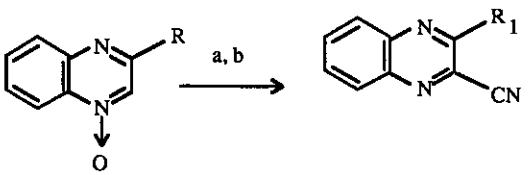
a: MCPBA; b: RNH_2/CH_3CN

Ref. 69

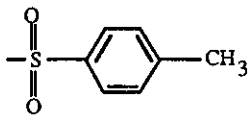


a: TEA/$(C_2H_5O)_2P(O)CH_2CN$;b: RNH_2, (X=NH);c: C_2H_5OH/OH^- (X=O)

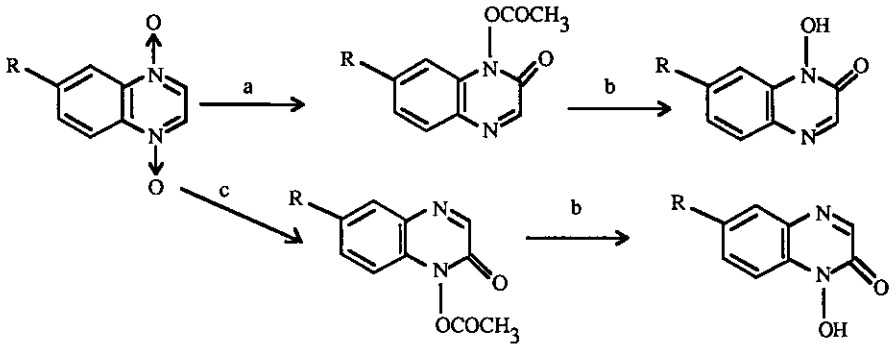
Ref. 70



a: $(CH_3)_3SiCN$/DBU (R=R_1);

b: R=  (R_1=CN)

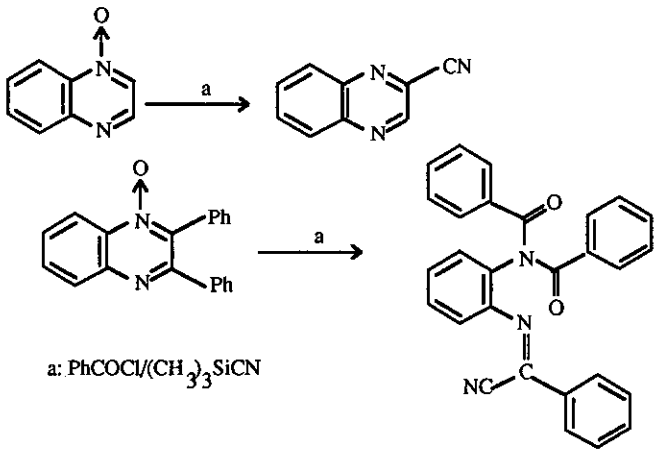
Ref. 71



R=Cl; a: Ac_2O; b:H_2O;

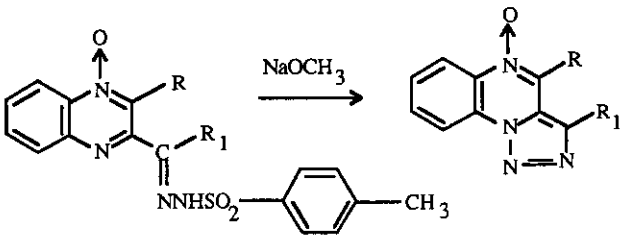
R=H, CH_3O, C_2H_5O, or CH_3; c:Ac_2O; b:H_2O

Ref. 72

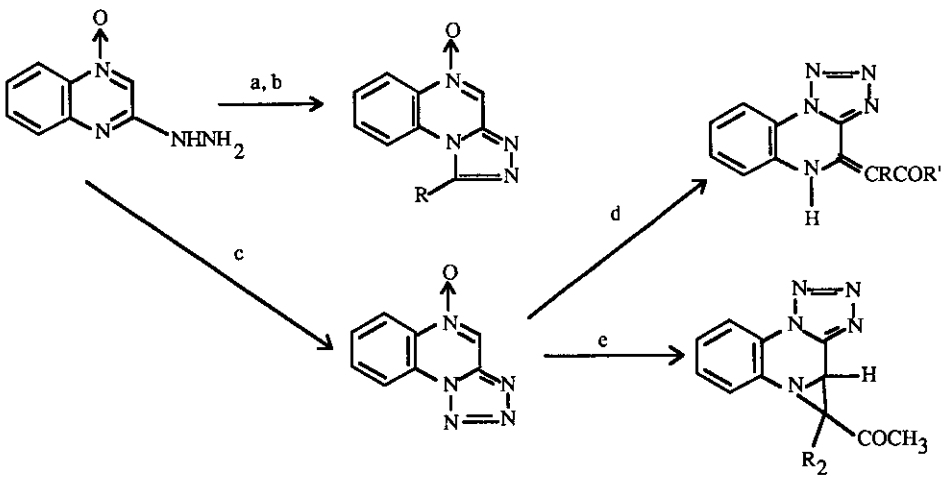


a: $PhCOCl/(CH_3)_3SiCN$

Ref. 73a



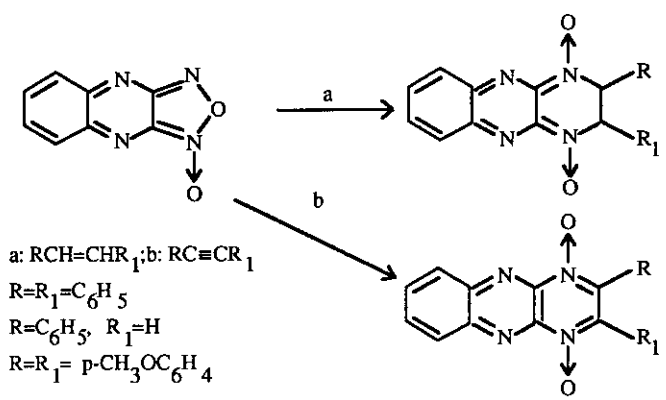
Ref. 73b,74



a: triethyl othoformate (R=H); b: CH_3COOH ($R=CH_3$); c: diazotization;

d: carbanion of β-diketones and β-keto esters; e: $R_2CH(COCH_3)_2$ ($R_2=CH_3$)

Ref. 75



a: $RCH=CHR_1$;b: $RC\equiv CR_1$

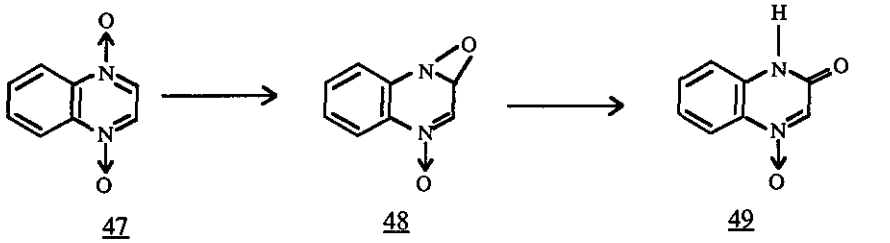
$R=R_1=C_6H_5$

$R=C_6H_5$, $R_1=H$

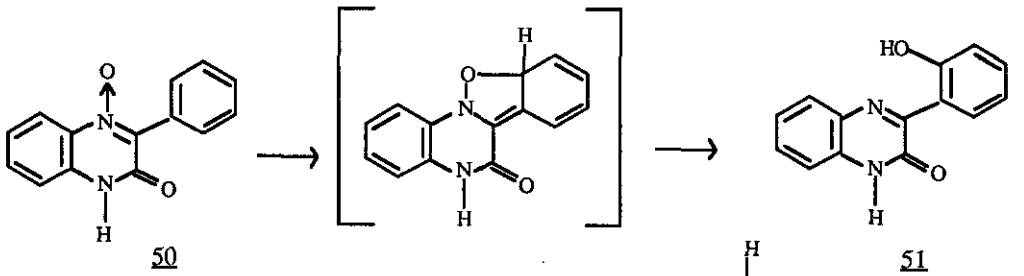
$R=R_1=$ p-$CH_3OC_6H_4$

d)Photochemical Reactions

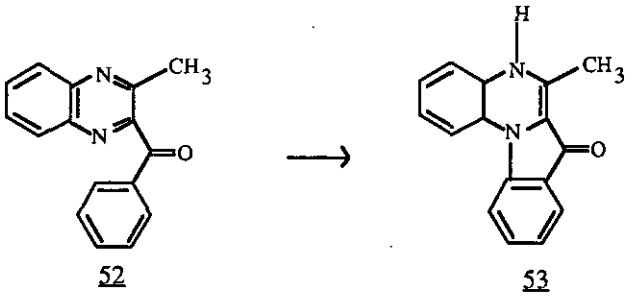
From the flash photolysis of quinoxaline 1,4-dioxide (47) in neutral aqueous solution, it was concluded that the conversion of 47 into 4(2*H*)-quinoxalinone oxide (49) involves the intermediacy of oxaziridine (48).[76] Furthermore, it is shown that oxaziridine (48) reverts back to 47 in addition to producing 49. The relative efficiency of formation of 47 and 49 is 3:2. The production of 49 is enhanced in acidic solution. Photolysis of a number of 4-quinoxalinone 4-oxides was reported;[77] for example, 3-phenyl-2-quinoxalinone 4-oxides (50) rearranged to quinoxalinone (51). Fast photochemical reaction of quinoxaline derivatives is demonstrated by the rearrangement of 52 into the purple methylindoloquinoxalinone (53).[78]



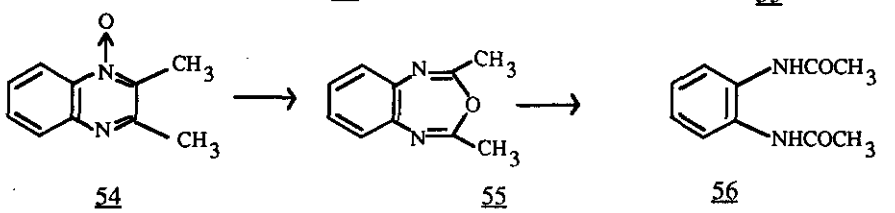
47 48 49



50 51

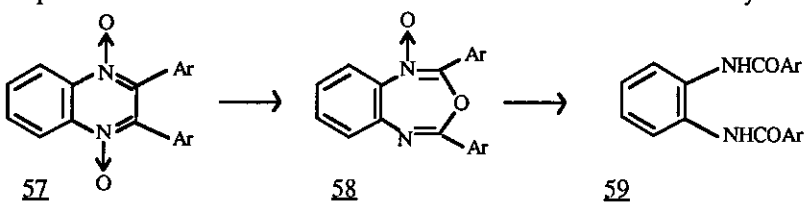


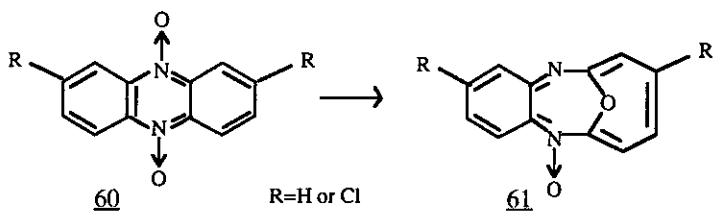
52 53

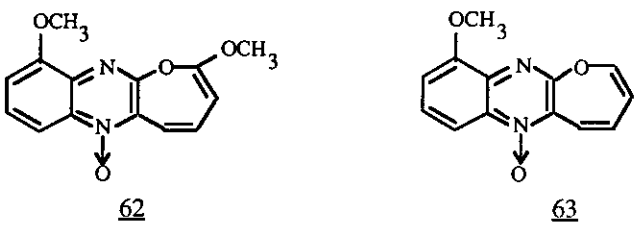


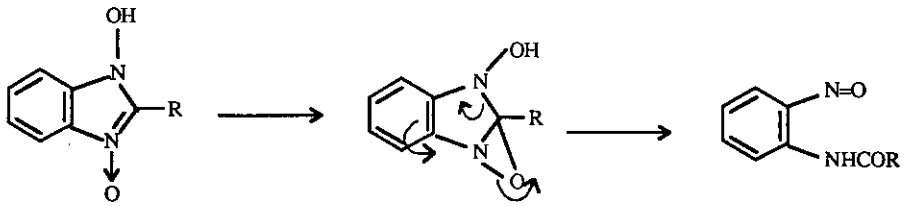
54 55 56

The photochemical products from irrradiation of quinoxaline 1-oxide depended on the solvent used and the nature of substituents at positions 2 and 3. For example, the solvent effect on the irradiation of 2,3-dimethylquinoxaline 1-oxide (54) in cyclohexane gave 2,4-dimethyl-3,1,5-benzoxadiazepine (55) as the main product[79] whereas in water, the hydrolysis product of 56 is obtained. In comparison with earlier studies that reported intractable mixtures, isolable products have been obtained from the photolysis reaction of a number of 2,3-diarylquinoxaline 1,4-dioxides (57).[80] The reaction involves a deoxygenation step followed by hydrolysis to give 59. Irradiation of some phenazine 9,10-dioxide (60) in various organic solvents was studied in detail. The reaction occurs from the lowest excited singlet state and in an intramolecular process. Benzo[*c*]-2-azoxy-5-aza-1,6-oxido[10]annulene derivatives (61) were formed.[81] On the other hand, photoisomerization of 1-methoxyphenazine 9,10-dioxide in protic solvents gave three products two of which are oxepinoquinoxaline *N*- oxides (62) and (63).[82] Furthermore, the photochemistry of phenazine mono *N*- oxide received earlier considerable study.[83]



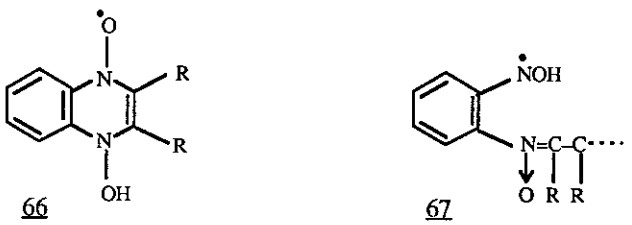






64 65

The structures of some 2,3,6(7)-trisubstituted quinoxaline 1,4-dioxides were assigned through their photochemical rearrangement into 1,3,5(6)-trisubstituted benzimidazolones.[84] Interestingly, the photolysis of some 1-hydroxybenzimidazole 3-oxides (64) gave the corresponding nitrosoaniline derivatives (65).[85] Studies aimed at the elucidation of structures of intermediates in the photolysis of quinoxaline 1,4-dioxides were reported using ESR and ENDOR techniques. Evidence supports the intermediacy of nitroxyl radical (66) in the photolysis of a number of 2,3-distributed quinoxaline 1,4-dioxides in protic organic solvents.[86] In another study,[87] intermediate (67) which appeared in the original publication in the incomplete form shown below was suggested, however no mechanistic justification was given to explain the cleavage of the heteroring that lead to 67. If the latter is formed, it would be difficult to explain the formation of benzimidazalones *via* this intermediate.



66 67

This review will not include the large number of reports on the antibacterial activities of quinoxaline 1,4-dioxides, nor will it list the extensive literature of patents in this area, however the interesting work on the relationship between reduction potentials and antibacterial activity should be cited, especially a hypothesis paper that discusses an integrated concept of amebicidal action through electron transfer and oxyradicals.[88] Furthermore, this group of researchers has reported cyclic voltammetry data for a number of phenazines, phenazine *N*- oxides, quinoxalines and quinoxaline *N*- oxides and correlated these data with structure. Some relationships exist

between reduction potential and reported antimicrobial activity, and a possible mechanism of drug action is proposed.[89]

It is clear from this review that the area of quinoxaline *N*- oxides continues to be of research interest to many heterocyclic chemists.

ACKNOWLEDGEMENT

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