SYNTHESIS AND REACTIONS OF QUINOXALINES

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By

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DECEMBER 1990

CERTIFICATE

Certified that the thesis entitled **"Synthesis and Reactions of Quinoxalines"** submitted by Shri Keshav Mohan is a bona fide work done by him under my guidance in the Department of Applied Chemistry, Cochin University of Science and Technology, and no part of this has been presented for any other degree.

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Chapter 1

INTRODUCTION

1. INTRODUCTION

Studies on the synthesis of new quinoxalines have been of considerable importance because of their interesting chemical as well as biological properties. Quinoxaline derivatives are widely distributed in nature and many of them, such as the antibiotics, levomycin and actinomycin possess very useful biological activity. In addition, a large number of synthetic quinoxalines have also shown antibacterial, fungicidal, insecticidal, antiinflammatory, tranquilizing and antidepresant properties.

The present work describes studies on some new reactions of quinoxaline-2-carboxaldehyde obtained by the periodic acid cleavage of the condensation product of D-glucose with o-phenylenediamine. Quinoxaline-2-carboxaldehyde was also used for the synthesis of a large number of new condensed quinoxalines and heteroaryl quinoxalines. Condensed quinoxalines were obtained by oxidative cyclisation of quinoxaline-2-carboxaldehyde hydrazone and phenylhydrazone using lead tetraacetate. While the hydrazone cyclised to give a condensed v-triazole derivative, the phenylhydrazone produced a pyrazoloquinoxaline (flavazole). The same type of results were also obtained when the hydrazone and phenylhydrazone of 2-acetylquinoxaline were treated with lead

tetraacetate. The different modes of cyclisation may apparently be due to the different mechanisms and the intermediates involved. As both the quinoxaline ring system and the triazole system are independently biologically active, the fused system is expected to have interesting biological properties.

2-Heteroaryl quinoxalines were synthesised by the addition of diazomethane to various anils prepared from quinoxaline-2-carboxaldehyde with different aromatic amines. Condensation of o-phenylenediamine with dehydro ascorbic acid and subsequent reactions also led to a few heteroaryl quinoxalines.

As sulphur containing heterocyclic systems have been reported to possess wide spectrum antibacterial properties, a number of condensed quinoxalines containing sulphur in the ring were obtained by the reaction of thiourea on quinoxaline derivatives. An apparently new heterocyclic derivative, 2-amino-4-oxo thiazino[5,6-b]quinoxaline was synthesised by the reaction of ethyl-2-chloroquinoxaline-3-carboxylate with thiourea. The structures of all the new compounds were established by elemental analysis and also by analysis of their spectral data.

All the newly synthesised compounds and some related compounds were subjected to preliminary screening for their antimicrobial activity. Three different pathogenic species of bacteria, Pseudomonas aeruginosa, Vibrio parahaemolyticus and Bacillus cereus were used for the screening tests. The results are highly encouraging as many new compounds show excellent growth inhibition properties. These compounds will be submitted for a detailed study of their biological activity.

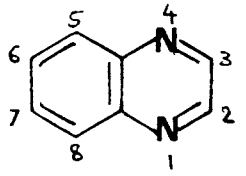
The work thus deals with the chemistry of some rare heterocyclic systems with a wide range of biological activity. As a number of new heterocyclic compounds have been synthesised using both known and new methods, and as some of them have been shown to possess excellent antimicrobial properties, the work provides important information from the aspects of both synthetic organic chemistry and biological studies of heterocyclic systems.

Chapter 2

HISTORICAL REVIEW

2. INTRODUCTION

Quinoxaline (1), which is also called 1,4-benzodiazine, benzoparadiazine and phenpiazine is numbered as



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shown and the 2 and 3 positions which are equivalent are also designated as α-positions. Quinoxalines are, in general easy to prepare and numerous derivatives have been reported in work designed to produce biologically active compounds.[1]

2.2 SYNTHESIS

Various quinoxaline derivatives have been prepared by the following methods:

(i) Condensation of aromatic diamines and α-dicarbonyl compounds.

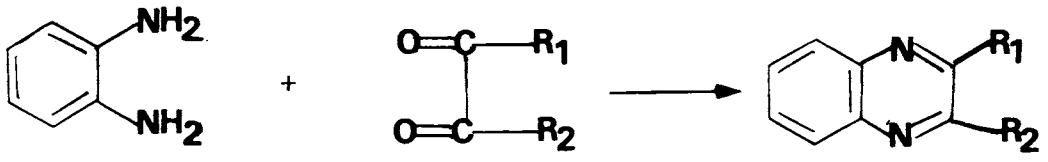
(ii) Intramolecular cyclisation of N-substituted aromatic ortho-diamines.

(iii) Ring transformation of benzodiazapines.

(iv) Condensation of benzofurazan-1-oxide and o-quinone dioximes to form quinoxaline-N-oxides.

2.2.1 From ortho-diamines and ∝-dicarbonyl compounds

The classical synthesis of quinoxalines involves the condensation of an aromatic o-diamine and an ∝-dicarbonyl compound.



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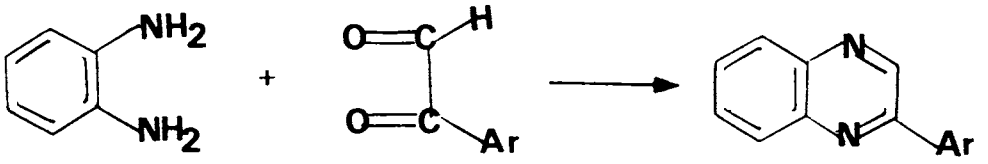
The reaction is very facile and is most widely used for the synthesis of quinoxaline itself and its alkyl substituted derivatives. The condensation of glyoxal with o-phenylene diamine yields quinoxaline in almost quantitative yield.[2] Substituted phenylglyoxals are the starting ∝-dicarbonyl compounds for the synthesis of 2-arylquinoxalines (3) and the corresponding aryl-∝-ketoacids yield 3-aryl-2-quinoxalinones (4).



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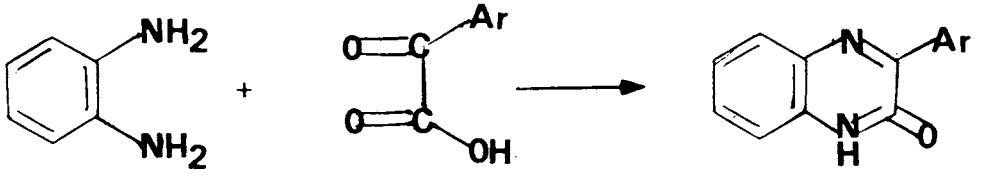

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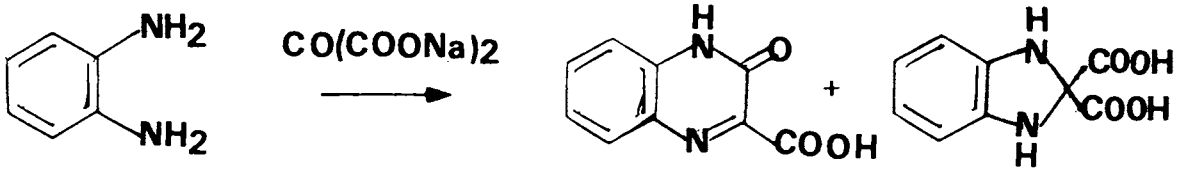
Condensation of mesoxalic acid and o-phenylenediamine proceeds as expected, whereas with sodium mesoxalate an anomalous reaction occurs.[3]



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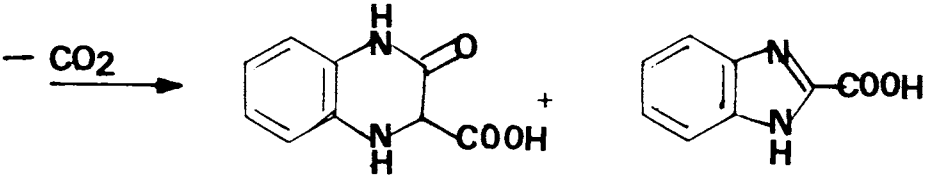

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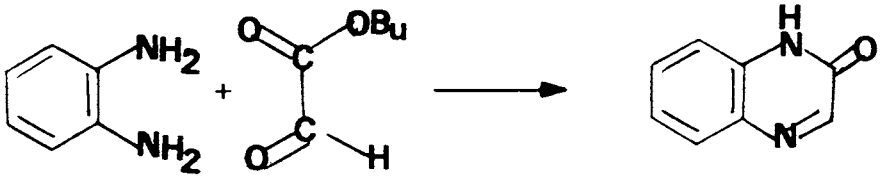
The initial product 2-hydroxyquinoxaline-3-carboxylic acid (5) and 1,2-dihydrobenzimidazole-2,2-dicarboxylic acid (6) undergo an intermolecular hydrogen transfer reaction to yield 1,2,3,4-tetrahydro-3-oxo quinoxaline-2-carboxylic acid (7) and benzimidazole-2-carboxylic acid (8). This type of hydrogen transfer occurs even when a vigorous stream of oxygen is passed through the reaction mixture. 1,2-Dihydro-benzimidazole-2,2-dicarboxylic acid (6) rather than its decarboxylation product is thought to be the reducing agent.[3]

The condensation of n-butylglyoxylate and o-phenylenediamine yields quinoxaline-2-ones (9) in excellent yield.[4]



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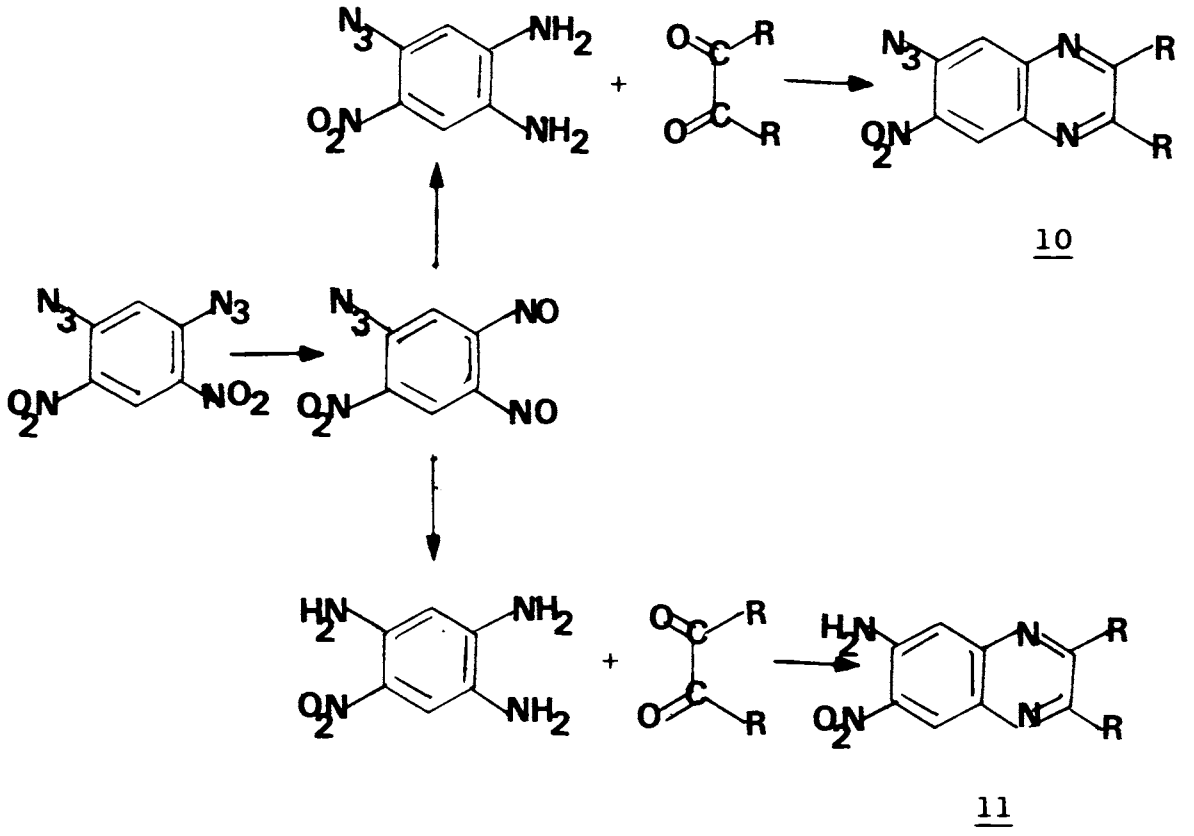
6,7-Disubstituted quinoxalines have been prepared from 2,4-diazido-1,5-dinitrobenzene which on pyrolysis is converted into 2-azido-1-nitro-4,5-dinitrosobenzene with the loss of nitrogen. Partial reduction of it with hydroiodic acid gives 1,2-diamino-4-azido-5-nitrobenzene and

treatment with excess of hydroiodic acid gives 2,4,5-triamino nitrobenzene. Reactions of these compounds[5,6] furnish the corresponding 6-azido-7-nitro (10) and 6-amino-7-nitro-quinoxalines (11).



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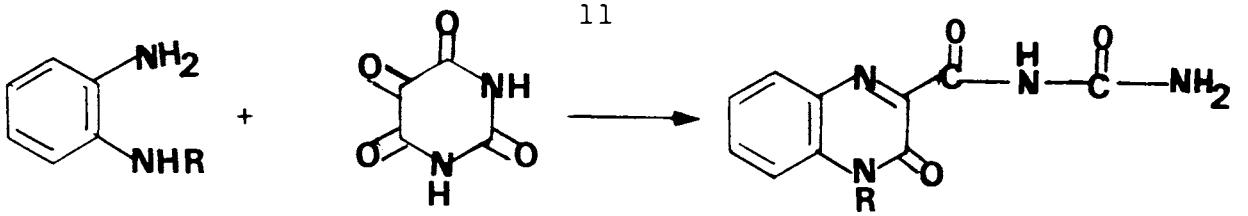
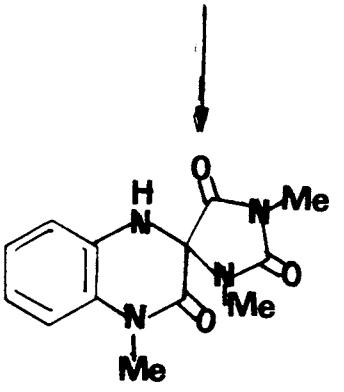
Condensation of o-phenylenediamine or N-methyl-o-phenylene-diamine with alloxan in neutral solution gives the ureides (12) and (13) respectively.[7]



12 R:H

13 R:Me



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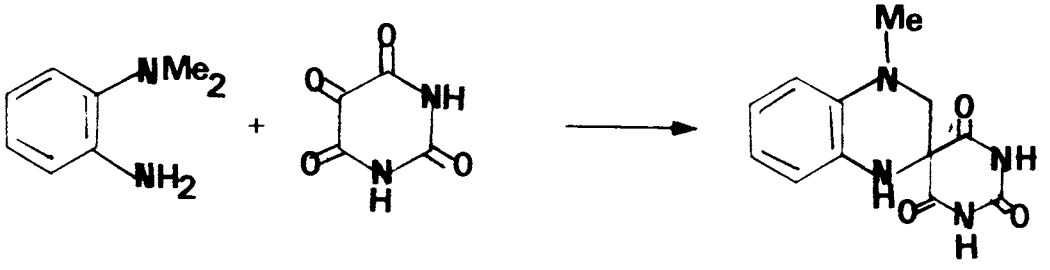
Methylation of 12 in acetone in the presence of potassium carbonate gives the spirohydentoin 14. A most unusual cyclisation occurs when N,N-dimethyl-o-phenylenediamine is treated



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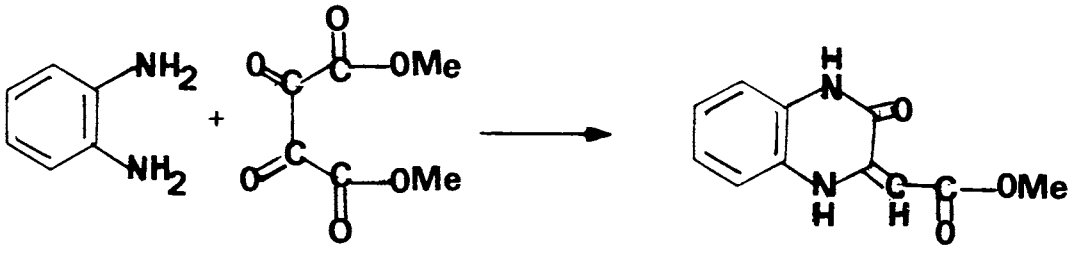
with alloxan in ethanolic solution. This apparently involves an N-methyl group and leads to the formation of spiro-barbituric acid 15, in good yield.[8]

The reaction of dimethyl acetylenedicarboxylate with o-phenylenediamine yields 3-methoxycarbonylmethelene-2-oxo-1,2,3,4-tetrahydroquinoxaline (16).[9]



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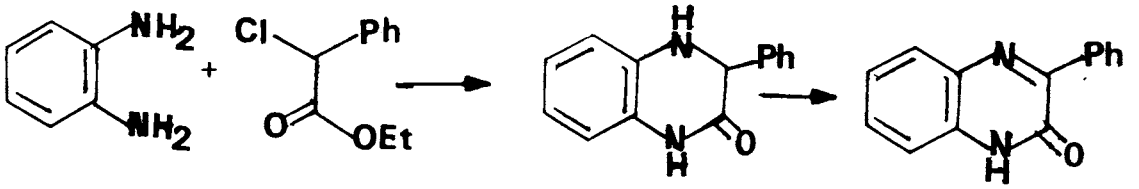

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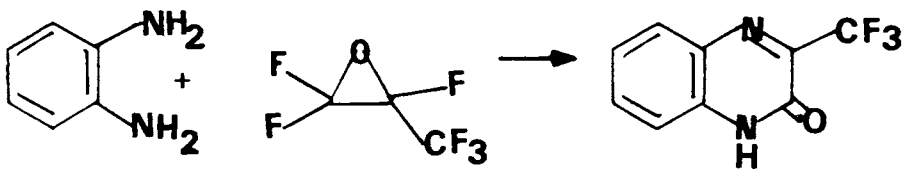
Ethyl-α-chlorophenyl acetate and o-phenylenediamine in the presence of triethylamine give 3-phenyl-1,2,3,4-tetrahydro-2-quinoxalinone[10] (17), which is oxidised to 3-phenyl-2-quinoxalinone (18). 3-Trifluoromethyl-2-quinoxalinones (19) have been obtained from hexafluoropropylene oxide and arylenediamines.[11]



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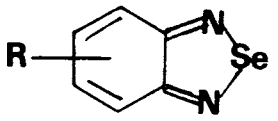
The preparation of quinoxaline derivatives carrying a substituent on the benzene ring requires suitably substituted o-phenylenediamines. These have been prepared by reductive cleavage of appropriately substituted 2,1,3-benzoselenadizoles (20).[12]



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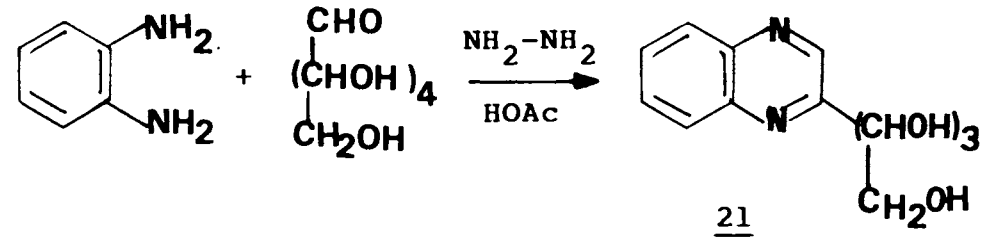
The condensation reactions of aromatic ortho-diamines and sugars and sugar derivatives have been studied in detail and quinoxaline derivatives have been prepared from osones, osonehydrazones and dehydro-L-ascorbic acid.[13,14] In this type of reaction, carbohydrates act as the carbonyl compounds. Glucose condense[14], with o-phenylenediamine

yielding 2-D-arabino tetrahydroxybutyl quinoxaline (21).



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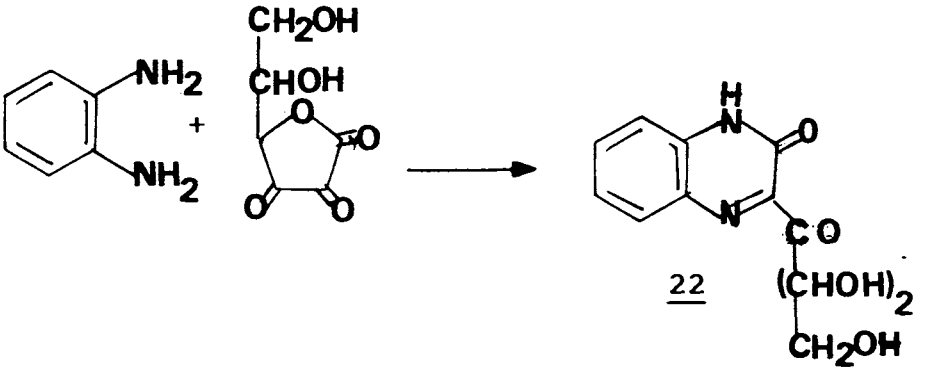

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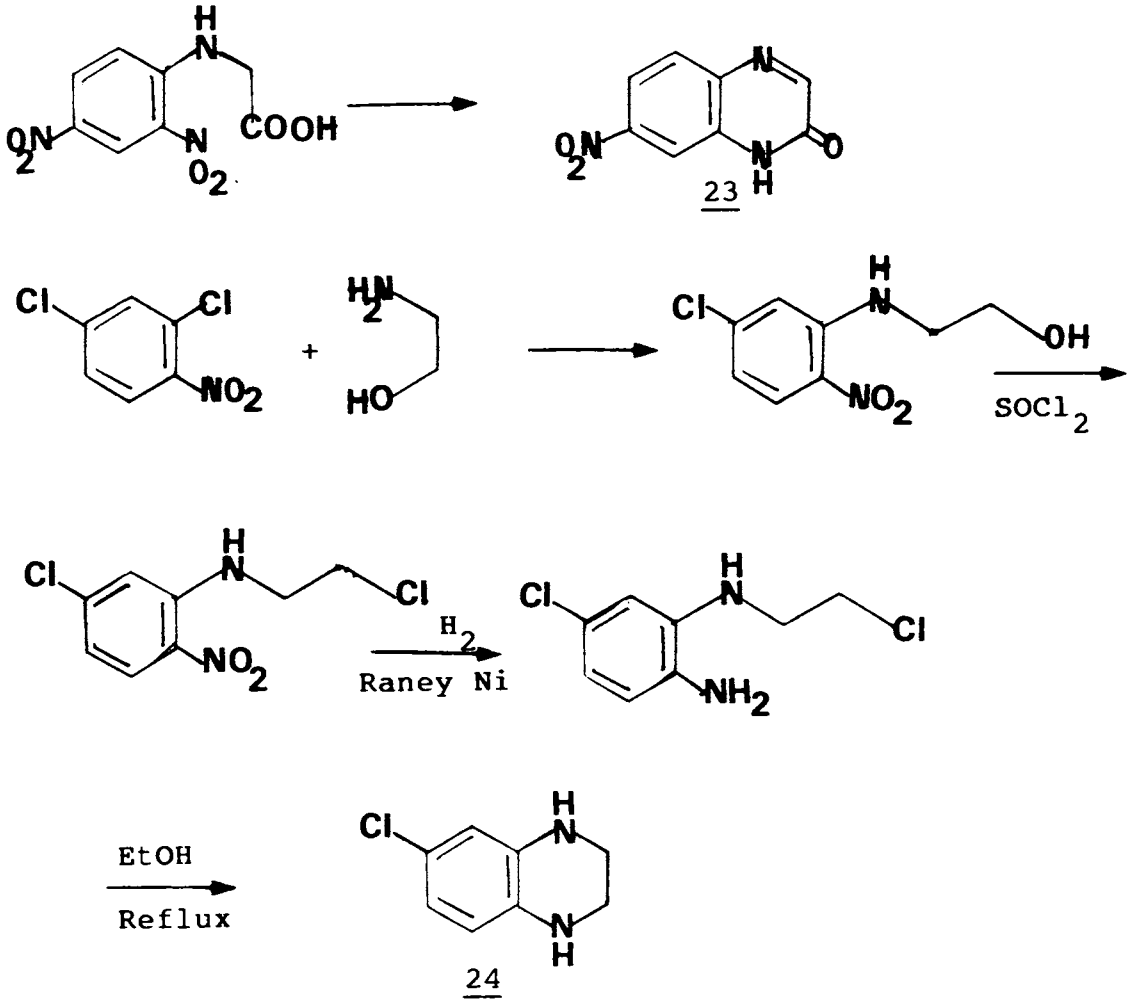
Similarly, o-phenylenediamine and dehydro ascorbic acid condense[15] giving 2-hydroxy-3-(1'-oxo-2',3',4'-trihydroxybutyl)quinoxaline (22).

2.2.2 Intramolecular cyclisation reactions

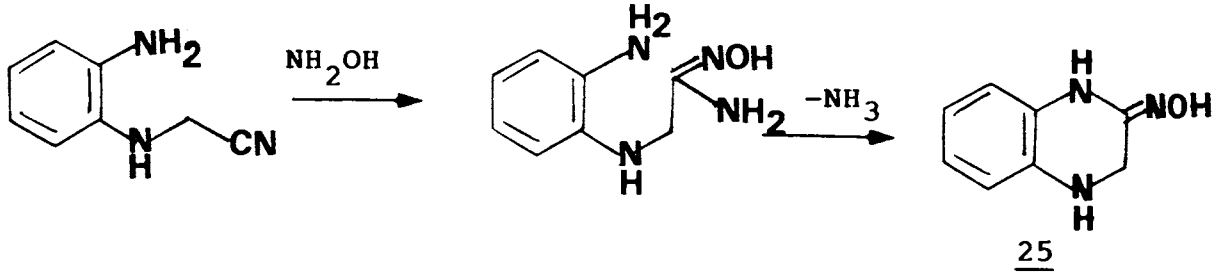
Cyclisation of α-amino acid intermediates formed from the amino acid and an o-nitrohalogenobenzene is an unambiguous method for the synthesis of quinoxaline-2-ones[16]

(23). 6-Chloro-1,2,3,4-tetrahydroquinoxaline (24) has been synthesised in 52% yield by cyclising the corresponding 6-(N-2'-chloroethylamino)aniline, which in turn was obtained from 2,4-dichloronitrobenzene.[17]



N-Cyanomethyl-o-phenylenediamine and hydroxylamine react together to give 2-hydroxyimino-1,2,3,4-tetrahydroquinoxaline[18] (25). Cyclodehydration of cis-phenylglyoxal-2-phenylhydrazone

with anhydrous $AlCl_3$-NaCl at 150-160°C yields some 2-phenylquinoxaline together with 4-phenylcinnoline.[19] 2-(o-Hydroxyphenyl)quinoxaline (26) was also prepared from o-hydroxyphenylglyloxal-2-phenylhydrazone under similar conditions.[20]



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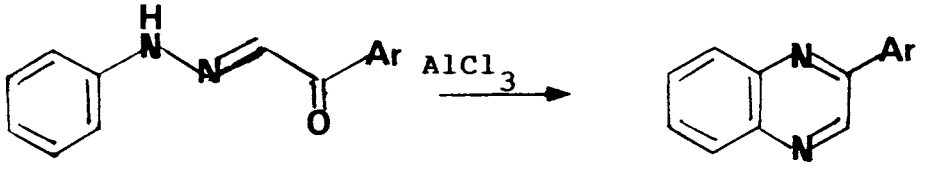

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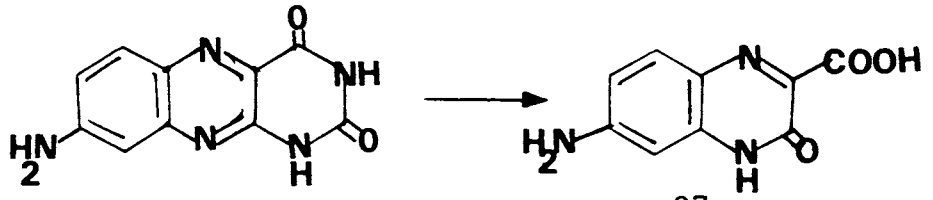
2.2.3 Ring transformations

Quinoxalines can be synthesised by the degradative reactions of larger ring systems. 1,2-Dihydro-2-oxoquinoxaline carboxylic acid (27) is isolated from alkaline hydrolysis of fused alloxazine.[21] The 1,5-benzodiazepine on irradiation

in benzene under oxygen undergoes oxidative ring contraction to 2-benzoyl-3-methylquinoxaline[22] (28). Similarly, photolysis of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine-4-oxide in benzene yields the N-benzoylquinoxaline (29). Related ring contractions of diazepines to reduced quinoxalines have also been observed.[23-25]



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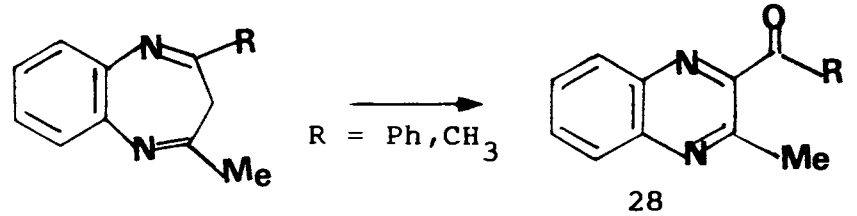

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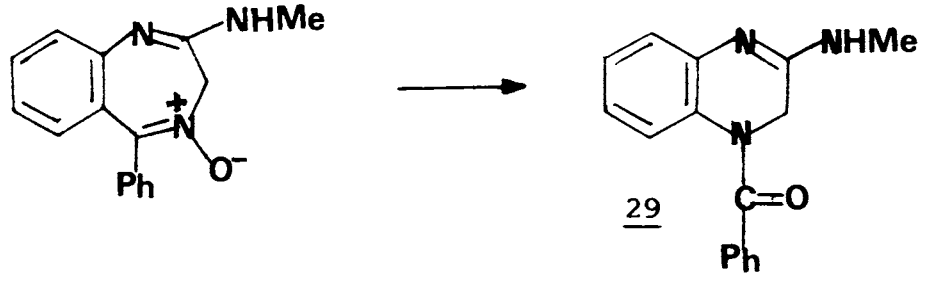

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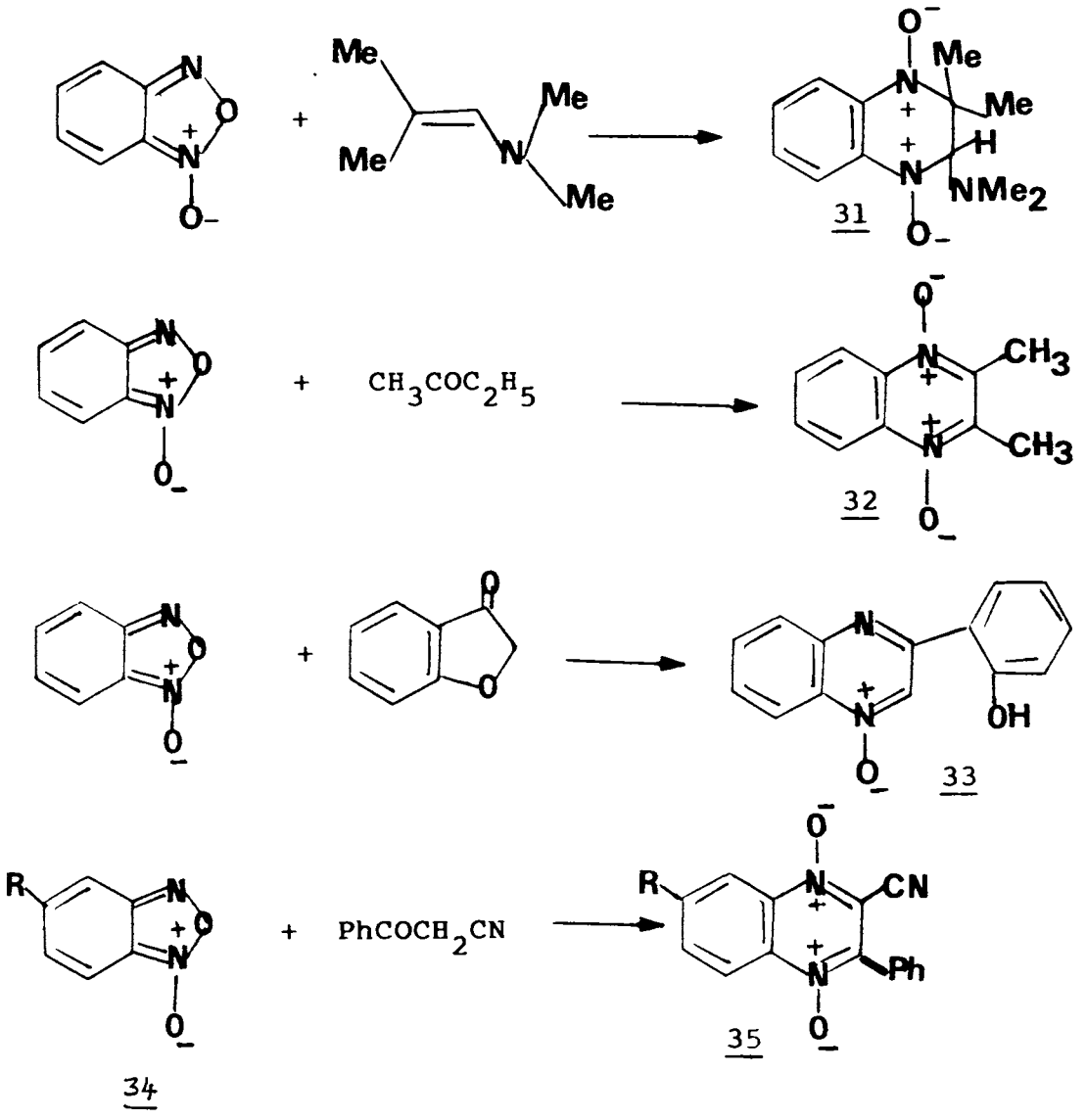
2.2.4 Quinoxaline-N-oxides

Haddadin and Issidorides first reported an elegant method for the synthesis of quinoxaline-1-1,4-dioxides from the reaction of benzo-furazan-1-oxide and an enamine or an active methylene compound, such as a β-diketone or a β-keto ester in the presence of a base.[26-27] Quinoxaline-1,4-dioxide formation involves loss of secondary amine in the enamine reaction and loss of water when an active methylene compound of the type $R_1CH_2COR_2$ is used. This reaction is now commonly referred to as the Beirut reaction.[28] The isolation of the dihydroquinoxaline-1,4-dioxide (31) from the reaction of (30) and N,N-dimethylisobutenyl amine ($Me_2C=CHNMe_2$) suggests that 2,3-dihydroquinoxalines are the likely intermediates in the Beirut reaction.[28]

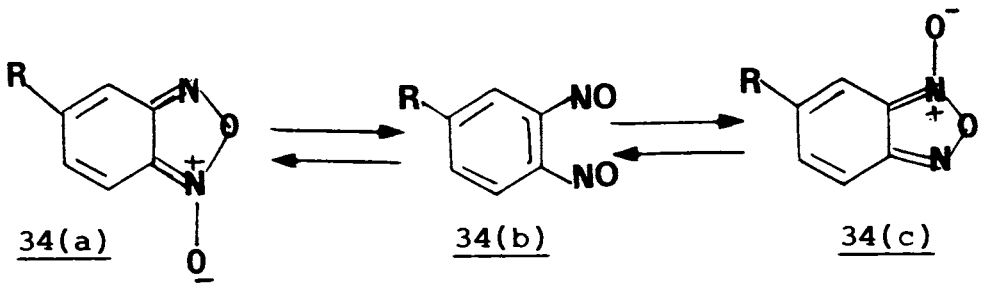
Work from several laboratories has demonstrated the utility of this method. In addition to enamines and 1,3-dicarbonyl compounds, simple carbonyl compounds condense with benzofurazan-1-oxide[29], for eg., methyl ethyl ketone gives 2,3-dimethylquinoxaline-1,4-dioxide (32). Benzofuran-3(2)-ones yield 3-(o-hydroxyphenyl)quinoxaline-1-oxides (33) involving reduction by the furanone.[30]

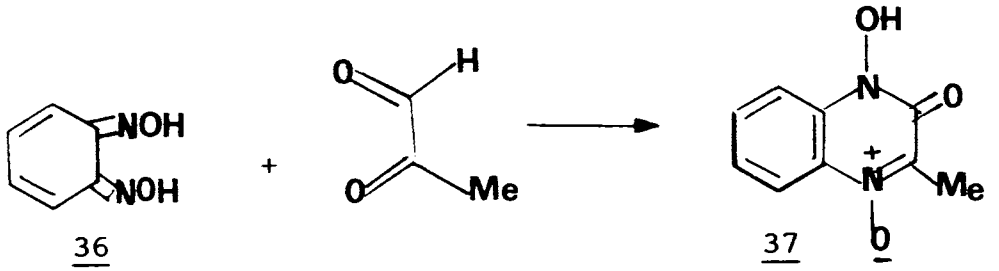
Mixtures of isomeric di-N-oxides are generally obtained when 5(6)-substituted benzofuran-1-oxides (34) are used in Beirut reaction.[31] However, only 7-substituted 2-cyano-3-phenylquinoxaline-1,4-dioxide (35) are isolated from benzoyl acetonitrile.[32]



It was concluded that benzofurazan-1-oxides react in their o-dinitrobenzene form 34(b) which is intermediate between the rapidly interconverting tautomers 34(a) and 34(c).

A further variation on this general method for preparing quinoxaline dioxides is the use of o-quinone-dioximes (36) rather than benzofurazan-1-oxides. The dioximes undergo cycloaddition with α-dicarbonyl and α-hydroxycarbonyl compounds, and hydroxamine acids of type (37) are easily prepared by this method.[33]





There are many patents on the Beirut reaction. Thus, 2-carbamoyl, 2-amino-3-carbamoyl,2-halomethyl-3-carboxy,2-mercatpto and 2-trifluoromethyl quinoxaline-1,4-

dioxides are just a few examples among the many quinoxaline derivatives prepared by this method.

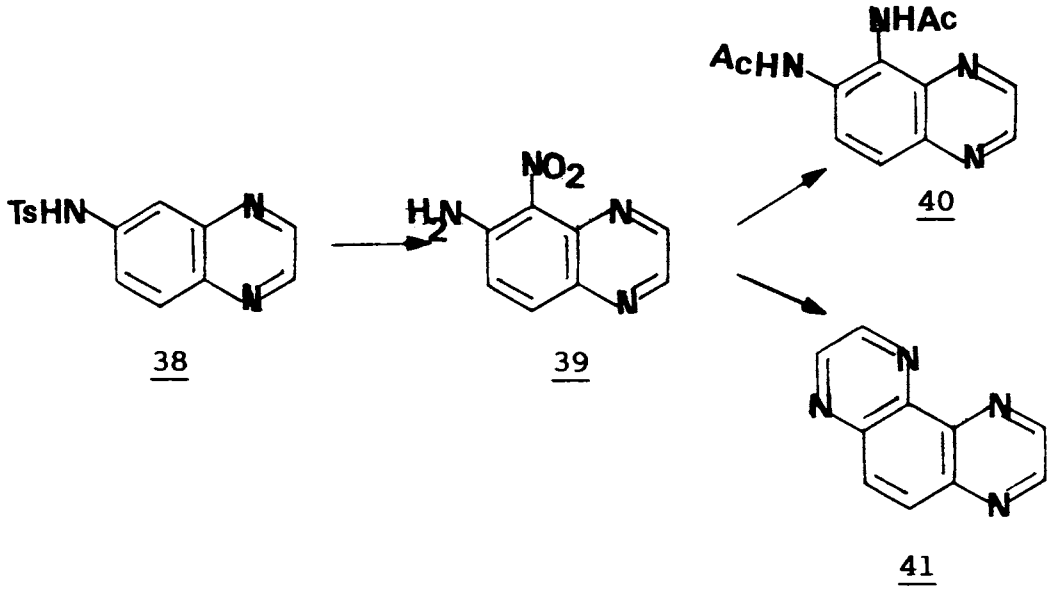
2.3 REACTIONS OF QUINOXALINES

2.3.1 Electrophilic and free-raidcal substitution

The known reluctance of pyridine to take part in electrophilic substitution reaction suggests that the introduction of a second nitrogen atom into the ring would render it even less reactive towards electrophiles. The symmetry of quinoxaline ring makes the 6-and 7-positions equivalent. When activating substituents are present in the benzene ring, substitution usually become more facile. When substitution is in the heterocyclic ring, the situation varies depending on the reaction conditions.

Quinoxaline is resistant to nitration under mild conditions. On treatment with a mixture of oleum and nitric acid at 90°C for 24 hrs.it gives 1.5% 5-nitroquinoxaline and 24% of 5,6 dinitroquinoxaline.[34] Reductive acetylation of the dinitro compound furnishes 5,6-diacetamidoquinoxaline (40). The structure of which has been confirmed by alternative synthesis[35] from 6-(p-toluene sulfonamido)quinoxaline (38). Nitration of 38 in glacial acetic acid gives the

5-nitro derivative and this on hydrolysis yields 6-amino-5-nitro derivative (39). Deamination of 39 gives 5-nitroquinoxaline and reductive acetylation furnishes 5,6-diacetamidoquinoxaline (40). Reducing 6-amino-5-nitroquinoxaline with stannous chloride and hydrochloric acid gives 5,6-diaminoquinoxaline which condenses with glyoxal sodium bisulphite to give 4,7-diaza-1,10-phenanthroline (41).



The reaction of 6-methoxyquinoxaline in concentrated sulphuric acid at 0°C gives 6-methoxy-5-nitroquinoxaline.[36] The position of the nitro group is confirmed by the reduction of the product to 5-amino-6-methoxyquinoxaline identical with a sample prepared from 2,3,4-triamino anisole and glyoxal.[36] Nitration of 5-methoxy quinoxaline furnishes

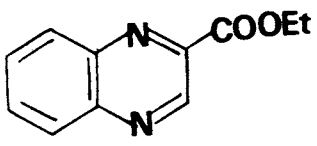
a dinitro derivative, presumably 5-methoxy-6,8-dinitro-quinoxaline, but no mononitro quinoxaline could be isolated.[36]

Sulfonation of quinoxaline-2,3-dione with fuming sulphuric acid yields the 6-sulfonic acid.[37] Similarly, if quinoxaline-2,3-dione is treated with chlorosulfonic acid at elevated temperatures, the 6-sulfonyl chloride is obtained. 6-Methyl quinoxaline-2,3-dione under these conditions yields the 7-sulfonyl chloride; and the 5-methyl derivative is reported to give 6- and 7-substituted products.[37] Reaction of 2,3-dimethyl quinoxaline with 20% HNO_3 at 90°C for 15 hrs. gives a mixture of 6-nitro- and 6,7-dinitroquinoxaline-2,3-dione.[38]

A careful study of the phenylation of quinoxaline with benzoyl peroxide, various benzenediazonium salts and N-nitrosoacetanilide indicates that the 2-position is most reactive to phenyl radicals and that the 5-position is more reactive than the 6-position.[39] Benzoyl peroxide and N-nitrosoacetanilide are the most effective phenylating reagents.[38]

When a mixture of quinoxaline and ferrous sulphate is treated with N-chloro-di-n-butylamine, exclusive 2-substitution occurs in 50% sulfuric acid, but in concentrated acid mixture of 2 and 6-(4-n-butyl aminobutyl)quinoxaline is obtained.[40] Abnormal substitution at position 6 is explained by postulating free radical attack on the diprotonated species.[40] The radicals are generated under oxidising conditions with hydrogen peroxide or t-butylhydroperoxide and ferrous sulphate. Thus 2-ethoxycarbonylquinoxaline (42) is obtained in good yield from quinoxaline and ethylpyruvate-hydrogen peroxide adduct. The latter is decomposed in the presence of aqueous ferrous sulphate generating EtO_2C radicals.[41]

Quinoxaline and formamide in the presence of 30% hydrogen peroxide, sulphuric acid and ferrous sulphate at 10°-15°, give 2-quinoxaline carboxamide (43) in good yield.[42] Quinoxaline-2-carboxaldehyde and quinoxaline-2-yl-ketones has also been obtained via homolytic acylation.[43] It has been reported that substitution of quinoxaline takes place at C-2 when it is irradiated in ether, methanol or ethanol.[44] The intermediate in the reaction is the quinoxaline radical (44).



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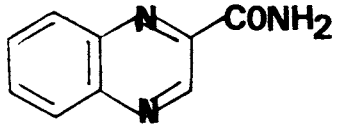

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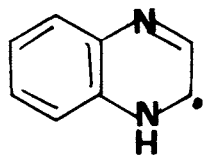

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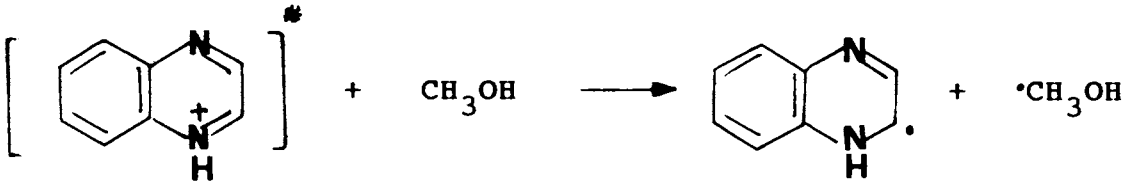
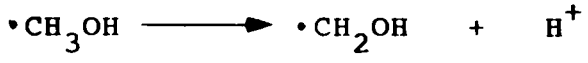
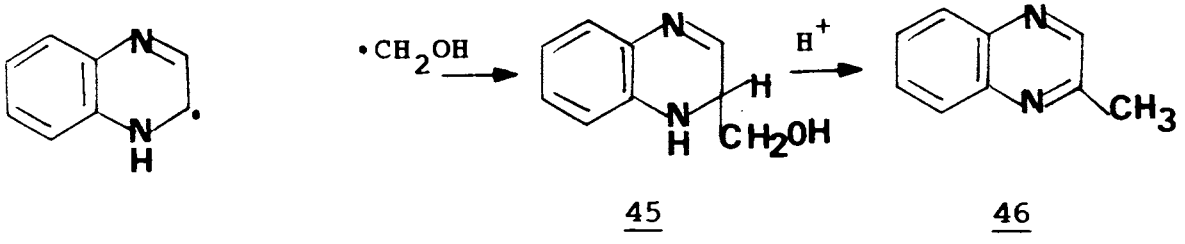
The UV irradiation of quinoxaline in methanol yields radicals not by hydrogen abstraction, but by the protonation of the first singlet excited state, followed by epiplex formation.[45] Irradiation of quinoxaline in



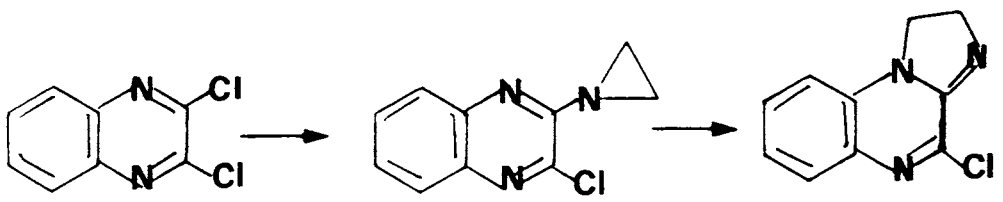




45 46

acidified methanol furnishes 2-methylquinoxaline and the reaction is suggested to go through a pathway involving electron transfer from the solvent to an excited state of the protonated quinoxaline.[46]

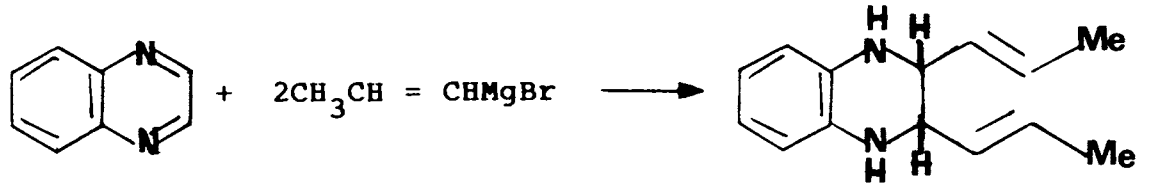
The case of displacement of α-chlorine in the quinoxaline series is of preparative value. Thus 2-alkoxy, 2-amino, 2-methylamino, 2-dimethylamino, 2-benzylamino, 2-mercapto-quinoxalines are all readily prepared from 2-chloroquinoxaline.[47] The displacement of two α-chlorine atoms of 2,3-dichloroquinoxaline has also been of synthetic significance.[48] Reaction of 2,3-dichloroquinoxaline with aziridine furnishes 2-(1-aziridinyl)-3-chloroquinoxaline which on rearrangement gives, 1,2-dihydro-4-chloro imidazo-(1,2-a)quinoxaline.[48] (48).



47 48

2.3.2 Nucleophilic addition reactions

Quinoxalines undergo facile addition reactions with nucleophilic reagents. Thus two molecular proportions of grignard reagent can be added across quinoxaline molecule.[49] The reaction of quinoxaline with allyl magnesium bromide gives after hydrolysis of initial adduct, 86% of 2,3-diallyl-1,2,3,4-tetrahydroquinoxaline. 2,3-Bis[3-(dimethylamino)propyl]-1,2,3,4-tetrahydroquinoxaline derivative (50)



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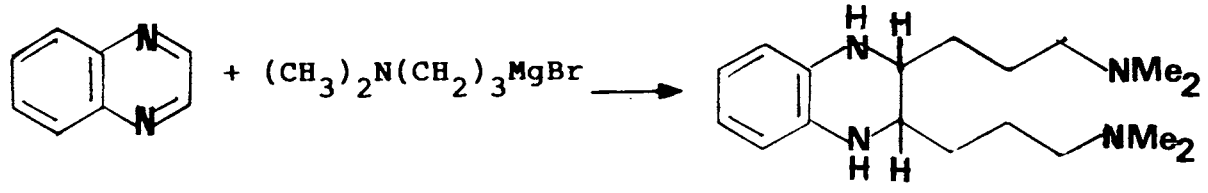

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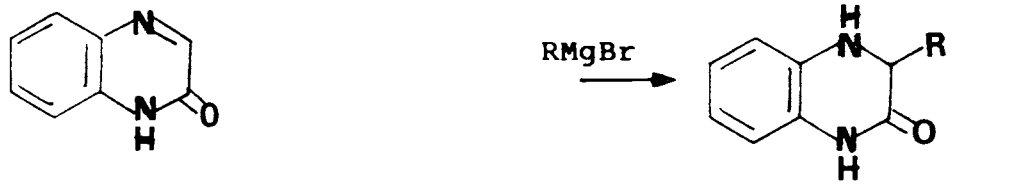
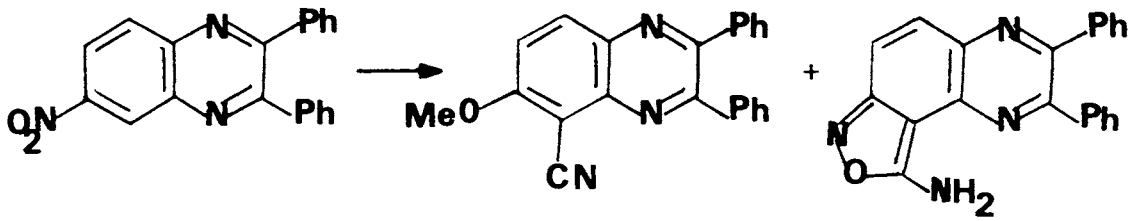


51 R : Me, Ph

results from quinoxaline and 3-(dimethylamino)propyl magnesium bromide.[49] 2-Quinoxalinone add one mole of grignard reagent to yield the corresponding 3-substituted tetrahydroquinoxalinones[49] (51).

6-Substituted quinoxalines undergo unusual reactions with nucleophiles. Thus 2,3-diphenyl-6-nitroquinoxaline (52) with potassium cyanide undergoes substitution in the 5-position, with simultaneous nucleophilic displacement of the nitro group to give the compounds (53) along with 5-aminoisoxazolo[3,4-f]-quinoxaline (54).[50]



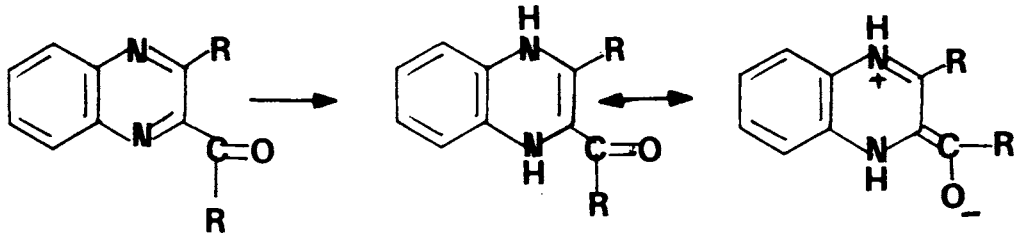
52 53 54

2.3.3 Reduction reactions

2.3.3.1 Dihydroquinoxalines

Catalytic reduction of 2-acetyl-3-methylquinoxaline (55) in ethanol with one mole of hydrogen, gives a deep

crimson solution, from which red-brown needles of 2-acetyl-1,4-dihydro-3-methylquinoxaline (56) are obtained.[51] Ethanolic solution of 56 reoxidise on exposure to air to 2-acetyl-3-methylquinoxaline, but the solid dye is stable, in air for several days. Similar results are obtained with 2-acetyl-3-phenylquinoxaline (57) from the reduction of which a purple dye, 2-acetyl-1,4-dihydro-3-phenylquinoxaline (58) is obtained.[51]

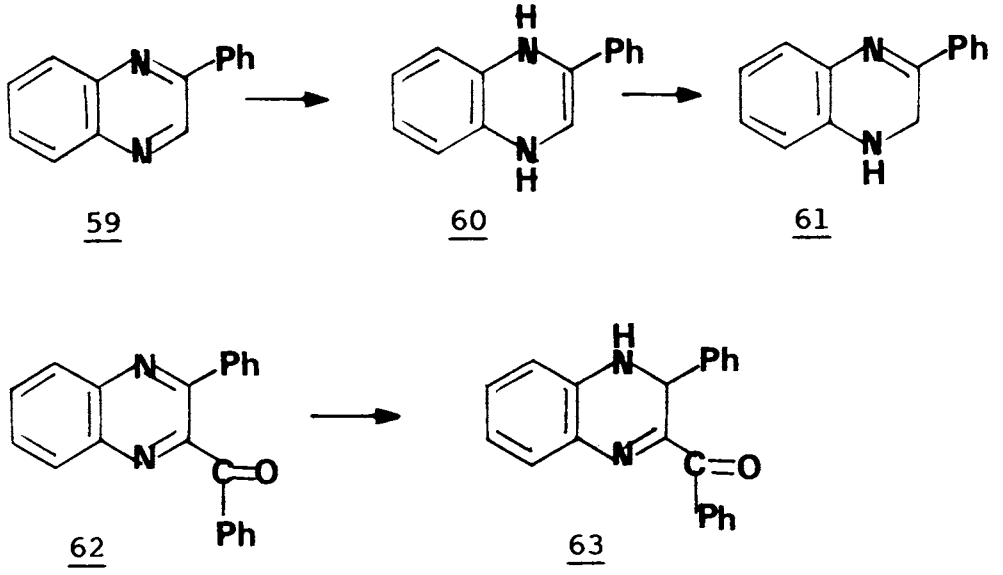


55 R : CH_3 56 R : CH_3

57 R : Ph 58 R : Ph

Reduction of quinoxaline with sodium in tetrahydrofuran at 20° yields the 1,4-dihydroquinoxaline.[52] The 1,4-dihydroquinoxaline (60) the first product of reduction of 2-phenylquinoxaline (59) readily rearranges to the thermodynamically more stable 1,2-dihydro

isomer (61).[53] 2-Benzoyl-3-phenylquinoxaline (62) is reduced by sodium amalgam to the red dye 2-benzoyl-3-4-dihydro-3-phenylquinoxaline (63).[54]

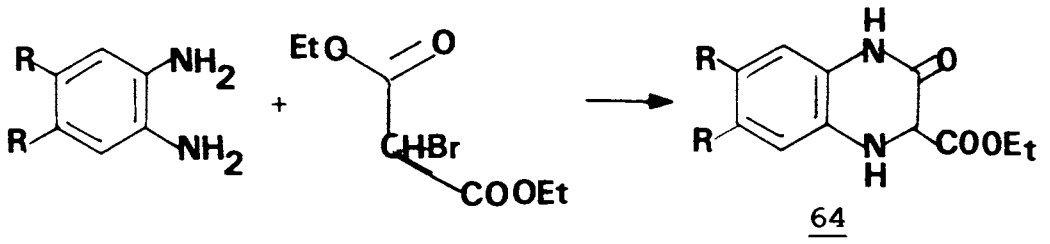


2.3.3.2 Tetrahydroquinoxalines

1,2,3,4-Tetrahydro derivatives are formed when quinoxalines are reduced with lithium aluminium hydride in ethereal solution.[55] Similar reduction of 2,3-dimethyl-quinoxaline in benzene also gives the meso(cis)-1,2,3,4-tetrahydro derivative. This is shown to be a stereospecific

reduction since the lithium aluminium hydride does not isomerise the dl-(trans) compounds. Low temperature, platinum catalysed hydrogenation of 2,3-dimethylquinoxaline in benzene also gives meso(cis)-1,2,3,4-tetrahydro-2,3-dimethylquinoxaline.[56] Sodium borohydride in acetic acid[57] and hydrogen and platinum[58] have been used to reduce 6-substituted quinoxalines to 1,2,3,4-tetrahydro compounds.

2-Ethoxycarbonyl-1,2,3,4-tetrahydroquinoxaline-2-ones (64) are obtained either by sodium dithionate reduction of the corresponding quinoxalinone esters or by direct synthesis from o-phenylenediamines and bromomalonic ester.[57]



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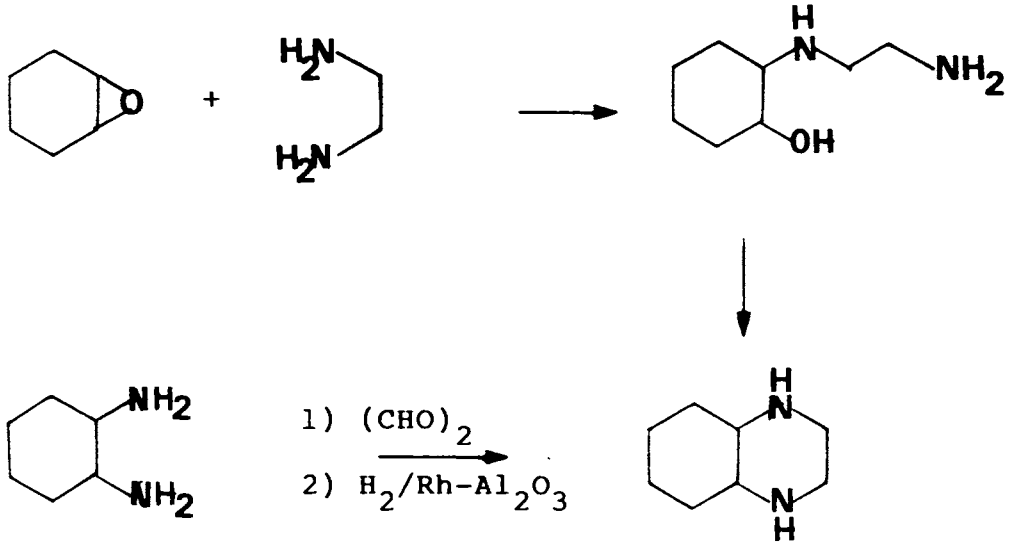
2.3.3.3 Decahydroquinoxalines

Hydrogenation of quinoxaline or 1,2,3,4-tetrahydroquinoxaline over a 5% rhodium-on-alumina catalyst at 100°C and 136 atmos. or over freshly prepared Raney nickel gives meso(cis)-decahydroquinoxaline in high yield.[60] The decahydroquinoxaline (65) is prepared by the reaction of ethylenediamine on cyclohexane oxide and catalytic



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dehydrative ring closure of the product.[61] It was shown to be dl(trans)-decahydroquinoxaline by its alternative synthesis from trans-1,2-diamino cyclohexane.

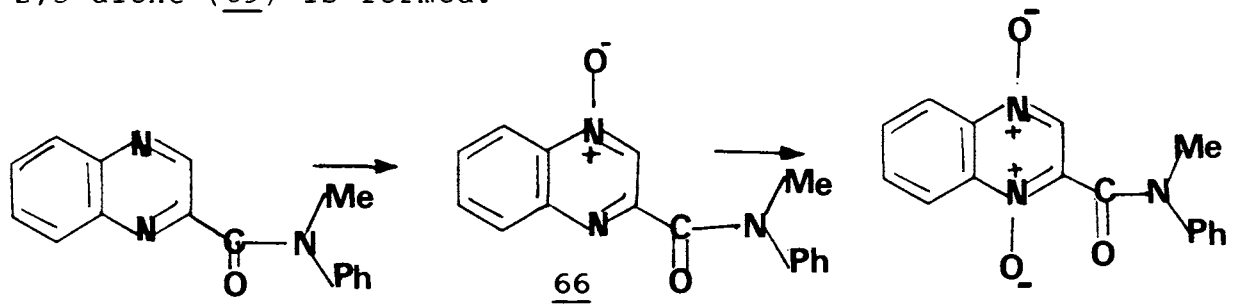
2.3.4 Oxidation reactions

Various methods have been used for N-oxidation of quinoxalines. Treatment of quinoxaline with one equivalent of peracetic acid in acetic acid gives quinoxaline-1-oxide and with excess of peracetic acid, quinoxaline-1,4-dioxide is formed.[62] Reaction of quinoxaline with 30% aqueous hydrogen peroxide in acetic acid gives quinoxaline-2,3-dione.[63]

Substituents in the 2-position generally inhibit 1-oxide formation, for example, oxidation of 2-alkoxy, 2-carbethoxy quinoxaline furnishes the 4-oxides.[64] Treatment of quinoxaline-2-carboxy-N-methyl anilide with one mole peracetic acid gives the 4-oxide (66) and oxidation with excess of peracetic acid; 1,4-dioxide (67).[64]

5-Substituted quinoxalines afford mono-N-oxides, presumably the 1-oxides and are resistant to further oxidation, though 5-methoxy quinoxaline is exceptional in forming

a 1,4-dioxide.[65] In the case of 6-substituted quinoxalines, as the substituents become more electron attracting, the yield of 1,4-dioxide decreases but more of the corresponding 2,3-dione (69) is formed.[65]



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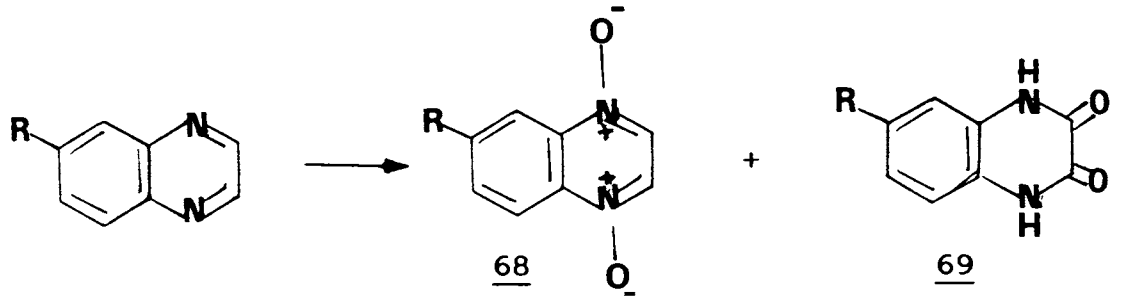
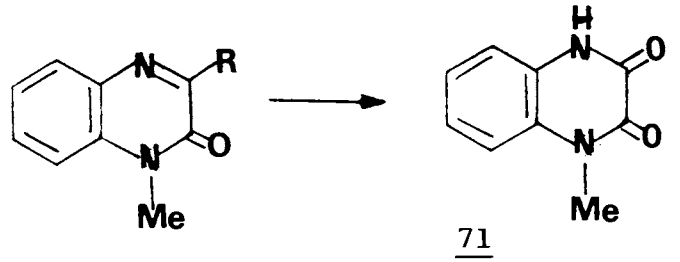


68 69



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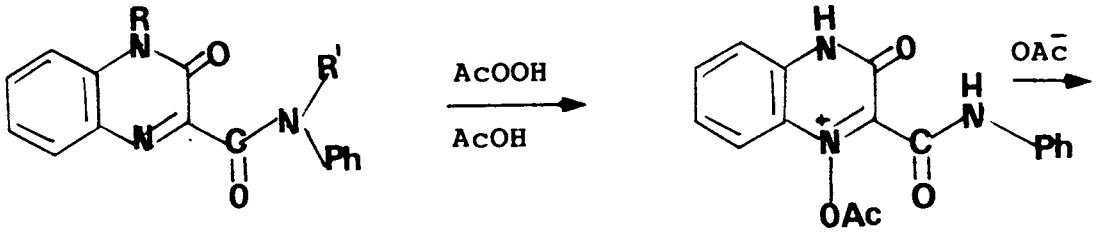
70 R : H ; CH_3

Peracetic acid oxidation of 1-methylquinoxaline-2-one (70) gives 1-methylquinoxaline-2,3-dione (71) in moderate yield and similar treatment of 1,3-dimethylquinoxaline-2-one yields a small quantity of the 4-oxide.[66]

Oxidation of 4-methylquinoxaline-3-one-2-carboxy-N-methylanilide (72) with hydrogen peroxide and acetic acid furnishes the 1-oxide but on removal of either one or both the N-methyl groups (72 a-c); oxidation with hydrogen peroxide or with peracetic or perbenzoic acid results in the removal of the carboxamide group and the formation of a quinoxaline-2,3-dione.[67,68]

The mechanism proposed for this abnormal reaction is illustrated by reference to the conversions of quinoxaline-3-one-2-carboxyamilide (72c) into quinoxaline-2,3-dione (76). Hydrolysis of the N-acetoxy derivative would yield the 1-oxide, acetic acid and hydrogen ion in the usual manner; but reaction with acetate ion is facilitated by the electrophilic nature of carbon-2, subsequent elimination followed by hydrolysis yields the quinoxaline-2,3-dione.

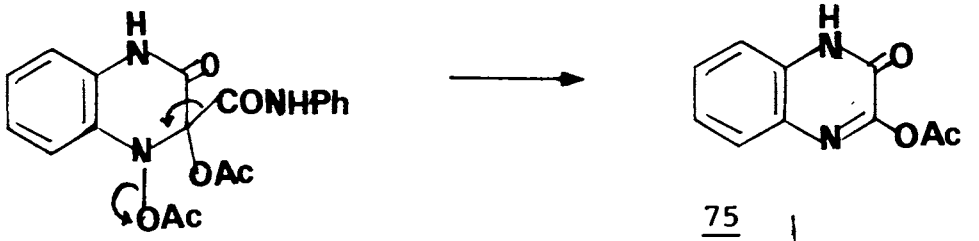


72 a) R = H, R' = CH_3

b) R = CH_3, R' = H

c) R = R' = H

73



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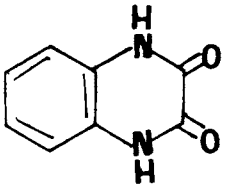

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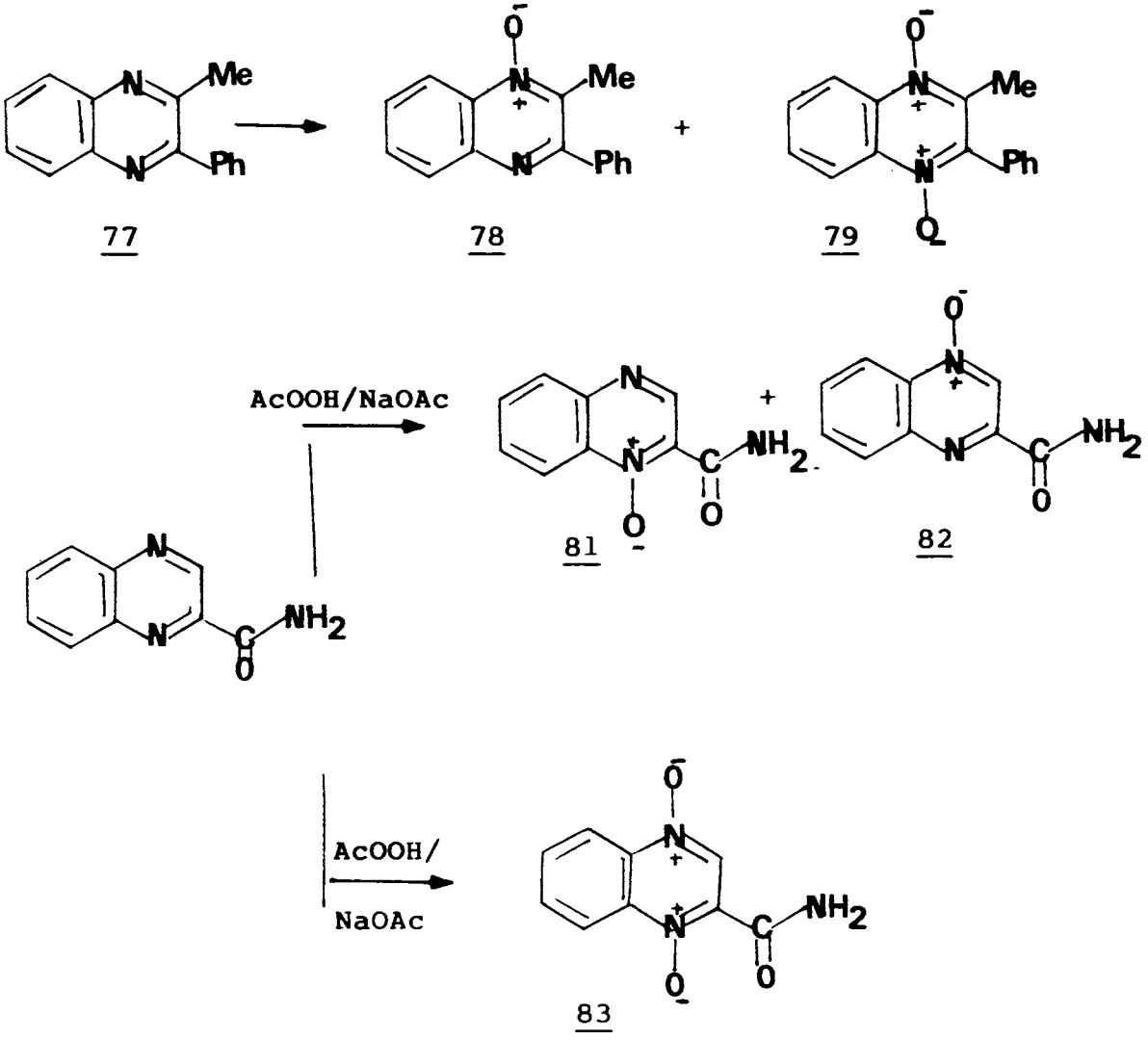
acid oxidation of 2-carbamoyl quinoxaline (80) at 20-25° gives the monoxide (81) and (82) and at higher temperatures the 1,4-dioxide (83) is isolated in 50% yield together with small amount of the 1,4-dioxide of 2-amino-3-quinoxalinone.[69]



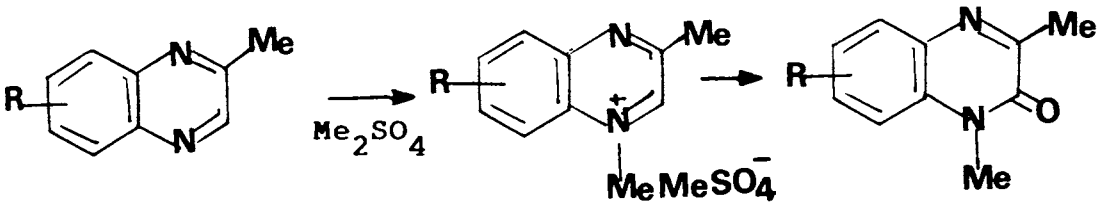
However, Hayastin and coworkers[70] report the isolation of only the 4-oxide from (75) using monoperphthalic acid in ether at 10°C. In their attempt to correlate the nature of 2-substitution with the formation of 1-versus 4-oxides, they examined the behaviour of some 2-substituted quinoxalines.[71] 2-Aminoquinoxaline is best oxidised with permaleic acid in ethanol in the presence of sodium bicarbonate. Exclusive 1-oxidation occurs and the product is conveniently isolated as the carbamic acid ester.[72]

The electrolytic oxidation of quinoxaline at a copper anode gives pyrazine-2,3-dicarboxylic acid in excellent yield.[73] A similar conversion may be effected with alkaline potassium permanganate.

2.3.5 Quaternary salts

During the last few years, numerous quaternary salts of quinoxalines have been prepared and their reactions studied. 2-Methylquinoxaline and some of their 6,7-substituted derivatives (84) form 4-methylquinoxalinium methosulphates and perchlorates (85).[74] On hydrolysis of these salts, the quinoxalinones (86) are formed. Similarly when 2,3-dimethylquinoxaline is quaternised with dimethylsulphate,

1,2,3-trimethylquinoxalinium methosulphate (87) is obtained which on standing in sodium phosphate buffer at pH 7.5-8 is dimerised into two coloured compounds, 88 (major) and 89 (minor).[75]



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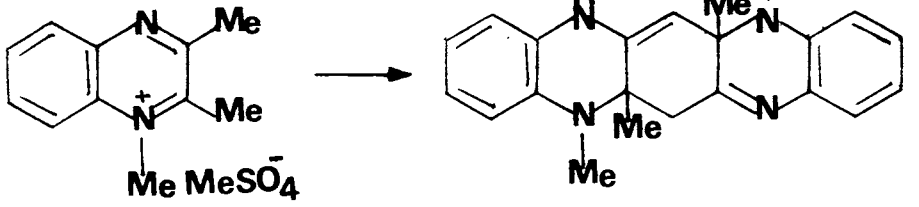

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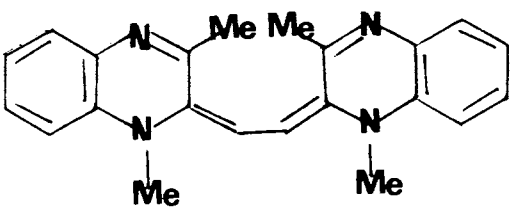

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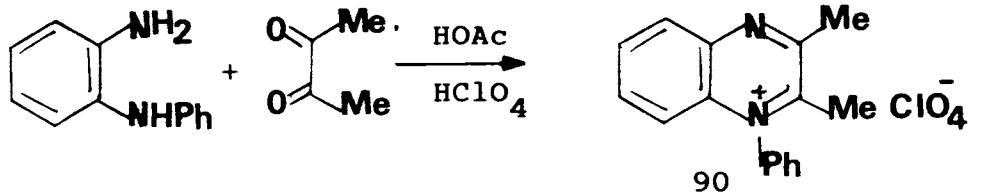
1-Alkyl and 1-aryl-2,3-dimethylquinoxaline perchlorates are synthesised by the condensation of biacetyl with suitably substituted o-phenylenediamine in perchloric acid. Thus 1-phenyl-2,3-dimethylquinoxalinium perchlorate (85) is obtained.[76] Tennant and Livingstone have reported the preparation and some substitution reactions of 1-acetoxy-3,4-dihydro-3-oxo-2-phenylquinoxalinium perchlorates (91) which with sodium acetate, gives the 6-acetoxyquinoxaline (93).[77]



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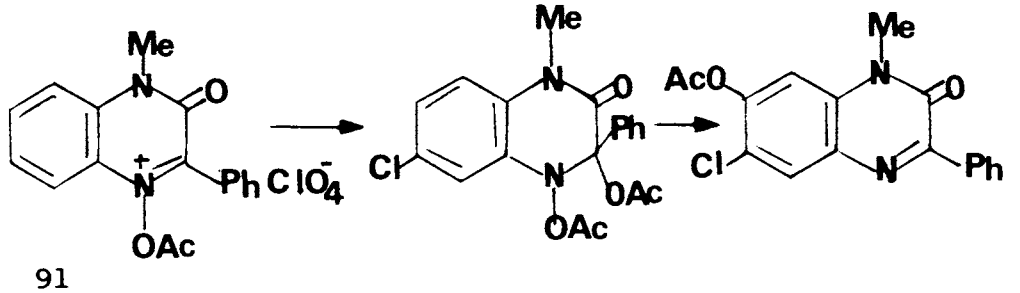

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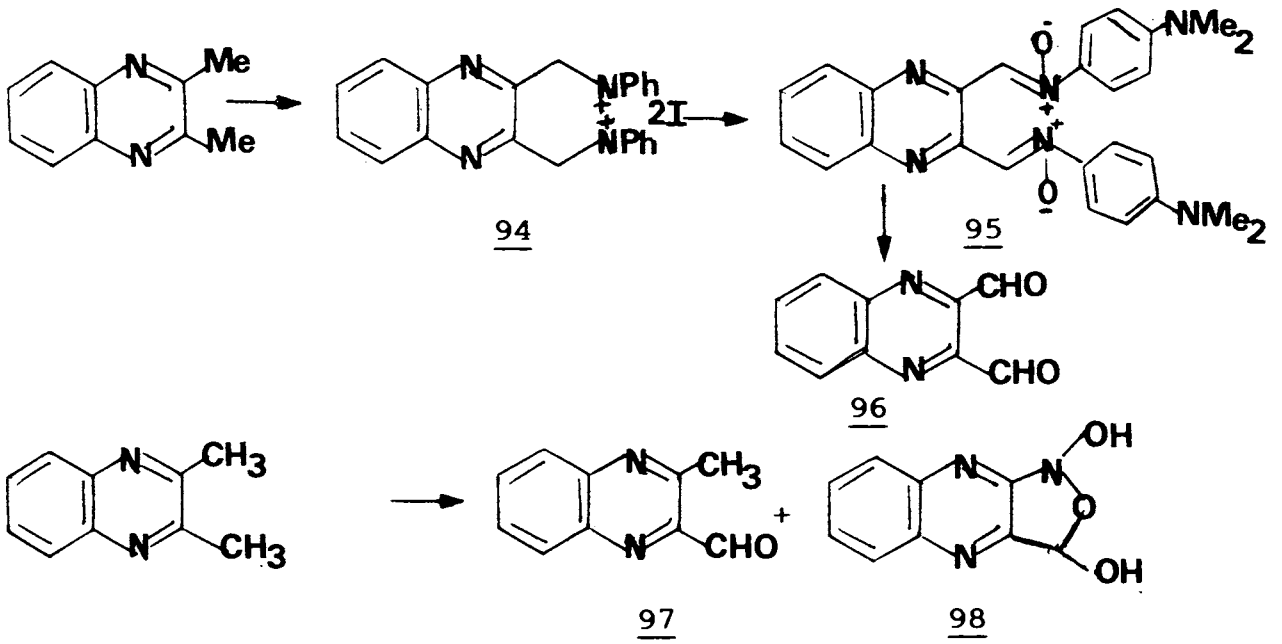
2.3.6 Reactions of substituted Quinoxalines

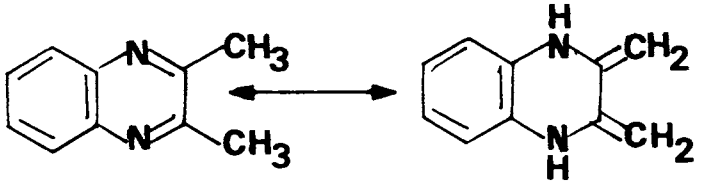
2.3.6.1 Methylquinoxalines

∝-Methylquinoxaline exhibit the typical reactivity of active methyl compounds such as condensation with aromatic and heterocyclic aldehydes[78,79], side chain bromination and base catalysed claisen condensation with esters. 2,3-Dimethylquinoxaline reacts with pyridine and iodine to form quinoxaline-2,3-bis(methylene pyridinium iodide) (94). Condensation of 94 with p-nitrosodimethylaniline in the presence of potassium carbonate yields the bis-(p-dimethylaminonitrone) (95) and this in acid hydrolysis gives quinoxaline-2,3-dialdehyde (96). The dialdehyde is also obtained by selenium dioxide oxidation of 2,3-dimethylquinoxaline.[80] However, K.Mustafa et.al[81] recently report that SeO_2 oxidation of 2,3-dimethylquinoxaline yields a mixture of compounds as shown below.



94 95 96 97 98

2,3-Dimethylquinoxaline undergoes reaction with typical dienophiles such as maleic anhydride, p-benzoquinone and N-phenylmaleimide.[82] The products are formulated as Diels-Alder adducts, primarily since analogous products are not isolated from reactions with other quinoxalines in which there are no possibility of tautomerism to a buta-1,3-diene system like (99).



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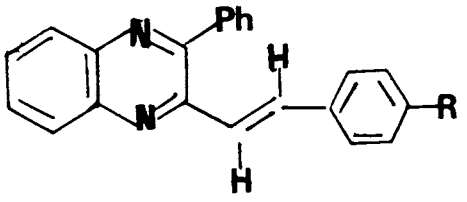
2-Methyl-3-phenylquinoxaline reacts with aryl-aldehydes to form 2-styryl derivatives (100) but forcing conditions are necessary to overcome the steric effect of the 3-phenyl group.[78] Direct N-amination of 2-phenyl-quinoxaline has been reported with o-methylsulphonylhydroxyl-amine.[83] The reactive nitrogen is N-4, the least sterically hindered, and the product was characterised by conversion into the N-benzoylimine (101).



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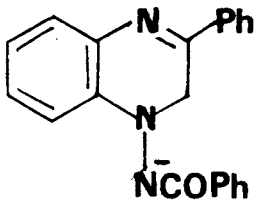

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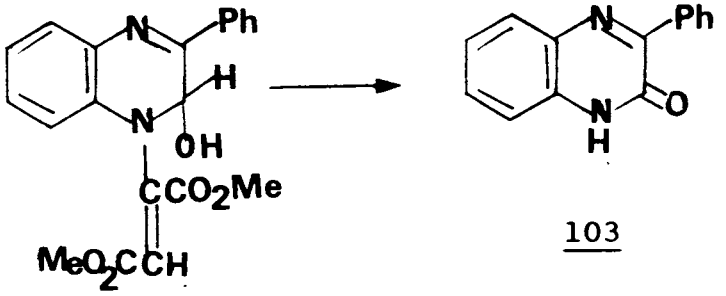
2-Phenylquinoxaline reacts with dimethyl acetylene-dicarboxylate to give a product which after exposure to the atmosphere is isolated as 102, and which on oxidation with potassium permanganate gives 3-phenylquinoxaline-2-one (103). 2,3-Diphenylquinoxaline reacts with dimethylacetylene-dicarboxylate in methanol to give a yellow adduct which consists of one mole each of the reactants and to which is assigned an analogous structure, 104. In acidic methanol the adduct forms salts of the type, 105.[84]



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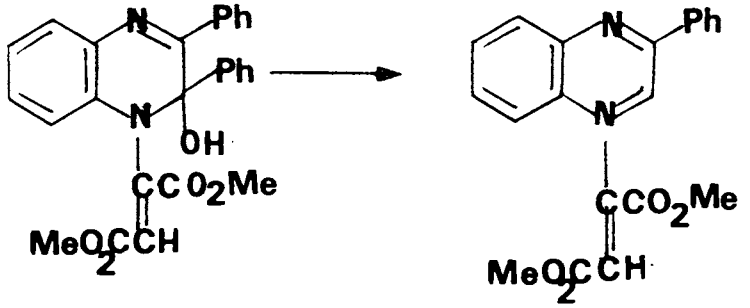

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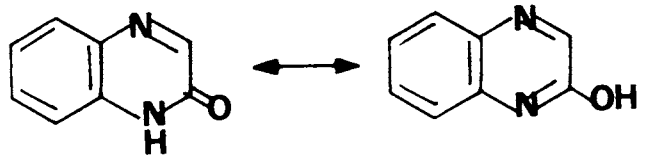
105

2.3.6.2 Quinoxaline-2-one and 2-3-dione

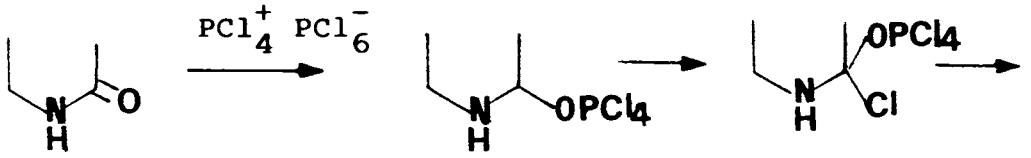
Quinoxaline-2-ones are readily converted into the corresponding 2-chloroquinoxalines by treatment with phosphoryl chloride; in the case of the highly insoluble 2,3-diones, chlorination is effected conveniently with a

mixture of phosphoryl chloride and dimethylaniline.[85] The use of phosphorous pentachloride may lead to side reactions, for example, quinoxaline-2-one is converted into 2,3-dichloroquinoxaline with this reagent. ∝-Chloroquinoxalines undergo facile displacement reactions with nucleophilic reagents and so the readily available quinoxaline-2-ones are useful intermediaries in many synthetic reactions.

Quinoxaline-2-one (106a) is in a mobile tautomeric equilibrium with 2-hydroxyquinoxaline (106b). The ready conversion of quinoxaline-2-ones into 2-chloroquinoxalines

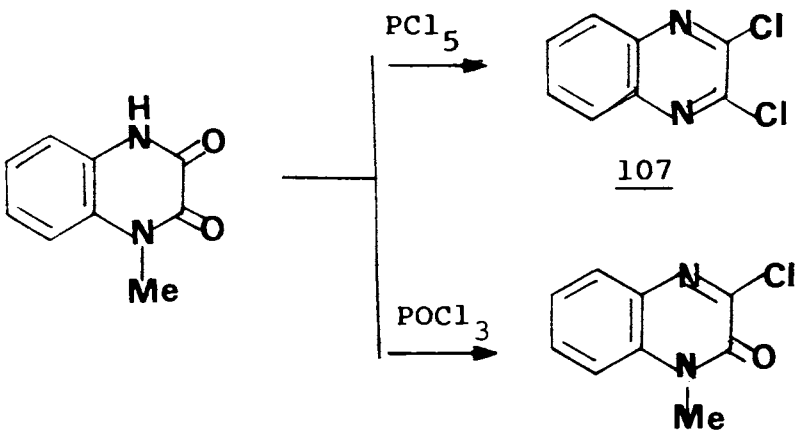


106a 106b



is not a chemical evidence for existence of hydroxy form. Phenolic hydroxyl groups are difficult to replace with chlorine, and this reaction is more correctly regarded as the transformation of a secondary amide into the corresponding imino chloride.

The conversion of -NMeCO ⟶ -N=CCl may also be effected with phosphorous pentachloride. This occurs with elimination of methyl chloride and further emphasises that formation of a chloroderivative is due to amide-carbonyl reactivity. Thus treatment of 1-methylquinoxaline-2,3-dione with phosphorous pentachloride gives 2,3-dichloroquinoxaline (107) and with phosphorylchloride, 3-chloro-1-methyl-quinoxaline-2-one (108).[86,87]



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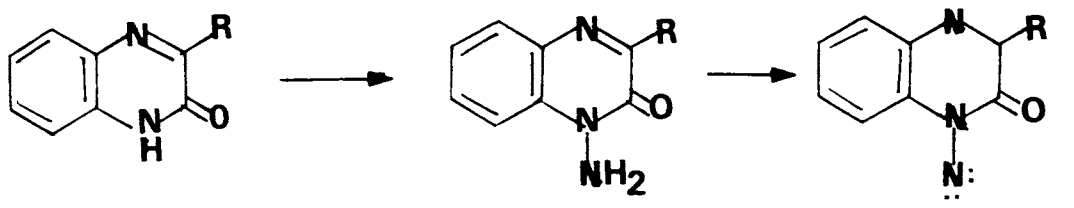
108

Direct amination of quinoxalinones with hydroxylamine-o-sulfonic acid produces the 1-amino derivatives (109) and subsequent oxidations with lead tetraacetate gives the 1,2,4-benzotriazines (112). Benzotriazine formation probably involves the formation of an intermediate nitrene (110), ring expansion to the benzotriazepinone (111) and subsequent loss of carbon monoxide. The nitrene (110) was trapped as the sulfoxide (113) when the oxidation was carried out in the presence of dimethyl sulfoxide.[88]



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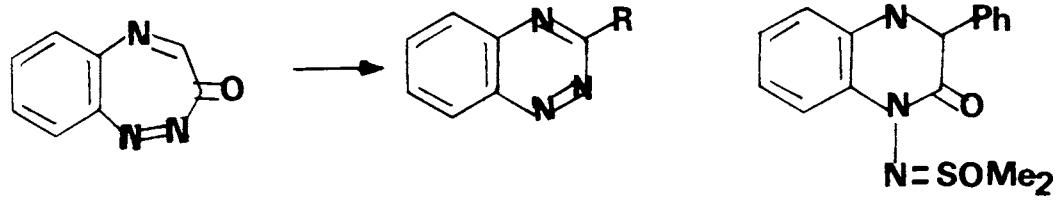
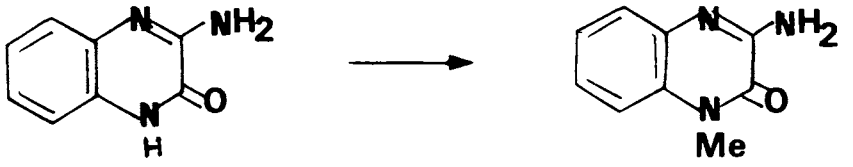
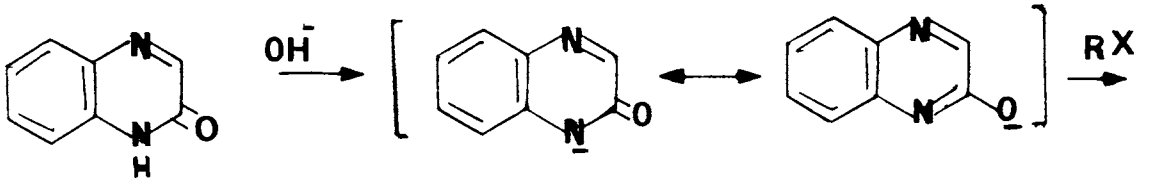


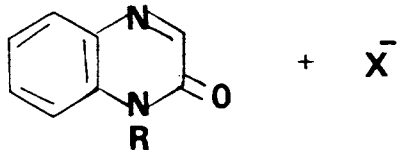
111 112 113

Treatment of an alkaline solution of quinoxaline-2-one or quinoxaline-2,3-dione with alkyl iodide or sulfate results in N-methylation. Thus methylation of 3-amino-quinoxaline-2-one (114) with methylsulfate and alkali gives 3-amino-1-methylquinoxaline-2-one (115)[87]. It, therefore, appears that the preferred nucleophilic centre in the resonant anions of the type shown in the scheme below, is nitrogen rather than oxygen.



114 115



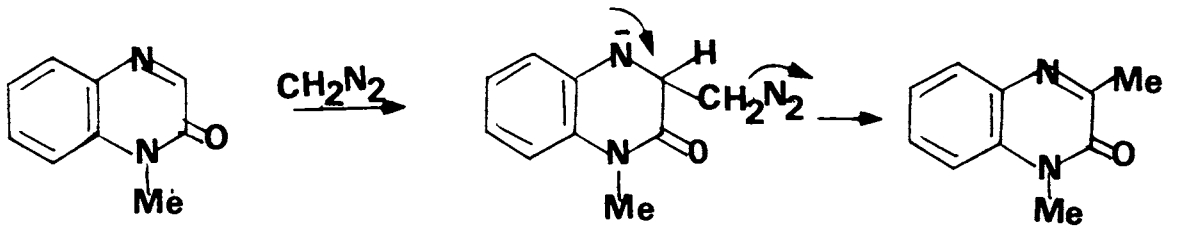


With diazomethane, quinoxaline-2-ones and quinoxaline-2,3-diones form mixtures of N- and O-methyl derivatives.[87] A consideration of the mechanism of these reactions is complicated by the fact that diazomethane may function as an electrophilic or nucleophilic reagent. However, it is certainly an oversimplification to assume that N-methyl derivative is formed necessarily from the cyclic amide form and the O-methyl derivative from the tautomeric hydroxy form.

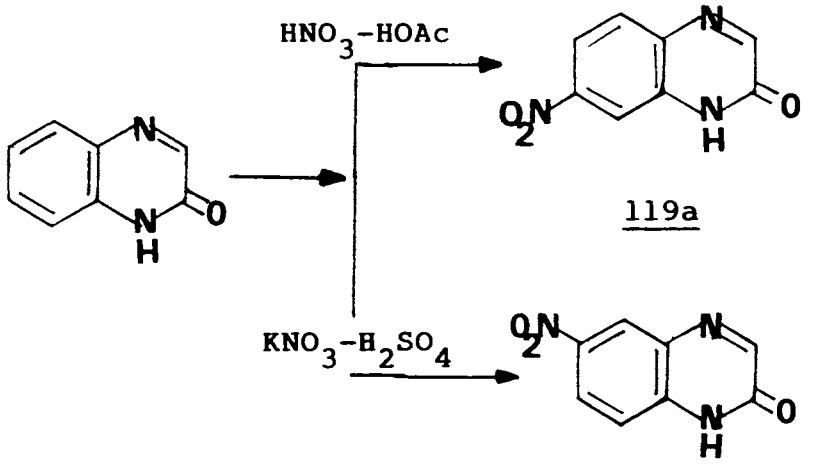
1-Methylquinoxaline-2-one (116) is converted into 1,3-dimethylquinoxaline-2-one (118) with diazomethane. This unusual C-methylation is probably a result of the electrophilic character of carbon-3 in the mono methyl compound and may occur by the mechanism as shown in the scheme.

Nitration of quinoxaline-2-one in acetic acid gives mainly the 7-nitro derivative (119a) and in sulphuric acid, the 6-nitro derivative (119b) is formed.

Quinoxaline-2-one is a weak base and so the different orientation of substitution in acetic acid and sulphuric acid may mean that in acetic acid, the principal species



116 117 118



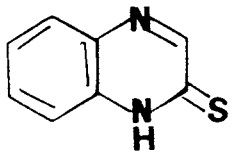
119a

119b

dione is obtained, presumably owing to oxidation and subsequent nitration. It, therefore, appears that substitution procedures offer a useful alternative to the classical quinoxaline synthesis, particularly when the required o-phenylenediamine is not readily available.

2.3.6.3 Quinoxaline-2-thione and 2,3-dithione

Treatment of quinoxaline-2-thione (120) with methyl iodide and alkali gives 2-methylthioquinoxaline (121) and apparently no 1-methylquinoxaline-2-thione (122). 2-Methylthioquinoxaline is oxidised by hydrogen peroxide in acetic acid at room temperature mainly to 2-methylsulfonylquinoxaline



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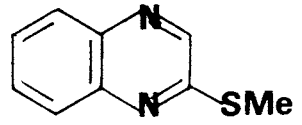

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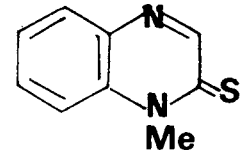

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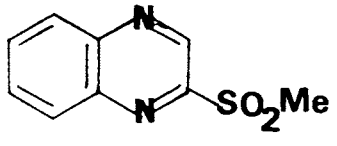

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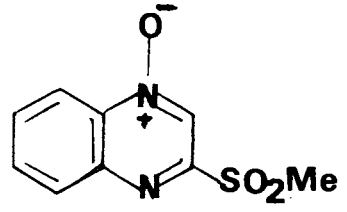
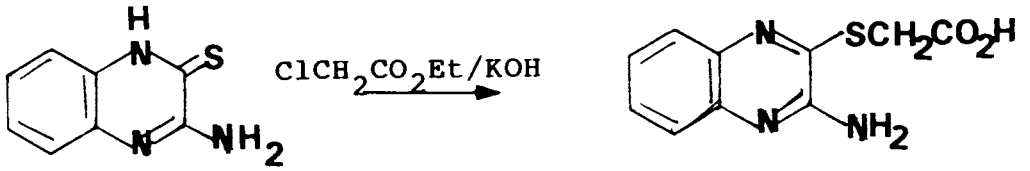


124

(123) at 55°C, 2-methylsulfonylquinoxaline-4-oxide (124) and quinoxaline-2,3-dione.[89] The methylsulfonyl group in 123 and 124 is very readily displaced by treatment with alkali.

Quinoxaline-2,3-dithione is useful for its coordinating properties with transition metals. The metal complexes of the dithione with Cu, Ni, Zn, Pd and Pt have been prepared and the spectral properties of the Ni and Pd complexes examined.[90] UV data indicate that quinoxaline-2,3-dithione is present as such rather than as 2,3-dimercaptoquinoxaline; the highly coloured nature of its complexes is attributed to charge transfer.

2-Aminoquinoxaline-3-thione (125) reacts with ∝-chloro esters under alkaline conditions and (2-aminoquinoxaline) thioglycolic acids (126) are obtained.[91]



125 126

2.3.6.4 2-Chloro and 2,3-Dichloroquinoxalines

2-Chloroquinoxalines undergo facile nucleophilic displacement reactions with amines to give the corresponding 2-substituted quinoxalines. With diamines, besides the 2-amino derivative, bis(quinoxalinyl) alkylenediamines are produced.[92]

Nucleophilic displacement of 2-chloro-3-phenyl-quinoxaline with methylamine at 100°-150°C and with sodium-phenoxide in excess of phenol at 100° gives the expected 2-methylamino and 2-phenoxy-3-phenylquinoxalines.[93]

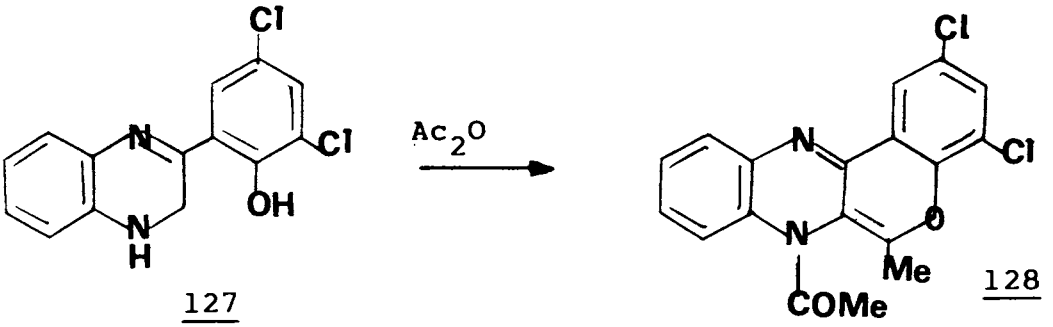
2,3-Dichloroquinoxaline with anhydrous potassium fluoride at 200° yields 2,3-difluoroquinoxalines which is readily hydrolysed to quinoxaline-2,3-dione.[94] Treatment of 2,3-dichloroquinoxaline with phosphorous pentachloride at 300° yields hexachloroquinoxaline which with potassium fluoride at 380° gives predominantly hexafluoroquinoxaline.[95]

Reactions of 2-chloro and 2,3-dichloroquinoxalines with carbanions give 2-quinoxalinyl ketones and 3-chloro-2-quinoxalinyl ketones. Thus 2-quinoxalinyl acetophenone has been formed from acetophenone anion.[96] However,

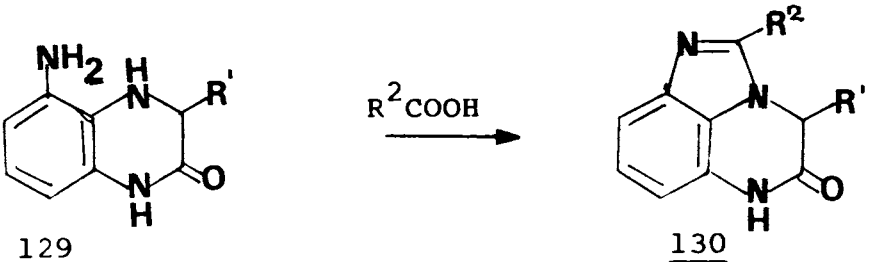
2,3-dimethoxyquinoxaline and 2,3-diethoxyquinoxaline with methyl ethyl ketone and sodamide in anhydrous benzene give 2-amino derivatives rather than the ketones.[97]

2.3.7 Condensed Quinoxalines

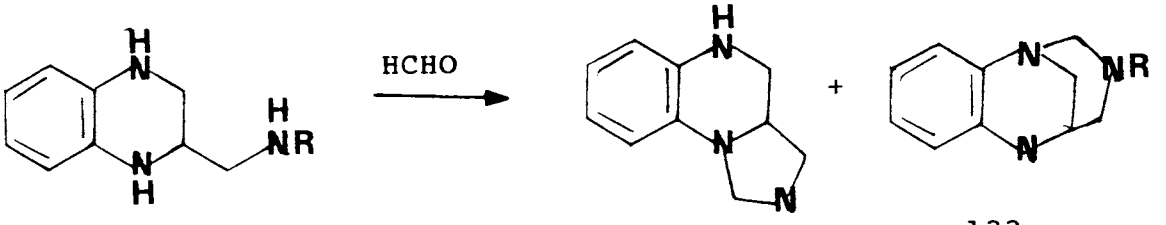
Acetic anhydride cyclisation of the 2-hydroxy-phenyl-3,4-dihydro quinoxaline (127) yields the benzopyrano-quinoxaline (128) derivatives.[98] 5-Amino-1,2,3,4-tetrahydro



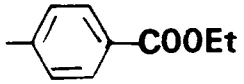
127 128



129 130



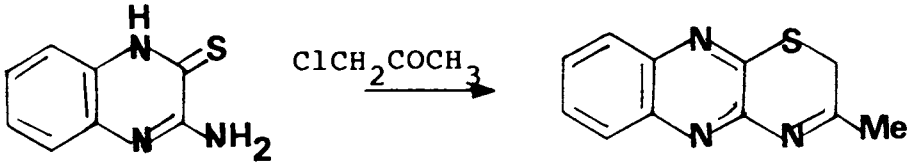
131 132 133

R = 

quinoxaline-2-one (129) undergoes ring closure with carboxylic acids and 5,6-dihydro-4H-imidazo[1,5-4-d,e] quinoxaline-2-ones (130) are obtained.[99] Tetrahydro-quinoxalines such as (131) are of interest as structural analoges of tetrahydrofolic acid, a compound with a vital role in one carbon metabolism. The reaction of 131 with formaldehyde leads to both imidazoline (132) and hexahydro-pyrimidine (133).[100,101]

when 2-aminoquinoxaline-3-thione reacts with α-haloketones in the presence of alkali, ring closure takes place and quinoxalines [2,3-b][1,4] thiazines (134) are isolated.[91] When 2-chloroquinoxaline is treated with sodium aryloxide in an excess of corresponding phenol, a mixture of the expected 2-aryloxyquinoxaline and the corresponding benzofuro[2,3-b]quinoxaline (135) are obtained.[102] Aryloxy-quinolxalines are readily cyclised with polyphosphoric acid to benzofuro[2,3-b]quinoxalines.[102] 2-Arylfuro[2,3-b]-quinoxalines (137) results from cyclisation of 2-phenyl-3-quinoxalinones.[103]

Quinoxaline-2-carboxaldehyde phenylhydrazone cyclise to 1-phenylflavazole (139).[13] 2-Chloro-3-quinoxaline carboxaldehyde on boiling with hydrazine hydrate in ethanol gave 1H-pyrazolo[3,4-b]quinoxaline (141).[104,105]



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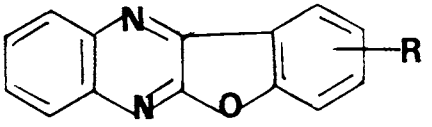

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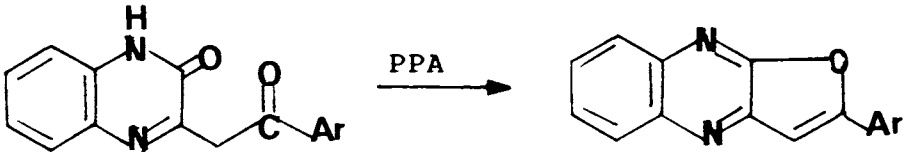
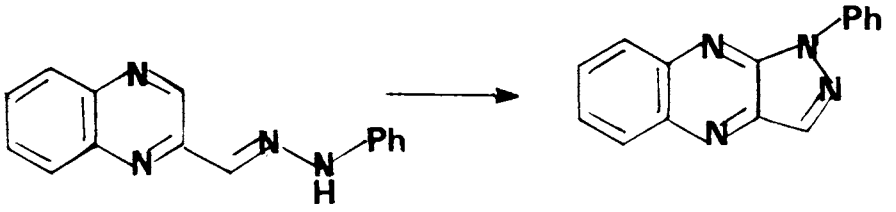
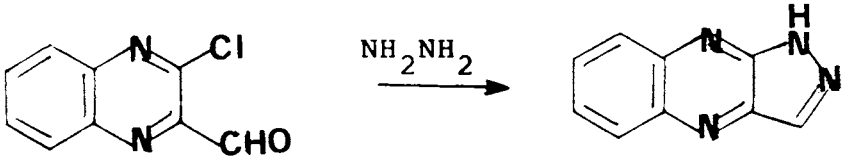


136 137



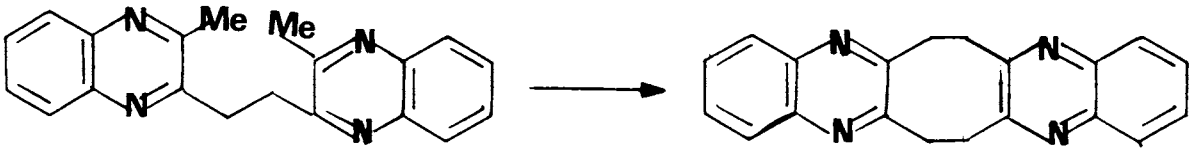
138 139



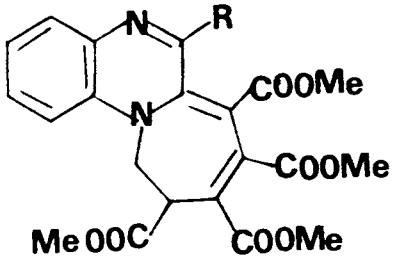
140 141

PPA - Poly Phosphoric Acid

2,3-Dimethylquinoxaline on treatment with phenyl lithium and Cu_2Cl_2 undergoes dehydrodimerisation to yield the compound (142). This has been further converted[106] into the pentacyclic compound (143). 2-Methylquinoxaline reacts with dimethyl acetylene dicarboxylate to give a mixture of azepino[1,2-a]quinoxalines (144) and (145).[107]



142 143



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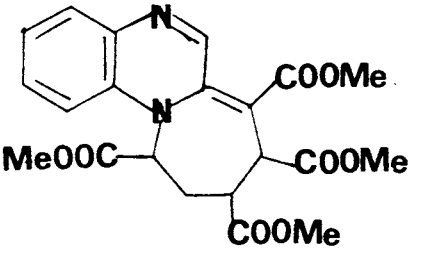
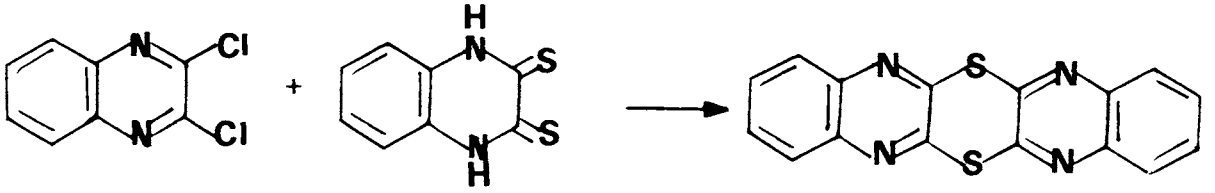


145

2,3-Dichloroquinoxaline is a good starting material for the synthesis of condensed quinoxaline system. Reactions of 2,3-dichloroquinoxaline with 2,3-dimercaptoquinoxaline yields the [1,4]dithieno[2,3-b:5,6-b']diquinoxaline (146).[108]

and with 4,5-diphenyl imidazoline-2-thione (147), the imidazo[2',1'-2,3]thiazolo[4,5-b]quinoxaline (148).[109,110]



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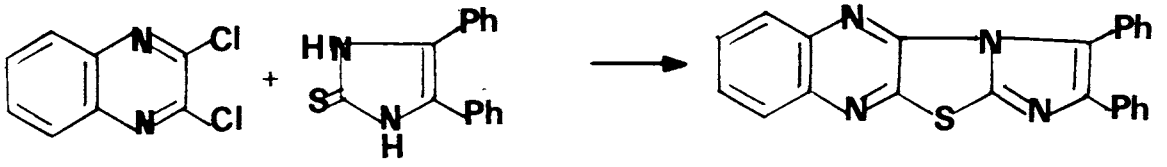
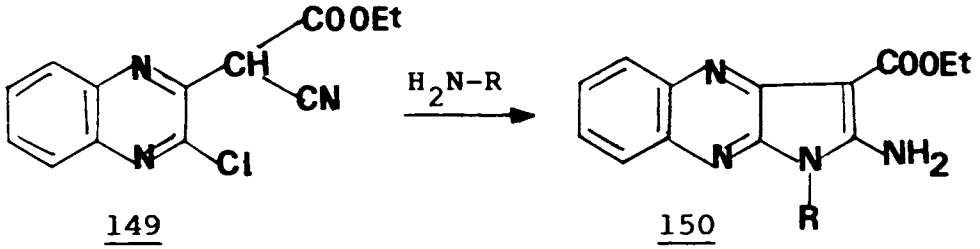
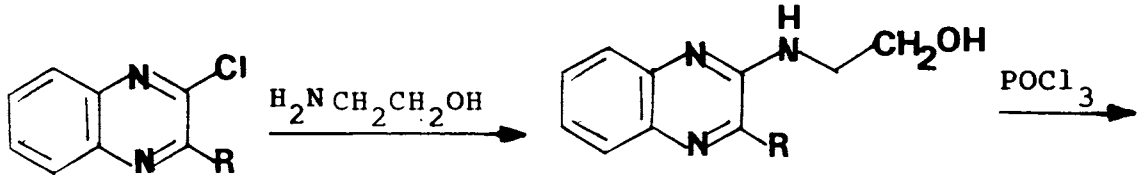


147 148

The reaction of ethyl-2-(3-chloro-2-quinoxalinyl)-2-cyanoacetate (149) with various amines gives the corresponding 1-substituted ethyl-2-aminopyrazolo[2,3-b]quinoxaline-3-carboxylate (150) in good yield.[111] 2-Chloroquinoxalines react with ethanolamine to give 2-(2-hydroxyethylamino)-quinoxaline (151). When 151 is refluxed in phosphorous oxychloride, 1,2-dihydroimidazo[1,2-a]quinoxaline (152) is obtained.[112] Catalytic hydrogenation of 5-acylamido-2,3-disubstituted quinoxalines (153) with palladised carbon in



149 150



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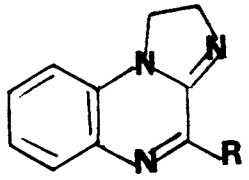

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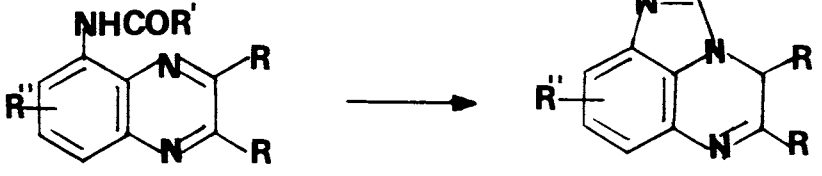
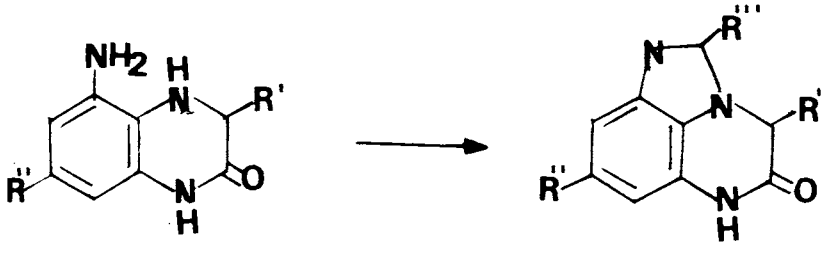


153 154

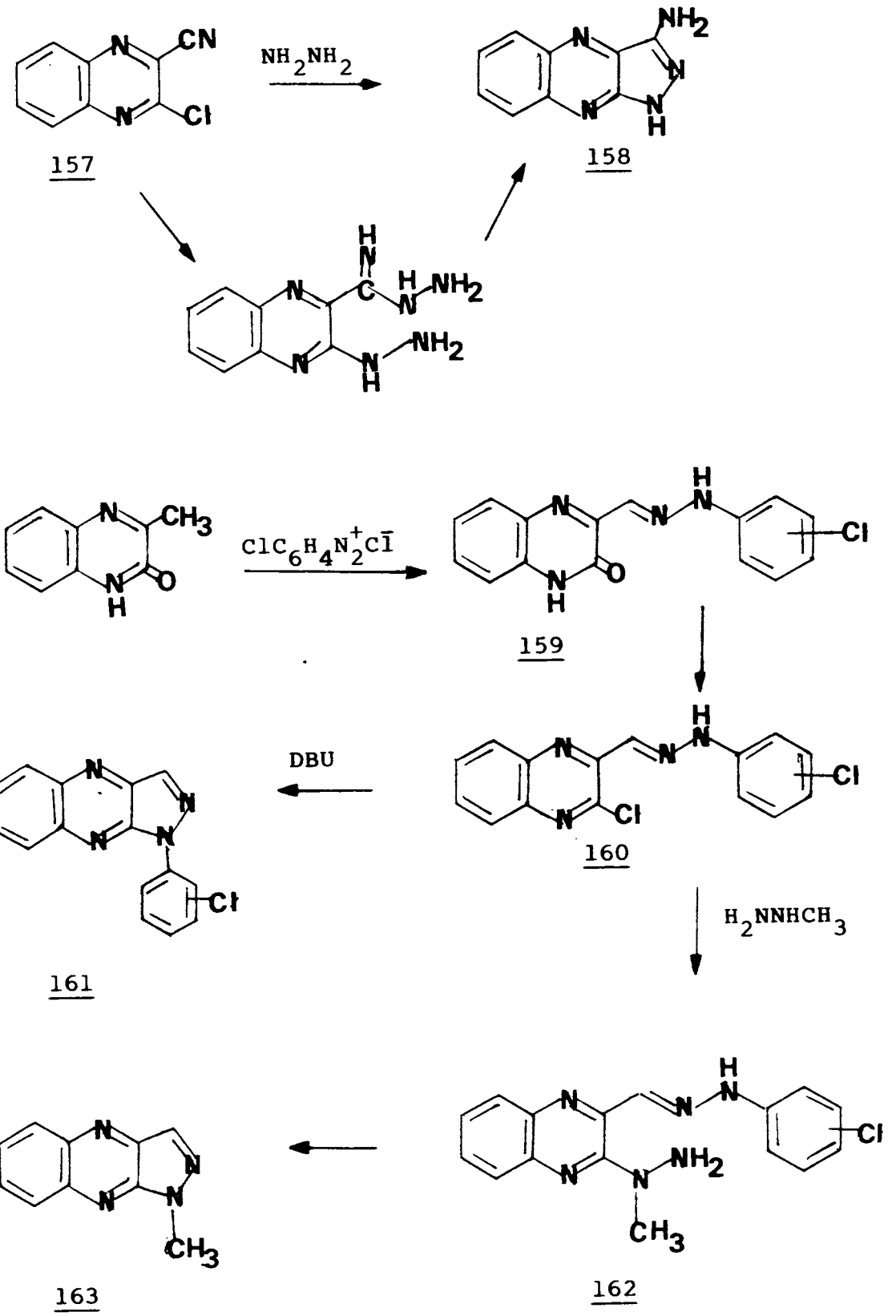


155 156

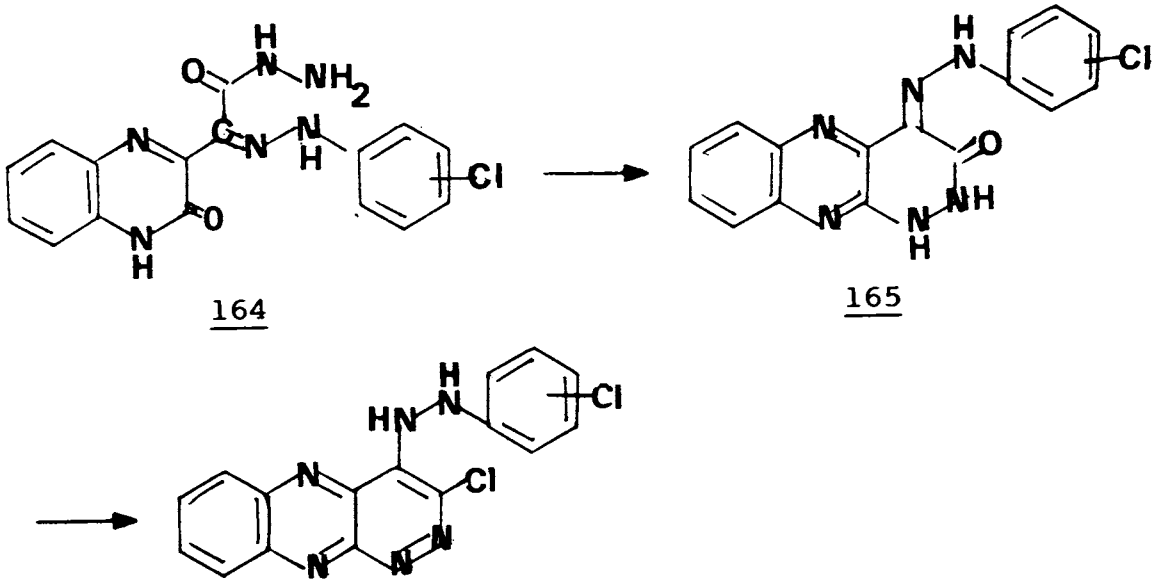
acetic acid affords 4,5-disubstituted 5,6-dihydro-4H-imidazo-[1,5,4-d,e]quinoxalines (154).[104] When 5-amino-1,2,3,4-tetrahydroquinoxaline-2-ones (155) are heated with carboxylic acids, ring closure reactions occur to form 5,6-dihydro-4H-imidazo[1,5,4-d,e]quinoxaline-2-ones (156).[99]

2-Chloroquinoxaline-3-nitrile (157) on treatment with hydrazine hydrate for 4 hours provide 3-aminopyrazolo-[3,4-b]quinoxalines (158).[113] The reaction of 3-methyl-2-oxo-1,2-dihydroquinoxaline with aryldiazonium chlorides gives the arylhydrazones (159), whose chlorination with $POCl_3$ afford the 2-chloro derivative (160). Refluxing of 160 and diazabicyclo undecene (DBU) in DMF effects the cyclization to provide 1-aryl-1H-pyrazolo[3,4-b]quinoxaline (161).[114]

α-Arylhydrazono hydrazides of quinoxaline (164) on refluxing with hydrazine dihydrochloride in ACOH results in dehydrative cyclisation to give (165) and on chlorination of

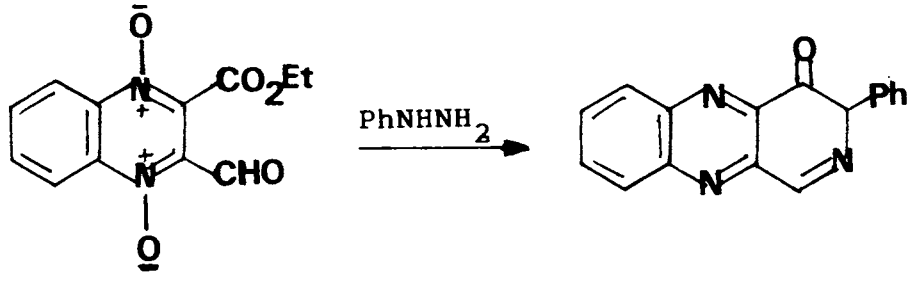

NH2NH2
157
158
ClC6H4N2+Cl−
159
DBU
160
H2NNHCH3
161
162
163

it with $POCl_3$ provides 3-chloro-4-(o-chlorophenyl)hydrazino pyridazino[3,4-b]quinoxaline (166).[115]



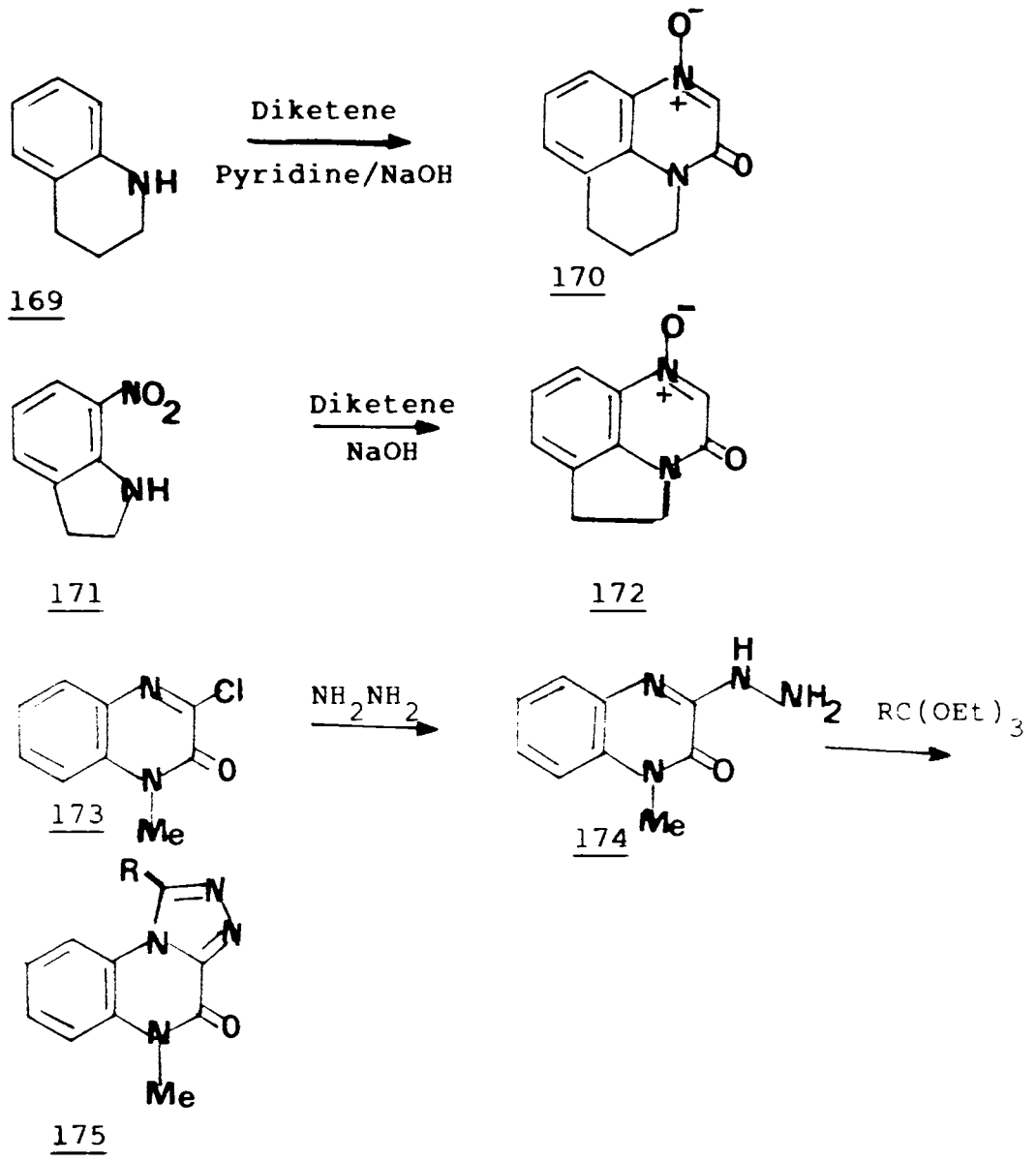
164 165 166

Reaction of 2-ethoxycarbonyl-3-formylquinoxaline-1,4-dioxide (167) with phenylhydrazine[116] provides 1,2-dihydro-1-oxo-2-phenylpyridazino[4,5-b]quinoxaline (168).



167 168

The reaction of the tetrahydroquinoxaline (169) with diketene and sodium hydroxide gives the pyrido[3,2,1-i,j]quinoxaline-7-oxide (170) and a similar reaction of the indoline (171) affords the pyrrolo[3,2,1-i,j]quinoxaline-6-oxide (172).[117] 3-Chloro-1-methylquinoxaline-2-one (173) on treatment with hydrazine hydrate gives (174) which with orthoesters provide the triazolo[4,3-a]quinoxalines (175).[118]

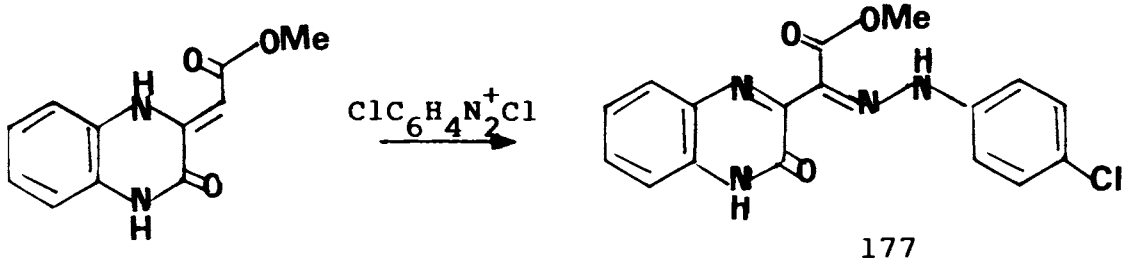


2.3.8 Heteroaryl Quinoxalines

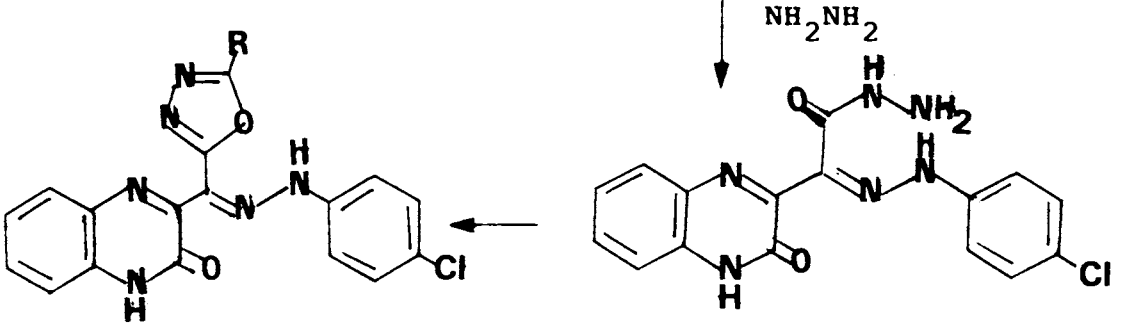
Reactions of the ester 176 with aryldiazonium chloride result in the methyleneic C-diazotization to give the α-arylhydrazono esters (177). The reaction of 177 with hydrazine hydrate afford the α-arylhydrazono hydrazides (178) in good yield.[119] Reaction of 178 with triethyl ortho esters provide 179, the 3-(α-arylhydrazono-1,3,4-oxadiazol-2-yl-methyl)-2-oxo-1,2-dihydroquinoxaline.[120] Reactions of 176 with pyrazole-5-diazonium chloride (180) gives the pyrazolylhydrazone (181) in good yield. Refluxing 181 in DMF or acetic acid result in cyclisation to afford the 3-quinoxalinyl pyrazolo[5,1-e][1,2,4] triazine (182).

Reaction of 2-quinoxalinyl hydrazine (183) with mucochloric acid (184) gives the 2-pyridazinyl quinoxaline (185) which is further derivitised.[121] Reactions of 2-amino-quinoxalines with dinitro halo benzene gives 2-(dinitro trifluoromethyl anilino)quinoxalines (186) which show excellent antifungal activity.[122]

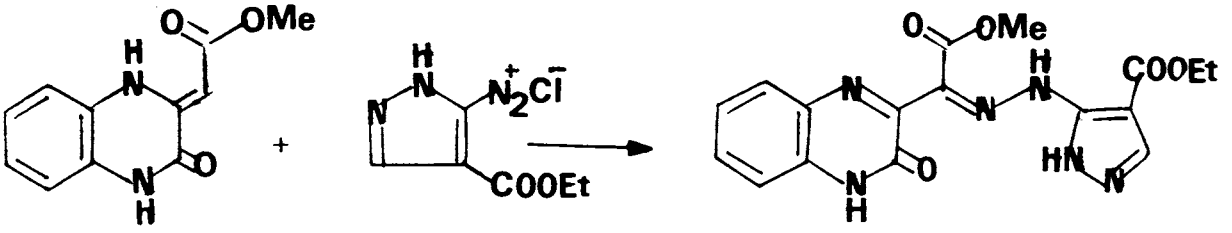
Nissan chemical industries elaborated synthesis of Quizalofop-Et (188) which is found to possess excellent grass hopper killer activity.[123,124] Thus reaction of



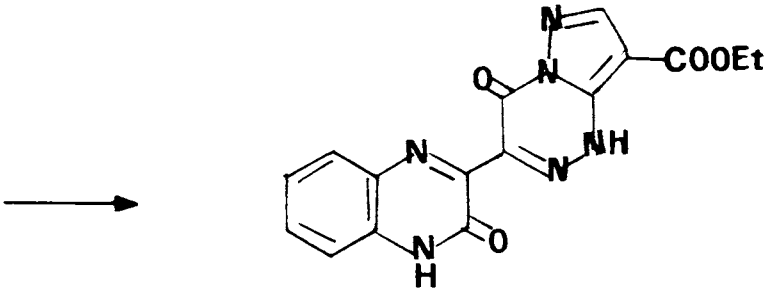
176 177



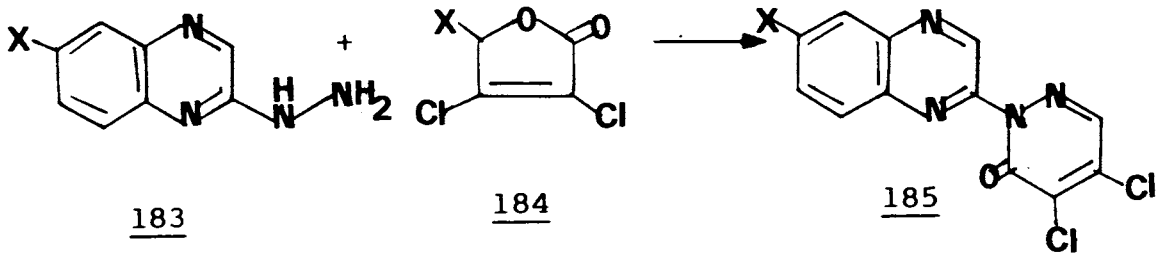
179 R = H, CH_3 178



176 180 181

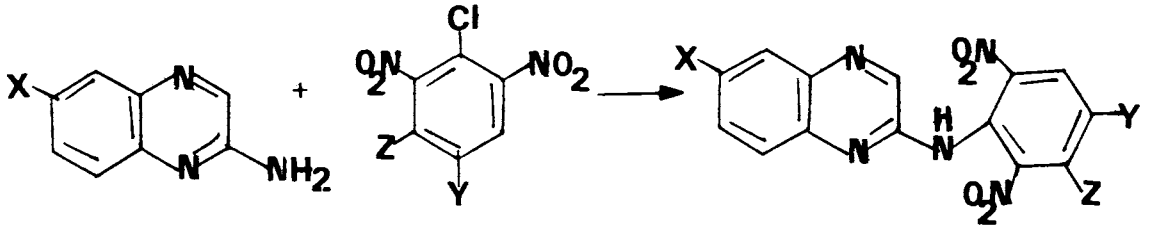


182



183 184 185

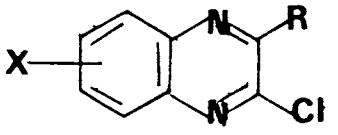
X = H, Cl, CF_3 X = OH, H



186 a) Y = CF_3, Z = Cl

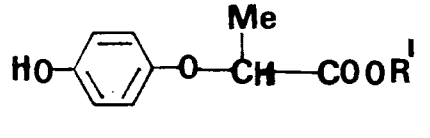
b) Y = CF_3, Z = H

c) Y = NO_2, Z = H

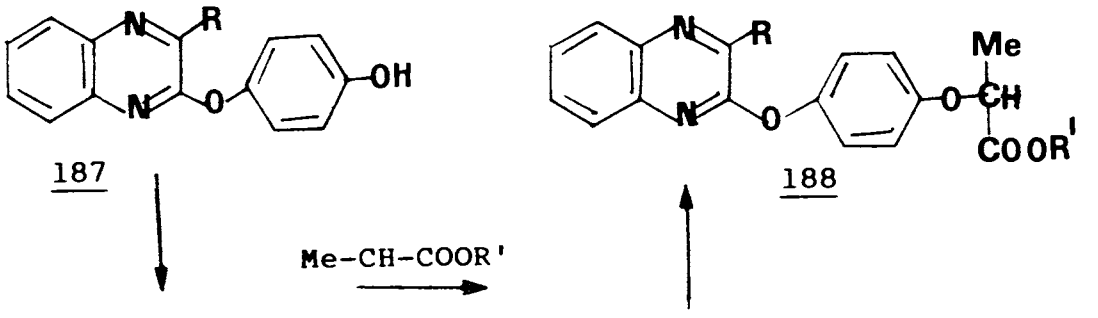


X = Cl, CF_3

R = CH_3, H



Hydroquinone

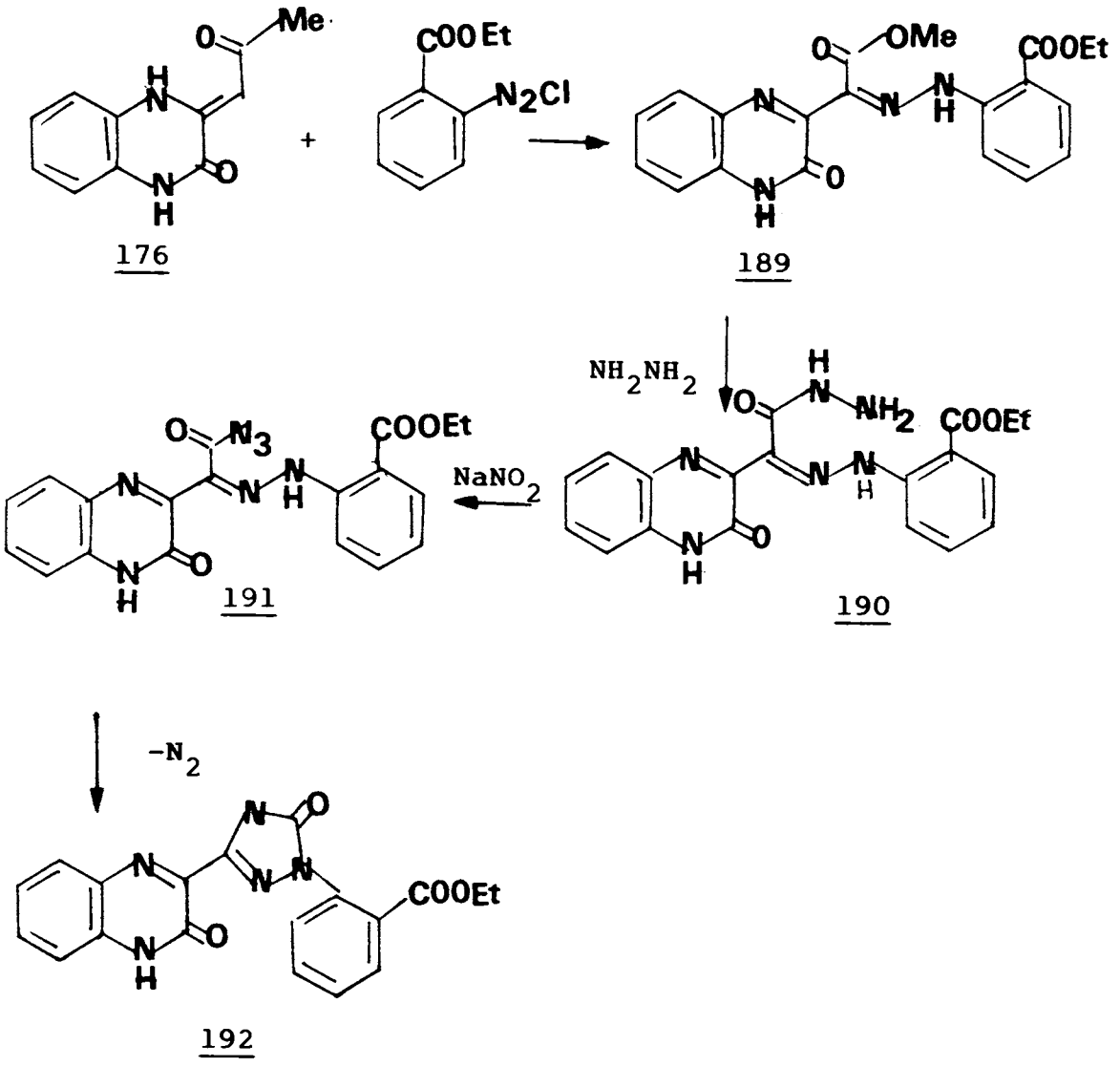


187 188

Me-CH-COOR'

2-chloroquinoxalines with 2-(4-hydroxy phenoxy)propionic acid derivatives give 2-[4-(2-quinoxalinyloxy)phenoxy]propionic acid (188) which is also obtained from the reaction of chloroquinoxalines with hydroquinone and then with 2-halo-propionic acid derivatives. The compound (188) is commercially called quizalofop.

The reaction of 3-methoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (176) with ethylbenzoate-2-diazonium chloride gave 3-[α-(o-ethoxycarbonylphenylhydrazono)-methoxy carbonylmethyl]-2-oxo-1,2-dihydroquinoxaline (189) whose reaction with hydrazine hydrate afford 3-[α-(o-ethoxy carbonyl phenylhydrazono]hydrazino carbonylmethyl]-2-oxo-1,2,dihydroquinoxaline (190). The reaction of 190 with sodium nitrite in water under cold conditions affords the azide (191) and subsequent heating of the reaction mixture resulted in the Curtius rearrangement[125] to provide 1-(o-ethoxy carbonylphenyl)-3-(3-oxo-3,4-dihydroquinoxaline-2-yl)-4,5-dihydro-1-H-1,2,4-triazol-5-one (192).



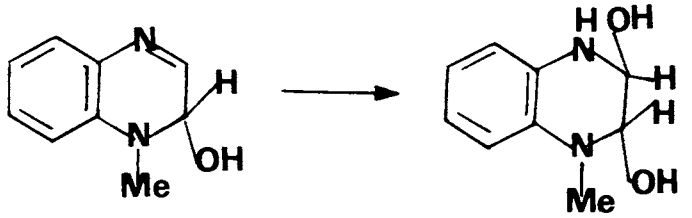
2.4 PHYSICAL METHODS OF CHARACTERISATION

2.4.1 Ultraviolet absorption spectra

The electronic spectra of quinoxaline and its 2-chloro,2-methoxy and 2-amino derivatives have been calculated by Pariser-Parr-Pople method.[126] Analysis of the UV

spectra of the monoprotonated 2-substituted quinoxalines and the Hammett correlation of the pKa shifts with the substituent constants, give two straight lines, corresponding to two sets of substituents and so reflecting a change in the position of protonation.[127] This may be why 2-methoxy quinoxaline was found to protonate at N-4 and 2-amino quinoxaline at N-1.[127]

The spectrum of 1-methylquinoxalinium iodide in dilute aqueous alkali at pH 10.5 shows absorption maxima at 301 and at 340 nm, and in methanolic sodium methoxide, a maxima at 304 and 344 nm.[128] The two maxima in aqueous alkali are attributed to the existence of an equilibrium mixture of the pseudo base (193) and the tetrahydro quinoxaline (194).[128] The pseudo base is the species that gives rise to the longer wavelength absorption maximum at



193 194

340 nm. It is formed by the nucleophilic attack of hydroxide ion at C-2 in aqueous alkali, and the tetrahydroquinoxaline is the result of covalent addition of water across the C_3-N_4 double bond of the pseudo base.[128]

2.4.2 Nuclear Magnetic Resonance Spectra

Nuclear magnetic resonance spectroscopy has become an indispensable tool for synthetic chemists, and an additional and very useful technique for examining tautomeric and conformational equilibria.

The H'-NMR spectrum of quinoxaline has been determined in carbontetrachloride and in acetone. The signal for H-2 and H-3 appears at δ 8.7 in carbontetrachloride and the computed chemical shifts for H-5(8), and H-6(7) are at δ 8.03 and δ 7.67 respectively.[124]

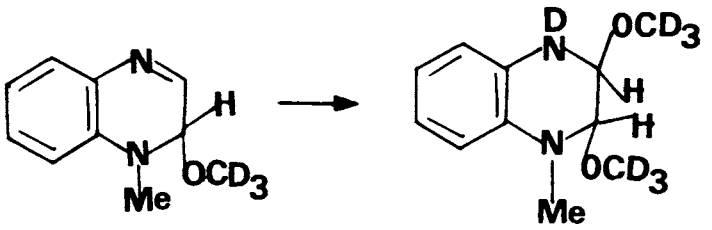
The H'-NMR spectra of a number of 2,5- and 6-monosubstituted quinoxalines have also been analysed and their chemical shifts and coupling constants reported.[129] A study of 'H-chemical shifts of 2,3,6-trimethylquinoxaline in carbontetrachloride, trifluoroacetic acid and fluorosulfonic

acid indicated that the carbocyclic ring participate in the positive charge distribution to the extent of about 25-30% in the mono protonated species and 15-20% in the diprotonated quinoxalines.

2,3-Diphenylquinoxaline forms a stable monocation in trifluoroacetic acid, as indicated by the down field hydrogen signals in this solvent, compared to those in CH_2Cl_2. Analysis of chemical shift values of quinoxaline-2,3-dicarboxylic acid in DMF and carbontetrachloride indicated the presence of an equilibrium between monomeric and dimeric species.

The existence of covalently hydrated quinoxaline (194) is confirmed by NMR examination of the 1-methyl-quinoxalinium cation in the basic methanol-d_4.[130] This prove to be complex and best interpreted by postulating the presence of the tetrahydroquinoxaline (196) in equilibrium with 195.

Chemical shifts and coupling constants of substituted 1,2,3,4-tetrahydroquinoxalines indicate that the arylated



195 196

heterocyclic ring in these derivatives is in the half chair form. The variation of the cis-vicinal and geminal couplings resulting from acylation on nitrogen indicates that the acylated derivatives have a slightly flattened half chair conformation.[130]

The ^{13}C chemical shifts for quinoxalines have been explained in terms of the inductive and resonance effects of the substituents. Resonance at 144.8 and 142.8 δ values in the spectrum of quinoxaline in deutro chloroform are assigned to carbon atoms 2 and 3; and 9 and 10 respectively. The C-5 and C-8 resonate[132] at δ 129.6 and C-6 and C-7 resonate at δ 129.4.

2.4.3 Mass Spectra

The mass spectra of a number of quinoxalines have been reported.[133] The parent heterocycle shows fragment ions resulting from the loss of one and two molecules of HCN. Similarly in the case of 2-alkyl and 2-arylquinoxalines, M^+-HCN, and M^+-RCN ions are observed.[133] A notable feature of the spectrum of 2-methyl-3-phenylquinoxaline is the formation of an intense $(M^+-1)^+$ ion. This was shown by deuterium labelling to be the result of hydrogen migration from the methyl group to the phenyl ring, followed by expulsion of a hydrogen atom to give the cation.[134]

The M^+-17 peak with the expected metastable ion was found to be a significant feature of the mass spectra of all substituted mono-N-oxides examined and is assigned to a one step elimination of the hydroxyl radical. For quinoxaline dioxides the M^+-16 peak is more important and is due to the preferential loss of an oxygen atom from the molecular ion.[133]

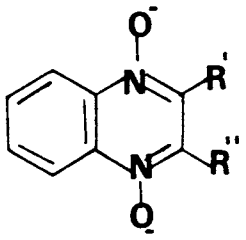
2.5 BIOLOGICAL STUDIES

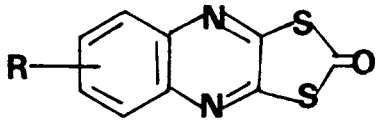
The present literature is abundant with reports of widespread usage of quinoxaline derivatives as antihypertensive agents and animal growth promoters.[113,120] It is also

interesting to note that several highly mutagenic and carcinogenic quinoxalines have been identified in heated meat and fried fish.[136] Buu-Hoc and co-workers among others, reported that certain condensed quinoxalines exhibit anti-bacterial, antiinflammatory, analgesic and tuberculostatic activities.[137]

Several biologically active polypeptides such as levomycin and echinomycin have been shown to possess one or more quinoxalinyl residues.[138] Antibiotics of the triostin and quinomycin series, isolated from streptomyces aureus, have been shown by degradative study to contain quinoxaline-2-carboxylic acid residue.[138]

The collaborative work by synthetic and screening research groups have continuously been carried out to create various biologically active quinoxalines. Thus quinoxaline 1,4-dioxides (197a-c) have been shown antibacterial[139] and quinoxaline-2,3-dithione cyclic dithio-carbonate (198a) (Morestan) and trithiocarbonate (198b) (Eradox) possess fungicidal and insecticidal effects.[140] The 2,3,7-trichloro-6-methylsulfamoyl quinoxaline (199) has been patented as anticancer agent.[141] 2-Phenyl-3-piperidino quinoxaline (200) and some of its derivatives are selective herbicides.[142]





197 a) R' = CH_3, R" = CH=NOCH$_3$

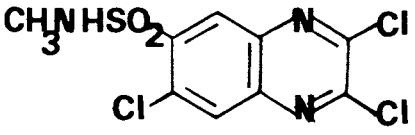
b) R' = H, R" = CH=NNHCOOMe

c) R' = CH_3, R" = CH_2OH

d) R' = R" = CH_2OH

198 a) R = CH_3,

b) R = H



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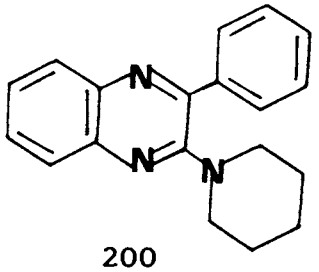

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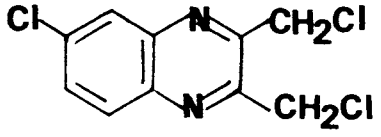

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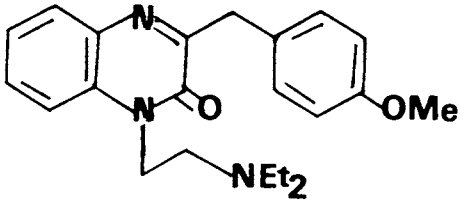

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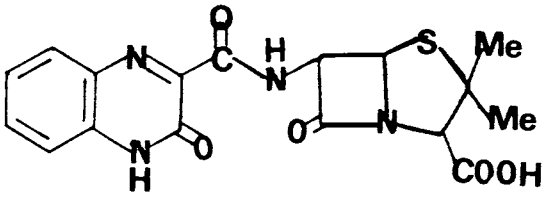


203

6-Chloro-2,3-bis (chloromethyl)-quinoxaline (201) has been patented as a foliar fungicide.[143] Caroverine (202) and Quinacilline (203) are used as antibacterial agents.[144,145] In addition to the above compounds, many other biologically active quinoxalines have also been reported. Studies in biosynthesis of quinoxaline antibiotics have also been reported by Konrad et al.[146] According to them quinoxaline antibiotics are chromodepsipeptides produced by several streptomyces strains.

Chapter 3

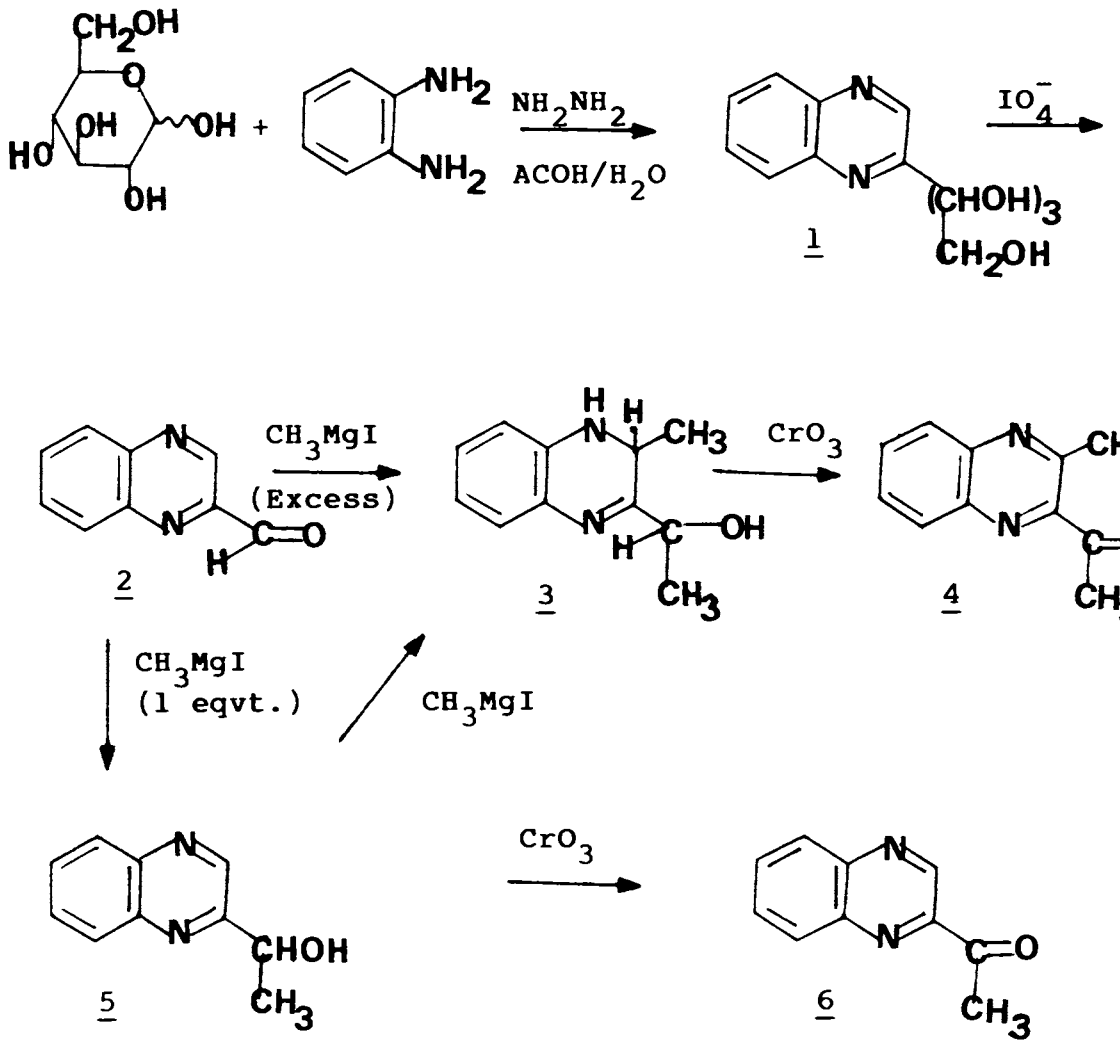
RESULTS AND DISCUSSION

3.1 ADDITION REACTIONS OF QUINOXALINE-2-CARBOXALDEHYDE

The synthesis of quinoxaline-2-carboxaldehyde (2) was carried out by the oxidation of 2-(D-arabino-tetrahydroxybutyl)quinoxaline (1) following the method reported by C.L.Leese and H.N.Rydon.[147] Treatment of D-glucose with o-phenylenediamine in the presence of hydrazine hydrate and acetic acid on a boiling water bath under a carbondioxide atmosphere provided by the addition of a pinch of sodium bicarbonate, gave the tetrahydroxybutyl quinoxaline derivative.[13,147] The carboxaldehyde 2 was obtained in 63% yield by the oxidation of 1 with sodium metaperiodate in water in the presence of acetic acid at laboratory temperature. The product was isolated by extraction with ether and purified by recrystallisation from petroleum ether.

Treatment of quinoxaline-2-carboxaldehyde (2) with excess of methylmagnesium iodide prepared from methyl iodide and magnesium in ether gave 3-methyl-3,4-dihydro-2-(α-hydroxyethyl)quinoxaline (3) in 94% yield as a red dye. The structure of 3 was established by spectral data as given below. The IR spectrum of 3 showed peaks at 3350 cm^{-1} (broad) for -OH and -NH and at 1650 cm^{-1} for C=N-. The nuclear magnetic resonance spectrum of 3 revealed the presence

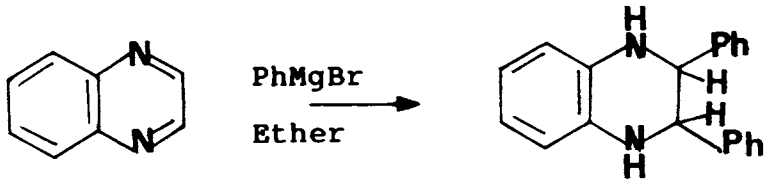
of two methyl absorption bands at δ 1.2 and at δ 2.2. The different positions of the absorption bands due to the methyl groups in the above nuclear magnetic resonance spectra are explicable on the basis that an increase of electron density causes shielding which is manifested by a displacement of the band in the direction of the increasing field strength. The two methyl absorption bands are doublets, consistent with the proposed structure of 3. Barltrop et al[51] who obtained 3 by a catalytic reduction of 2-acetyl-3-methylquinoxaline (4) established that the colored dye is a dihydro derivative resulting from the partial reduction of the quinoxaline ring. It is also thus established that the 1,2-dihydro isomer is thermodynamically more stable than the 1,4-dihydro isomer.[53] Treatment of 3 with Jones' reagent at 0°C oxidised both the -C-NH- and the -CH-OH groups to give 94% of 2-acetyl-3-methylquinoxaline (4). The NMR and IR spectra of 4 were in agreement with the reported values.[22] Although the oxidation of a -CH-NH is not expected under the above conditions, the facile oxidation of the 1,2 position to give 3 may be due to the fact that a stable aromatic system is produced.



Addition of one equivalent of methylmagnesium iodide in ether to an ether solution of quinoxaline-2-carboxaldehyde (2) (reverse addition) cooled in a freezing

mixture, followed by addition of water, extraction with ether and recrystallisation from hexane gave 97% of 2-(α-hydroxyethyl)quinoxaline (5). Nuclear magnetic resonance spectra of compound 5 showed multiplet at δ 7.6-8 for the aromatic protons and a doublet centered at δ 1.6 for the methyl protons. The other absorptions were a multiplet at δ 5.2 for -CH and a doublet at δ 4.3 for OH. The infrared spectrum of 5 showed an absorption band at 3230 cm^{-1} for OH. Oxidation of 5 with Jone's reagent at 0°C gave 91% of the known 2-acetylquinoxaline (6).[80] The IR and NMR spectra of 6 were consistent with its structure (see experimental section for details).

The formation of 3 from 2 may be considered as a result of addition of two moles of methylmagnesium iodide, one across the 1,2 - C=N and the other on the aldehyde group It may be noted here that Grignard reagents are known to add across the C=N of the quinoxaline ring.[148] Thus, addition of phenylmagnesium iodide to quinoxaline (7) itself has been reported to give 2,3-diphenyl-1,2,3,4-tetrahydro quinoxaline (8).



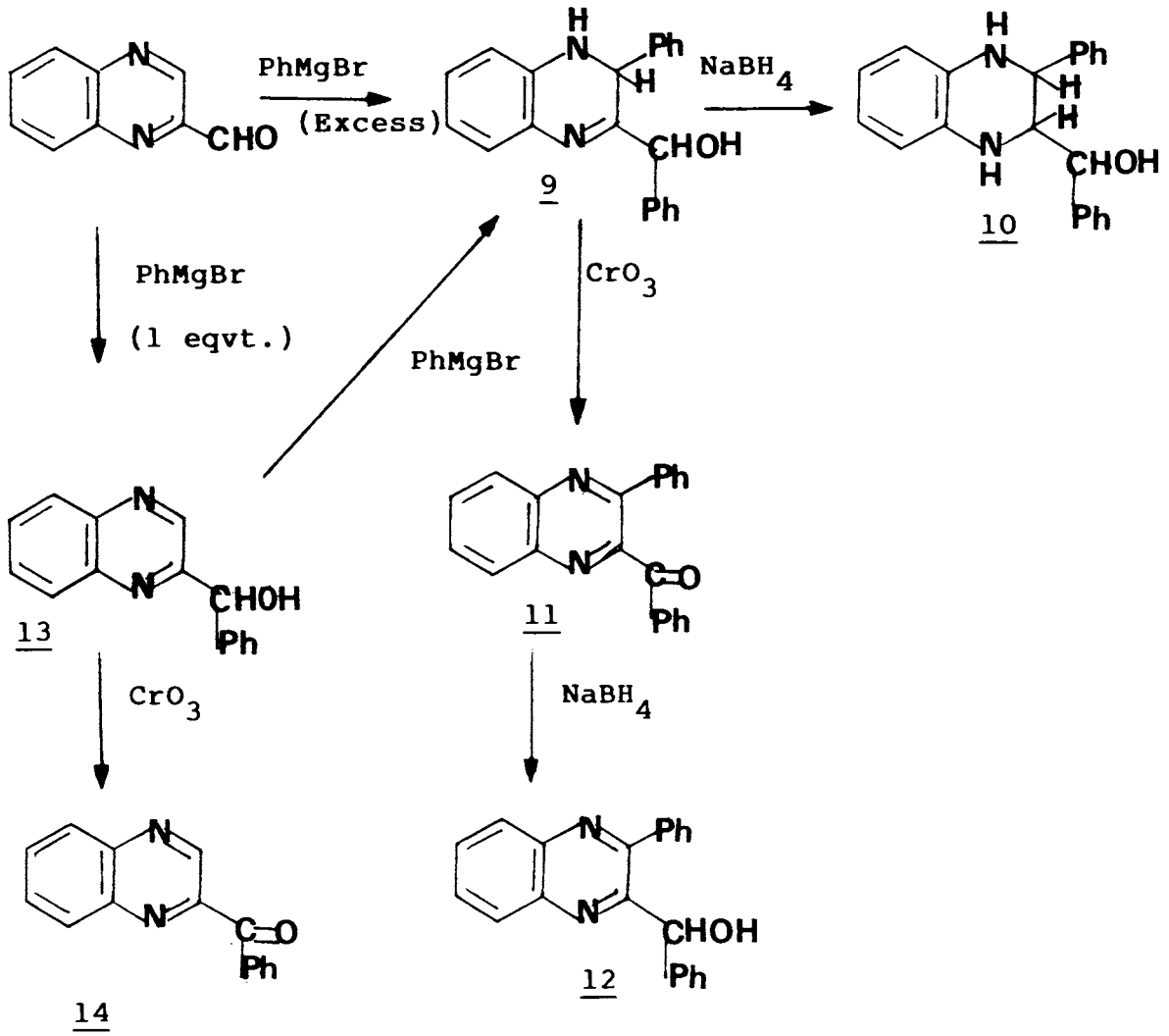
7 8

The additions of methylmagnesium iodide to 2 might have been stepwise, the first molecule getting added across the more reactive aldehydic group giving 5 followed by addition of a second molecule to the C=N to give 3. The fact that the reaction of 5 with an excess of methylmagnesium iodide gave compound 3 supported this view. Although the addition of one more molecule of methylmagnesium iodide to the second C=N is possible, this does not take place probably because the carbon end of that C=N- is already substituted by CH_3-CH-O group and thus both the steric effect and the negative charge on the oxygen prevent further addition of the negative end of methylmagnesium iodide to that bond.

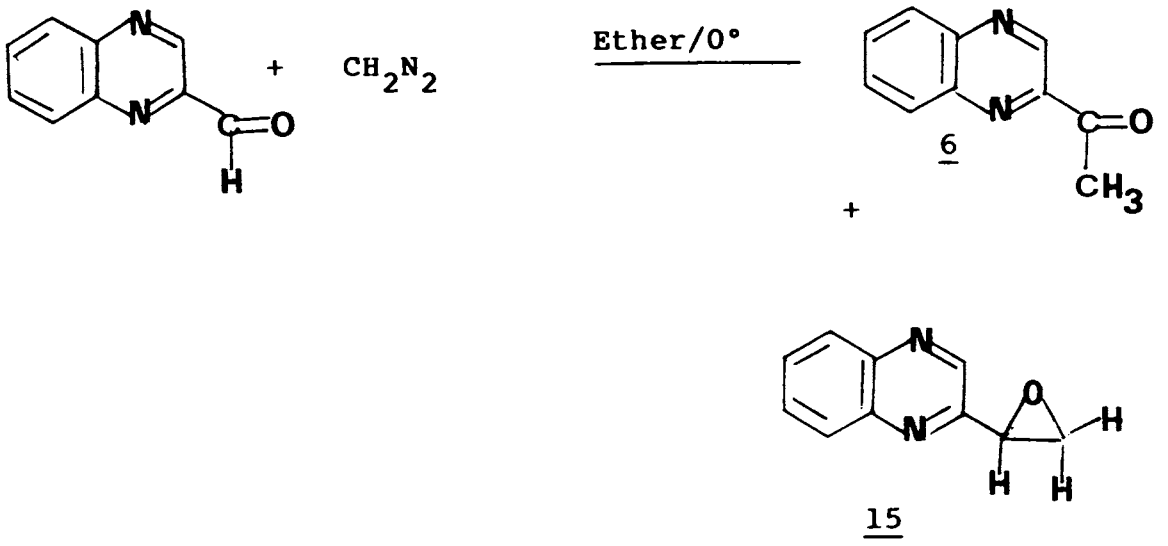
Similarly, treatment of quinoxaline-2-carboxaldehyde (2) with excess of phenylmagnesium bromide prepared from bromobenzene and magnesium in absolute ether gave 2-(α-hydroxybenzyl)-3,4-dihydro-3-phenylquinoxaline (9) in 66% yield.[149] The mass spectra of 9 showed a weak molecular ion peak at m/z 314, a strong peak at m/z 313 (M^+-H), the base peak at m/z 312 (M^+-2H) and other strong peaks at m/z 283 (313-CHOH), m/z 235 (312-C_6H_5), m/z 207 (M^+-C_6H_5CHOH) etc. The IR spectra showed peaks at 3350 cm^{-1} (OH and NH) and 1650 cm^{-1} (C=N).

Reduction of 9 with sodium borohydride in methanol at room temperature gave 1,2,3,4-tetrahydro-2-(α-hydroxybenzyl)-3-phenylquinoxaline (10) in 81% yield. Treatment of 9 with Jone's reagent oxidised both the -CHNH and -CHOH to give 2-benzoyl-3-phenylquinoxaline (11) in excellent yield. The structure of 11 was confirmed by its IR, NMR and mass spectral data. Reduction of 11 with sodium borohydride gave 2-(α-hydroxybenzyl)-3-phenylquinoxaline (12). Addition of one equivalent of phenylmagnesium bromide in ether to an ether solution of 2 gave 76% of 2-(α-hydroxybenzyl)quinoxaline (13). Oxidation of 13 with Jone's reagent at 0°C gave 89% of the known 2-benzoylquinoxaline (14). Reduction of 14 using sodium borohydride in methanol gave

back the alcohol 13. Reaction of 13 with excess of phenylmagnesium bromide gave 9 in good yield as expected.



Treatment of a solution of quinoxaline-2-carboxaldehyde (2) in ether with diazomethane in ether gave the expoxide, quinoxaline-2-yl-ethylene oxide (15) in 27.5% yield in addition to the expected 2-acetylequinoxaline (56).[150] The structure of 15 was established by using spectral data and elemental analysis. The mass spectra of 15 showed a weak molecular ion peak at m/z 172, and other peaks at 144 (M^+ -CO) and 116 (144-N_2). The IR spectrum showed peaks at 3050 cm^{-1} (C-H stretching), 1680 cm^{-1} (C=N) and 1100 cm^{-1} corresponding to the symmetrical stretching of the epoxide ring.[151] The nuclear magnetic resonance spectrum of the compound showed a multiplet centered at δ 8, for aromatic H, a triplet at δ 5.8 and a doublet at δ 4.1 for the -CH and $-CH_2$ protons respectively of the epoxide ring. Results of elemental analysis were in agreement with the calculated values.



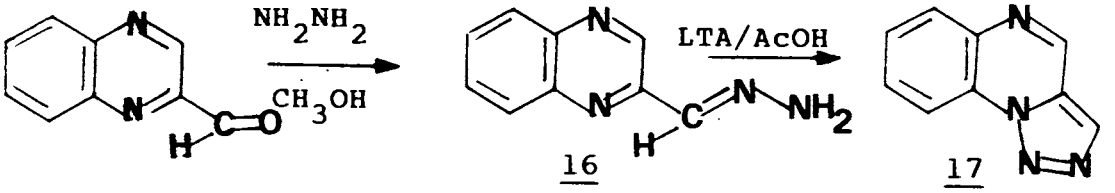
3.2 SYNTHESIS OF CONDENSED QUINOXALINES

Certain condensed quinoxalines are reported to exhibit antibacterial, antiinflammatory, analgesic and tuberculostatic activities.[137,161] Triazoles are found to be both medicinally and industrially important as they are widely used as drugs, optical brightners and polymer additives.[152] Hence the synthesis of quinoxalines with fused triazole ring system is of paramount interest.

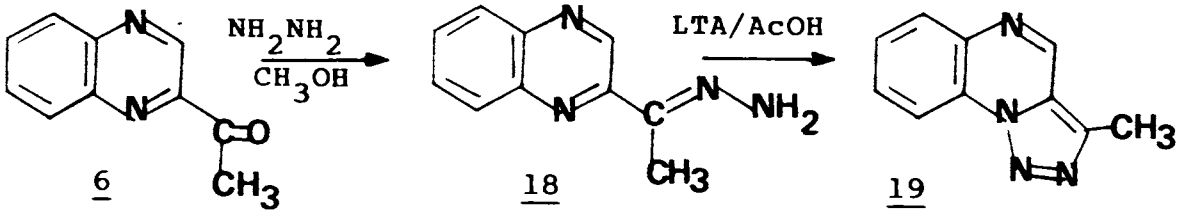
Synthesis of nitrogen heterocycles by the oxidative cyclisation of aldehyde hydrazones having potential cyclisation sites using lead tetraacetate as the reagent

has been reported previously.[153] This reaction can be successfully applied for the synthesis of condensed quinoxalines.

Quinoxaline-2-carboxaldehyde hydrazone (16) was prepared by stirring quinoxaline-2-carboxaldehyde (2) with 80% hydrazine hydrate in methanol at room temperature for 30 minutes in 75% yield.[154] Treatment of quinoxaline-2-carboxaldehyde hydrazone (16) with freshly prepared lead tetraacetate in glacial acetic acid for 8 hours gave v-triazolo[3,4-a]quinoxaline (17) in 70% yield.



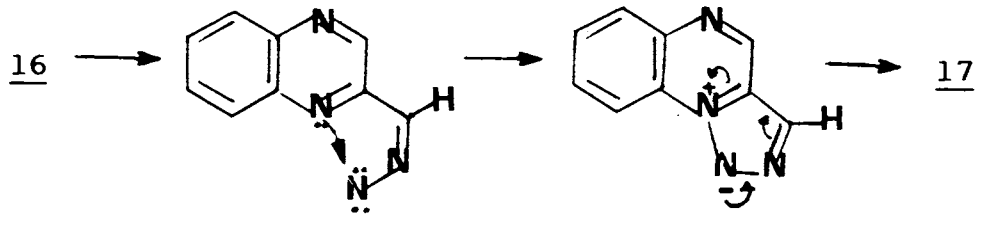
16 17



6 18 19

The structure of the new condensed quinoxaline was established by spectral data and elemental analysis. Compound 17 showed a strong molecular ion peak at m/z 170, a weak M^++1 peak, the base peak at m/z 142 (M^+-N_2) and other strong peaks at m/z 115 (M^+-N_2,HCN) and m/z 102. The mass spectra of fused triazoles are characterised by the loss of nitrogen and HCN from the molecular ion peak.[155] The nuclear magnetic resonance spectrum of the compound showed a multiplet centered at δ 8, for the aromatic protons. The peak at δ 9.4 represented the lone proton on the triazole ring. The infrared spectrum showed peaks at 3080 cm^{-1} for C-H stretching, 1650 cm^{-1} for -N=N- and 950-990 cm^{-1} characteristic of triazole nucleus.

The mechanism of this cyclisation may be postulated as follows. An initial attack at the amino nitrogen by lead tetraacetate to give an intermediate nitrene[158] (16a) followed by internal nucleophilic displacement could account for the formation of the product.

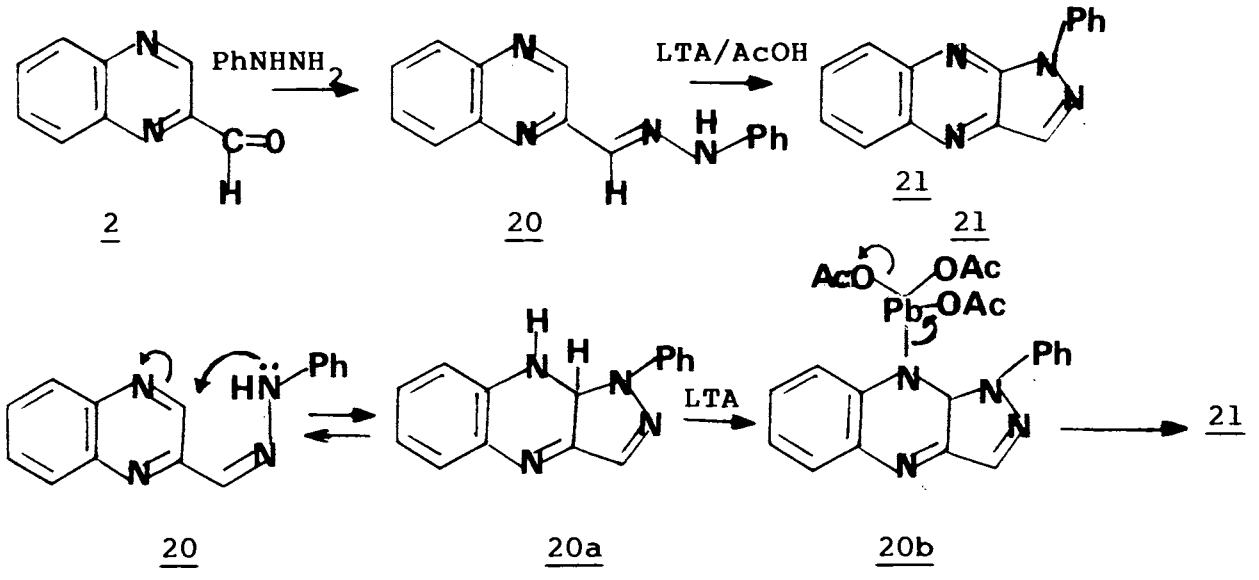


16a 16b

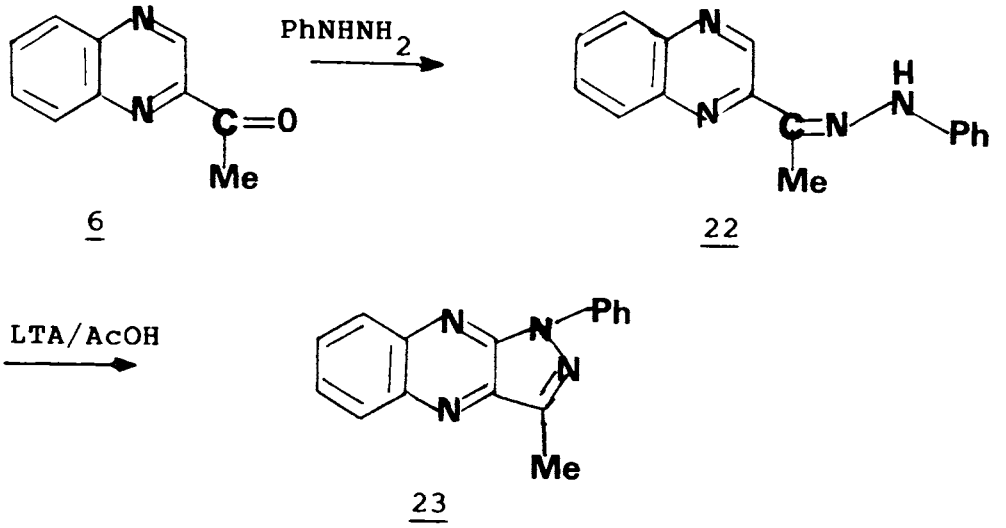
Similarly, 2-acetylquinoxaline (6) with hydrazine hydrate in methanol have 2-acetylquinoxaline hydrazone (18). Treatment of 2-acetylquinoxaline hydrazone (18) with equimolar quantity of freshly prepared lead tetraacetate in glacial acetic acid for 5 hours gave 5-methyl-v-triazolo-[3,4-a]quinoxaline (19) in 87% yield. The mass spectrum of the compound showed a strong molecular ion peak at m/z 184 and weak peaks at 185 (M^++1) and 183 (M^+-1). The other characteristic peaks were 169 (M^+-CH_3), m/z 142 (M^+-CH_3,HCN) and 116 (M^+-CH_3,HCN & N_2). The nuclear magnetic resonance spectra of the compound showed peaks at δ 2.8 for the methyl protons and a multiplet at δ 7.3-8.3 corresponding to the aromatic protons. The large change in chemical shift observed for the absorption of methyl protons was due to the low electron density at the $-CH_3$ substituted carbon. The infrared spectrum and results of elemental analysis were also consistent with the structure of the compound.

Quinoxaline-2-carboxaldehyde phenylhydrazone (20) was obtained in 81% yield by treating a solution of quinoxaline-2-carboxaldehyde (2) with freshly distilled phenylhydrazine in methanol at room temperature for one hour.[4] Treatment of the hydrazone 20 with an equivalent quantity of freshly prepared lead tetraacetate in glacial

acetic acid gave 1-phenylpyrazolo[3,4-b]quinoxaline (21) in 66.6% yield. The compound 21 was identified by direct comparison with a standard sample using spectral and analytical data which were identical in all respects.[149,157] It is known that quinoxaline-2-carboxaldehyde phenylhydrazone readily undergoes oxidative cyclisation in the presence of phenylhydrazine or azobenzene[149] to give 1-phenyl pyrazoloquinoxaline. Here we report for the first time the successful cyclisation of 20 using lead tetraacetate as the oxidising agent. It is also noteworthy that the reaction requires only a shorter period and the product is formed in a better yield. The mechanism of this cyclisation may be proposed as follows. The reversible nucleophilic addition of the $NH-C_6H_5$ across the C=N-band of quinoxaline to give 20a followed by oxidation with lead tetraacetate as shown in 20b will give the product.



Similarly 2-acetylquinoxaline on treatment with phenylhydrazine in methanol gave 2-acetylquinoxaline phenylhydrazone (22) in 84% yield. Treatment of this phenylhydrazone 22 with an equivalent quantity of freshly prepared lead tetraacetate in glacial acetic acid at ambient temperature for 5 hours gave 3-methyl-1-phenyl pyrazolo[3,4-b]quinoxaline (23) in 66% yield. Compound 23 showed in its mass spectrum a molecular ion peak at m/z 260, as the base peak. The other characteristic peaks were at m/z 192, (219-HCN). The nuclear magnetic resonance spectrum of the compound showed a singlet at δ 2.7 for the $-CH_3$ proton and a



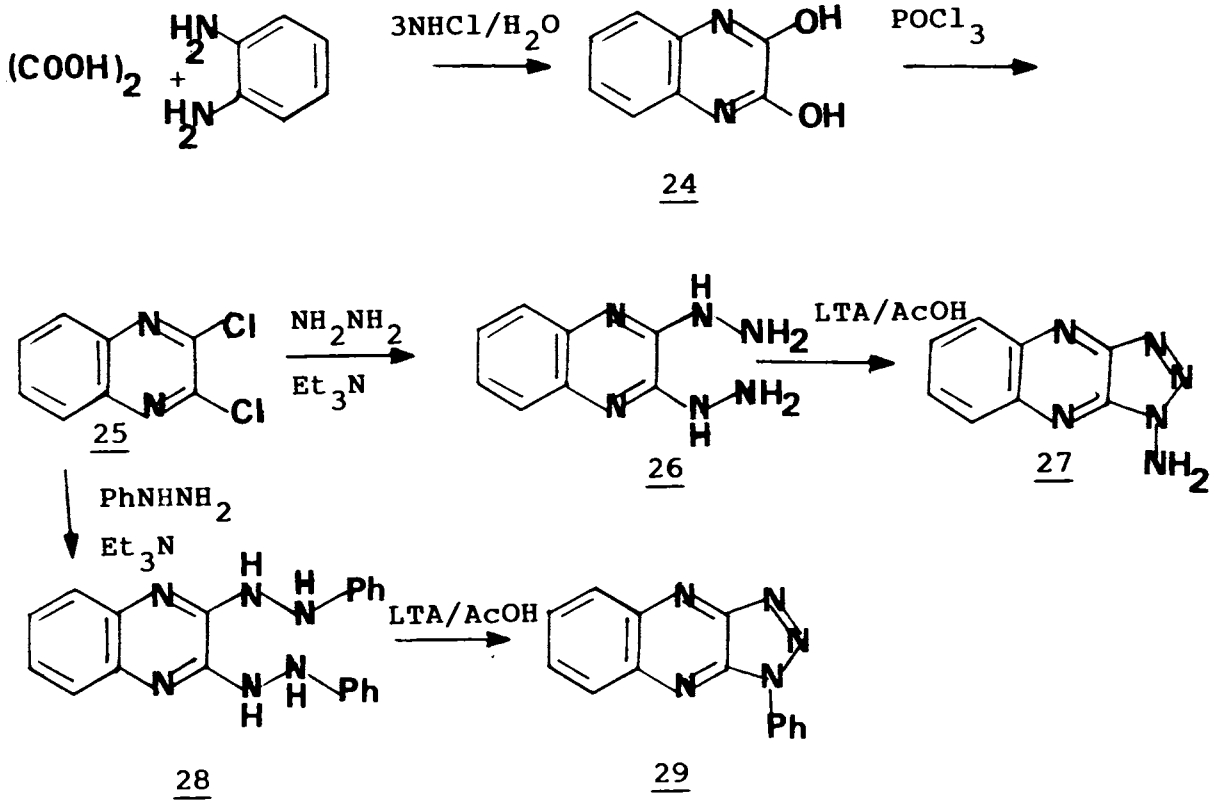
6 22 23

multiplet at δ 7.2 to 8.4 for the aromatic protons. The infrared spectra of the compound showed bands at 2900 cm^{-1} for the C-H stretching and at 1650 cm^{-1} for the C=N. The elemental analysis of the compound was also consistent with its structure.

Alexandroue and Curtin reported in 1963 that osazones and substituted hydrazones of α-diketones undergo oxidative dehydrogenation to give substituted 1,2,3-triazoles.[158] We have now successfully applied this reaction for the synthesis of triazoloquinoxalines as follows.

2,3-Dihydroxyquinoxaline (24) was obtained by refluxing a 1:1 mixture of oxalic acid and o-phenylenediamine in 3N aqueous hydrochloric acid for one hour over a boiling water bath.[159] 2,3-Dichloroquinoxaline (25) was obtained in good yield by treating 24 with excess of phosphorous oxychloride.[85] 2,3-Bis hydrazinoquinoxaline (26) was obtained in 92% yield by heating a solution of 25 in methanol with 80% hydrazine hydrate and a few drops of triethylamine. 2,3-Dichloroquinoxaline (25) in methanol with phenylhydrazine and a few drops of triethylamine for half an hour gave 2,3-bis phenylhydrazinoquinoxaline (28) in good

yield. The two bis hydrazino derivatives were cyclised to triazoloquinoxalines using lead tetraacetate.

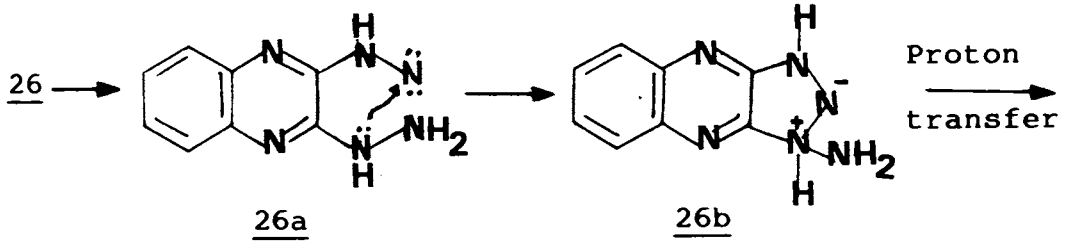


Thus, 2,3-bis hydrazinoquinoxaline (26) on treatment with freshly prepared lead tetraacetate in glacial acetic acid gave 1-amino[4,5-b]triazoloquinoxaline (27) in 86% yield. The mass spectrum of the compound showed a weak molecular ion peak and a prominent (M^+-1) peak at m/z 185. The sharp (M^+-1) peak in the mass spectrum indicated the presence of $-NH_2$ group. Other important peaks in the mass

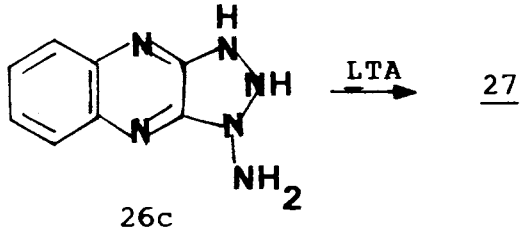
spectrum of the compound are at m/z 158 (M^+-N_2), m/z 131 (158-HCN) and a peak at m/z 28 which were all characteristic of the triazole ring system. The infrared spectrum of the compound showed two bands at 3400 cm^{-1} and at 3150 cm^{-1} for the primary amino group[151], one band at 3000 cm^{-1} for the C-H stretching and other significant bands at 1640 cm^{-1} and 1560 cm^{-1}. The nuclear magnetic resonance spectra recorded in DMSO and the results of the elemental analysis were consistent with the structure of 27.

Treatment of 2,3-bis phenylhydrazinoquinoxaline (28) with an equivalent quantity of freshly prepared lead tetraacetate gave 1-phenyl[4,5-b]triazoloquinoxaline (29) in 83.3% yield. The mass spectrum of 1-phenyl[4,5-b]triazoloquinoxaline showed a molecular ion peak at m/z 247 and a (M^+-1) peak at m/z 246. Other important peaks were at m/z 219 (M^+-N_2) and m/z 192 (219-HCN), characteristic of triazolo ring system, along with other peaks. The nuclear magnetic resonance spectrum of the compound showed only characteristic absorption for the aromatic protons as multiplet in the region δ 7.4-8.4. The infrared spectrum and results of elemental analysis were also consistent with the structure of 29.

The mechanisms of these reactions are not well understood. The formation of a nitrene intermediate 26a followed by nucleophilic addition to give 26c and subsequent oxidation of 26c with another equivalent of lead tetraacetate would explain how 27 is obtained. The formation of 29 would necessarily involve a phenyl migration and may be postulated as follows.

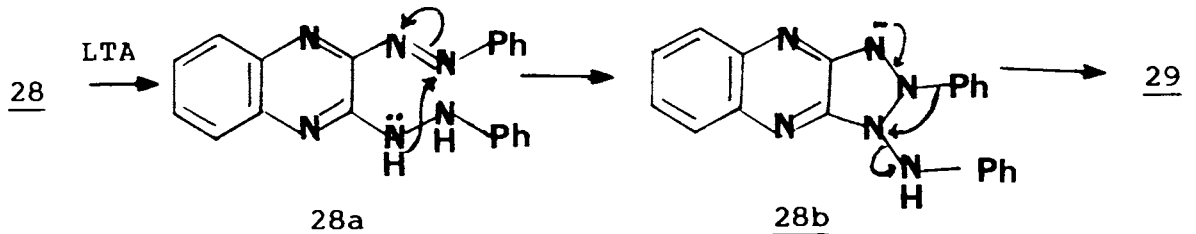


26a 26b



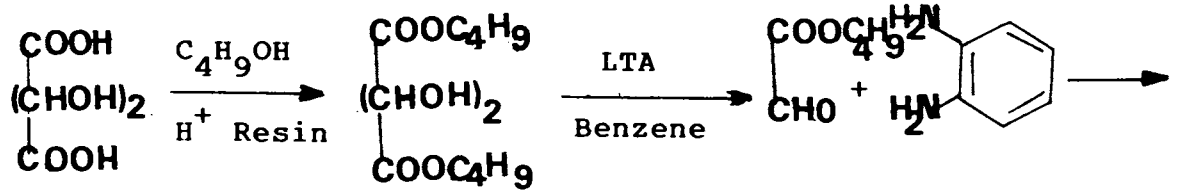
27

26c



28a 28b

2-Hydroxyquinoxaline (32) was obtained by the condensation [4] reaction of o-phenylenediamine and n-butylglyoxylate (31) in benzene. n-Butylglyoxylate was in turn prepared by the oxidative cleavage of the di-n-butyltartarate (30) using lead tetraacetate in dry benzene.[160] Treatment of 2-hydroxyquinoxaline (32) with excess of phosphorous oxychloride and catalytic amount of DMF gave 2-chloroquinoxaline (33) in 97.5% yield.[47] 2-Hydrazinoquinoxaline



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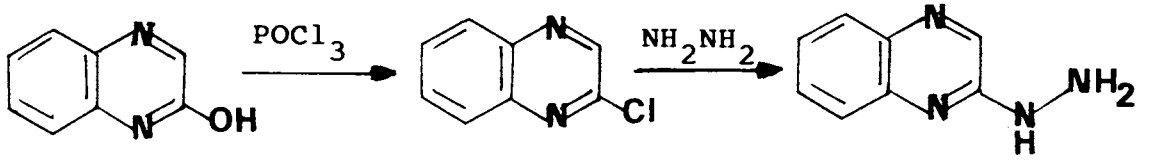
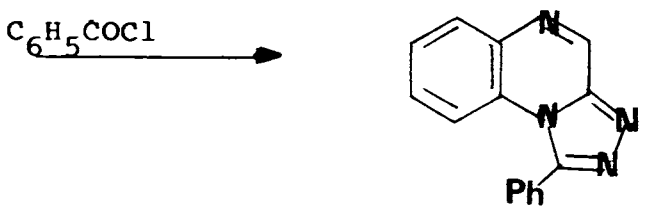


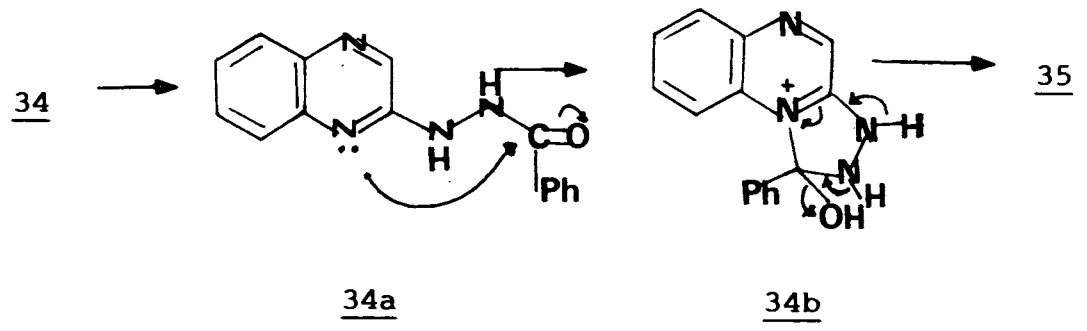
32 33 34



35

(34) was obtained in good yield by treating a solution of 33 in methanol with 80% hydrazine hydrate and a few drops of triethylamine. 2-Hydrazinoquinoxaline thus obtained was used as an intermediate for the synthesis of condensed quinoxalines.

Refluxing 2-hydrazinoquinoxaline (34) with benzoyl chloride over a water bath for 2 hours gave on work up 75% of 5-phenyl-1,2,4-triazolo[3,4-b]quinoxaline (35). The compound was characterised using spectral and analytical data. The mass spectrum of the compound showed a molecular ion peak at m/z 246, followed by a peak at m/z 214 (M^+-N_2) which is characteristic of a triazole ring. The nuclear magnetic resonance spectra showed multiplet at δ 8.2 to 8.4 for the protons on the heterocyclic ring and at δ 7.5 for the phenyl protons. The infrared spectrum showed bands at 2990 cm^{-1} (CH), 1601 cm^{-1} (C=N), 1546 cm^{-1} and at 1452 cm^{-1}. Results of elemental analysis were in agreement with the calculated values. The mechanism of the formation of 35 may be indicated as proceeding through the intermediates 34a and 34b.



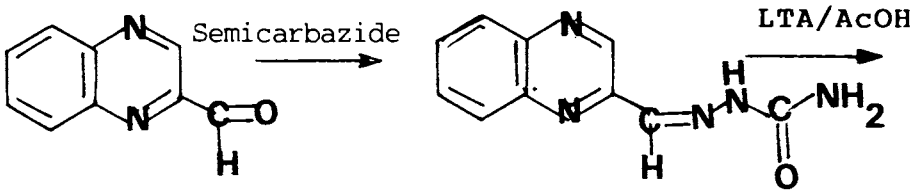
34a 34b

3.3 SYNTHESIS OF 2-HETEROARYL QUINOXALINES

The strong antibacterial activity possessed by quinoxalines and condensed quinoxalines[137] prompted us to undertake the synthesis and evaluation of quinoxalines substituted with heteroaryl systems. Moreover, there appear only very few reports on the synthesis and biological studies of heteroarylquinoxalines.[161]

Quinoxaline-2-carboxaldehyde semicarbazone (36) was obtained by treating quinoxaline-2-carboxaldehyde (2) with semicarbazide hydrochloride. Treatment of 36 with an equivalent quantity of freshly prepared lead tetraacetate in glacial acetic acid gave 2-(2-amino-1,3,4-oxadiazol-5-yl)-quinoxaline (38) in 75% yield. The mass spectrum of 36 showed a molecular ion peak at m/z 213 and an (M^++1) peak at m/z 214. The mass spectrum of the compound also showed a

prominent peak at m/z 170 (M^+-HNCO) which is very significant of 2-amino-1,3,4-oxadiozole.[155] The nuclear magnetic resonance spectrum of the compound showed a broad peak at δ 2.4 ($-NH_2$) and a multiplet at δ 7.5 to 8.5 (Aromatic). The infrared spectra of the compound showed two absorption bands at 3380 cm^{-1} and at 3280 cm^{-1} for the $-NH_2$ group and two



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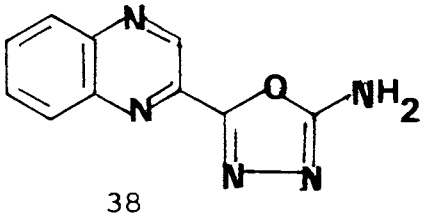

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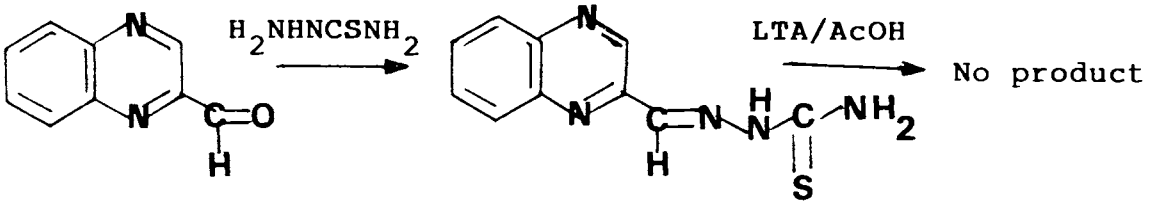
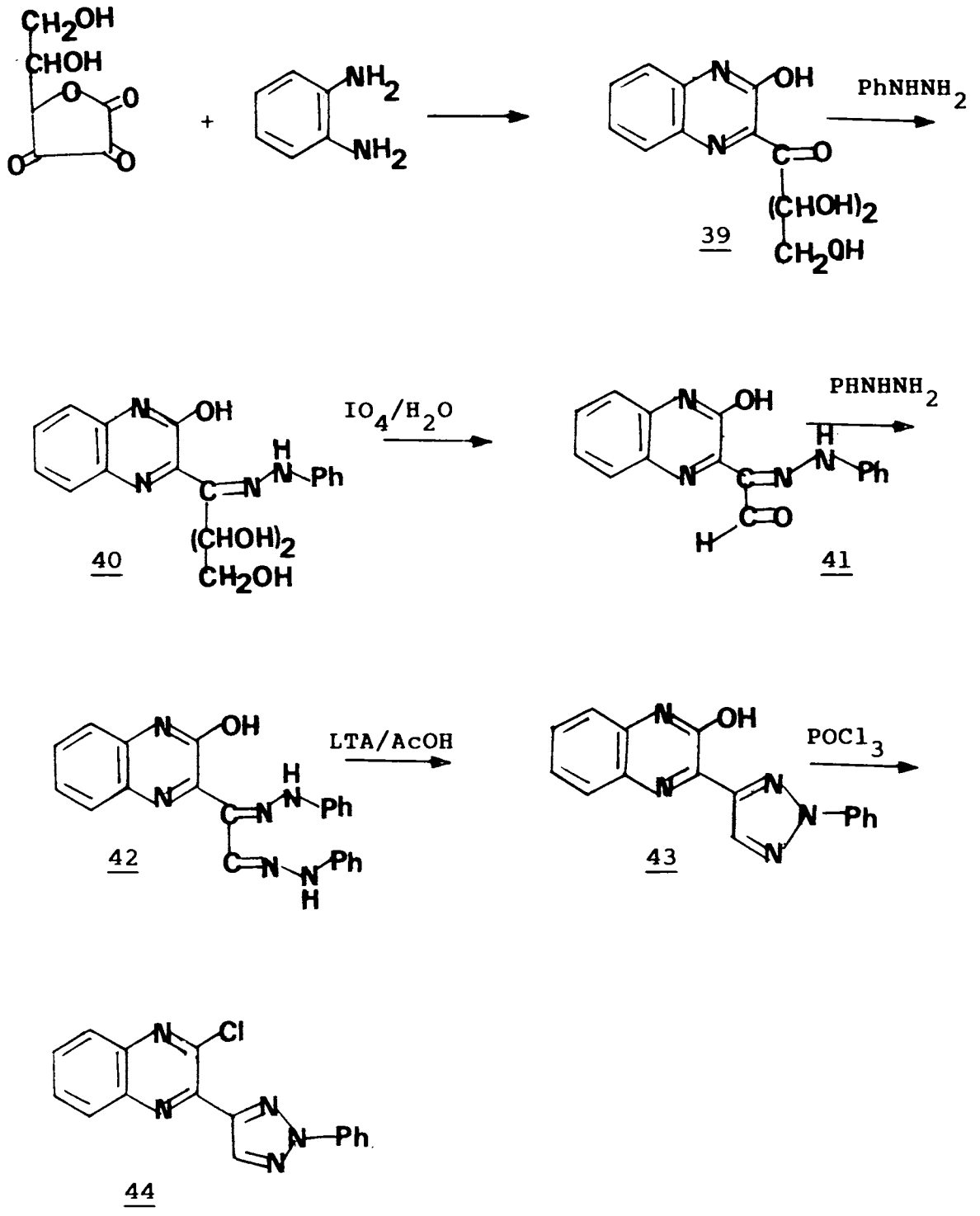


2 37

bands at 1030 cm^{-1} and 1020 cm^{-1} for the C-O-stretching. The elemental analysis of the compound was in agreement with its structure.

Quinoxaline-2-carboxaldehyde thiosemicarbazone (37) was prepared by treating the aldehyde 2 with thiosemicarbazide. Attempts to obtain cyclisation product of the thiosemicarbazone (37) by treatment with lead tetraacetate in acetic acid or benzene at room temperature or at higher temperatures proved unsuccessful.

2-Hydroxy-3-(1-oxo-2,3,4-trihydroxybutyl)quinoxaline (39)[162] was obtained by the condensation of dehydro ascorbic acid with o-phenylenediamine. Treating a suspension of 39 in methanol with freshly distilled phenylhydrazine and a few drops of acetic acid under reflux on a boiling water bath gave 2-hydroxy-3(1-phenylhydrazono-2,3,4-trihydroxybutyl)quinoxaline (40).[163] When the compound 40 was stirred in the dark with a cold aqueous solution of sodium metaperiodate, 2-hydroxy-3-(1-phenylhydrazono glyoxalyl)quinoxaline (41)[163] was obtained in 97.6% yield by the oxidative cleavage of the side chain. Compound 41 is a versatile starting material for the synthesis of heteroaryl quinoxalines. 2-Hydroxy-3-(1,2-bis phenylhydrazono glyoxalyl)quinoxaline (42)[163] was obtained in good yield by the treatment of 41



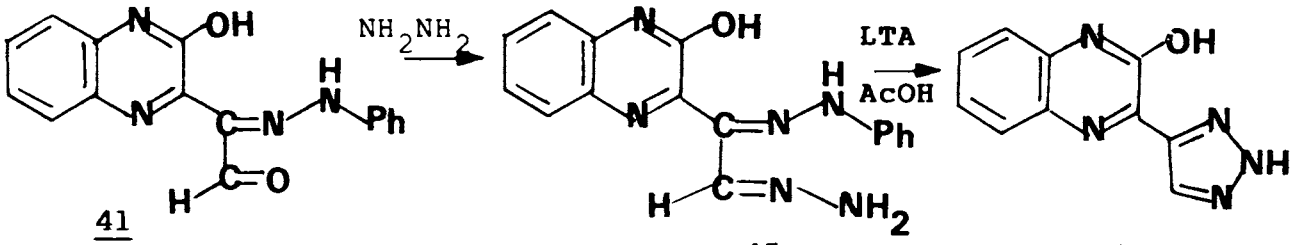
with freshly distilled phenylhydrazine in methanol with a few drops of acetic acid.

Alexandroue and Curtin reported that ozazones and bis hydrazones of 1,2-dicarbonyl compounds when treated with a range of oxidising agents undergo oxidative dehydrogenation to give 1,2,3-triazoles.[153] We have successfully applied this reaction in the synthesis of heteroaryl quinoxalines.

Treatment of the bis hydrazone 42 with an equivalent quantity of freshly prepared lead tetraacetate in glacial acetic acid gave 87.7% 2-hydroxy-3-(2-phenyl-1,2,3-triazolo-4-yl)quinoxaline (43). The mass spectrum of the compound showed a molecular ion peak at m/z 289. The other prominent peaks in the mass spectra are at m/z 261, ($M^+ - N_2$); m/z 169, (261-C_6H_5 NH); and m/z 149. The nuclear magnetic resonance spectrum of the compound showed multiplet at δ 7.2-8.2 for the aromatic protons and a singlet at δ 8.9 characteristic of the proton on the triazolyl ring. The infrared spectrum of the compound showed bands at 3500 cm^{-1} (broad, -NH, -OH), 1720 cm^{-1} (-$\overset{O}{\overset{\|}{C}}$-N- of the quinoxaline moiety) and 1630 cm^{-1} for C=N. The elemental analysis of the compound gave results consistent with the molecular formulae of the compound.

Treatment of the triazolylquinoxaline (43) with phosphorous oxychloride gave 2-chloro-3-(2-phenyl-1,2,3-triazol-4-yl)quinoxaline (44) in good yield. The spectral data and elemental analysis of the compound were consistent with the structure.

Reaction of 2-hydroxy-3-(1-phenylhydrazono glyoxalyl)quinoxaline (41) with 80% hydrazine hydrate in methanol gave 2-hydroxy-3-(1-phenylhydrazono-2-hydrazono glyoxalyl)quinoxaline (45) in 67% yield. Compound 45 underwent oxidative cyclisation on treating with lead tetraacetate in glacial acetic acid at room temperatures to give 2-hydroxy-3-(2(H)1,2,3-triazol-4-yl)quinoxaline (46) in 63% yield. Compound 46 was characterised spectroscopically. The mass spectrum of the compound showed molecular ion peak at m/z 213. The other significant peaks were at m/z 185, ($M^+ - N_2$); and m/z 158, (185-HCN). It is to be noted here that the loss of N_2 and HCN in the fragmentation is characteristic of the triazole ring system. The nuclear magnetic resonance spectrum of the compound recorded in DMSO showed characteristic peaks at δ 7.5-8.5 (multiplet for the aromatic protons) and δ 8.9 (singlet for the C_5'H of the triazole ring). The infrared spectrum of the compound showed bands at 3500 cm^{-1} (-NH, -OH), 2900 cm^{-1} (C-H-stretching) and at 1660 cm^{-1} (C=N).



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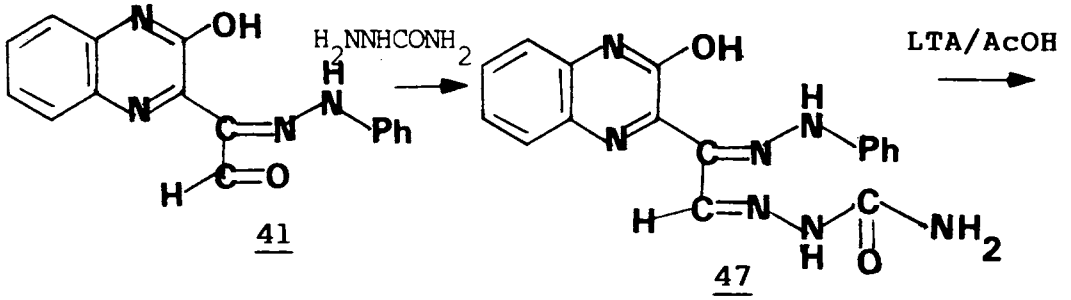
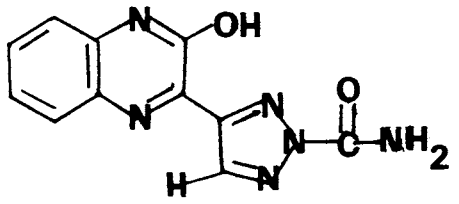


41 47



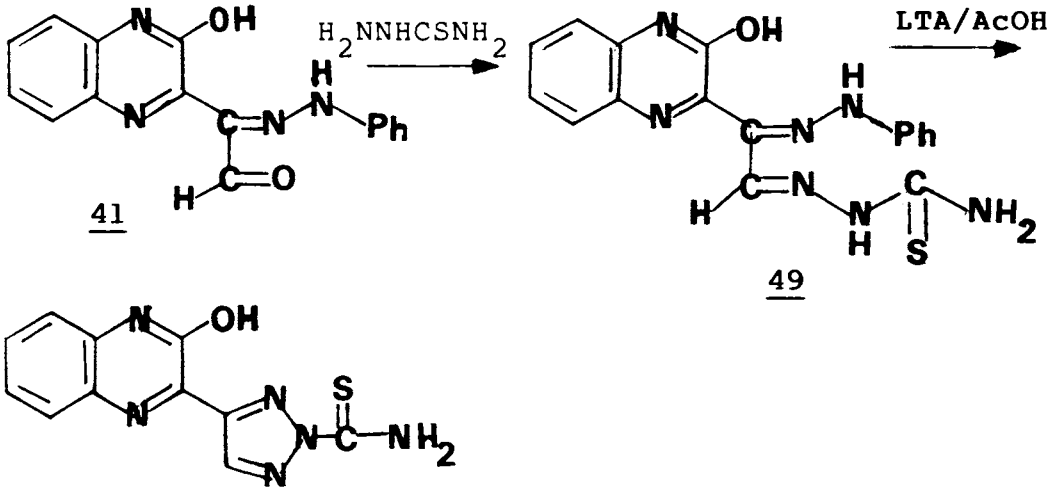
48

On stirring a suspension of 2-hydroxy-3-(1-phenylhydrazono glyoxalyl)quinoxaline (41) in water with semicarbazide hydrochloride and sodium acetate resulted in the formation of 2-hydroxy-3-(1-phenylhydrazono-2-semicarbazone glyoxalyl)quinoxaline (47). Treating 47 with an equimolar quantity of freshly prepared lead tetraacetate in glacial acetic acid gave 2-hydroxy-3-(2-amido-1,2,3-triazol-4-yl)-quinoxaline (48) in 91.6% yield.

The mass spectrum of the compound 48 showed molecular ion peak at m/z 256, (M^+ +1) peak at m/z 257 and (M^+ -1) peak at 255. The other important peaks were at m/z 214, (257-CONH) and m/z 188, (214-HCN). Nuclear magnetic resonance spectrum of the compound taken in DMSO showed a singlet at δ 9.2 for the proton on the triazole ring system in addition to the multiplet between δ 8 to 7 for aromatic protons. The infrared spectrum of the compound showed broad absorption at 3700 cm^{-1} (-NH, OH), two sharp peaks at 3300 cm^{-1} and 3200 cm^{-1} ($-CONH_2$) and a band at 1650 cm^{-1} (-C=N-). The results of elemental analysis of the compound were consistent with the molecular formula of the compound.

Similarly, 2-hydroxy-3-(1-phenylhydrazono glyoxalyl) quinoxaline (41) on treating with thiosemicarbazide in water gave 98% of 2-hydroxy-3-(1-phenylhydrazono-2-thiosemicarbazone glyoxalyl)quinoxaline (49). Cyclisation of 49 using lead tetraacetate in glacial acetic acid gave the cyclised product, 2-hydroxy-3-(2-thioamido-1,2,3-triazol-4-yl)quinoxaline (50) in 95.8% yield. The mass spectrum of the compound showed molecular ion peak at m/z 272 and (M^+ +2) peak at 274. Other prominent peaks were at m/z 258, ($274-NH_2$) and m/z 246, ($274-N_2$). The infrared spectrum of

the compound showed absorption bands at 3700 cm^{-1} (-NH, OH, broad), 3450 cm^{-1} ($-CSNH_2$), 1630 (-C=N-) and at 1260 cm^{-1} (C=S), all characteristic of the structure, 50. The nuclear magnetic resonance spectrum and elemental analysis were all in agreement with the structure of the compound.

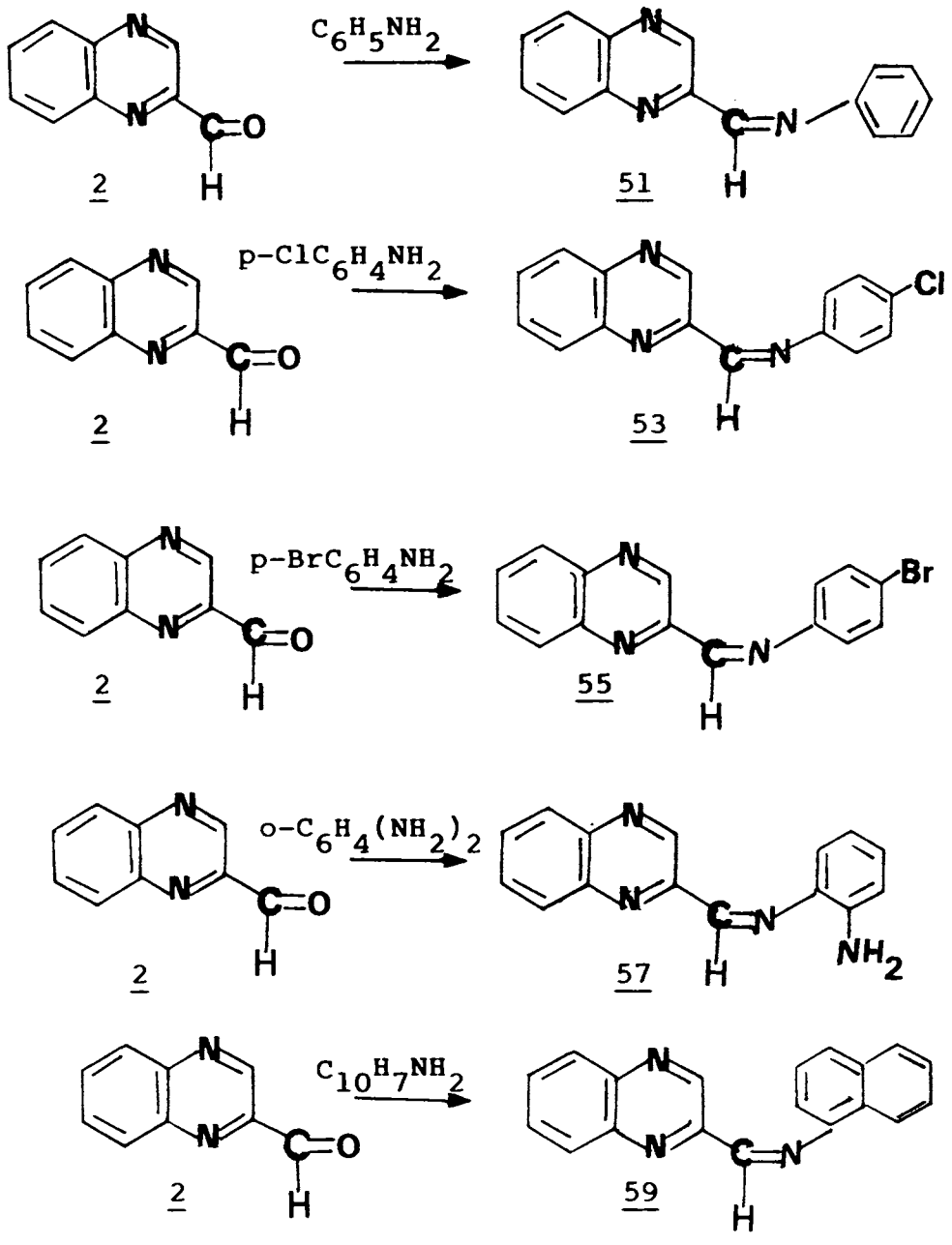


Kabada and Edward reported in 1961 that diazomethane readily add across -C=N of Schiff's bases giving triazolines.[164] Keeping this report in view, an investigation of the action of diazomethane on the Schiff's bases of quinoxaline-2-carboxaldehyde was undertaken.

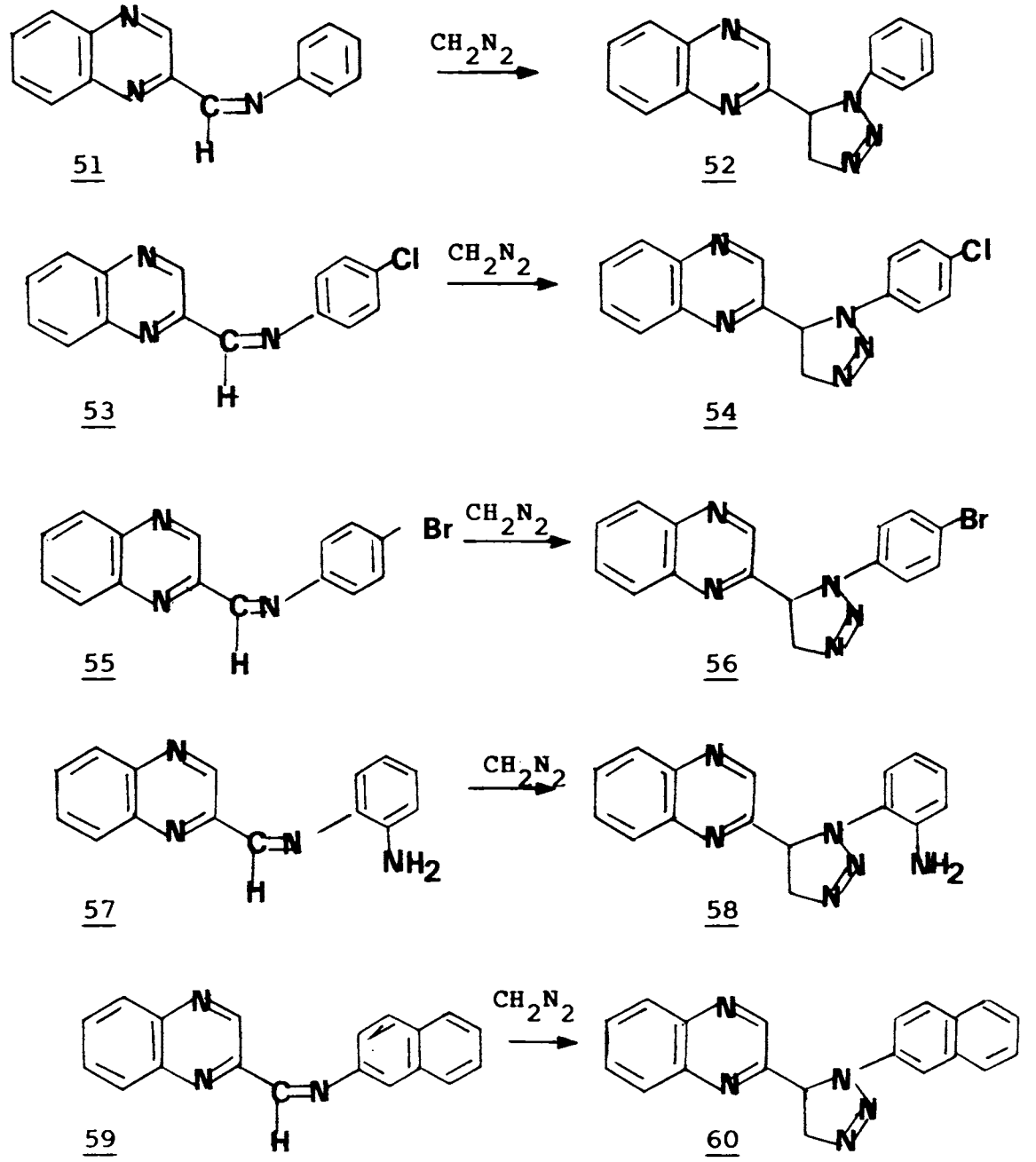
A few anils of quinoxaline-2-carboxaldehyde (2) were prepared by the treatment of 2 in methanol with the required amine.[165] Reaction of the anils with freshly prepared diazomethane in dioxane successfully gave the triazolinyl quinoxalines as addition products in good yield.

Thus quinoxaline-2-carboxaldehyde (2) on stirring with aniline in methanol gave 2-(phenyliminomethyl)quinoxaline (51). Treating 51 with freshly prepared diazomethane in dioxane for several hours gave 58.18% of 2-(1-phenyl-1,2,3-triazolin-5-yl)quinoxaline (52). Similarly treatment of 2 with p-chloro aniline, p-bromo aniline, O-phenylenediamine and naphthylamine in methanol gave 2-(p-chlorophenyliminomethyl)quinoxaline (53), 2-(p-bromophenyliminomethyl)quinoxaline (55), 2-(O-aminophenyliminomethyl)quinoxaline (57) and 2-(naphthyliminomethyl)quinoxaline (59) respectively.

Reaction of the above anils with diazomethane in dioxane for several hours gave 2-(1-p-chlorophenyl-1,2,3-triazolin-5-yl)quinoxaline (54), 2-(1-p-bromophenyl-1,2,3-

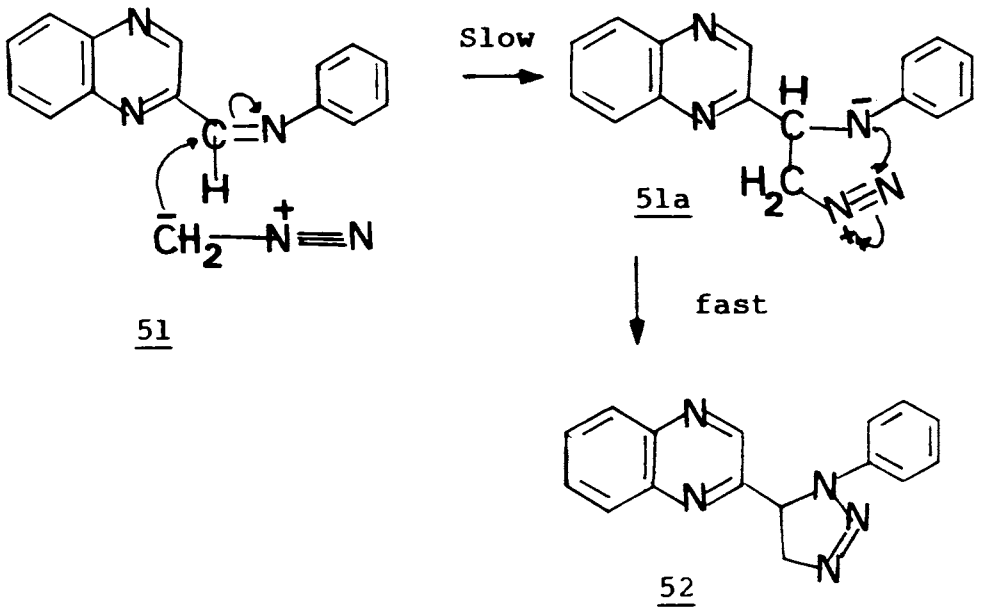


triazolin-5-yl)quinoxaline (56), 2-(1-o-aminophenyl-1,2,3-triazolin-5-yl)quinoxaline (58) and 2-(1-naphthyl-1,2,3-triazolin-5-yl)quinoxaline (60) respectively.



The above reactions have been persumed to consist of two steps, a slow rate determining step in which a nucleophilic attack by the carbon in diazomethane on the double

bond carbon of the anil takes place to give the intermediate 52. It is pertinent to note here that the carbon of diazomethane is often been postulated to have nucleophilic character.[164] The subsequent step is a rapid ring closure to form the triazoline ring.



51 51a 52

The mass spectra of the triazolines were all characteristic of (M^+-42) peaks. It accounted for the easy loss of $-CH_2N_2$ from triazolines. This peak (M^+-42) remains to be

the base peak also. The nuclear magnetic resonance spectrum of the compounds showed triplet at δ 5.2 (^{4}CH), doublet at 4.7 ($^{5}CH_2$) and multiplet at δ 7.5 to 8.5 for the aromatic protons. The infrared spectra of all the compounds showed bands at 3060 cm^{-1} for the -CH stretching and bands between 990 cm^{-1} and 950 cm^{-1} significant of the triazoline ring system.[155] Results of elemental analysis of all the triazolines were consistent with their molecular formula.

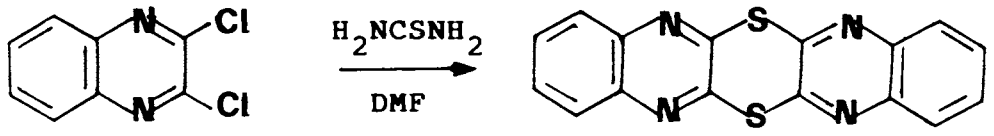
All the triazolines underwent decomposition on heating.

3.4 SYNTHESIS OF CONDENSED QUINOXALINES CONTAINING SULPHUR

There are numerous reports about the use of sulphur heterocycles as wide spectrum, antibacterials.[166,167] However, only very few reports have appeared in the literature on the synthesis of quinoxalines containing sulphur heretocycles. Saikachi and Tagami reported the synthesis of thiazoloquinoxalines using 2-mercapto-3-aminoquinoxaline as the starting material.[168] Subsequently, the above system was reported as synthesised by the interaction of 2,3-dichloroquinoxaline and N-substituted thiourea.[169] Since the thiourea molecule has several nucleophilic centres[89], the

reaction between thiourea and dichloroquinoxaline may lead to the formation of several products. This and a few other aspects prompted us to re-investigate the reaction of thiourea with quinoxaline derivatives with a view to synthesising condensed quinoxalines containing sulphur heterocycles for possible evaluation of their biological activities.

Heating an equimolar mixture of 2,3-dichloroquinoxaline (25) and thiourea in dimethylformamide for 5 hours over a boiling water bath provided diquinoxalino[2,3-b:2',3'-e]-1,4-dithiene (61) in 76.73% yield. This method



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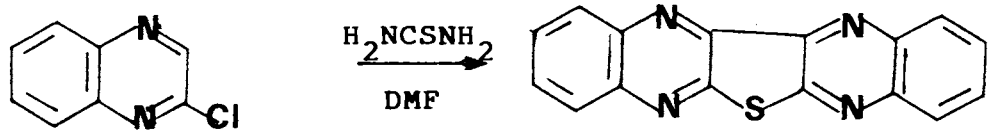
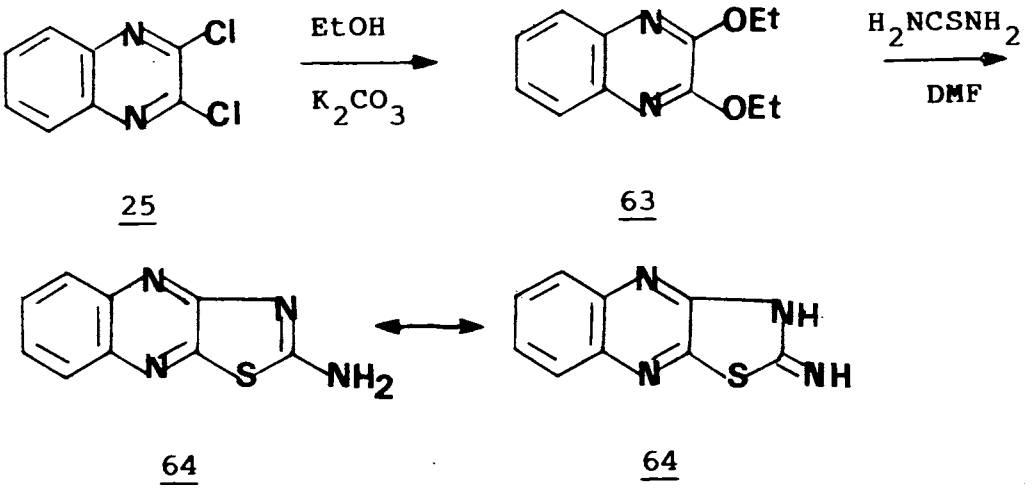


33 62

thus provides the product in a considerably better yield than the one reported by Ismail and Sauer[170] who had reported the synthesis in only 30.6% yield. The reaction time was also reduced. The improvement in yield may be due to the change of solvent employed. The mass spectrum of diquinoxalino[2,3-b:2',3'-e]-1,4-dithiiene (61) showed molecular ion peak at m/z 320, which was also the base peak. The spectrum also showed very weak (M^++1) and (M^++2) peaks. The other characteristics of the compound were in agreement with the reported values.[170]

Treating 2-chloroquinoxaline (33) with equimolar quantity of thiourea in DMF over boiling water bath for 3 hours gave diquinoxalino[2,3-b:2',3'-d]thiiene (62) in 64.2% yield. Compound 62 was characterised using spectral and analytical data. Mass spectra of the compound 62 showed a sharp molecular ion peak at m/z 288 which is also the base peak. The mass spectrum showed very weak (M^++1) and (M^++2) peaks also. The nuclear magnetic resonance spectrum of the compound showed characteristic multiplet at δ 7.7 to δ 8.5. The infrared spectra and results of elemental analysis were consistent with the structure of 62.

2,3-Dichloroquinoxaline (25) on refluxing with absolute ethanol in the presence of potassium carbonate gave 2,3-diethoxyquinoxaline (63) in good yield.[47] Refluxing equimolar quantities of 2,3-diethoxyquinoxaline (63) and thiourea in DMF gave 2-aminothiazolo[4,5-b]quinoxaline (64) in 86.39% yield. Incidentally the same compound was obtained by Ismail and Sauer, but only in 6% yield in their experiment with dichloroquinoxaline in ethanol.[170] The structure of 64 was established using spectral data. The mass spectra of the compound showed peaks at m/z 206 (M^+ +4) which was the base peak also. The spectra showed (M^+ +1) and (M^+ +2) peaks in addition to the (M^+ +4) peak. Other peaks in the spectra were at m/z 207 (17.7%), m/z 205 (10.57%), m/z 204 (7.64%) (M^+ +2), 178 (206-N_2) and 162 (178-NH_2). The nuclear magnetic resonance spectrum of the compound showed characteristic peaks for aromatic protons at δ 7.9. The peak at δ 1.7



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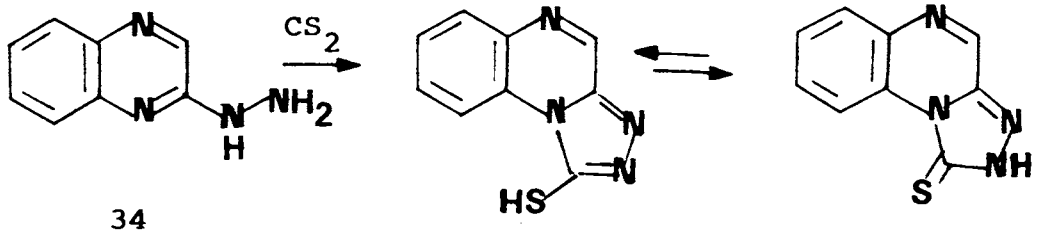
64 64

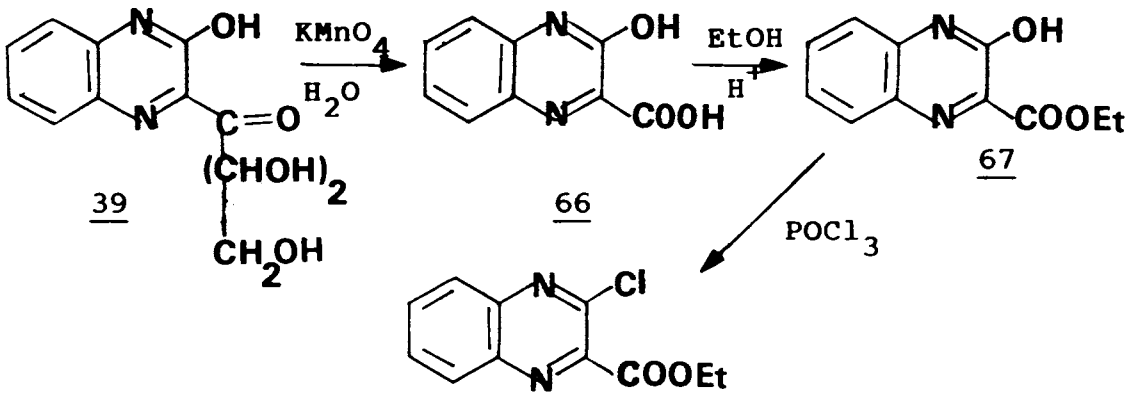
corresponds to the amino protons. The compound may be existing as a mixture of both the amino and imino forms.

Interaction between 2-hydrazinoquinoxaline (34) and carbondisulphide gave 5-mercapto-1,2,4-triazolo[3,4-a]quinoxaline (65) in 71.4% yield. The mass spectrum of the compound 65 showed molecular ion peak at m/z 202 which was also the base peak. Other peaks at m/z 203, (M^+ +1); and m/z 204, (M^+ +2), were also observed. Peaks at m/z 170, (M^+ -32); m/z 144, (170-HCN) and m/z 116, (144-N_2) support the structure of 5-mercapto-1,2,4-triazoloquinoxaline (65). The infrared spectra of the compound showed characteristic bands at 4000 cm^{-1} (broad SH, NH) and 1265 cm^{-1} (C=S). Results of elemental analysis were in agreement with the structure of 65

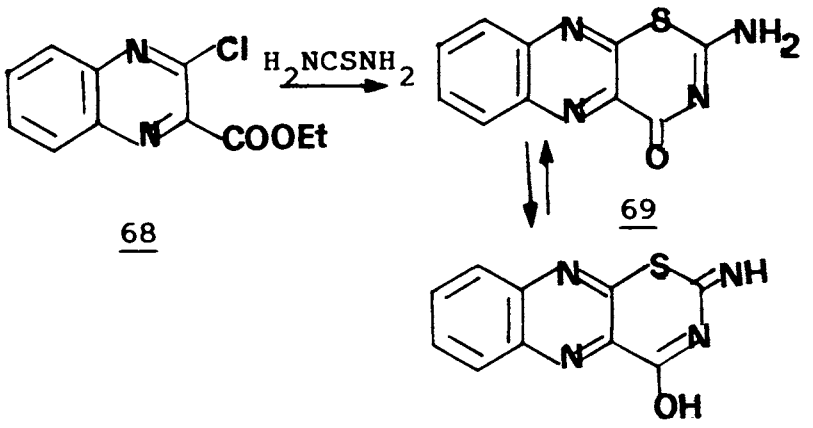


34 65 65

2-Hydroxy-3(1'-oxo-2',3',4'-trihydroxybutyl)quinoxaline (39) on treating with aquous 5% potassium permanganate gave 2-hydroxy-3-quinoxaline carboxylic acid (66).[171] Refluxing 66 in absolute alcohol with seralite-SRC-120, a strongly cationic resin, for 3 hours gave ethyl-2-hydroxyquinoxaline-3-carboxylate (67) in good yield. Treating 67 with phosphorous oxychloride and catalytic amount of DMF gave ethyl-2-chloroquinoxaline-3-carboxylate (68).[47]



Interaction of equimolar quantities of ethyl-2-chloroquinoxaline-3-carboxylate (68) and thiourea in DMF gave 2-amino-4-oxo-thiazino[5,6-b]quinoxaline (69) in 66.6% yield.



68 69

69

The structure of the compound 69 was established using spectral and analytical data as follows. The infrared spectrum of the compound 69 showed a broad band at 3900 cm^{-1} (-OH,NH) and two bands at 3700 cm^{-1} and 3600 cm^{-1} ($-NH_2$). The band at 1740 cm^{-1} corresponds to the -NH-C=O group in the ring of 69. The nuclear magnetic spectrum of the compound showed characteristic peaks at δ 7.6 (aromatic) and a peak at δ 1.7 (amino or imino protons). The compound 69 may exist in the amino form or imino form or as a mixture of both the forms. The mass spectra of 69 gave the molecular ion peak at m/z 230 and a characteristic (M^+ +4) peak at m/z 234. The results of elemental analysis were consistent with the molecular formula of the compound.

Chapter 4

EXPERIMENTAL PROCEDURES

All melting points were taken using capillary tubes on a melting point bath containing liquid paraffin or sulphuric acid and are not corrected. Thin layer chromatography was performed on 5x20 cm glass plates coated with silica gel G. Chloroform was used as the eluent unless otherwise mentioned. Compounds were detected either by their colour or by developing with iodine. Ultraviolet spectra were taken on a Hitachi-200-20-UV-Vis spectrophotometer using methanol as solvent. NMR spectra were recorded using a Hitachi R-600 Perkin Elmer-FT NMR spectrometer using TMS as internal standard. Mass spectra were recorded at RSIC, Punjab University using Finnigan Mat 8230 GC-MS spectrometer. Infrared spectra were recorded using Perkin Elmer PE 983 Infrared spectrometer at RSIC, IIT, Madras and elemental analysis were determined using carbo erba 1106 Elemental analyser at RSIC, CDRI, Lucknow.

4.1 2-(D-Arabino-tetrahydroxybutyl)quinoxaline (1)

A solution of 36.0 g (0.2 mol) of D-glucose in 54 ml of water was mixed with 6 ml of glacial acetic acid, 21.6 g (0.2 mol) of o-phenylenediamine, 5 ml (0.1 mol) of hydrazine hydrate and a pinch of sodium bicarbonate and the mixture was heated for 5 hours on a boiling water bath.

The solution was cooled in ice and the precipitated product was filtered and washed with water. It was recrystallised from hot water and dried to give 17.0 g (34%) of 2-(D-arabino-tetrahydroxybutyl)quinoxaline (1) m.p. 192° (decomp.) (lit.[13] m.p. 192°).

4.2 Quinoxaline-2-carboxaldehyde (2)

A mixture of 5.0 g (0.02 mol) of 2-(D-arabino-tetrahydroxybutyl)quinoxaline (1) and 13.0 g (0.06 mol) of sodium metaperiodate in 300 ml of water and 10 ml of glacial acetic acid was kept at room temperature with occasional shaking for 16 hours. The mixture was filtered and the filterate neutralised with sodium bicarbonate. The neutral solution was extracted with ether, the ether extract was dried with anhydrous sodium sulphate, filtered and evaporated to dryness. The residue was recrystallised from petroleum ether (60°-80°) to give 2.0 g (63%) of quinoxaline-2-carbo-xaldehyde (2) m.p. 107° (lit.[147] m.p. 107°-8).

4.3 3-Methyl-3,4-dihydro-2-(α-hydroxyethyl)quinoxaline (3)

A solution of 1.6 g (0.01 mol) of quinoxaline-2-carboxaldehyde (2) in 200 ml of dry ether was added dropwise to a stirred, cooled (freezing mixture) solution of

4 equivalents of methylmagnesium iodide.[165] After the completion of addition, the mixture was stirred for 30 minutes, 100 ml of cold water was added dropwise and stirring continued for another 2 hours. The ether layer was separated, washed with water and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the residue purified on a silica gel column using chloroform as eluent to get 1.78 g (93%) of 3-methyl-3,4-dihydro-2-(α-hydroxyethyl)quinoxaline (3) as a red liquid identical in all respects to the reported compound.[51]

IR: (KBr); 3440 cm^{-1} (broad, OH, NH)

NMR: ($CDCl_3$); δ 7.3 to 8 (4, m, Aromatic), 4.9 (1, d, OH); 2.9 (1, m, CH); 2.3 (3, d, CH_3); 1.2 (3, d, CH_3).

4.4 2-Acetyl-3-methylquinoxaline (4)

A solution of 1.0 g (0.005 ml) of 3 in 50 ml of acetone was cooled in an ice bath. To the cold solution 1.5 ml of Jones' reagent (prepared from 26.72 g of CrO_3 and 100 ml of sulfuric acid obtained by diluting 23 ml of the concentrated acid)[165] was added dropwise with constant stirring at 0°C. After the addition was complete, the

mixture was stirred for another 30 minutes at 0°C, 20 ml of ice cold water was added and the mixture extracted with ether. The ether extract was washed with 5% sodium bicarbonate solution followed by water, dried over anhydrous sodium sulphate and concentrated to dryness under reduced pressure. The residue was recrystallised from hexane to give 850 mg (94.1%) of 2-acetyl-3-methylquinoxaline (4) m.p. 86° (lit.[22] m.p. 86.7°).

IR: (KBr): 1690 cm^{-1} (C=O).

NMR: ($CDCl_3$): δ 7.3 to 8 (4, m, aromatic); 2.9 (3, s, $COCH_3$); 1.2 (3, s, CH_3).

4.5 2-(α-hydroxyethyl)quinoxaline (5)

To a cooled (freezing mixture) solution of 1.6 g (0.01 mol) of quinoxaline-2-carboxaldehyde (2) in ether was added dropwise with stirring a solution of one equivalent methylmagnesium iodide under a nitrogen atmosphere. After the completion of addition, the mixture was stirred 30 minutes more and 400 ml of cold water was added slowly with stirring and the mixture was kept overnight at room temperature. The ether layer was separated, dried over anhydrous sodium sulphate and concentrated to dryness under

reduced pressure. The residue was leached with petroleum ether to remove any unreacted starting material and the residue recrystallised from chloroform-hexane (1:9) to give 1.7 g (97%) of 2-(α-hydroxyethyl)quinoxaline (5) m.p. 51°.

IR: (KBr); 3230 cm^{-1} (OH).

NMR: ($CDCl_3$); δ 7.6 to 8 (5, m, aromatic); 5.2 (1, m, CH); 4.3 (1, d, OH); 1.6 (3, d, CH_3).

Anal: Calcd: for $C_{10}H_{10}N_2O$: C, 68.96; H, 5.75; N, 16.09.
Found: C, 67.00; H, 6.01; N, 16.09.

4.6 2-Acetylquinoxaline (6)

A solution of 870 mg (0.005 mol) of 2-(α-hydroxyethyl)quinoxaline (5) in 40 ml of acetone was cooled in an ice bath. To this solution was added dropwise 1.5 ml of Jone's reagent (prepared from 26.72 g of CrO_3 and 100 ml of sulfuric acid)[165] with stirring. After the completion of addition the mixture was stirred for another 30 minutes at 0°, 20 ml of ice cold water was added and the mixture was extracted with ether. The extract was washed with 5% sodium bicarbonate solution followed by water, dried with anhydrous sodium sulphate and concentrated to dryness under reduced pressure. The residue was recrystallised from hexane to give 800 mg (91%) of 2-acetylquinoxaline (6) m.p. 75° (lit.[80] m.p. 76°).

IR: (KBr); 1690 cm^{-1} (C=O).

NMR: ($CDCl_3$); δ 7.5 to 8 (5, m, aromatic); 2.7 (3, s, $-COCH_3$).

4.7 2-(α-HYdroxybenzyl)-3,4-dihydro-3-phenyl-quinoxaline (9)[149]

(a) By addition of phenylmagnesium bromide to quinoxaline-2-carboxaldehyde (2)

A solution of 4.7 g (0.03 mol) of quinoxaline-2-carboxaldehyde (2) in 200 ml of dry ether was added dropwise to a stirred, cooled solution of phenylmagnesium bromide. After the completion of addition, the mixture was stirred for 30 minutes and 100 ml of water was added dropwise, stirred for 2 hours more and kept overnight at room temperature. The ether layer was separated, washed with water and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the residue recrystallised from hexane to give 6.2 g (66%) of 2-(α-hydroxybenzyl)-3,4-dihydro-3-phenyl-quinoxaline (9) m.p. 130° (decomp).

IR: (KBr); 3350 (OH, NH); 1650 cm^{-1} (C=N).

MS: m/z 314, (M^+); 313, 312, 283 (M^+ -H, CHOH); 235 (M^+ -2H, C_6H_5); 207 (M^+ -C_6H_5CHOH) etc.

UV: $\lambda_{max.}^{MeOH}$ 269.2 nm (ε 1.05×10^5).

Anal: Calcd: for $C_{21}H_{18}N_2O$; C, 80.23; H, 5.72; N, 8.74.

Found: C, 80.45; H, 5.80; N, 8.74.

(b) By addition of phenylmagnesium bromide to 2(α-hydroxybenzyl)quinoxaline

A solution of 1.2 g (0.005 mol) of 2-(α-hydroxybenzyl)quinoxaline (13) in dry ether was added dropwise to a stirred solution of phenylmagnesium bromide. After the completion of addition, the mixture was stirred for 30 minutes and 100 ml of water was added dropwise and stirred. The ether layer was separated, washed with water and dried over anhydrous sodium sulphate. The solvent was evaporated and the residue recrystallised from hexane to give 1.3 g (81.25%) of 9, identical in all respects with the sample prepared under (a) above.

4.8 1,2,3,4-Tetrahydro-2-(α-hydroxybenzyl)-3-phenylquinoxaline (10)[149]

To a solution of 160 mg (0.0005 mol) of 2-(α-hydroxybenzyl)-3,4-dihydro-3-phenylquinoxaline (9) in 10 ml of methanol was added 10 mg of sodium borohydride and

stirred for 30 minutes. The colour of the solution changed from blood red to yellow. It was concentrated to 5 ml under reduced pressure, diluted to 100 ml with water, stirred well, filtered, washed with water and dried and recrystallised from hexane-chloroform (9:1) to give 130 mg (81%) of 1,2,3,4-tetrahydro-2-(α -hydroxybenzyl)-3-phenylquinoxaline (10) m.p. 80°.

IR: (KBr); 3400 cm^{-1} (broad, NH, OH).

MS: m/z 316 ($M^+ - C_6H_5CHOH$); 132, 77 etc.

UV: $\lambda_{max.}^{MeOH}$ 219 nm (ε 2.4×10^5); 316.4 nm (ε 4.0×10^4).

Anal: Calcd: for $C_{21}H_{20}N_2O$: C, 79.72; H, 6.37; N, 8.86.
Found: C, 79.99; H, 6.50; N, 8.74.

4.9 2-Benzoyl-3-phenylquinoxaline (11)[149]

A solution of 940 mg (0.003 mol) of 2-(α-hydroxybenyl)-3,4-dihydro-3-phenylquinoxaline (9) in 50 ml acetone was cooled in an ice bath. To the cold solution, 1.5 ml of Jone's reagent was added dropwise with constant stirring at 0°. After the completion of the addition, the mixture was stirred 30 minutes at 0°, 20 ml of ice cold water was added and the mixture extracted with ether. The ether

extract was washed with 5% sodium bicarbonate solution followed by water, dried with anhydrous sodium sulphate and evaporated to dryness. The residue was recrystallised from hexane to give 810 mg (91%) of 2-benzoyl-3-phenyl-quinoxaline (11) m.p. 153°.

IR: (KBr); 1670 cm^{-1} (C=O); 1595 cm^{-1} (aromatic).

NMR: ($CDCl_3$); absorption only at δ 7.7 (m, aromatic).

UV: $\lambda_{max.}^{MeOH}$ 250 nm (ε 3.54×10^5); 334 nm (ε 8.9×10^4).

MS: m/z 310 (M^+); 282 ($M^+ - CO$); 233 ($M^+ - C_6H_5$).

Anal: Calcd: for $C_{21}H_{14}N_2O$; C, 81.27; H, 4.55; N, 9.03.

Found: C, 81.20; H, 4.70; N, 9.13.

4.10 2-(α-Hydroxybenzyl)-3-phenylquinoxaline (12)[149]

To a solution of 310 mg (0.001 mol) of 2-benzoyl-3-phenylquinoxaline (11) in 100 ml of methanol was added 30 mg of sodium borohydride and the mixture was stirred at room temperature for 2 hours. The solution was concentrated to 20 ml under reduced pressure and diluted to 100 ml with water. The mixture was cooled overnight in a refrigerator, the crystals were filtered, washed with water, dried and

recrystallised from hexane to give 250 mg (83%) of 2-(α-hydroxybenzyl)-3-phenylquinoxaline (12) m.p. 125°.

IR: (KBr); 3310 cm^{-1} (broad, OH).

NMR: ($CDCl_3$); δ 8.1 to 7.8 (m) 7.2 (5, m, phenyl)
5.5 (1, d, OH); 6.1 (1, d, benzylic-H).

MS: m/z 312 (M^+); 310 (M^+ - 2H); 295 (M^+ - OH); 282 (M^+-CHOH).

UV: $\lambda_{max.}^{MeOH}$ 241.8 nm (ε $1.5x10^5$); 326.3 nm (ε $4.0x10^4$).

Anal: Calcd: for $C_{21}H_{16}N_2O$; C, 80.74; H, 5.16; N, 8.97.
Found: C, 80.96' H, 5.03; N, 8.65.

4.11 2-(α-Hydroxybenzyl)quinoxaline (13)

(a) By the reverse addition of phenylmagnesium bromide to quinoxaline-2-carboxaldehyde.

To a cooled solution of 12.5 g (0.08 mol) of quinoxaline-2-carboxaldehyde (2) was added dropwise with stirring a solution of phenylmagnesium bromide prepared from 12.0 ml of freshly distilled bromobenzene and 2.5 g of magnesium turnings under nitrogen atmosphere.[165] After the completion of addition, the mixture was stirred 30 minutes and 400 ml of cold water was added slowly with stirring and

the mixture was kept overnight at room temperature. The ether layer was separated, dried over anhydrous sodium sulphate and concentrated to dryness under reduced pressure. The residue was leached with petroleum ether to remove any unreacted starting material and the residue recrystallised from chloroform-hexane (1:9) to give 14.3 g (76%) of 2-(α-hydroxybenzyl)quinoxaline (13) m.p. 138° (decomp.).

IR: (KBr); 3250 cm^{-1} (broad, OH).

NMR: ($CDCl_3$); δ 8.7, 8.1 (m), 7.3 (5, s, phenyl); 5.9 (1, d, benzylic H); 5 (1, d, OH).

MS: m/z 236 (M^+); 217 (M^+ - OH); 159 (M^+ - C_6H_5); 129, 103 etc.

UV: λ_{max}^{MeOH} 237.2 nm (ε 1.18×10^5); 319 nm (ε 2.9×10^4).

Anal: Calcd: for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86.
Found: C, 75.96; H, 4.85; N, 11.95.

(b) By the reduction of 2-benzoylquinoxaline (14) with sodium borohydride

To a solution of 1.2 g (0.005 mol) of benzoylquinoxaline (14) in 10 ml of methanol was added to 10 mg of

sodium borohydride and stirred for 30 minutes, under a calcium chloride guard tube. After the completion of the reaction, the mixture was concentrated under reduced pressure, diluted with water, stirred well, filtered, dried and recrystallised from chloroform-hexane to give 1.08 g (90%) of 2-(α-hydroxybenzyl)quinoxaline (13), identical in all respects with the sample prepared under (a) above.

4.12 2-Benzoylquinoxaline (14)

A solution of 1.2 g (0.005 mol) of 2-(α-hydroxybenzyl)quinoxaline (13) in 40 ml acetone was cooled in an ice bath. To this solution was added dropwise 1.5 ml of Jone's reagent.[165] After the completion of addition, the mixture was stirred for another 30 minutes at 0°. The reaction mixture was stirred with 20 ml cold water and extracted with ether. The extract was washed with sodium bicarbonate solution and concentrated to dryness under reduced pressure. The residue was recrystallised from hexane to get 1.04 g (89%) of 2-benzoylquinoxaline m.p. 80° (lit.[150] m.p. 80°).

IR: (KBr); 1660 cm^{-1} (C=O).

UV: $\lambda_{max.}^{MeOH}$ 249.8 nm (ϵ 2.5×10^5).

Anal: Calcd: for $C_{15}H_{10}N_2O$; C, 76.91; H, 4.30; N, 11.95.

Found: C, 76.77; H, 4.51; N, 12.23.

4.13 Quinoxaline-2-yl-ethyleneoxide (15)

A solution of diazomethane[165], (0.025 mol) in ether generated from 4.0 g of nitrosomethyl urea, was added dropwise to a stirred and cooled solution of 1.6 g (0.01 mol) of quinoxaline-2-carboxaldehyde (2) in ether. After the completion of addition, the mixture was stirred for another 30 minutes at 0°. Ether was removed under reduced pressure. The residue was chromatographed over silica gel column using chloroform as the eluent to give 1.05 g (52.5%) of the known 2-acetylquinoxaline (6) as the first fraction.

On continued elution of the column with the eluent chloroform, a second fraction was obtained which on evaporation and recrystallisation from hexane gave 0.55 g (27.5%) of quinoxaline-2-yl-ethylene oxide (15) m.p.139°.

IR: (KBr); 3100 (C-H stretching), 1100, 950, 810 and 760 cm^{-1} (12 band of epoxy ring).

MS: m/z 172 (M^+); 144 (M^+ - CO); 116 (144-N_2).

Anal: Calcd: for $C_{10}H_8N_2O$; C, 69.76; H, 9.65; N, 16.27.

Found: C, 69.77; H, 4.65; N, 16.26.

4.14 Quinoxaline-2-carboxaldehyde hydrazone (16)

A solution of 1.6 g (0.01 mol) of quinoxaline-2-carboxaldehyde (2) in methanol was mixed with 10 ml of 80% hydrazine hydrate. The mixture was refluxed on a boiling water bath for 30 minutes. After completion of reaction, volume of methanol was reduced under diminished pressure and cooled in a refrigerator overnight. The crystals were filtered and recrystallised from methanol, to give 1.3 g (75.58%) of quinoxaline-2-carboxaldehyde hydrazone (16) m.p. 145° (lit.[154] m.p. 147°)

IR: (KBr); 3800, 3500, 1650 cm^{-1}.

NMR: ($CDCl_3$); δ 9.4 (1, s, H-C=N); 8 (m, aromatic), 2 (broad).

UV: $\lambda_{max.}^{MeOH}$ 349 nm (ε 5.7x10^4), 265 nm (ε 5.4x10^4).

4.15 Preparation of lead tetraacetate[165]

A mixture of 550 g of glacial acetic acid and 185 g of acetic anhydride was placed in a one litre, three

necked flask provided with a thermometer and a mercury sealed stirrer. The liquid was vigorously stirred, heated to 55-60° and 300 g of dry red lead powder was added in portions of 15-20 g at a time. A fresh addition was made only after the colour due to the preceeding addition had largely disappeared. The temperature of the reaction mixture was maintained around 65°. After the addition was completed, the mixture was heated to 80° in order to complete the reaction. At the end of the reaction, the thick and dark solution was cooled, the precipitated lead tetraacetate was filtered out and washed with glacial acetic acid. The crude product was recrystallised from hot acetic acid containing a little acetic anhydride and decolourising carbon to obtain 150 g of the colourless crystals, of lead tetraacetate.

4.16 v-Triazolo[3,4-a]quinoxaline (17)

A solution of 0.86 g (0.005 mol) of quinoxaline-2-carboxaldehyde hydrazone (16) in 10 ml of glacial acetic acid was mixed with 2.2 g (0.005 mol) of freshly prepared lead tetraacetate in a 50 ml round bottom flask fitted with a calcium chloride guard tube. The reaction mixture was stirred at room temperature for 8 hours. When the reaction was completed, 15 ml of cold water was added to the mixture

and neutralised with sodium bicarbonate solution. The mixture was extracted with chloroform repeatedly and the extract washed with water. The chloroform solution was then dried over anhydrous sodium sulphate and evaporated to dryness under reduced pressure. The residue was chromatographed over a silica column using chloroform as the eluent to give 0.6 g (70.5%) of v-triazolo[3,4-a]quinoxaline (17) m.p. 155°.

IR: (KBr); 3080 (C-H); 2360, 1650, 990-950 cm^{-1}.

NMR: ($CDCl_3$); δ 9.2 (1, s, H-C-N=N); 7.8 to 8.5 (5, m, aromatic).

MS: m/z 170 (M^+), 142 ($M^+ - 28$), 115 (142-HCN), 102, 88.

UV: $\lambda_{max.}^{MeOH}$ 300 nm (ε 5.1×10^4), 249 nm (ε 4.9×10^4).

Anal: Calcd: for $C_9H_6N_4$; C, 63.53; H, 3.52; N, 32.94.

Found: C, 62.92; H, 2.83; N, 32.94.

4.17 2-Acetylquinoxaline hydrazone

A solution of 1.72 g (0.01 mol) of 2-acetylquinoxaline (6) in 10 ml of methanol was taken in a 100 ml round bottom flask and mixed with 10 ml of hydrazine hydrate. The mixture was stirred at room temperature for 30 minutes

and then allowed to stand. The product crystallised out and was filtered, dried and recrystallised from methanol to give 1.1 g (75.2%) 2-acetylquinoxaline hydrazone (18) m.p. 140°.

IR: (KBr); 3800, 3650 cm^{-1}.

NMR: ($CDCl_3$); δ 9.4 (1, s, H-C=N); 8.4 to 7.2 (5, m, aromatic); 2.8 (3, s, CH_3).

UV: $\lambda_{max.}^{MeOH}$ 392 nm (ε 2.5×10^4), 308 nm (ε 2.6×10^4).

Anal: Calcd: for $C_9H_8N_4$; C, 62.79; H, 4.65; N, 32.56.

Found: C, 62.65, H, 4.72; N, 31.82.

4.18 5-Methyl-v-triazolo[3,4-a]quinoxaline (19)

A solution of 2.2 g (0.005 mol) of lead tetra-acetate in 10 ml of glacial acetic acid was mixed with 0.93 g (0.005 mol) of 2-acetylquinoxaline hydrazone and was stirred at room temperature for 5 hours under a calcium chloride guard tube. After the completion of the reaction, 15 ml of water was added to the mixture and neutralised with aqueous sodium bicarbonate. It was then extracted with chloroform and the chloroform extract was washed repeatedly with water. The chloroform extract was dried over anhydrous

sodium sulphate. The solution was concentrated under reduced pressure and cooled to give 0.72 g of 5-methyl-v-triazolo[3,4-a]quinoxaline (19) in 87% yield, m.p. 205°.

IR: (KBr); 3100 (CH), 2400, 1620 (C=N), 1600 cm^{-1}.

NMR: ($CDCl_3$); δ 8.3 to 7.3 (m, 5, aromatic);
2.8 (3, s, - CH_3).

MS: m/z 184 (M^+), 169 ($M^+ - CH_3$), 142 (169-HCN),
116 (142-N_2).

UV: $\lambda_{max.}^{MeOH}$ 219 nm (ϵ 4.0×10^4).

Anal: Calcd: for $C_{10}H_8N_4$; C, 65.22; H, 4.34; N, 30.44.
Found: C, 65.20; H, 4.36; N, 30.41.

4.19 Quinoxaline-2-carboxaldehyde phenylhydrazone (20)

A solution of 1.6 g (0.01 mol) of quinoxaline-2-carboxaldehyde (2) and 1.1 g (0.01 mol) of phenylhydrazine in 20 ml of methanol was stirred at room temperature for one hour. Yellow crystals of quinoxaline-2-carboxaldehyde phenylhydrazone were formed. The mixture was cooled in ice, filtered and washed with a small amount of cold methanol and the product recrystallised from methanol to give 2.0 g (81%)

of quinoxaline-2-carboxaldehyde phenylhydrazone (20) m.p.230° (lit.[154] m.p. 229-230°).

4.20 1-Phenylpyrazolo[3,4-b]quinoxaline (21)

A mixture of 1.0 g (0.004 mol) of quinoxaline-2-carboxaldehyde phenylhydrazone (20), 1.7 g (0.004 mol) of freshly prepared lead tetraacetate and 10 ml of glacial acetic acid was stirred at room temperature for 9 hours, under a calcium chloride guard tube. After the completion of the reaction, 15 ml of water was added to the reaction mixture, stirred and neutralised with aqueous sodium bicarbonate solution. It was then extracted with chloroform, the extract washed with water repeatedly and dried over anhydrous sodium sulphate. The chloroform solution was concentrated under diminished pressure and purified by passing through a silica column using chloroform as the eluent to give 600 mg (66.6%) of 1-phenylpyrazolo[3,4-b]quinoxaline (21) identical in all respects to the one reported m.p. 152° (lit.[157] m.p. 152°).

4.21 2-Acetylquinoxaline phenylhydrazone (22)

A solution of 1.72 g (0.01 mol) of 2-acetylquinoxaline and 1.1 g (0.01 mol) of phenylhydrazine in 20 ml

methanol was stirred at room temperature for one hour. Yellow crystals of 2-acetylquinoxaline phenylhydrazone was formed. The mixture was cooled in a refrigerator, filtered and washed with cold methanol. The product was recrystallised from methanol to give 2.2 g (84%) of 2-acetylquinoxaline phenylhydrazone (22) m.p. 205°.

IR: (KBr); 1600 cm^{-1}.

NMR: ($CDCl_3$); δ 9 to 8 (5H, m), 7.6 (5H, phenyl)
3 (3H, s, CH_3)

UV: $\lambda_{max.}^{MeOH}$ 340 nm (ϵ 4.6×10^4), 287 nm (ϵ 4.6×10^4).

4.22 3-Methyl-1-phenylpyrazolo[3,4-b]quinoxaline (23)

To a solution of 2.2 g (0.005 mol) of lead tetra-acetate in 10 ml of glacial acetic acid was added 1.31 g (0.005 mol) of 2-acetylquinoxaline phenylhydrazone (22) under a calcium chloride guard tube, and the mixture was stirred at room temperature for 5 hours. After the completion of reaction, 20 ml of water was added, the mixture was stirred and neutralised with sodium bicarbonate solution. The mixture was then extracted with chloroform and the extract washed repeatedly with water. The extract was dried

over anhydrous sodium sulphate and concentrated under reduced pressure, and chromatographed over silica gel using chloroform as eluent to get 0.86 g (66%) of 3-methyl-1-phenylpyrazolo[3,4-b]quinoxaline (23) m.p. 135-7°.

IR: (KBr); 2900 (C-H), 1650 (C=N), 1600 cm^{-1}.

NMR: ($CDCl_3$); δ 8.4 to 7.6 (4, m, hetero),
7.4 to 7.2 (5, m, aromatic), 2.7 (3, s, CH_3).

MS: m/z 260 (M^+, 100%), 245 ($M^+ - CH_3$, 14.25%),
219 (245-HCN, 61.98%), 192 (219-HCN, 8.8%).

UV: $\lambda_{max.}^{MeOH}$ 332 nm (ε 8.3×10^4), 280 nm (ε 8.2×10^4).

Anal: Calcd: for $C_{16}H_{12}N_4$; C, 62.23; H, 4.01; N, 21.54.
Found: C, 62.13; H, 4.64; N, 21.53.

4.23 2,3-Dihydroxyquinoxaline (24)

A mixture of 6.3 g (0.05 mol) of oxalic acid and 5.4 g (0.05 mol) of o-phenylenediamine in 25 ml of 3N hydrochloric acid was heated on a boiling water bath for one hour. The mixture was cooled and the crystals filtered out. It was washed repeatedly with water and dried to give 6.0 g (95%) of 2,3-dihydroxyquinoxaline (24) m.p. $> 260°$ (lit.[159] m.p. 300°).

4.24 2,3-Dichloroquinoxaline (25)

A mixture of 4.05 g (0.025 mol) of 2,3-hydroxyquinoxaline, 6 ml of phosphorous oxychloride and a catalytic amount of dimethylformamide was heated over water bath for 3 hours under a calcium chloride guard tube. It was cooled and poured into crushed ice with vigorous stirring. The precipitate was filtered, washed repeatedly with ice cold water and dried. The product was recrystallised from hexane to give 4.5 g (90.9%) of 2,3-dichloroquinoxaline (25) m.p. 151° (lit.[85] m.p. 152°).

4.25 2,3-Bis hydrazinoquinoxaline (26)

A solution of 3.96 g (0.02 mol) of dichloroquinoxaline in methanol was treated with 5 ml of 80% hydrazine hydrate in methanol and 5 drops of triethylamine. The mixture was heated over a boiling water bath for 30 minutes. When the reaction was complete, it was cooled and filtered. The product was recrystallised from methanol to get 3.5 g (92.1%) of 2,3-bis hydrazinoquinoxaline m.p. 280° (decomp).

IR: (KBr); 3860, 3470 (NH), 1650 cm^{-1} (C=N).

UV: $\lambda_{max.}^{MeOH}$ 340 nm (ϵ 5.8x10^4), 215 nm (ϵ 5.7x10^4).

Anal: Calcd: for $C_8H_{10}N_6O$; C, 50.52; H, 5.26; N, 44.21.

Found: C, 50.43; H, 5.28; N, 44.31.

4.26 1-Amino-v-triazolo[4,5-b]quinoxaline (27)

To a solution of 4.4 g (0.01 mol) of lead tetra-acetate in 15 ml of glacial acetic acid was added with stirring 1.9 g (0.01 mol) of 2,3-bis hydrazinoquinoxaline. The mixture was stirred for 8 hours. After completion of the reaction, water was added to the reaction mixture. The precipitate was filtered and washed with water. The product was dried and recrystallised from methanol to get 1.6 g (86%) of 1-amino-v-triazolo[4,5-b]quinoxaline m.p. 260° (decomp).

IR: (KBr); 3400, 3150 ($-NH_2$), 3000 (C-H), 1640, 1560 cm^{-1}.

NMR: (DMSO-d_6); δ 7.5 to 7 (4, m, aromatic), 3.5 (2, broad, NH_2).

MS: m/z 186 (M^+); 185 (M^+ -1); 158 ($M^+ - N_2$);
131 (158-HCN) and 28.

UV: $\lambda_{max.}^{MeOH}$ 290 nm (ϵ 3.8x10^4), 251 nm (ϵ 4.9x10^4).

Anal: Calcd: for $C_8H_6N_6$; C, 51.61; H, 3.22; N, 45.16.

Found: C, 51.52; H, 3.33; N, 45.16.

4.27 2,3-Bis phenylhydrazinoquinoxaline (28)

A solution of 1.9 g (0.01 mol) of dichloroquinoxaline in 20 ml of methanol was mixed with 5 ml of pure phenylhydrazine and 5 drops of triethylamine. The mixture was heated over a boiling water bath for 30 minutes. After the completion of the reaction, the reaction mixture was cooled and filtered. The product was recrystallised from methanol to give 2.4 g (70.1%) of 2,3-bis phenylhydrazinoquinoxaline (28) m.p. 280°.

IR: (KBr); 3800 cm^{-1} (broad, NH).

UV: $\lambda_{max.}^{MeOH}$ 320 nm (ε 1.04×10^5).

4.28 1-Phenyl-v-triazolo[4,5-b]quinoxaline (29)

To a solution of 2.2 g (0.005 mol) of lead tetraacetate in 10 ml of glacial acetic acid was added 1.7 g (0.005 mol) of 2,3-bis phenylhydrazinoquinoxaline. The mixture was stirred at lab.temp. for 8 hours under a calcium chloride guard tube. After the completion of the reaction, water was added to the reaction mixture. The precipitate was filtered, washed with water and dried. The product was purified by passing over a silica gel column using chloroform as eluent to give 1.0 g (83.3%) of 1-phenyl-v-triazolo-[4,5-b]quinoxaline m.p. 124°.

IR: (KBr); 3050, 2400, 1600 cm^{-1}.

NMR: ($CDCl_3$); δ 8.4 to 7.9 (4, m, hetero ring);
7.6 (5, s, phenyl H).

MS: m/z 247 (M^+); 219 (M^+ -28); 192 (219-HCN).

UV: $\lambda_{max.}^{MeOH}$ 324 nm (ε 7.6×10^4).

Anal: Calcd: for $C_{14}H_9N_5$; C, 68.01; H, 3.64; N, 28.34.
Found: C, 68.00; H, 3.68; N, 28.34.

4.29 Di-n-butyltartarate (30)[160]

A mixture of 75.0 g (0.5 mol) d-tartaric acid, 10.0 g zeo karb 225/H^+, 110 g (135 ml) of redistilled n-butyl alcohol and 150 ml of sodium dried benzene were placed in a one litre round bottom flask. The mixture was refluxed over a boiling water bath under a calcium chloride guard tube for 10 hours. It was filtered and the filterate was washed successively with aqueous sodium bicarbonate and water. The benzene layer was dried over anhydrous sodium sulphate. The excess solvent was removed under reduced pressure to give 95 g (81.8%) of di-n-butyltartarate.[160]

4.30 n-Butylglyoxylate (31)[160]

In a three necked round bottom flask was placed 125 ml of dry benzene and 32.5 g of di-n-butyltartarate (0.124 mol). The mixture was stirred with addition of small portions of 57.8 g (0.13 mol) of lead tetraacetate during 25 minutes while keeping the temperature below 30° by occasional cooling. After the completion of addition, the mixture was stirred for one hour more during which time a gummy salt separated. The salts were removed by filteration. The residue was washed with more benzene. The combined filterate was concentrated by distillation to give 24.8 g (77%) of n-butylglyoxylate (31).

4.31 2-Hydroxyquinoxaline (32)[4]

A solution of 14.0 g (0.1 mol) of n-butylglyoxylate in benzene was stirred with 10.8 g (0.1 mol) of o-phenylenediamine for 5 hours. The solid that separated was filtered, dried and recrystallised from methanol to give 8.5 g (58.2%) of 2-hydroxyquinoxaline m.p. 270 (lit.[4] m.p. 271-272°).

4.32 2-Chloroquinoxaline (33)

A mixture of 7.3 g (0.05 mol) of 2-hydroxyquinoxaline, 10 ml of phosphorous oxychloride and a catalytic

amount of dimethylformamide was heated over a boiling water bath for 3 hours. The reaction mixture was cooled and poured in a narrow stream to crushed ice with vigorous stirring. The precipitate was filtered, washed with water and dried. The product was recrystallised from hexane to give 8.0 g (97.5%) of 2-chloroquinoxaline m.p. 46° (lit.[47] m.p. 46-47).

4.33 2-Hydrazinoquinoxaline (34)

A solution of 3.2 g (0.02 mol) of 2-chloroquinoxaline in methanol was treated with 5 ml of 80% hydrazine hydrate and 5 drops of triethylamine and the mixture was heated under reflux over a boiling water bath for 30 minutes. When the reaction was completed, it was cooled, filtered and dried. the product was recrystallised from methanol to give 3.0 g (96.09%) of 2-hydrazinoquinoxaline (34) m.p. 172°.

IR: (KBr); 3800, 3600 cm^{-1} (broad, NH)

UV: $\lambda_{max.}^{MeOH}$ 302 nm (ε 4.4×10^4), 257 nm (ε 4.4×10^4).

Anal: Calcd: for $C_8H_7N_4$; C, 60.37; H, 4.40; N, 35.22.

Found: C, 60.25; H, 4.46; N, 35.06.

4.34 5-Phenyl-1,2,4-triazolo[3,4-a]quinoxaline (35)

A mixture of 500 mg (0.0003 mol) of 2-hydrazinoquinoxaline and 5.0 ml of benzoylchloride was heated two hours over a boiling water bath in a RB flask fitted with a calcium chloride guard tube. When the reaction was complete, the mixture was cooled and poured into cold water with stirring. The solid product was filtered, dried and purified by passing over a silica gel column using chloroform as eluent to give 600 mg (75%) of 5-phenyl-1,2,4-triazolo[3,4-a]-quinoxaline (35) m.p. 95-7°.

IR: (KBr); 2990 (CH), 1601 (C=N), 1546, 1452 cm^{-1}.

NMR: ($CDCl_3$); δ 8.4 to 8.2 (m, 4, hetero H),
7.5 (s, 5, phenyl).

MS: m/z 246 (M^+); 214 (M^+ -28).

UV: $\lambda_{max.}^{MeOH}$ 360 nm (ε 7.7×10^4), 289 nm (ε 7.5×10^4).

Anal: Calcd: for $C_{15}H_{10}N_4$; C, 73.17; H, 4.06; N, 22.7.
Found: C, 72.16; H, 4.17; N, 22.76.

4.35 Quinoxaline-2-carboxaldehyde semicarbazone (36)

A solution of 1.6 g (0.01 mol) of quinoxaline-2-carboxaldehyde (2) in methanol was treated with a solution

of 2 g of semicarbazide hydrochloride and 3 g of crystallised sodium acetate in 20 ml of water. The mixture was stirred for 30 minutes. The product crystallised on standing. It was filtered and recrystallised from alcohol to give 1.8 g (83.7%) of quinoxaline-2-carboxaldehyde semicarbazone (36) m.p. 255° (lit.[64] m.p. 256°).

4.36 Quinoxaline-2-carboxaldehyde thiosemicarbazone (37)

A solution of 1.6 g (0.01 mol) of quinoxaline-2-carboxaldehyde in methanol was treated with 0.9 g (0.01 mol) of thiosemicarbazide. The mixture was stirred for 30 minutes and allowed to stand. The product that crystallised was filtered and recrystallised from methanol to give 1.9 g (82%) of quinoxaline-2-carboxaldehyde thiosemicarbazone (37) m.p. 240° (decomp) (lit.[64] m.p. 240°).

4.37 2-(2-Amino-1,3,4-oxadiazol-5-yl)quinoxaline (38)

A solution of 2.15 g (0.01 mol) of quinoxaline-2-carboxaldehyde semicarbazone (36) in 10 ml glacial acetic acid was treated with 4.5 g (0.01 mol) of freshly prepared lead tetraacetate in a 50 ml round bottom flask fitted with calcium chloride guard tube. The mixture was stirred for

9 hours at room temperature. After completion of the reaction, 15 ml of cold water was added and neutralised with sodium bicarbonate solution. The mixture was extracted with chloroform. The extract was washed repeatedly with water and dried over anhydrous sodium sulphate. The chloroform solution was then evaporated to dryness. The residue was recrystallised from chloroform-hexane to give 1.6 g (75%) of 2-(2-amino-1,3,4-oxadiazol-5-yl)quinoxaline m.p. 155°.

IR: (KBr); 3380, 3280 ($-NH_2$), 1030, cm^{-1} (C-O-C).

NMR: ($CDCl_3$); δ 8.5 to 7.5 (m, 5, aromatic).
2.4 (2, broad, NH_2).

MS: m/z 213, 212 (M^+ -1); 214 (M^+ +1); 188 (M^+ -25);
170 (M^+ - HNCO).

UV: $\lambda_{max.}^{MeOH}$ 320 nm (ε $2.7x10^4$), 297 nm (ε $2.9x10^4$),
244 nm (ε $5.7x10^4$).

Anal: Calcd: for $C_{10}H_7N_4O$; C, 56.33; H, 3.75; N, 32.86.
Found: C, 57.55; H, 3.28; N, 32.85.

3.38 Attempted cyclisation of (37) using lead tetraacetate

To a suspension of 1.15 g (0.005 mol) of 37 in glacial acetic acid taken in a 50 ml round bottom flask was

added 2.2 g (0.005 mol) of freshly prepared lead tetra-acetate. The flask was fitted with a calcium chloride guard tube. The mixture was stirred at room temperature for 9 hours. Water was added and stirring continued for a while and allowed to stand. The starting thiosemicarbazone was isolated on usual work up without any change.

4.39 2-Hydroxy-3-(1-oxo-2,3,4-trihydroxybutyl)-quinoxaline (39)

A solution of 17.5 g (0.1 mol) of ascorbic acid in 100 ml of water at 10°C was stirred with 10.8 g (0.1 mol) of p-benzoquinone for one hour. After this period, 10.8 g (0.1 mol) of recrystallised o-phenylenediamine was added to the reaction mixture and stirring continued for another two hours. Yellow crystals that separated were filtered, washed with water and recrystallised from methanol to get 22.0 g (89.06%) of 2-hydroxy-3-(1-oxo-2,3,4-trihydroxybutyl)quinoxaline (39) m.p. 125° (lit.[15] m.p. 125°).

4.40 2-Hydroxy-3-(1-phenylhydrazono-2,3,4-trihydroxybutyl)-quinoxaline (40)

To a suspension of 120 g (0.05 mol) of 2-hydroxy-3-(1-oxo-2,3,4-trihydroxybutyl)quinoxaline in methanol was

added a methanol solution of 6.0 ml of freshly distilled phenylhydrazine and 1 ml of glacial acetic acid. The mixture was boiled under reflux for one hour. The red crystalline products formed on cooling was filtered, washed with water and methanol and dried to get 13 g (77.38%) of 2-hydroxy-3-(1-phenylhydrazono-2,3,4-trihydroxybutyl)quinoxaline (40) m.p. 205° (lit.[163] m.p. 205°).

4.41 2-Hydroxy-3-(1-phenylhydrazono glyoxalyl)-quinoxaline (41)

To a stirred solution of sodium metaperiodate (10.0 g) in 30 ml water was added 9.8 g (0.03 mol) of 2-hydroxy-3-(1-phenylhydrazono-2,3,4-trihydroxybutyl)quinoxaline with stirring. The reaction flask was covered with a brown paper and the mixture stirred overnight. The suspension was filtered and the product recrystallised from butanol to give 7.8 g (97.6%) of orange coloured, needle shaped aldehyde (41) m.p. 242°(lit.[163] m.p. 244°).

4.42 2-Hydroxy-3-(1,2-bis phenylhydrazono glyoxalyl)-quinoxaline (42)

A suspension of 1.5 g (0.005 mol) of 2-hydroxy-3-(1-phenylhydrazono glyoxalyl)quinoxaline (41) in 50 ml of

n-butanol was mixed with a few drops of glacial acetic acid and boiled over water bath. Freshly distilled phenylhydrazine (1 ml) was added to the reaction mixture and boiled for 5 minutes. When the reaction was complete, the mixture was cooled and the product filtered, dried and recrystallised from n-butanol to give 1.4 g (70.35%) of 2-hydroxy-3-(1,2-bis phenylhydrazone glyoxalyl)quinoxaline (42) m.p. 220° (lit.[163] m.p. 220°).

4.43 2-Hydroxy-3-(2-phenyl-1,2,3-triazol-4-yl)-quinoxaline (43)

To a mixture of 1.0 g (0.0025 mol) of lead tetra-acetate in 15 ml of glacial acetic acid taken in a 50 ml round bottom flask fitted with a calcium chloride guard tube was added 0.75 g (0.0005 mol) of 42. The reaction mixture was stirred at room temperature for 8 hours. After the completion of the reaction 25 ml of cold water was added and cooled. The product that formed was filtered, washed with water and dried to get 0.5 g (87.7%) of 2-hydroxy-3-(2-phenyl-1,2,3-triazol-4-yl)quinoxaline (43) m.p. 195-97°.

IR: (KBr); 3500 (NH, OH), 2340, 1720 (-OCN), 1630 cm^{-1} (C=N).

NMR: (DMSO-d_6); δ 8.9 (1, s, C-H of triazol),
7.9 to 8.2 (4, m, quinoxaline), 7.2 (5, s, phenyl H).

MS: m/z 289 (M^+); 261 ($M^+ - N_2$); 169 (261-HM-C_6H_5) and 149.

UV: $\lambda_{max.}^{MeOH}$ 380 nm (ε 5.7x10^4).

Anal: Calcd: for $C_{16}H_{11}N_5O$; C, 66.43; H, 3.8; N, 24.22.
Found: C, 65.84; H, 4.2; N, 24.22.

4.44 2-Chloro-3-(2-phenyl-1,2,3-triazol-4-yl)-quinoxaline (44)

A mixture of 700 mg (0.0025 mol) of 43 and 5 ml of phosphorous oxychloride and a catalytic quantity of dimethylformamide was heated in a 50 ml round bottom flask fitted with a water condenser and calcium chloride guard tube over a boiling water bath for 3 hours. After the reaction time, the mixture was cooled and poured onto crushed ice with vigorous stirring. The precipitate was filtered, dried and recrystallised from chloroform-hexane to give 600 mg (80%) of 2-chloro-3-(2-phenyl-1,2,3-triazol-4-yl)quinoxaline (44) m.p. 142°.

IR: 1600 (C=N), 800 cm^{-1}.

NMR: ($CDCl_3$); δ 8.9 (1, s, H-C-triazole),
8.2 to 7.9 (m, 4, quinoxaline), 7.2 (5, phenyl).

MS: m/z 307 (M^+); 308 (M^+ +1); 309 (M^+ +2).

Anal: Calcd: for $C_{16}H_{10}N_5OCl$; C, 62.54; H, 3.26; N, 22.8.
Found: C, 61.80; H, 3.5; N, 22.60.

4.45 2-Hydroxy-3-(1-phenylhydrazono-2-hydrazono glyoxalyl)-quinoxaline (45)

A suspension of 1.3 g (0.005 mol) of 2-hydroxy-3-(1-phenylhydrazono glyoxalyl)quinoxaline (41) in 50 ml of methanol was stirred with the dropwise addition of 2 ml of hydrazine hydrate in methanol. The product was filtered and dried to give 0.92 g of (67.15%) of 2-hydroxy-3-(1-phenyl-hydrazono-2-hydrazono glyoxalyl)quinoxaline (45) m.p. above 260° (lit.[163] m.p. 260°).

4.46 2-Hydroxy-3-(2(H),1,2,3-triazol-4-yl)quinoxaline (46)

To a mixture of 0.7 g (0.0015 mol) of freshly prepared lead tetraacetate and 10 ml of glacial acetic acid, taken in a 50 ml round bottom flask fitted with a calcium chloride guard tube was added 0.45 g (0.0015 mol) of the

hydrazone (45). The mixture was stirred at room temperature for 8 hours. After completion of the reaction 20 ml of cold water was added to it and the precipitate was filtered, dried and recrystallised from methanol to give 0.3 g of (63.19%) of 2-hydroxy-3-(2(H),1,2,3-triazol-4-yl)quinoxaline (46) m.p. 195°.

IR: (KBr); 3500 (broad, -OH, NH); 2950 (C-H); 2400, 1720 (-OCN); 1660 (C=N) cm^{-1}.

NMR: (DMSO-s_6); δ 8.4 to 7.9 (aromatic), 8.9 (1H, s, CH of triazol).

MS: m/z 213 (M^+); 185 ($M^+ - N_2$); 158 (185-HCN).

Anal: Calcd: for $C_{10}H_7N_5O$; C, 56.33; H, 3.28; N, 32.86.
Found: C, 56.80; H, 3.30; N, 32.85.

4.47 2-Hydroxy-3-(1-phenylhydrazono-2-semicarbazone glyoxalyl)quinoxaline (47)

To a mixture of 2 g of semicarbazide hydrochloride and 3.0 g of sodium acetate dissolved in 10 ml of water was added 1.58 g (0.005 mol) of 2-hydroxy-3-(phenylhydrazono glyoxalyl)quinoxaline (41) in 5 ml of n-butanol. The mixture

was stirred for 2 hours and then allowed to stand. The product that formed was filtered, washed with water and dried to give 1.6 g of the semicarbazone (47), (89.38%). m.p. 272° (lit.[163] m.p. 273°).

4.48 2-Hydroxy-3-(2-amido-1,2,3-triazol-4-yl)quinoxaline (48)

To a solution of 1 g (0.0025 mol) of lead tetra-acetate in 15 ml of glacial acetic acid taken in a 50 ml round bottom flask fitted with a calcium chloride guard tube was added 0.670 g (0.002 mol) of 47. The reaction mixture was stirred for 8 hours. After the completion of the reaction, 20 ml of cold water was added and the product filtered out, washed with water and dried to give 0.45 g (91.6%) of 2-hydroxy-3-(2-amido-1,2,3-triazol-4-yl)-quinoxaline (48) m.p. 210°.

IR: (KBr); 3700 (OH, NH); 3300, 3200 (two bands, $-C-NH_2$); 1740, 1728 (-OCN), 1650 cm^{-1} (-C=N).

NMR: (DMSO-d_6); δ 9.2 (C-H-triazol); 8 to 6 (aromatic).

MS: m/z 256 (M^+), 257 (M^++1), 255 (M^+-1), 214 (257-CONH), 188 (214-HCN).

Anal: Calcd: for $C_{11}H_8N_6O_2$; C, 51.60; H, 3.12; N, 32.81.
Found: C, 52.10; H, 3.33; N, 32.80.

4.49 2-Hydroxy-3-(1-phenylhydrazono-2-thiosemicarbazone-glyoxalyl)quinoxaline (49)

To a solution of 1.0 g of thiosemicarbazide and 1.5 g sodium acetate in 10 ml water was added 0.73 g (0.0025 mol) of the 2-hydroxy-3-(1-phenylhydrazono glyoxalyl)-quinoxaline (41). The mixture was stirred for 2 hours and the product filtered, washed with water and dried to give 0.92 g (98.18%) of 2-hydroxy-3-(1-phenylhydrazono-2-thiosemi-carbazone glyoxalyl)quinoxaline (49) m.p. 220° (lit.[163] m.p.220°).

4.50 2-Hydroxy-3-(2-thioamido-1,2,3-triazol-4-yl)-quinoxaline (50)

To a solution of 1.0 g of lead tetraacetate in 15 ml of glacial acetic acid taken in a 50 ml round bottom flask fitted with a calcium chloride guard tube was added 0.7 g (0.002 mol) of (49). The mixture was stirred continuously for 8 hours. After completion of the reaction, 25 ml of cold water was added and the product formed was filtered washed with water and dried to give 0.5 g (95.85%) of 2-hydroxy-3-(2-thioamido-1,2,3-triazol-4-yl)quinoxaline (50) m.p. 205°.

IR: (KBr); 3700 (NH, OH), 3570, 3450 (NH_2), 1754, 1630 (C=N), 1260 (C=S) cm^{-1}.

NMR: (DMSO-d_6); δ 9.2 (C-H, triazole), 8 to 7 (aromatic).

MS: m/z 272 (M^+); 274 (M^+ +2); 258 (274-NH_2), 246 (274-N_2).

Anal: Calcd: for $C_{11}H_8N_6OS$; C, 48.52; H, 2.94; N, 30.88.
Found: C, 49.33; H, 2.85; N, 31.50.

4.51 2-(Phenyliminomethyl)quinoxaline (51)

A sample of 1.0 ml of dry, freshly distilled aniline was added to a solution of 1.58 g (0.01 mol) of quinoxaline-2-carboxaldehyde (2) in methanol and the mixture heated over a boiling water bath for one hour. After completion of the reaction, it was cooled and the solid product filtered. The product was recrystallised from methanol to give 2.0 g (85.83%) of 2-(phenyliminomethyl)quinoxaline (51) m.p. 125-28°.

IR: (KBr); 3020 (C-H), 1600 (C=N) cm^{-1}.

NMR: ($CDCl_3$); δ 9.7 (1, s, HC=N), 8.7, 8.2 to 7.7 (m, aromatic), 7.4 (5H, phenyl).

Anal: Calcd: for $C_{15}H_{11}N_3$; C, 77.25; H, 4.72; N, 18.02.

Found: C, 76.85; H, 4.81; N, 18.05.

4.52 Diazomethane in dioxane[164]

To a mixture of 12 ml of 50% aqueous potassium hydroxide and 25 ml of dioxane kept in an ice bath was added 4.0 g of nitrosomethylurea with shaking. The yellow dioxane layer containing the generated diazomethane was separated in a separating funnel and used immediately for the next reaction. The solution contained approximately 1.0 g of diazomethane.

4.53 2-(1-Phenyl-1,2,3-triazolin-5-yl)quinoxaline (52)

To a solution of 0.507 g (0.0025 mol) of 51 in 15 ml of dioxane was added a solution of 1.0 g of diazomethane in 25 ml moist dioxane. The reaction mixture was kept tightly corked at laboratory temperature for 120 hours. When the reaction was complete as followed by tlc, 50 ml of cold water was added to it and cooled again. The yellow crystals that separated was filtered, washed with water and dried to give 400 mg (58.18%) of 2-(1-phenyl-1,2,3-triazolin-5-yl)quinoxaline (52) m.p. 120-22°.

IR: (KBr); 3067 (CH), 1680, 981, 955 cm^{-1}.

NMR: ($CDCl_3$); δ 8.7 (1, s), 8.3 to 7.7 (4H, m), 7.3 (phenyl H), 5.2 (1H, t), 4.7 (2H, d).

MS: m/z 275 (M^+, 15%); 247 ($M^+ - N_2$, 87%); 232 ($M^+ - CH_2N_2$, 14%).

UV: $\lambda_{max.}^{MeOH}$ 315 nm (ϵ 7.1×10^4), 280 nm (ϵ 3.9×10^4).

Anal: Calcd: for $C_{16}H_{13}N_5$; C, 69.81; H, 4.72; N, 25.45.
Found: C, 69.82; H, 4.63; N, 25.4.

4.54 2(p-chlorophenyliminomethyl)quinoxaline (53)

A solution of 1.58 g (0.01 mol) of quinoxaline-2-carboxaldehyde in methanol was stirred at room temperature with 1.3 g (0.012 mol) of p-chloroaniline for one hour. After the completion of reaction, the product was filtered dried and recrystallised from methanol to give 2.0 g (76.9%) of the anil (53) m.p. 168-69°.

IR: (KBr); 3000, 1500, 850 cm^{-1}.

NMR: ($CDCl_3$); δ 9.7 (1H, s, H-C=N), 8.7, 8.2 to 7.7 (m, aromatic), 7.4 (4H, phenyl).

Anal: Calcd: for $C_{15}H_{10}N_3Cl$; C, 67.41; H, 3.75; N, 15.73.
Found: C, 67.35; H, 3.82; N, 15.72.

4.55 2-(1-p-chlorophenyl-1,2,3-triazolin-5-yl)-quinoxaline (54)

A solution of 1.0 g of diazomethane in 25 ml moist dioxane generated from 4 g of nitrosomethylurea was added to a solution of 0.513 g (0.0025 mol) of 2-(p-chlorophenyliminomethyl)quinoxaline in 10 ml of dioxane. The mixture was allowed to stand at laboratory temperature for 168 hours. After the completion of reaction as followed by tlc, 50 ml of cold water was added to the reaction mixture, cooled, the product filtered and dried to give 400 mg (77.8%) of 2-(1-p-chlorophenyl-1,2,3-triazolin-5-yl)quinoxaline (54) m.p. 82-85°.

IR: (KBr); 2953, 1546, 1008, 950, 943, 850 cm^{-1}.

NMR: ($CDCl_3$); δ 8.7 (1H, s),8.3 to 7.7 (4H, m, 7.3 (4H, phenyl), 5.2 (1H, t, CH), 4.7 (2H, d, CH_2).

MS: m/z 309 (M^+), 267 ($M^+ - CH_2N_2$), 142 (267-C_6H_4ClN).

UV: $\lambda_{max.}^{MeOH}$ 311 nm (ε 8.7x10^4), 247 nm (ε8.03x10^4).

Anal: Calcd: for $C_{16}H_{12}N_5Cl$; C, 62.13; H, 3.86; N, 22.65.
Found: C, 62.24; H, 3.9; N, 22.5.

4.56 2-(p-Bromophenyliminomethyl)quinoxaline (55)

A solution of 1.58 g (0.01 mol) of quinoxaline-2-carboxaldehyde in methanol was kept at room temperature with 1.8 g (0.01 mol) of p-bromoaniline for 2 hours. The product formed was filtered, and recrystallised from methanol to give 2.0 g (64.5%) of the anil 55 m.p. 174°.

IR: (KBr); 3020, 1550, 550 cm^{-1}.

NMR: ($CDCl_3$); δ 9.7 (1H, s, H-C=N), 8.7, 8.2 to 7.7 (m, aromatic), 7.4 (4H, phenyl).

4.57 2-(1-p-Bromophenyl-1,2,3-triazolin-5-yl)-quinoxaline (56)

A solution of 1 g of diazomethane in 25 ml of moist dioxane generated from 4.0 g of nitrosomethylurea was added to a solution of 800 mg (0.0025 mol) of 2-(p-bromophenyliminomethyl)quinoxaline in 10 ml of dioxane. The mixture was allowed to stand at laboratory temperature for 168 hours. After the completion of reaction, 50 ml of cold water was added to the reaction mixture, cooled, the product filtered out, washed with water and dried to give 500 mg (62.5%) of 2-(1-p-bromophenyl-1,2,3-triazolin-5-yl)quinoxaline (56) m.p. 86°.

IR: (KBr); 3050, 1500, 980, 950, 550 cm^{-1}.

NMR: ($CDCl_3$); δ 8.7 (1H, s), 8.3 to 8.6 (4H, m, hetero), 7.3 (4H, phenyl), 5.2 (1H, t, CH), 4.7 (2H, d, CH_2).

MS: m/z 359 (M^+), 316 ($M^+ - CH_2N_2$).

UV: $\lambda_{max.}^{MeOH}$ 316 nm (ε 1.01×10^5), 248 nm (ε 1.02×10^5).

Anal: Calcd: for $C_{16}H_{12}N_5Br$; C, 53.48; H, 3.34; N, 19.09.
Found: C, 53.48; H, 3.40; N, 19.50.

4.58 2-(o-Aminophenyliminomethyl)quinoxaline (57)

A solution of 1.58 g (0.01 mol) of quinoxaline-2-carboxaldehyde in methanol was stirred with 1.02 g (0.01 mol) of o-phenylenediamine, at room temperature for 2 hours. The product was filtered and recrystallised from methanol to give 2 g of (86.9%) of the anil m.p. 192°.

IR: (KBr); 4050, 3800, 1650 cm^{-1}.

Anal: Calcd: for $C_{15}H_{12}N_4$; C, 72.58; H, 4.84; N, 22.58.
Found: C, 73.0; H, 4.67; N, 22.48.

4.59 2-(1-o-Aminophenyl-1,2,3-triazolin-5-yl)-quinoxaline (58)

A solution of 1.0 g of diazomethane in 25 ml of moist dioxane generated from 4.0 g of nitrosomethyl urea was added to a solution of 0.512 g (0.0025 mol) of 2-(o-aminophenyliminomethyl)quinoxaline (57) in 10 ml of dioxane. The mixture was allowed to stand at room temperature for 168 hours. After the completion of the reaction, 50 ml of cold water was added, cooled and the product filtered and dried to give 0.4 g (50%) of 2-(1-o-aminophenyl-1,2,3-triazolin-5-yl)quinoxaline (58) m.p. 180°.

IR: (KBr); 4058, 3802 (NH), 2921 (H-C), 1554, 1051, 964 cm^{-1}

MS: m/z 290 (M^+), 248 ($M^+ - CH_2N_2$), 232 (248-NH_2), 144.

UV: $\lambda_{max.}^{MeOH}$ 355 nm (ε 8.6×10^4), 316 nm (ε 8.4×10^4).

Anal: Calcd: for $C_{16}H_{14}N_6$; C, 66.2; H, 4.82; N, 28.96.
Found: C, 66.08; H, 4.63; N, 28.94.

4.60 2-(Naphthaliminomethyl)quinoxaline (59)

A solution of 1.58 g (0.01 mol) of quinoxaline-2-carboxaldehyde in methanol was stirred with 1.45 g (0.01 mol)

of naphthalamine for 2 hours. The product was filtered and recrystallised from methanol to give 2.5 g (89.2%) of the anil m.p. 155°.

IR: (KBr); 3050, 1620 cm^{-1}.

NMR: ($CDCl_3$); δ 9.7 (1H, s, H-C=N-), 8.7 to 7.8 (m, aromatic), 7.4 (naphthyl).

Anal: Calcd: for $C_{19}H_{13}N_3$; C, 80.56; H, 4.59; N, 14.84.
Found: C, 80.07; H, 5.02; N, 15.01.

4.61 2-(1-Naphthyl-1,2,3-triazol-5-yl)quinoxaline (60)

A solution of 1.0 g of diazomethane in 25 ml of moist dioxane generated from 4.0 g of nitrosomethyl urea was added to a solution of 0.511 g (0.0025 mol) of the anil 59 in 10 ml of dioxane. The mixture was allowed to stand at room temperature for 168 hours. After completion of the reaction as followed by tlc, 50 ml of cold water was added to the reaction mixture, cooled and the product was filtered and dried to give 0.45 g (75%) of 2-(1-naphthyl-1,2,3-triazolin-5-yl)quinoxaline (60) m.p. 121°.

IR: (KBr); 3043, 1422, 1012, 940 cm^{-1}.

NMR: ($CDCl_3$); δ 8.7 (1H, s, H-C=N), 8.3 to 8.6 (m, hetero), 7.3 (naphthyl), 5.2 (1H, t, CH), 4.7 (2H, d, CH_2).

MS: m/z 325 (M^+), 297 ($M^+ - N_2$), 282 ($M^+ - CH_2N_2$).

UV: $\lambda_{max.}^{MeOH}$ 304 nm (ϵ $9.9x10^4$).

Anal: Calcd: for $C_{20}H_{16}N_5$; C, 73.84; H, 4.61; N, 21.53.
Found: C, 73.44; H, 4.52; N, 21.52.

4.62 Diquinoxalino[2,3-b:2',3'-e]-1,4-dithiiene (61)

A mixture of 1.0 g (0.005 mol) of dichloroquinoxaline and 700 mg of thiourea in 10 ml of dimethylformamide was heated over a water bath for 5 hours. After completion of the reaction as monitored by tlc, the reaction mixture was cooled and poured into crushed ice with vigorous stirring. The crystals that formed were filtered out and recrystallised from methanol to give 0.620 g of (76.7%) of diquinoxalino-[2,3-b:2',3'-e]-1,4-dithiiene (61) m.p. 375° (decomp.) (lit.[168] m.p. 378°).

IR: (KBr); 3050, 1600 cm^{-1}.

NMR: ($CDCl_3$); δ 7.5 (m, aromatic).

MS: m/z 320 (M^+), 321 (M^+ +1), 322 (M^+ +2), 323 (M^+ +3), very week; 288, 276, 244, 192.

UV: $\lambda_{max.}^{MeOH}$ 320 nm (ε 9.5×10^4).

Anal: Calcd: for $C_{16}H_8N_4S_2$; C, 60.0; H, 2.5; N, 17.5.
Found: C, 59.2; H, 3.1; N, 17.8.

4.63 Diquinoxalino[2,3-b:2'3'-d]thiiene (62)

A mixture of 1.6 g (0.01 mol) of 2-chloroquinoxaline and 0.35 g of thiourea in 10 ml of dimethylformamide was heated over a boiling water bath for 3 hours. After the completion of the reaction as monitored by tlc, the reaction mixture was cooled and poured into crushed ice with vigorous stirring. The product that formed was filtered out, dried and purified by column chromatography over silica gel column using chloroform as eluent to give 900 mg (64.2%) of diquinoxaline[2,3-b:2'3'-d]thiiene (62) m.p.280° (decomp).

IR: (KBr); 3050, 1600 cm^{-1}.

NMR: ($CDCl_3$); δ 8 to 7.5 (aromatic).

MS: m/z 288 (M^+), 289, 290, 160, 149 etc.

UV: $\lambda_{max.}^{MeOH}$ 300 nm (ϵ 9.1×10^4).

Anal: Calcd: for $C_{16}H_8N_4S$; C, 66.6; H, 2.7; N, 19.44.
Found: C, 65.6; H, 2.85; N, 20.01.

4.64 2,3-Diethoxyquinoxaline (63)

To 3.96 g (0.02 mol) of 2,3-dichloroquinoxaline (25) in 15 ml of absolute ethanol taken in a 50 ml round bottom flask was added 2.0 g of potassium carbonate and fitted with a reflux condenser and calcium chloride guard tube. The mixture was refluxed over a boiling water bath for 3 hours. After the completion of the reaction, the mixture was filtered and the solvent removed under reduced pressure. The residue was recrystallised from hexane to give 3.0 g of (80%) of 2,3-diethoxyquinoxaline (63) m.p. 78° (lit.[47] m.p. 78°).

4.65 2-Aminothiazolo[4,5-b]quinoxaline (64)

A mixture of 1.0 g (0.005 mol) of diethoxyquinoxaline and 700 mg of thiorurea in 10 ml of dimethylformamide was heated over a boiling water bath for 10 hours. After

completion of the reaction, as monitored by tlc, the reaction mixture was poured into crushed ice, the product formed was filtered out, dried and purified by column chromatography over silica gel using chloroform as eluent to get 800 mg (86.39%) of 2-aminothiazolo[4,5-b]quinoxaline m.p. 210°.

IR: (KBr); 3720, 3440 cm^{-1} (broad, NH), 3030, 2360 cm^{-1}.

NMR: ($CDCl_3$); δ7.9 (m, aromatic), 1.7 (broad, NH_2).

MS: m/z 206 (M^+ +4), 204 (M^+ +2), 203 (M^+ +1), 178 (206-N_2), 162 (172-NH_2).

UV: $\lambda_{max.}^{MeOH}$ 356 nm (ε 6.4×10^4), 348 nm (ε 6.4×10^4).

Anal: Calcd: for $C_9C_6N_4S$; C, 53.46; H, 2.97; N, 27.72.
Found: C, 53.5; H, 3.0; N, 27.62.

4.66 5-Mercapto-1,2,4-triazolo[3,4-a]quinoxaline (65)

A mixture of 800 mg of 2-hydrazinoquinoxaline (34) (0.005 mol) and 5.0 ml of carbondisulphide in 5 ml of dimethylformamide was heated over a boiling water bath for 5 hours. After completion of the reaction the reaction mixture was added to crushed ice with vigorous stirring and

the product formed was filtered out. It was dried and recrystallised from methanol to give 750 mg (71.43%) of 5-mercapto-1,2,4-triazolo[3,4-a]quinoxaline (65) m.p. 230° (decomp).

IR: (KBr); 4080, 3295 (HS, NH), 2365, 1722, 1607, 1265 cm^{-1}.

NMR: was not determined as the sample was insoluble.

MS: m/z 202 (M^+), 170 (M^+ -5), 144 (170-HCN), 116 (144-N_2).

UV: $\lambda_{max.}^{MeOH}$ 330 nm (ε $6.1x10^4$), 320 nm (ε $6.3x10^4$).

Anal: Calcd: for $C_9H_6N_4S$; C, 53.4; H, 2.90; N, 27.7.

Found: C, 53.46; H, 288; N, 27.6.

4.67 2-Hydroxy-3-quinoxaline carboxalyic acid (66)

To a suspension of 12 g (0.05 mol) of 2-hydroxy-3-(1-oxo-2,3,4-trihydroxybutyl)quinoxaline (39) in water was added an aqueous solution of 6 g of potassium permanganate. The mixture was stirred for one hour. The excess potassium permanganate was removed by adding sodiumbisulphite solution. The reaction mixture was filtered, acidified with concentrated hydrochloric acid and the product filtered and

dried to give 7.0 g of (81.36%) of 2-hydroxy-3-quinoxaline carboxylic acid (66) m.p. 264° (lit.[171] m.p. 165°).

4.68 Ethyl-2-hydroxyquinoxaline-3-carboxylate (67)

A mixture of 5.7 g (0.003 mol) of 2-hydroxy-quinoxaline-3-carboxylic acid (67), 10 g of seralite-SRC-120 resin and 20 ml of absolute ethanol in a 100 ml round bottom flask was heated under reflux over water bath for 10 hours. After the completion of the reaction, the mixture was filtered, the filterate was concentrated and cooled to give 4.8 g (80%) of ethyl-2-hydroxyquinoxaline-3-carboxylate (67) m.p. 176° (lit.[172,47] m.p. 175.5°).

4.69 Ethyl-2-chloroquinoxaline-3-carboxylate (68)

A mixture of 4.36 g (0.002 mol) of ethyl-2-hydroxy-quinoxaline-3-carboxylate and 50 ml of freshly distilled phosphorous oxychloride was heated on a steam bath for three hours, under a calcium chloride guard tube. The mixture was cooled and poured into 500 g of crushed ice with stirring. The precipitate was filtered, washed with ice cold water, dried and recrystallised from hexane to give 3.7 g (85%) of ethyl-2-chloroquinoxaline-3-carboxylate (68) m.p. 42-43° (lit.[47] m.p. 42.5°).

4.70 2-Amino-4-oxo thiazino[5,6-b]quinoxaline (69)

A mixture of 1.08 g (0.005 mol) of 2-chloroquinoxaline-3-carboxylate and 0.65 g of thiourea in 10 ml dimethylformamide was heated over water bath for three hours. After completion of the reaction as monitored, by tlc, the reaction mixture was cooled and poured into crushed ice with vigorous stirring. The product formed was filtered and dried. It was dissolved in minimum quantity of methanol-chloroform and chromatographed over silica gel to get 700 mg (66.72%) of 2-amino-4-oxo- thiazino[5,6-b]quinoxaline (69) m.p. 170°.

IR: (KBr); 3900 (broad, NH, OH), 3700, 3600 (NH_2), 1730 cm^{-1} (NH-C=O).

NMR: ($CDCl_3$); δ 7.9 (4, m, aromatic), 1.7 (broad, NH_2).

MS: m/z 234 (M^+ +4), 190, 162.

UV: $\lambda_{max.}^{MeOH}$ 330 nm (ε 6.1×10^4), 320 nm (ε 6.3×10^4).

Anal: Calcd: for $C_{10}H_6N_4OS$; C, 52.17; H, 2.6; N, 24.34.
Found: C, 52.28; H, 2.51; N, 24.35.

Chapter 5

BIOLOGICAL STUDIES

5.1 INTRODUCTION

Many quinoxaline derivatives have been reported to have interesting antimicrobial activity. The newly synthesised compounds and some related quinoxaline derivatives were, therefore, tested for their activity against three different strains of microorganisms each under three different concentrations.

Pseudomonas aeruginosa, Vibrio parahaemolyticus, Bacillus cereus, were selected as the test organisms as they were readily available in our laboratory. All the three are pathogenic organisms and infect humans.[173] Infections of healthy individuals with P.aeruginosa are rare and usually mild. Cutaneous infections acquired in swimming pools or bath tubs are usually brief and self limiting. However, serious P.aeruginosa infections are seen to occur in chronically debitilated patients and the nature of the underlying conditions generally determines the outcome. In cystic fibrosis patients the respiratory track is colonised by P.aeruginosa and death often results from pulmonary complications. Highly destructive occular infections may be caused by P.aeruginosa originating from

contaminated ophthalmologic solutions or following severe facial burns. Long term intravenous or urinary catheterization in various surgical procedures and severe burns can also allow the organism to circumvent the protective layers of the skin and colonize various tissues often leading to septicemia.

Vibrio parahaemolyticus is found in marine and estuarine environments throughout the world. It has been recovered from sea foods and often found with increasing frequency in cases of food poisoning in various countries. In Japan, it accounts for half the cases of bacterial food poisoning. The disease ranges from the usual moderate short term illness to severe cases of gastroenteritis. Infections of the eyes, ears, as well as blood streams have also recently been recognised in the US in persons scratched by the sharp edges of clams or oysters.

Bacillus cereus found on many grains, vegetables and dairy products also can cause outbreaks of food poisoning. The prominent forms of food poisoning caused by it are diarrheal syndrome and emetic syndrome. Diarrheal

syndrome is caused by heat labile enterotoxin and emetic syndrome is associated with heat stable enterotoxin.

5.2 PREPARATION OF TEST SOLUTIONS

Stock solutions of concentration 100 ppm of the test compounds were prepared by accurately weighing out 10 mg of the compound into 100 ml standard flask. The solutions were prepared in 1:1 aqueous ethanol. Solutions of concentration 50 ppm and 10 ppm were prepared by accurately pipetting out 12.5 ml and 2.5 ml respectively of the stock solution into 25 ml standard flasks and diluting to the required volume.

5.3 NUTRIENT BROTH

Nutrient broth (1000 ml) supplied by Hi-Media, Bombay were used after sterilising by autoclaving at 15 lbs pressure, 121°C for 15 minutes.

5.4 PREPARATION OF INOCULUM[174,175]

Pseudomonas aeruginosa, Vibrio parahaemolyticus and Bacillus cereus preserved in the microbiology division were first subcultured before preparing the final test

culture. Three Erlenmayer flasks containing 25 ml of the nutrient broth were autoclaved, cooled to the laboratory temperature and inoculated with the stock culture (10^6 cells/ml) under sterile conditions, and incubated for 18 hours at room temperature (28±2°C). Fresh test cultures were prepared from these subcultures following the same procedure.

5.5 METHODOLOGY[174,175]

Solutions of the test compounds (1 ml) at three different concentrations, 10 ppm, 50 ppm and 100 ppm were added to 3 ml of nutrient broth dispensed in clean test tubes. A control was also kept for every set with 3 ml of the nutrient broth and 1 ml of the solvent so that the total volume remained constant. The prepared media were autoclaved, cooled and inoculated under sterile conditions with 0.1 ml (10^6 cells/ml) of previously prepared inoculum. The tubes were incubated for 48 hours at 28±2°C. Growth of microorganism was measured in terms of optical density of the solutions using a Hitachi 800 UV-Vis spectrophotometer. Duplicates were maintained for each concentration. The optical density obtained for the control was considered as 100% growth of microorganism for computation purpose.

From the optical density data, percentage of growth inhibition was calculated.

Optical density of control = ODC $\equiv$ 100% Growth

Optical density of test solution = ODT

Percentage growth in test/solution = $\frac{ODT \times 100}{ODC}$ = x

Percentage growth inhibition = 100 - x

5.6 RESULTS

Percentage growth inhibition of the test organisms by the test organic compounds at different concentrations were tabulated.

The data showed that all the quinoxaline derivatives were active against all the three bacteria (Table 1). In most cases the growth inhibition properties of the compounds were considerably high only at higher concentrations of the compounds, such as at 50 ppm and 100 ppm. The various anils of quinoxaline-2-carboxaldehyde showed above 70% growth inhibition against P.aeruginosa and V.parahaemolyticus at 50 ppm and 100 ppm concentrations.

But the activity against B.cereus was only moderate to very low at 10 ppm and only below 50% growth inhibition observed even at 100 ppm concentration of the compounds.

The various hydrazones in the quinoxaline series showed moderate to good growth inhibition properties. It was found that the hydrazones were considerably active against B.cereus also even at 10 ppm concentration. 2-Hydrazinoquinoxaline (34) exhibited above 90% growth inhibition against all the three bacteria at 100 ppm concentration.

Activity of condensed quinoxalines (Table II) was also moderate to good with increase in concentration of the test compounds. It was observed that P.aeruginosa showed certain extent of insensitivity to triazoloquinoxalines even at 100 ppm concentration whereas the growth of V.parahaemolyticus and B.cereus were inhibited to an extent of 50% at 50 ppm concentration. It is to be particularly noted that the pyrazoloquinoxalines 23 were uniformly active against all the three bacteria. At 100 ppm concentration, compounds 21 and 23 exhibited 76.52% and 70.92% growth inhibition respectively against

P.aeruginosa, 86.66% and 84.24% growth inhibition respectively against V.parahaemolyticus and 82% and 79.65% of growth inhibition against B.cereus. Among the triazoloquinoxalines, 17, 27 and 35 were found to be 73.15%, 75.9% and 97% active against P.aeruginosa at 100 ppm concentration.

The heteroaryl quinoxalines showed excellent growth inhibition properties against all the three bacteria even at lower concentrations (Table III). It was found that 2-chloro-3-(2-phenyl triazol-4-yl)quinoxaline (44) exhibited 58.48% growth inhibition against P.aeruginosa, 48.5% against V.parahaemolyticus and 36.1% against B.cereus at 10 ppm concentration. The triazolinylquinoxalines also showed considerable growth inhibition properties, but the activity was less prominent at 10 ppm concentration.

All the condensed quinoxalines containing sulphur showed excellent growth inhibition properties against all the bacteria (Table IV). For instance, diquinoxalinodithiiene (61) exhibited 86.25% activity against P.aeruginosa, 84.45% activity against V.parahaemolyticus and 35.7% activity against B.cereus whereas the

thiazoloquinoxaline (64) exhibited 80.53% activity against, P.aeruginosa 47.21% activity against V.parahaemolyticus and 4.76% activity against B.cereus at 10 ppm concentration. Diquinoxalinothiiene (62) exhibited uniformly good activity against all the three bacteria.

It is to be concluded from our preliminary biological studies that the condensed quinoxalines, heteroarylquinoxalines and condensed quinoxalines containing sulphur are excellent antibacterial agents worth further explorations.

No other biological studies of these compounds were conducted during the course of this work.

Table 1

QUINOXALINE DERIVATIVES

PERCENTAGE GROWTH INHIBITION

Sl. No.	Compound No.	P.aeruginosa			V.parahaemolyticus			B.cereus		
		10 ppm	50 ppm	100 ppm	10 ppm	50 ppm	100 ppm	10 ppm	50 ppm	100 ppm
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
1.	1	11.33	18.95	25.27	0.00	16.00	12.90	10.00	14.58	25.52
2.	2	0.00	10.94	91.01	48.17	66.67	80.86	7.55	23.44	24.74
3.	16	1.50	14.99	52.35	6.61	19.70	64.17	12.70	15.48	33.90
4.	18	48.77	49.89	69.57	32.86	81.45	81.83	79.83	81.39	82.60
5.	20	12.0	37.14	59.28	16.9	66.33	86.66	64.35	72.52	75.20
6.	22	65.77	76.51	76.50	78.27	84.50	89.20	31.83	56.70	78.78
7.	25	44.09	46.36	63.64	72.03	93.48	94.68	66.28	73.72	84.65
8.	26	24.77	25.91	35.00	0.00	8.99	12.61	48.37	55.81	92.33

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
9.	28	4.32	28.86	44.00	13.19	49.71	90.58	93.02	96.51	97.44
10.	34	40.68	49.77	97.27	27.10	51.89	96.38	45.35	56.51	74.42
11.	36	74.04	74.04	76.29	44.60	83.35	83.48	2.78	57.83	40.26
12.	42	61.81	90.60	94.24	65.07	69.85	69.48	46.36	46.90	48.70
13.	45	86.66	89.39	83.30	77.94	80.51	85.22	63.07	72.23	85.71
14.	47	93.30	96.30	96.30	87.80	88.90	91.90	47.16	53.63	86.79
15.	49	93.63	97.87	99.39	87.13	90.80	93.38	73.30	76.62	95.26
16.	51	2.34	85.94	87.30	2.15	50.97	72.47	13.80	25.00	35.16
17.	53	25.78	71.48	71.48	40.43	61.51	69.25	9.38	36.98	37.50
18.	55	17.58	38.28	87.70	0.00	57.42	67.90	0.00	20.57	21.09
19.	57	0.00	11.72	29.60	0.00	0.00	1.06	10.94	11.22	11.22
20.	59	0.00	18.38	18.95	51.61	54.84	68.82	20.00	24.72	44.79
21.	63	7.07	21.68	61.60	87.90	90.00	91.50	47.76	11.90	28.50
22.	68	93.80	94.46	95.35	85.22	94.24	97.88	14.28	38.09	50.00

Table II

CONDENSED QUINOXALINES

PERCENTAGE GROWTH INHIBITION

Sl. No.	Compound No.	P.aeruginosa			V.parahaemolyticus			B.cereus		
		10 ppm	50 ppm	100 ppm	10 ppm	50 ppm	100 ppm	10 ppm	50 ppm	100 ppm
1.	17	14.99	20.13	73.15	0.89	6.48	21.47	1.30	5.39	15.65
2.	19	6.26	6.49	7.83	8.13	73.57	74.59	21.39	69.91	76.00
3.	21	12.30	71.14	76.51	30.11	86.91	90.72	34.61	61.74	82.09
4.	23	11.63	56.15	70.92	81.58	81.83	84.24	49.74	77.91	79.18
5.	27	28.41	53.18	75.90	6.67	11.16	18.12	43.49	69.53	95.33
6.	29	4.55	36.82	39.09	59.42	96.67	97.10	65.58	91.63	91.63
7.	35	45.00	61.80	97.20	33.10	65.60	96.00	50.35	60.00	80.12

Table III

HETEROARYL QUINOXALINES

PERCENTAGE GROWTH INHIBITION

Sl. No.	Compound No.	P.aeruginosa			V.parahaemolyticus			B.cereus		
		10 ppm	50 ppm	100 ppm	10 ppm	50 ppm	100 ppm	10 ppm	50 ppm	100 ppm
1.	43	21.23	24.55	47.34	28.59	67.56	76.00	4.76	21.40	52.33
2.	44	55.48	64.54	67.57	48.52	58.48	82.35	36.10	60.80	76.00
3.	46	89.30	90.10	93.00	85.20	86.00	92.60	93.53	96.22	98.92
4.	48	94.24	94.44	97.27	83.08	86.02	97.50	51.48	58.76	63.61
5.	50	85.75	87.87	88.78	82.35	84.55	86.75	87.38	80.80	90.02
6.	52	15.20	86.00	92.30	22.25	60.97	75.40	23.80	45.00	75.16
7.	54	35.00	71.40	75.00	40.50	65.20	80.20	29.30	36.98	57.50
8.	56	38.20	87.70	87.00	38.00	67.40	87.90	20.50	40.10	57.90
9.	58	15.00	38.25	60.60	15.00	20.55	40.10	20.90	31.20	51.20
10.	60	20.00	36.68	37.90	68.22	70.20	88.80	30.00	34.70	74.79

Table IV

CONDENSED QUINOXALINES CONTAINING SULPHUR

PERCENTAGE GROWTH INHIBITION

Sl. No.	Compound No.	P.aeruginosa			V.parahaemolyticus			B.cereus		
		10 ppm	50 ppm	100 ppm	10 ppm	50 ppm	100 ppm	10 ppm	50 ppm	100 ppm
1.	61	86.25	89.15	90.70	84.45	91.17	92.70	35.70	64.28	88.00
2.	62	74.33	89.60	91.37	78.85	89.63	92.50	52.33	59.55	71.42
3.	64	80.53	85.39	86.94	47.21	76.58	88.67	4.76	23.80	61.90
4.	65	81.20	90.20	99.00	54.00	75.20	96.38	50.30	76.70	82.00
5.	69	38.00	87.38	96.46	60.00	82.70	94.00	61.90	71.42	81.70

Chapter 6

SUMMARY AND CONCLUSIONS

6. SUMMARY AND CONCLUSIONS

Quinoxalines are bicyclic heterofused systems, widely distributed in nature having biological activity. Numerous synthetic quinoxalines are reported which also have useful biological properties.

A few reactions of quinoxaline-2-carboxaldehyde have been carried out in order to get some quinoxaline derivatives starting materials for their further conversions. The present work has developed a method for the synthesis of a tricyclic hetrofused ring system-condensed quinoxalines and heteroaryl quinoxalines. In addition to it, synthesis of a few condensed quinoxalines containing sulphur in the ring was also carried out. All the new compounds and some related compounds were screened to establish their activity against Pseudomonas aeruginosa, Vibrio parahaemolyticus and Bacillus cereus at different concentrations.

Reactions of quinoxaline-2-carboxaldehyde with grignard reagent followed addition of one or two molecules of the reagent depending on the reaction conditions. Inter-conversions of the addition products were also investigated.

Synthesis of a novel tricyclic heterofused system triazoloquinoxaline is reported starting from quinoxaline derivatives. Thus oxidative cyclisation of quinoxaline-2-carboxaldehyde hydrazone and 2-acetylquinoxaline hydrazone using lead tetraacetate gave v-triazolo[3,4-a]quinoxaline and 5-methyl-v-triazolo[3,4-a]quinoxaline respectively in excellent yields. Cyclisation of 2,3-bis hydrazinoquinoxaline in the presence of lead tetraacetate yielded 1-amino triazolo[4,5-b]-quinoxaline whereas 2,3-bis phenylhydrazinoquinoxaline provided 1-phenyltriazolo[4,5-b]quinoxaline. The known 1-phenylpyrazolo[3,4-b]quinoxaline and 3-methyl-1-phenyl pyrazolo[3,4-b]quinoxaline were obtained from the phenyl-hydrazones of quinoxaline-2-carboxaldehyde and 2-acetylquino-xaline. Treatment of 2-hydrazinoquinoxaline and benzoyl chloride gave 5-phenyl-1,2,4-triazolo[3,4-a]quinoxaline. The mechanism for these cyclisations have been discussed and the structure proof for all the new compounds have been presented.

Synthesis of some new heteroaryl quinoxalines were carried out starting from quinoxaline-2-carboxaldehyde. Thus cyclisation of quinoxaline-2-carboxaldehyde semicarbazone using lead tetraacetate gave 2-(2-amino-1,3,4-oxadiazol-5-yl)-quinoxaline. 2-Hydroxy-(1,2-bis phenylhydrazonoglyoxalyl)-quinoxaline on treatment with lead tetraacetate gave

2-hydroxy-3-(2-phenyl-1,2,3-triazol-4-yl)quinoxaline in good yield. Similarly, cyclisation of hydrazone, semicarbazone and thiosemicarbazone of 2-hydroxy-3-(phenylhydrazone glyoxalyl)quinoxaline using lead tetraacetate gave triazolyl-quinoxalines. Reaction of the anils of quinoxaline-2-carboxaldehyde with freshly prepared diazomethane in dioxane successfully gave the triazolinyl quinoxalines as addition products and their structures were established using analytical and spectral data.

Reaction of thiourea with quinoxalines gave interesting heterofused ring systems incorporating sulphur in the ring. Thus, diquinoxalino[2,3-b:2',3'-e]1,4-dithiiene and diquinoxalino[2,3-b :2',3'-d]thiiene were obtained in better yield from 2,3-dichloroquinoxaline and 2-chloroquino-xaline respectively. 2-Aminothiazolo[4,5-b]quinoxaline was obtained by reaction between 2,3-diethoxyquinoxaline and thiourea. Treatment of thiourea with ethyl-2-chloroquino-xaline-3-carboxylate gave the new 2-amino-4-oxo thiazino-[5,6-b]quinoxaline in excellent yield. As thiourea molecule has different nucleophilic centres, reaction with it may lead to different products. It has also been observed that dimethyl formamide is the most suitable solvent in such reactions. Interaction of 2-hydrazinoquinoxaline and

carbondisulphide gave 5-mercapto-1,2,4-triazolo[3,4-a]quinoxaline. The proof for the structure of the new compounds were obtained from their analytical and spectral data.

All the newly synthesised and some related compounds were screened for their activity against Pseudomonas aeruginosa, Vibrio parahaemolyticus and Bacillus cereus. The test cultures were charged with 10 ppm, 50 ppm and 100 ppm solutions of the compounds under sterilised conditions. After the incubation period, the growth of the test micro-organisms were measured in terms of optical density of the test solutions from which the growth inhibition property of the compounds were computed. It is to be concluded from the preliminary biological studies that the condensed quinoxalines, heteroarylquinoxalines and condensed quinoxalines incorporated with sulphur are excellent antibacterial agents worth further investigations. Previous reports on quinoxaline derivatives have shown that they possess antimicrobial, diuretic, anti-inflammatory, analgesic, antileukemic, antitumer and tuberculostatic properties. Also some quinoxalines have applications as agricultural chemicals. Therefore, all new compounds reported in this work will be submitted for studying their various biological properties.

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