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Synthesis of Novel Heterocyclic Fused Systems as Potential Leads – Oxazino [5,6-b], Pyrazino [5,6-b] and Imidazolo [4,5-b]- Quinoxalines.

Sreela Dasgupta*.

Department of Chemistry, Jai Hind College Autonomous, Churchgate, Mumbai 400020, India.

ABSTRACT

Heterocyclic systems such as piperazines and pyrazines have been known to exhibit a wide range of biological activity. Fused systems incorporating these two heterocyclic moieties have shown enhanced activity in having a rigid conformation. In an attempt to further 'freeze' the conformation, extended fusion with bidentate nucleophiles has been explored in this paper giving rise to oxazino[5,6-b], pyrazino[5,6-b] and imidazole[4,5-b] quinoxalines. Such transformations have been brought about by the cyclo-condensation of the quinoxaline ring with aliphatic bidentate nucleophiles as possible pharmacophores. These novel molecules which have been synthesized holds significance in being probable potential leads as two pharmacophoric moieties are embedded in their system – the heterocyclic ring and the aliphatic bidentate nucleophile.

Keywords: Quinoxalines, Bidentate nucleophile, Oxazino [5,6-b] quinoxaline, Pyrazino [5,6-b] quinoxaline, Imidazole[4,5-b] quinoxaline, Pharmacophore

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Corresponding author

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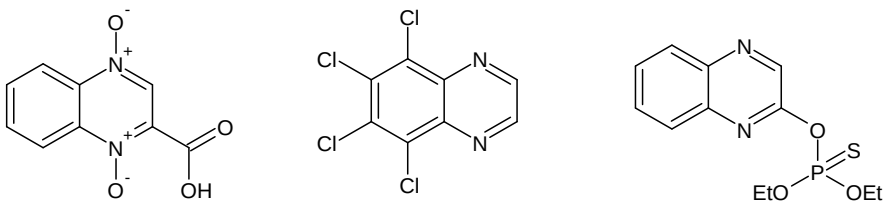
INTRODUCTION

Fused pyrazines, such as the quinoxaline ring system has been reported to possess a wide range of biological activities [1] such as antifungal, antibacterial, CNS depressant and radioprotective activities; a few examples being shown in Figure 1:



Antibiotic Fungicidal Anthelmintic

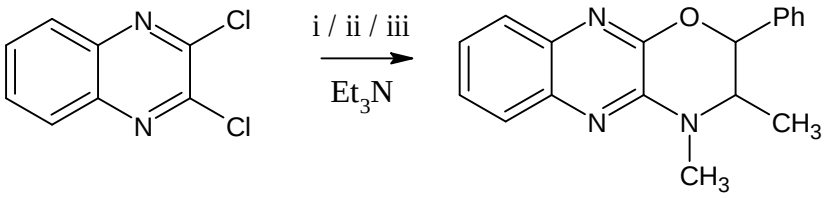
Figure 1

Many such synthetic quinoxalines have been designed having a diverse range of biological activity [2]. Keeping this aspect in mind, the present work has focussed on the synthesis of some novel heterocyclic ring systems incorporating the pyrazine ring system as the quinoxaline moiety, and coupling it with various other pharmacophores. Coupling of the quinoxaline ring system with various bidentate nucleophiles to give oxazino -, thiazino-, dioxino- [5,6-b] quinoxalines has been well researched and a number of them have been found to possess significant activity such as antibacterial, antiprotozoal, antifungal, etc [3-10]. Although a number of aromatic bidentate nucleophiles such as 2-aminopyridine, 2-aminobenzimidazole, 2-mercaptobenzimidazole, o-aminophenol, etc have been coupled with the quinoxaline system [11], very few reports of condensation with aliphatic bidentate nucleophiles have been reported [12-15]. Hence it was thought worthwhile to explore this area and synthesize novel fused heterocyclic systems through reaction between the quinoxaline ring and aliphatic bidentate nucleophiles capable of being possible pharmacophores.

MATERIALS AND METHODS

IR spectra were recorded with a Perkin-Elmer 15 spectrometer while the PMR spectra was recorded with a Perkin Elmer R-32 (90MHz) using TM S as internal standard. Mass spectra was recorded on a Jeol JMS D-300 spectrometer. All melting points were recorded in open capillary tubes on an electrothermal apparatus and are uncorrected. Chemicals and solvents have been procured from Sigma Aldrich and S.D. Fine Chem Ltd.

Scheme 1 was based on the cyclo-condensation of the 2,3-dichloroquinoxaline ring with ephedrine and *ψ*-ephedrine to give 2*H*-oxazino[5,6-b] quinoxalines [**1], [2], and [3**], novel heterocyclic systems that incorporate a quinoxaline moiety with ephedrine. Ephedrine was chosen as the bidentate nucleophile as it exhibits *α*- and *β*- adrenergic activity, CNS stimulant activity, in addition to being a bronchodilator and a respiratory centre stimulant. Hence the product formed may possibly act as a lead with potential activity.



i. ***d* – *ψ* – ephedrine**
ii. ***l*- *ψ* – ephedrine**
iii. ***l*-ephedrine**

1 = 2S, 3S
2 = 2R, 3R
3 = 2R, 3S

Scheme 1

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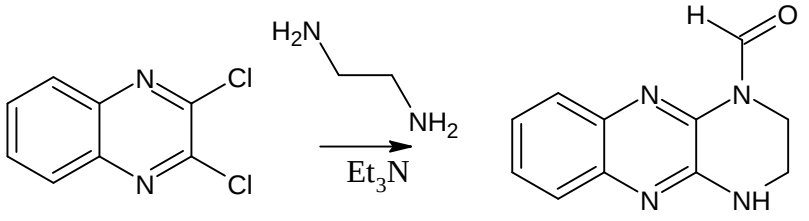
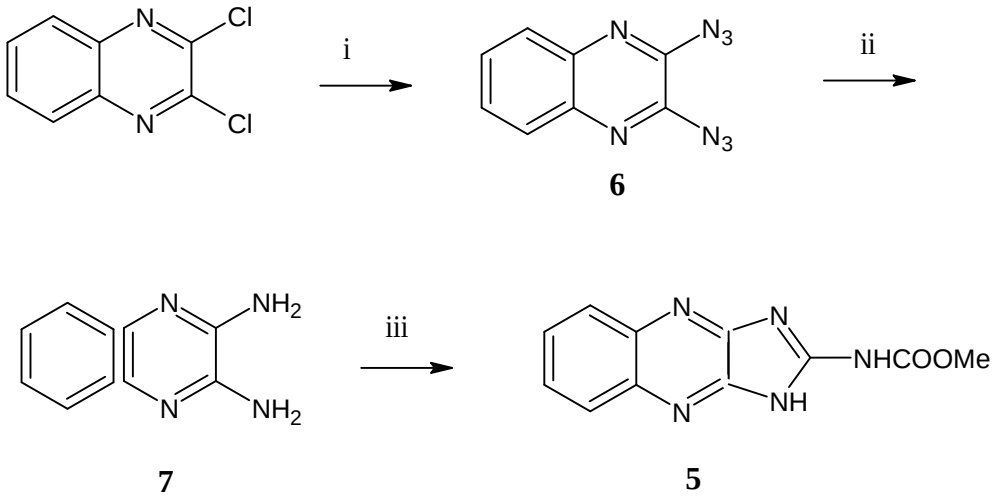
Apart from the N, O bidentate nucleophile in the ephedrine series, reaction was also successfully attempted with other bidentate nucleophiles such as ethylenediamine, to synthesize N-formyl-1,2,3,4 – tetrahydropyrazino [5,6-b] quinoxaline, **4**, **Scheme-2**.



4

Scheme 2

Synthesis of another novel fused heterocyclic system, **5** was inspired by the anthelmintic activity of several benzimidazoles such as mebendazole, albendazole and thiabendazole. Hence **Scheme 3** was devised to synthesize 2-(N-carbomethoxy) aminoimidazolo [4,5-b] quinoxaline, **5** with a view to obtain a potential anthelmintic lead molecule.



i = NaN_3, 50°C

ii =10 % Pd/C/H_2 , 30p.s.i

iii = MeCOO-NH-C(SMe)=NCOOMe, DMF, reflux

Scheme 3

Experimental

Synthesis of (*2S, 3S*) – 2-phenyl-3,4-dimethyl-3,4-dihydro-2*H*-1,4-oxazino [5,6-b] quinoxaline, 1

A mixture of 0.005 mol each of 2,3-dichloroquinoxaline and *d*-*ψ*-ephedrine dissolved in 20 cm^3 of DMF was heated at reflux in the presence of 0.006 mol of Et_3N as base, for 10 hours. On completion of reaction, it was poured into ice-cold water and extracted with ethyl acetate. The combined organic extracts were then washed with 1N citric acid solution, water, brine, dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The product was obtained as a dark yellow solid and was recrystallized with n-hexane.

Yield: 62.00% ; M. p. 123-25°C

Synthesis of (*2R, 3R*) – 2-phenyl-3,4-dimethyl-3,4-dihydro-2*H*-1,4-oxazino [5,6-b] quinoxaline, 2

Synthesis of compound **2** followed the same procedure as **1**; excepting that *l*-*ψ*-ephedrine was used in place of *d*-*ψ*-ephedrine

The product **2** was obtained as an orangish-yellow solid which was recrystallized with hexane-ether.

Yield: 56.00% ; M. p. 136-38^{o}C

Synthesis of (*2R, 3S*) – 2-phenyl-3,4-dimethyl-3,4-dihydro-2*H*-1,4-oxazino [5,6-b] quinoxaline, 3

Synthesis of compound **3** followed the same procedure as **1**; excepting that *l*-ephedrine was used in place of *d*-*ψ*-ephedrine

The product **3** was obtained as a pale-yellow solid which was recrystallized with benzene-hexane.

Yield: 47.10%; M. p. 144 - 46^{o}C

Synthesis of N-formyl – 1,2,3,4 - tetrahydropyrazino [5,6-b] quinoxaline, 4

A mixture of 0.005 mol each of 2,3-dichloroquinoxaline and ethylenediamine dissolved in 20 cm^3 of DMF was heated at reflux for 10 hours. On completion of reaction, it was poured into ice-cold water and extracted with ethyl acetate. The combined organic extracts were then washed with 1N citric acid solution, water, brine, dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The product was obtained as a yellow solid and was recrystallized with benzene-hexane.

Yield: 50.00%

Synthesis of 2,3-diazidoquinoxaline, 6

A mixture of 0.005 mol each of 2,3-dichloroquinoxaline and 0.015 mol of sodium azide dissolved in 15 cm^3 of DMF was stirred at 50^{o}C for 3 hours. On completion of reaction, it was poured into ice-cold water, the product filtered, washed with aqueous alcohol and acetone to give the product as a white crystalline solid.

Yield: 86.30 %; M. p. 260 - 262^{o}C

Synthesis of 2,3-diaminoquinoxaline, 7

A mixture of 0.0014 mol of 2,3-diazidoquinoxaline, **6**, in 60 cm^3 of glacial acetic acid 40cm^3 of methanol was hydrogenated with 10% Pd-C under 30 p.s.i. pressure at room temperature for 4 hours. On completion of reaction, the catalyst was filtered off and washed with a little methanol and the combined filtrate evaporated under suction. The residue was then cooled and basified with 50% KOH solution to yield the product. It was filtered, dried to obtain a white solid.

Yield: 61.50 %; M. p. 216-18^{o}C

Synthesis of 2- (N- Carbomethoxy) aminoimidazolo [4,5-b] quinoxaline, 5

A mixture of 0.00075 mol of 2,3-diaminoquinoxaline, **7** and 0.00075mol of 1,3-dicarbomethoxy-S-methylisothiourea dissolved in 10 cm^3 of DMF was heated at reflux for 14 hours. On completion of reaction, it was poured into ice-cold water to yield the product as a solid which was filtered, dried to obtain a yellow compound.

Yield: 69.70 %; M. p. 245-47^{o}C

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RESULTS AND DISCUSSION

Spectral analysis of 1

IR (KBr) ν_{max}: 3040 (aromatic -CH stretch), cm^{-1}
^1H NMR ($CDCl_3$, 90 MHz): δ 7.08 – 7.22 (m, 9H, Ar**H**), 5.08 – 5.18 (d, 1H, - OC**H**Ph, J = 4Hz), 3.62 – 3.94 (m, 1H, - C**H**NCH_3), 3.12-3.22 (m, 3H, N-C**H**$_3$), 1.22-1.42 (d, 3H, -CHC**H**$_3$)
Mass (m/z, %): 291 (M^+, 100), 276 (M^+-15, 45), 129 (M^+- 162, 10)

Spectral analysis of 2

IR (KBr) ν_{max}: 3040 (aromatic -CH stretch), cm^{-1}
^1H NMR ($CDCl_3$, 90 MHz): δ 7.08 – 7.22 (m, 9H, Ar**H**), 5.02 – 5.14 (d, 1H, - OC**H**Ph), 3.62 – 3.92 (m, 1H, - C**H**NCH_3), 3.12-3.22 (m, 3H, N-C**H**$_3$), 1.24-1.40 (d, 3H, -CHC**H**$_3$)
Mass (m/z, %): 291 (M^+, 100), 276 (M^+-15, 45), 129 (M^+- 162, 10)

Spectral analysis of 3

IR (KBr) ν_{max}: 3040 (aromatic -CH stretch), cm^{-1}
^1H NMR ($CDCl_3$, 90 MHz): δ 7.12 – 7.26 (m, 9H, Ar**H**), 5.06 – 5.18 (d, 1H, - OC**H**Ph, J= 7Hz), 3.62 – 3.96 (m, 1H, - C**H**NCH_3), 3.12-3.22 (m, 3H, N-C**H**$_3$), 1.22-1.42 (d, 3H, -CHC**H**$_3$)
Mass (m/z, %): 291 (M^+, 100), 276 (M^+-15, 45), 129 (M^+- 162, 10)

Spectral analysis of 4

IR (KBr) ν_{max}: 3040 (aromatic -CH stretch), 1680 (N-C=O) cm^{-1}
^1H NMR ($CDCl_3$, 90 MHz): δ 7.08 – 7.55 (m, 5H, Ar**H,** N-C**H**O), 2.54 – 2.68 (m, 5H, -N**H**-C**H**$_2$-C**H**$_2$-N)
Mass (m/z, %): 214 (M^+, 68), 171 (M^+- 43, 18), 156 (M^+- 58, 21), 142 (M^+- 72, 39)

Spectral analysis of 6

IR (KBr) ν_{max}: 3040 (aromatic -CH stretch), 2150 (-N_3 stretch) cm^{-1}
Mass (m/z, %): 212 (M^+, 14), 184 (M^+- 28, 11), 156 (M^+- 56, 34), 104 (M^+- 108, 100)

Spectral analysis of 7

IR (KBr) ν_{max}: 3400-3300 (-NH_2 stretch), 3040 (aromatic -CH stretch) cm^{-1}
Mass (m/z, %): 158 (M^+ - 2, 100), 130 (M^+- 30, 2), 105 (M^+- 55, 30)

Spectral analysis of 5

IR (KBr) ν_{max}: 3050 (aromatic -CH stretch) , 1650 (-NHCOOMe) cm^{-1}
Mass (m/z, %): 243 (M^+, 5), 186 (M^+- 58, 15), 158 (M^+- 85, 100)

The choice of the right base holds the key to the formation of the novel fused systems. Stronger bases such as KOH results in the formation of undesired products such as **8** due to the formation of dimethylamine from DMF (action of KOH on DMF) and its subsequent reaction with 2,3-dichloroquinoxaline. The formation of **8**, **Figure 2,** prevents the bidentate nucleophile to fuse with the quinoxaline moiety. Hence a milder nucleophilic base such as triethylamine is preferred.

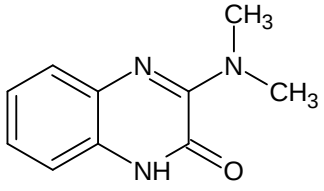

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Figure 2

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Formation of the 6-membered oxazino ring is confirmed from its ^{1}HNMR spectrum in which the -OC**H**(Ph) proton appears as a doublet at δ5.08-5.18 ppm whereas the (Me)N-C**H**-CH_3 proton appears as a multiplet at δ 3.62-3.94 ppm. The J value (4Hz) of the methine proton at C-2 in **1**, indicates trans configuration at C-2with respect to C3 indicating retention of geometry in the product as in *d*-*ψ*-ephedrine. Hence the cyclo-condensation proceeds via an addition-elimination sequence in which the N nucleophile of the ephedrine moiety first attacks the electron deficient site at C-3, in 2,3-dichloroquinoxaline, followed by elimination of the -Cl. This is followed by the attack of the oxanin at C-2 and a similar elimination sequence as before, to give the desired product **1**. Formation of **2, 3** also follow similar pathways.

The reaction of the N, N bidentate nucleophile (ethlylenediamine) follow the sequence as shown in **Figure 3**

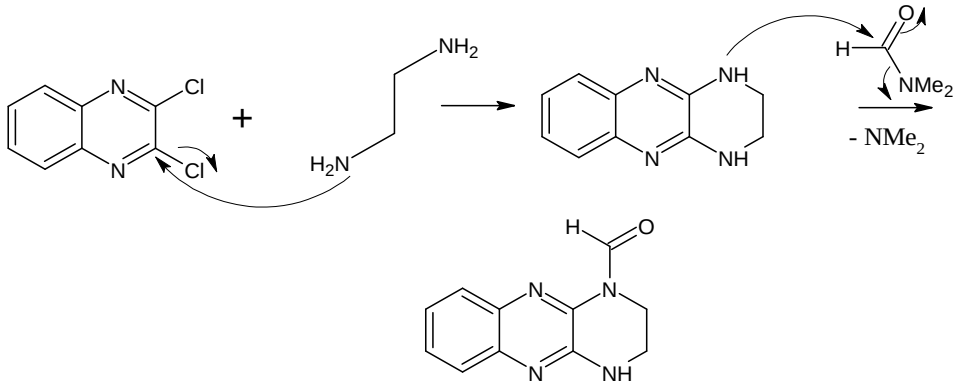

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Figure 3

CONCLUSION

The fused oxazino and imidazole quinoxalines thus synthesized may act as potential lead compounds by virtue of incorporating an ephedrine moiety onto the fused pyrazine ring system (quinoxaline). Such fused systems by virtue of having a rigid conformational mobility show great promise in exhibiting potential biological activity.

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