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Research Article

SYNTHESIS OF CERTAIN SUBSTITUTED QUINOXALINES AS ANTI INFLAMMATORY AGENTS

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ABSTRACT

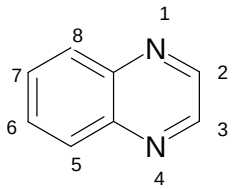
Substituted Quinoxaline have received considerable attention during last two decades as they are endowed with variety of biological activities and have wide range of therapeutic properties. A literature survey indicates that quinoxaline derivatives possess different pharmacological and biological activities, of which the most potent is anti-inflammatory activity. In view of above literature survey, we thought to synthesize a novel substituted quinoxaline system.

Keywords: Quinoxaline, Isoniazide, Anti-inflammatory activity Synthesis.

INTRODUCTION

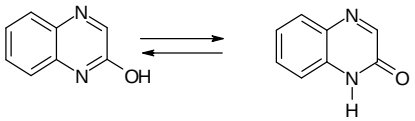
Quinoxaline is the subject of considerable interest from both academic and industrial Perceptive. Among the various classes of the nitrogen containing heterocyclic compounds Quinoxaline are important component of severally pharmacologically active compounds. Although rarely described in nature synthetic quinoxaline ring is a part of number of antibiotics which are known to inhibit the growth of Gram Positive bacteria and are also active against various transplantable tumors.

Quinoxaline is commonly called as *1,4-diazanaphthalene* or *benzopyrine*. The approved numbering of the ring atom is shown below.



Quinoxaline and its derivatives are mostly of synthetic origin. Some quinoxaline derivatives are known to posse's antibacterial activities .The quinoxaline antibiotics are agents of bicyclic desipeptide antibiotic that have been reported activity against gram-positive bacteria and certain tumors and to inhibit RNA synthesis[1]. Quinoxaline has also been used in reactive dyes and pigments, azo dyes, fluroscein dyes and it also forms a part of certain antibiotics.

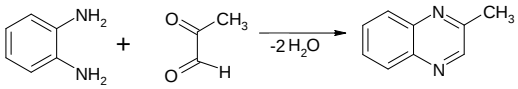
Quinoxaline is a low melting solid m.p. 29-30 °C and is miscible with water. It is weakly basic (*p*ka 0.56) and thus considerably weaker base than the isomeric diazonapthalenes namely cinnoline (*p*ka 2.42), pthalizine (*p*ka 3.47) or quinazoline (*p*ka 1.95). 2-Hydroxy-but not 2-amino quinoxaline exist in tautomeric forms.



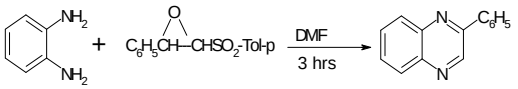
The fusion of one or two benzene rings in quinoxaline and phenazine increases the number of resonance structure, which are available to these systems. It posses the dipole moment of zero.

Quinoxaline itself is prepared by the reaction of *o*-phenyldiamine and glyxol [2].

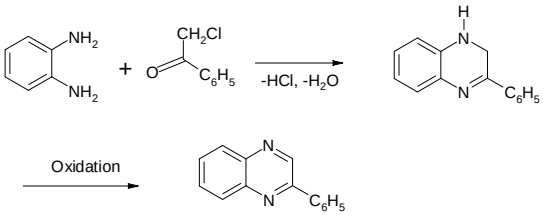
Simillarly 2-Methyl Quinoxaline has been prepared by the reaction of *o*-phenyldiamine and pyruvaldehyde.



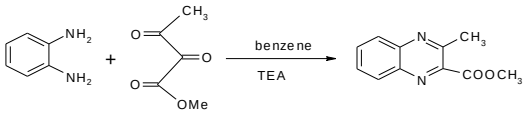
Taylor[3] recently reported that 1-(*p*-tolysulfonyl)-2-phenyloxirane, obtained from the condensation of chloromethyl *p*-tolysulfone with benzaldehyde, on reaction with *o*-Phenylenediamine yields 2-phenyl quinoxaline in good yield.



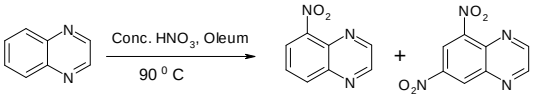
A number of simple variations of the dialdehyde diamine reaction appear to work well. Thus replacement of the dialdehyde with a α-halogenketone results in the formation of 2-substituted quinoxaline.2-phenylquinoxaline has been prepared in this manner from phenacyl chloride and *o*-phenylenediamine[4].



Compounds containing 1,2,3-tricarbonyl functionality have been used in the synthesis of a variety of Heterocyclic derivatives[5]. The tricarbonyl group containing compounds can be prepared by treating 3-keto ester with *p*-nitro sulphonyl peroxide[6], to give 2-(p- nitro phenyl)-sulfonyl) oxy)-3-keto esters.

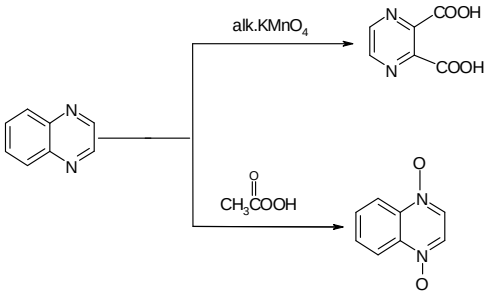


Treatment of the resulting 2-(nosyloxy)-3-ketoesters with triethyl amine (TEA) in benzene at room temperature results in *vic* tricarbonyl compound. The tricarbonyl compound can be trapped *in situ* with *o*-phenylenediamine to give quinoxaline derivatives. Quinoxaline forms salt with acids. Nitration occurs only under forcing conditions (Conc.HNO_3, Oleum) to give 5-nitroquinoxaline (1.5%) and 5,7 dinitroquinoxaline (95%).



2-chloroquinoxaline has been prepared by the action of phosphorous oxychloride on quinoxaline -2-one or quinoxaline-1- oxide[7].

Oxidation of quinoxaline results in the formation of the product depending upon the nature of the oxidizing agent employed. With alkaline potassium permagnate pyrazine 2, 3-dicarboxylic acid is formed, while with peracid quinoxaline *di*-N-oxide results. 2-methylquinoxalineon selenium dioxide oxidation affords quinoxaline 2-carboxaldehyde.



Alkyl radicals produced from acyl peroxide or alkyl hydroperoxide give high yields of 2-substituted alkyl derivatives. Reduction (Na, C_2H_5OH) of quinoxaline gives a 1,2,3,4-tetrahydro derivatives.

OBJECTIVES

Most of the present diseases are due to the invasion by the pathogenic organisms like bacteria, fungal, virus, ricketsia. To treat these diseases many potent and broad spectrum antibiotics were discovered eg: Ampicillin, Amoxicillin, Carbenicillin, Oflaxacin, Tetracyclines, and Ciproflaxcine etc. Even though antibiotics are life saving drugs in therapeutics but they are potentially harmful. These effects include allergic and anaphylactic reaction, superinfection, development of resistance, destruction of normal non-pathogenic bacterial flora and selective toxicity like aplastic anemia, kidney damage etc.

A considerable amount of research activity is directed towards a potent, more specific and less toxic antibiotics. Substituted quinoxaline have received considerable attention during last two decades as they are endowed with variety of biological activities and have wide range of therapeutic properties. A literature survey indicates that a quinoxaline derivative possesses different pharmacological and biological activities, which of most potent activity is anti-microbial, anti-fungal, anti-inflammatory and analgesic activity. We thought to synthesize novel substituted quinoxaline moiety.

Quinoxaline derivatives are widely distributed in nature and they have been shown to have very interesting biological activities like, anti-bacterial, anti-fungal, anti-inflammatory and analgesic activity. Hence in present study we plan to synthesize novel substituted quinoxaline derivatives.

Isoniazide is a antitubercular agent used for the treatment of tuberculosis. It is a first line drug and is used along with the refampicin and ethambutol.

By considering the above facts here with we have planned to synthesize substituted quinoxaline derivatives by incorporating the isoniazide moiety into the quinoxaline moiety and evaluate them for biological activities like anti-bacterial potency and anti-inflammatory activity.

METHODOLOGY

Preparation of 6-methyl -2,3-dihydroxy Quinoxaline (Ib)

In to a clean dry round bottom flask introduced 4-methyl- o-phenylene diamine (10.7 gms, 0.1 mole) and diethyl oxalate (14.6 ml, 0.1 mole) and the contents were refluxed for 1hr. Cooled and the separated solid was collected by filtration, washed with 25 ml ether and dried. The obtained 6-methyl-2,3-dihydroxy quinoxaline was recrystallized from DMF, the yield was 80% and the melting point was above 360 °C **(Ib).**

Preparation of 6-methyl -2,3- dichloro Quinoxaline (IIb)

In a clean dry round bottom flask introduced 6-methyl-2,3-dihydroxy quinoxaline (1.67 gms, 0.01 mole), phosphorous oxy chloride (6.25 ml, 0.01mole) and DMF (1ml). The contents of the flask were refluxed for 90 min. The resulting solution was cooled for 4-5 hr, and then the cold solution was poured into a

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filtration, washed with 25 ml of water and dried.

The obtained 6-methyl-2,3-dichloro quinoxaline was recrystallized from solution of chloroform and *n*-hexane (1:1), the yield was was 70% and was recrystallized from methanol and melting point was 120 °C **(IIb).**

Preparation of 6-methyl- 3-chloro-2-hydrazino quinoxaline (IIIb)

In a clean dry round bottom flask introduced 6-methyl-2,3-dichloro quinoxaline (1.60 gms, 0.01mole), hydrazine hydrate (1ml 0.01mole), methanol (25ml) and all the contents of the flask were refluxed for 20 min at refluxing temperature. Cooled and separated solid was collected by filtration, washed with 25 ml water and dried. The obtained 6-methyl 3-chloro-2-hydrazino quinoxaline was recrystallized from the solution of methanol and acetone (1:1), the yield was 70% and the melting point was 200°C. **(IIIb)**

Preparation of 3-chloro-2-(p-methoxybenzyl idene hydrazinyl)-6-methyl quinoxaline (IV b_1)

In a clean dry round bottom flask introduced 6-methyl-3-chloro-2-hydrazino quinoxaline **(IIIb)** (2.08 gms, 0.01 mole) and 4-methoxybenzaldehyde (1.20 ml, 0.01 mole) and glacial acetic acid (15 ml). The contents were refluxed for 2 hr, cooled and the solution was poured into crushed ice with continuous stirring with glass rod. The solid which was separated was collected by filtration and washed with 25 ml water and dried.

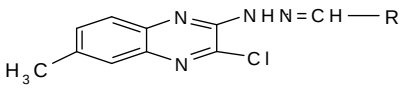
The obtained 3-chloro-2-(p-methoxy benzylidene hydrazinyl)-6-methyl quinoxaline **(IVb_1)** was recrystallized by using ethanol (90%), the yield was 61% and the melting point was 104-108 °C **(IV b_1).** The other Schiff's bases were prepared by using same procedure as above **(IVb_2-b_{10}).** The physical characterization data was given in the Table 1

Preparation of 6-methyl-N-(3-(isoniazidyl)-N'-(2-(2'-(p-methoxy benzylidene hydrazinyl))-quinoxaline(Vb_1)

Procedure

In to a clean dry round bottom flask introduced 3-chloro-2-(p-methoxy benzylidene hydrazinyl)-6-methyl quinoxaline **(IVb_1)** (3.26 gms, 0.01 mole), isoniazide (1.37 gms, 0.01 mole) and pyridine (25ml). The reaction mixture was refluxed for 24 hrs. Cooled and the solution was poured onto the ice cold water with continuous stirring. Then the solid that separated was collected by filtration and washed with 25 ml water and dried. The obtained 6-methyl-N-(3-(isoniazidyl)-N'-(2-(2'-(p-methoxy benzylidene hydrazinyl))-quinoxaline was recrystallized by using aqueous DMF, the yield was 55% and the melting point was 230-232 °C **(Vb_1).** The other compounds of the series were prepared by using same procedure as above **(Vb_2-Vb_{10}).** The physical characterization data was given in the Table 2.

Table 1: Characterization Data of Synthesized Compounds (IVb_1-IVb_{10})



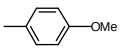
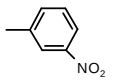
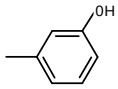
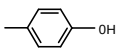
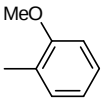
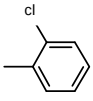
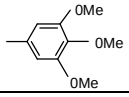
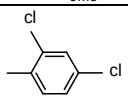
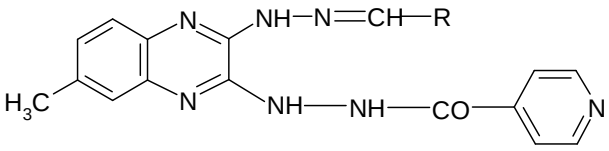
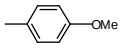
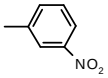
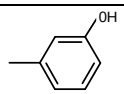
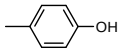
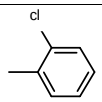
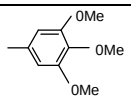
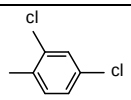
S.No	Compound code	R	Melting point	Molecular Formula	Molecular Weight	%Yield
1	IVb_1		104-108 °C	$C_{17}H_{15}N_4OCl$	326	61
2	IVb_2		170-174 °C	$C_{16}H_{12}N_5O_2Cl$	341	58
3	IVb_3		184-188 °C	$C_{16}H_{13}N_4OCl$	312	67
4	IVb_4		198-202 °C	$C_{16}H_{13}N_4OCl$	312	70
5	IVb_5		118-122 °C	$C_{20}H_{15}N_4Cl$	346	68
6	IVb_6		138-140 °C	$C_{17}H_{15}N_4OCl$	326	65
7	IVb_7		98-102 °C	$C_{16}H_{12}N_4Cl_2$	331	59
8	IVb_8		194-196 °C	$C_{19}H_{19}N_4O_3Cl$	386	52
9	IVb_9		158-162 °C	$C_{16}H_{11}N_4Cl_3$	365	55
10	IVb_{10}		130-132 °C	$C_{16}H_{12}N_4Cl_2$	331	63

Table 2: Physical Data of Quinoxaline Derivatives (Vb_1-Vb_{10})



S.No.	Compound Code	R	Mol. Formula	Molecular Wt.	Melting Point (°C)	Yield %
1	Vb_1		$C_{23}H_{21}N_7O_2$	427	230-232	55
2	Vb_2		$C_{22}H_{18}N_8O_3$	442	134-136	60
3	Vb_3		$C_{22}H_{19}N_7O_2$	413	200-206	56
4	Vb_4		$C_{22}H_{19}N_7O_2$	413	174-176	58
5	Vb_5		$C_{26}H_{21}N_7O$	447	142-144	53
6	Vb_6		$C_{23}H_{21}N_7O_2$	427	154-156	54
7	Vb_7		$C_{22}H_{18}N_7OCl$	431	158-160	59
8	Vb_8		$C_{25}H_{25}N_7O_4$	487	164-166	50
9	Vb_9		$C_{22}H_{17}N_7OCl_2$	466	124-126	62
10	Vb_{10}		$C_{22}H_{18}N_7OCl$	431	168-170	61

PHARMACOLOGICAL ACTIVITY

Anti- inflammatory activity

Inflammation is a normal protective response to tissue injury caused by physical trauma, noxious chemicals or microbiological agents. Inflammation is body response for tissue repair. Inflammation is triggered by the release of chemical mediators vary with the types of inflammatory process and include amines such as histamine, serotonin and lipids such as prostaglandins and small peptides such as kinins. The acute inflammatory response has 3 main functions.

1. A transient material called the acute inflammatory exudates occupies the affected area. The exudates carry proteins, fluid and cells from local blood vessels in to the damaged area to mediate local proteins.
2. If an infective causative agent (e.g. bacteria) is present in the damaged area it can be destroyed and eliminated by components of the exudates.
3. The damaged tissue can be broken down and partially liquefied and the debris removed from the site of damage.

Table 3: Data Showing Anti-inflammatory Activity of Quinoxaline Derivatives (Vb_1-Vb_9)

Group	Treatment	Dose mg/kg	Paw oedema volume							
			After 1st hr		After 2nd hr		After 3rd hr		After 4th hr	
			Mean	% ROV	Mean	% ROV	Mean	% ROV	Mean	% ROV
1	Control	0.5ml	0.70	-	0.81	-	0.9	-	1.21	-
2	Standard Diclofenac Sod.	20	0.48	31.4	0.44	45.6	0.50	44.4	0.36	70.2
3	Vb_1	200	0.55	21.4	0.53	34.5	0.54	40	0.46	61.9
4	Vb_2	200	0.55	21.4	0.58	28.3	0.61	32.2	0.47	61.1
5	Vb_3	200	0.54	22.8	0.55	32	0.56	37.7	0.49	59.5
6	Vb_4	200	0.58	17.1	0.64	20.9	0.61	32.2	0.52	57
7	Vb_5	200	0.54	22.8	0.53	34.5	0.57	36.6	0.50	58.6
8	Vb_6	200	0.54	22.8	0.49	39.5	0.53	41.1	0.43	64.4
9	Vb_7	200	0.55	21.4	0.59	27.1	0.56	37.7	0.45	62.8
10	Vb_8	200	0.49	30	0.45	44.4	0.51	43.3	0.38	68.5
11	Vb_9	200	0.6	14.2	0.63	22.2	0.63	30	0.50	58.6

ROV-Reduction in paw oedema volume

RESULTS AND DISCUSSION

Anti-inflammatory activity

From anti-inflammatory activity studies it was found that compounds showed significant activity. Perhaps the presence of OCH_3 on phenyl nucleus attached to second position of the quinaxaline nucleus may be responsible for marked anti-inflammatory activity.

From Anti-inflammatory activity evaluation, it was found that compounds showed significant activity. Perhaps the presence of OCH_3 on aromatic system present in 2^{nd} position of quinaxaline nucleus, which may be responsible for marked anti-inflammatory activity.

The above results establish the fact that substituted quinoxaline can be studied further to search for new anti-inflammatory compounds.

CONCLUSION

From the anti-inflammatory activity evaluation it is very clear that the tested compounds showed near to equipotent activity to that of standard diclofenac sodium employed for the study. From anti-inflammatory activity evaluations, it was found that compounds showed significant activity. Perhaps the presence of OCH_3 group at aromatic system and presence of heterocyclic nucleus may be responsible for marked anti-inflammatory activity.

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