CHAPTER ONE

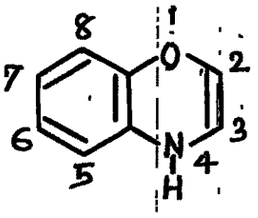
INTRODUCTION, LITERATURE SURVEY AND SCOPE OF WORK

Introduction :

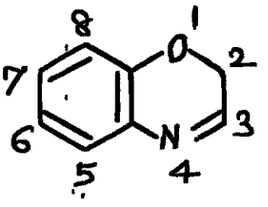
Oxazine is a very interesting class of heterocyclic compounds having wide range of applications in medicinal and polymer chemistry. Most of the synthetic compounds having heteroatoms like oxygen and nitrogen are commercially valuable.

The term oxazine was first introduced in chemical literature by Widman[1] in 1888, who defined an oxazine as a six membered ring compound containing a nitrogen and oxygen and four carbon atoms, all being joined together by eight bonds in one ring structure. They are divided into three types depending upon position of nitrogen with respect to oxygen, as 1:2-oxazine, 1:3-oxazine, 1:4-oxazine.

When the benzene ring fused with six membered oxazine ring containing one double bond is called as benzoxazine. Out of eight possible isomers of benzoxazine two of them are more important which are represented by the following structures



(I)
1,4-benzoxazine



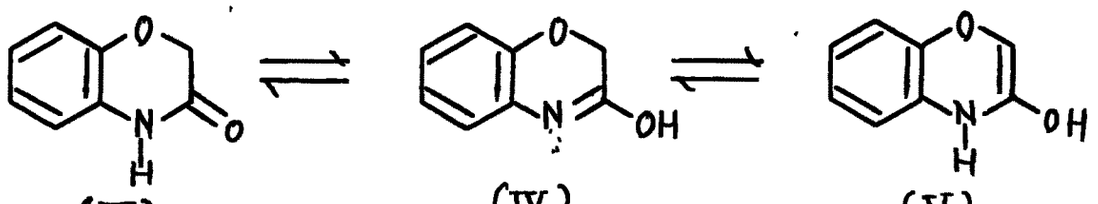
(II)
1,4,2-benzoxazine

They are named according to Ring Index[2] which are shown in above formulae. In the Chemical Abstract the position of methylene group is denoted by supplementary hydrogen. Thus

1,4,2-benzoxazine is referred as 1,4-2H-benzoxazine. It is clear that 1,4,2-benzoxazine is a tautomer of 1,4-benzoxazine due to 1,3 shift of hydrogen. Due to tautomeric nature above two forms are inseparable. The majority of the compounds reported in the literature are the derivatives of 2H-1,4-benzoxazine.

Benzoxazine derivatives which are reported in the literature are biologically active heterocyclic compounds having antibiotic[3], antiinflammatory[4,5], antibacterial[6], antifungal[7], antihelmintic[8], antituberculatic[9], anticancer[10] activities. Most of them are reported to be insecticides[11] and herbicides[12]. The oxazines with olefin substituent were considered as polymerizable monomer and plasticizer for cellulose acetate[13], tanning agent[14] and corrosion inhibitor[15]. Due to immense pharmaceutical and industrial importance, we have undertaken the research work on the synthesis and biological screening of some of 1,4-benzoxazin-3-one derivatives.

Out of three tautomeric forms III, IV and V. Spectroscopic study indicates that the keto form (III) is preferred[16a] over enol forms IV and V. This is referred as 1,4-benzoxazin-3(2H)-one as per new nomenclature[16b].



(III) (IV) (V)

In the present study, we report the synthesis of hydrazide and triazole derivatives of 1,4-benzoxazin-3(2H)-ones.

Literature Survey :

The parent member of 1,4-benzoxazine has not been prepared. However several derivatives of it are known. The reduced derivative of 1,4-benzoxazine which is commonly called as phenomorpholine or benzomorpholine was first prepared by Knorr[17] starting with O-aminophenol, Fair bourne and Toms[18] synthesized 6-aminomorpholine from 2,4-dinitrochlorobenzene. In vacuum pyrolysis of 3-aryl propane sulphonyl and 2-aryloxy ethane sulphonyl azides, 1,4-benzoxazine was also isolated by Rudolph et al.[19] The several derivatives of 3 keto morpholine have been reported in the literature. Two general methods of synthesis and some derivatives of 2H-1,4-benzoxazin-3-one have been revealed in the literature. Auwers and Frese[20] synthesized 1,4-benzoxazin-3(2H)-one by base catalyzed cyclization of o-haloacylaminophenol. Paxeddu and Sanna[21] had observed the formation of isomers when 2H-1,4-benzoxazin-3-one derived from 5-chloroacetylamino eugenol on bromination. Coles and Christiansen[22,23] obtained same compound, by reduction of o-nitrophenoxy acetic acid, in acetic acid with Pd as catalyst in quantitative yields. The formation of N-alkyl-3-keto-1,4-benzoxazine was also obtained by Lewis acid $AlCl_3$ catalysed, chloroacet-O-anisidides on heating for 1 hour at 180°. By this procedure at lower temperature 80-100° heating for 30 min., the main product was o-chloroaceta-mido phenol. This on treatment with alkali was converted into 3-keto-1,4-benzoxazine. The synthesis[20] of 2,3-dihydro-5-methyl-3-oxo-benz-1,4-oxazine was carried out by hydrogenating 3-methyl-2-nitro-phenoxy-acetic acid

over Pd in acetic acid. Two isomeric methyl derivatives have been reported[24] and their structures were assigned on the basis of their behaviour towards hydrochloric acid. The derivative to which O-methyl structure was assigned regenerated 2H-1,4-benzoxazin-3-one, with hydrochloric acid in cold, N-methyl 2H-1,4-benzoxazin-3-one is also prepared by action of methyl iodide and potassium hydroxide on 2H-1,4-benzoxazin-3-one in acetone[25]. Methyl[24] and benzyl[26] derivatives prepared from the sodium salts of various 2H-1,4-benzoxazin-3-ones were the N-alkyl compounds. The reduction of N-methyl 2H-1,4-benzoxazin-3-one with Lithium Aluminium hydride gives 4-methyl-phenomorpholine[25].

N-methyl-3-phenomorpholine rearranges on heating at 220° to oxyindole[25]. Newberry and Phillips[22] obtained 6-nitro derivative of 3-keto-phenomorpholine by nitration. The 3-keto morpholine-6-arsenic acid with potassium nitrate and sulphuric acid gives 70 % of total nitro derivatives, 5-nitro and 7-nitro derivatives with different amounts depending upon temperature, along with small quantity of 8-nitro derivative[27]. Paxeddu and Sanna[28] obtained 2,3-diketo-1,4-benzoxazine by condensing ortho amino phenol with oxalyl chloride or diethyl oxalate along with other by-products.

The studies on 2H-1,4-benzoxazin-3-one and its thio and N-methyl derivatives have been done by Mazharuddin and Thygarajan[29] and they have proved with UV, IR and PMR studies, the predominant tautomeric forms. The behaviour of 3-styryl-2H-1,4-benzoxazin-3-ones towards amines, hydrazines and Grignard reagent and the

spectroscopic studies of the products obtained, have been done by Mohamad Ali Elsayed and coworkers[30]. The effect of ammonia, primary amines, hydrazine, phenyl hydrazine and Grignard reagent on 2-p-anisyl-3(4H)-1-benzoxazin-4-one has been studied by Zaher and others[31]. Some new 2-substituted styryl-3,1-benzoxazin-4-ones and 2-substituted-3-alkyl-quinazolin-4-ones have been synthesized by Messiha et al.[32] Some pyrazino-1,4-benzoxazine compounds have been prepared by Gupta et al.[33] A convenient and simple method of synthesis of 1,4-benzoxazino-(2,3)-phenoxazines has been suggested by Gupta and his coworkers[34,35]. Several new 3-[2-(heteroaryl)-vinyl]-2H-1,4-benzoxazin-2-ones have been synthesized and were tested for antibacterial, antifungal, anti-helmintic, antiamoebic and antitrichomonal activities by Shridhar et al.[36] Shridhar and his coworkers[37] have synthesized 9-substituted-4-[2-(5'-nitro-2'-furyl and 5'-nitro-2'-thienyl)-vinyl]-8,10-dihydro-2H-pyrano-[2,3] [1,3]-benzoxazin-2-ones. They have studied the biological activities of the products obtained. The moderate anti-inflammatory activity of 3-aryl-2H-1,4-benzoxazin-3-ones-6-alkanoic acid ester has been described by Shridhar et al.[38] 2H-5,6-dihydro-1,4-oxazines[39] have been synthesized to study their different biological activities. A number of methyl-4-(6,8-substituted-2H-1,4-benzoxazin-2-one-3-yl)-phenyl acetate[40] and the corresponding α-methyl acetates have also been synthesized and evaluated for their anti-inflammatory activity against carrageenam induced oedema in rats. Some methyl-4H-imidazo[2,1c][1,4]-benzoxazine and methyl-4H-imidazo [2,1c][1,4]-benzothiazine-2-carbamates have been synthesized

and tested for ant helmintic activity[41]. Dhar and Bag[42] reacted hydroxy aromatic acid chlorides with chlorosuphonyl isocyanate in the presence of triethylamine to synthesise 2H-1,3-benzoxazine-2,4-3H-diones and 2H-naphth-[2,1]-1,3-oxazine-2,4-3H-diones.

Fourteen new derivatives[43] of 3,4-dihydro-2H-1,4-benzoxazin-3-ones have been synthesized by condensing N-chloro-acetyl 3,4-dihydro-2H-1,4-benzoxazin-3-one with either potassium -o-alkyl xanthate or ammonium N-alkyl/aryl dithio carbamic acid. The compounds were tested for possible anthelmintic activity.

Some new oxime ethers and alkanoic acid derivatives[44] were derived from 6-acetyl-2H-1,4-benzoxazin and benzothiazin-3-(4H)-ones for their pharmacological studies. Similarly, a number of ethyl-3-aryl-2H-1,4-benzoxazin-6-acetates and 6-α-methyl acetates, 3-aryl-2H-benzoxazin-6-acetic acids and 6-α-methyl acetic acid and methyl-4-(6-chloro and 6-nitro-2H-1,4-benzoxazin-3-yl) phenyl acetates[45] have been synthesized and evaluated for their anti-inflammatory and CNS activities. A number of new 7-isothiocyanato-3-N-heterocyclyl and 3-N,N-disubstituted amino 2H-1,4-benzoxazines and benzothiazines[46] have been synthesized and tested for their anthelmintic activity. 7-Isothiocyanato-3-N-pyrrolidinyl and 3-N-piperidinyl-2H-1,4-benzoxazines were proved to be more potent than thiabendazole and equipotent to the well known drug bitoscanate.

Hashimoto[47] has studied some nucleophilic and rearrangement reactions of N-acetyl-2H-1,4-benzoxazin-3-one to give 2,5,6,7-substituted derivatives of benzoxazine according to

reaction conditions. The formation of 5 and 6-substituted products were interpreted in terms of nucleophilic attack on the cation formed by heterolysis of N-O-bond in above compound. Antiedema and analgesic[48] derivatives of 2,3-dihydro-1,4-benzoxazin-3-one were prepared with alkyl, halo, nitro substituents at 2 and 6 positions, having N_4-CH_2-CHOH-CH_2OH linkage. The rapid and efficient synthesis of thio derivatives of 2H-1,4-benzoxazin-3-one has been reported, by Shridhar[49] with different substituents like -Cl, -Me, $-NO_2$, -Br, -NHCOOMe, -NHAC, -NHCoph in the benzene ring by treatment with P_2S_5 and $NaHCO_3$ at 80°. The conversion of benzoxazin-3-one to benzoxazin-3-thione using tertiary amine solublise P_2S_5 have been reported by Rao and Dave[50] with 85 to 90 % yield. By treating the same compound with P_2S_5 in methyl cyanide (1:1) for 2 hours at room temperature the yield increased to 95 %. The reactions 4-acetoxy-2H-1,4-benzoxazin-3-one with some nucleophiles were studied by Hashimoto et al.[51] O-acetates of 4-hydroxy-7-methoxy and 4-hydroxy-2H-1,4-benzoxazin-3-ones when reacted with nucleophiles like phenols, indoles, EtSH, the major reaction centre was positively charged N-atom. The quantitative determination of 1,4-benzoxazin-3-one in maize by gas liquid chromatography has been done by Woodward[52]. Similarly trimethyl silyl derivative of substituted 2-hydroxy 2H-1,4-benzoxazin-3(4H)-ones is reported for quantitation by gas chromatography[52].

A number of derivatives of 4H-[1,2,4]-triazolo-(3,4c)-1,4-benzoxazine have been synthesised and screened for their anti-inflammatory and CNS activity. Most of the compounds in

8

this series found to possess significant anti-inflammatory[53] and diuretic activities[54].

Recently Rajmohan and Subba Rao[55] have synthesised 2H-1,4-benzoxazin-3-ones from o-amino phenols and screened for bacterostatic and fungistatic activity and have been shown that they exhibit considerable fungistatic activity.

Scope of Present work :

Though antimicrobial and anti-inflammatory properties of benzoxazines have been reported, the information available about similar properties of various 1,4-benzoxazine derivatives is scanty. Also, some work has been done with a view to determine the relationship between molecular structure and its biological activity.

The main interest in the synthesis of hydrazido derivatives of 1,4-benzoxazin-3(2H)-one is in the fact that most of them are expected to be water soluble, can easily be absorbed in the blood stream and expected to show high biological activity. The title compounds in the present study are synthesized by new route and tested for antibacterial activity against different types of bacteria.