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NOTE

Novel Synthesis of 2*H*-3-Aryl-3,4-dihydro-1,3-chlorobenzoxazine-aryl-3,4-dihydro-4-methyl-1,3-chlorobenzoxazines

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2-Chlorobenzaldehyde and 1-(2-hydroxyphenyl)ethanol on the reaction with different primary aromatic amines gave 2-(arylimino)-methylphenols and 2-[1-arylimino)ethyl]phenol, respectively. On reduction with sodium borohydride gave 2-(arylamino)methylphenols and 2-[1-(aryl amino)ethyl]phenols, which further cyclic with formaldehyde to form 2*H*-3-aryl-3,4-dihydro-1,3-chlorobenzoxazines and 2*H*-3-aryl-3,4-dihydro-4-methyl-1,3-Chlorobenzoxazines, respectively.

Key Words: Azoles, Oxazoles, Benzoxazines, Chlorobenzoxazine, Heterocyclic.

The 1,3-chlorbenzoxazine structures has attracted considerable interest due to its wide range of biological and chemical properties[1,2]. The 1,3-chlorobenzoxazine nucleus is present in a large number of pharmacologically active molecule[3,4]. Calcium channel antagonists, central nervous system drugs, analgesic and others. Moreover, disubstituted-1,3-benzoxazines constitute an interesting group, which could find important application intermediates in several synthetic pathways directed towards the preparation of bioactive polycyclic hetero systems. Unfortunately, these applications have not been rigorously studied[5] and only a few synthetic methods are available for their preparation. In the course of research directed towards the synthesis of new therapeutic related to natural products[6], several polycyclic compounds containing the 1,3-benzodioxine substructure have been prepared, but the analogous 2,3-disubstituted-1,3-chlorobenzoxazine has not yet been described[7,8]. As part of this, we investigated the preparation of 2,3-disubstituted-1,3-benzoxazines which could be used as key intermediate the synthesis of other polycyclic heterocyclic compounds, in particular the bioisostere of 1,3-benzo derivatives[9,10].

Melting point were determined in open capillaries on a Campbell apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 297 spectrophotometer and ^{1}H NMR spectra on a Bruker 80 MHz instrument (CDRI, Lucknow). Elemental analysis was found satisfactory for the compounds.

Step-1: Preparation of 2-(arylimino)-5-chloromethyl-phenols: 5-Chlorosalicylaldehyde 2 g and appropriate aromatic amine 2 g were refluxed in ethanol (20 mL) for 0.5 h crystalline residue deposited on cooling was further purified by crystallization from chloroform-petroleum ether (2:8 v/v) to furnish the amines taken were aniline, [Clbenzx. 1] *p*-chloro aniline, [Clbenzx. 2] *o*-nitro aniline, [Clbenzx. 3] *m*-nitro aniline, [Clbenzx. 4] *p*-nitro aniline and [Clbenzx. 5] *p*-bromo-aniline.

Step-2: Preparation of 2-(arylamino-5-chloromethyl) phenols: Sodium borohydride (0.5 g) was added to solution of 2-(arylimino)-5-chloromethyl phenol (2 g) in methanol (10 mL) and the mixture stirred for 0.5 h at room temperature. The residue obtained on pouring the solution in to cold water was further crystallized from ethanol to afford (**III**).

Step-3: Preparation of 2*H*-3-aryl-3,4-dihydro-1,3-chlorobenzoxazines: 2-(Aryl amino)-5-chloromethylphenol 2 g and formalin (35 % 10 mL) were refluxed in ethanol (10 mL) for 6 h. The residue obtained after pouring the reaction mixture into cold water was crystallized from ethanol. For 2*H*-3-(*o*-nitrophenyl)-3,4-dihydro-chloro-1,3-benzoxazine yield 85 %, m.p. 129 ºC, m.w. 276.5, m.f. $C_{14}H_{11}NO_3Cl$, elemental analysis calcd. (%) C: 60.75, H: 3.97, N: 5.06, found (%) C: 60.72, H: 3.95, N: 5.05.

All the compounds show key IR bands at 730-800 cm^{-1} (C-H bending), 1600-1450 cm^{-1} (C-C multiple band stretching), 700-600 cm^{-1} (C-Br). 1360-1250 cm^{-1}  1240-1090 cm^{-1} (C-O-C), 1360-1310 cm^{-1} (C-N vibration) 1456-1380 cm^{-1} (C-CH_3) bending, 1190-1120 cm^{-1} (C-OCH_3). These prepared 1,3-

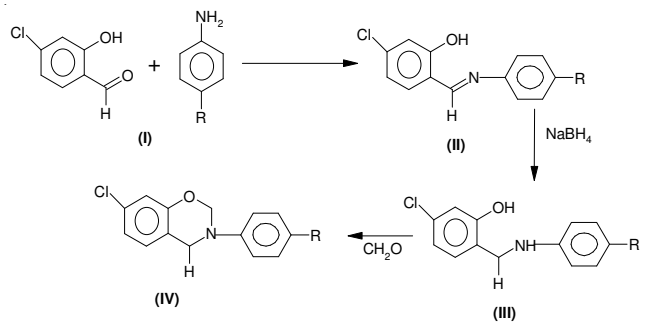
TABLE-1
KEY IR BANDS (cm^{-1}) OF CHLOROBENZOXAZINE DERIVATIVES

Compound code	Substituent	Benzoxazine ring				Disubstituted ring	
		C=N	C-O	C-H (str) in NCH_2	C-H (bend) in N-CH_2	Ar-Cl, NO_2, Br	C=C (str)
Clbenzx.-1	4-Cl	1279.5	1056.8	2846.10	1472.4	767.4	1610.7
Clbenzx.-2	2-NO_2	1269.6	1062.8	2843.10	1441.4	769.9	1605.6
Clbenzx.-3	3-NO_2	1271.5	1056.7	2840.20	1452.4	770.9	1608.7
Clbenzx.-4	4-NO_2	1277.5	1058.6	2838.12	1456.4	774.8	1604.7
Clbenzx.-5	4-Br	1278.6	1062.8	2842.20	1473.5	621.4	1597.7

TABLE-4
ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY OF CHLOROBENZOXAZINE DERIVATIVES

Compound code	*E. coli*		*Bacillus subtalis*		*Pseudomonas alcaligens*		*Salmonella sp.*		*Penicillium citrinum*		*Aspergillus flavus*		*Rhizoctonia bataticola*		*Aspergillus niger*	
	2 (%)	4 (%)	2 (%)	4 (%)	2 (%)	4 (%)	2 (%)	4 (%)	2 (%)	4 (%)	2 (%)	4 (%)	2 (%)	4 (%)	2 (%)	4 (%)
Mebenzx.-1	08	10	8	11	12	14	10	12	11	09	12	10	11	14	12	16
Mebenzx.-2	11	12	10	12	9	11	12	15	10	15	12	07	9	11	15	15
Mebenzx.-3	9	11	13	16	10	14	14	14	08	10	09	11	13	12	10	14
Mebenzx.-4	12	14	15	12	14	13	13	14	15	14	10	12	12	10	12	12
Mebenzx.-5	14	13	12	14	14	11	12	14	12	14	10	14	12	10	14	12
Standard drug	14	12	15	20	14	13	14	15	11	10	10	11	12	13	16	12

oxazines were screened for their antimicrobial and antifungal activities.



R = *o*-nitro aniline, *m*-nitro-aniline, *p*-nitro-aniline, *p*-chloro-aniline, *p*-bromo-aniline

We report the formation of 1,3-benzoxazine derivatives which indicate that the new approach enables the synthesis of 2,3-disubstituted-1,3-chlorobenzoxazines as the lactone[10], considered on useful intermediate preparation of new polycyclic systems. Directed *ortho*-lithiation of protected benzoxazines allows facile go for 2,3-disubstituted-1,3-benzoxazines. Moreover, the removal of the N-protecting group in the alkylation provides the unprotected 1,3-benzoxazines as central scaffolds for designed pharmaceutical compounds.

It is evident form IR and NMR data (Tables 1 and 2) that the respective substituent have influence the structural molecular dynamics exactly in the sequence of the electrometric behaviour of the groups and their positions. Table-3 shows the electrical polarizability and the dipole moment values (calculated) as obtained using PC model data. An almost linear variation between the electrical polarizability values and dipole moment justify the influence of these substituents on the molecular dynamics. Table-4 indicates the results on the biological activity of the compounds. A general perusal shows a direct relationship between the dipole moment and the magnitude of the inhibition zone. This may attribute to a dipole governed lipophilicity in the drug molecules, which on its turn influence the biological activity.

TABLE-2
H^1 NMR DATA OF CHLOROBENZOXAZINE DERIVATIVES

Signal No.	Chemical shift (δ ppm)	Multiplicity	Relative No. of protons	Inference
1	7.00-7.73	Multiplet	7	Ar-H
2	4.66	Singlet	2	-OCH_2 of bnzoxazine ring
3	3.56	Singlet	2	-NCH_2 of bnzoxazine ring

TABLE-3
ELECTRICAL POLARIZABILITY AS OBTAINED BY HANSCH TABLE FOR VARIOUS DERIVATIVES OF SERIES AND THEIR DIPOLE MOMENT VALUES

Compound No.	Clbenzx.-17	Clbenz.-18	Clbenz.-19	Clbenz.-20	Clbenz.-21
Elec. pol.	2.780	2.340	2.030	2.230	2.780
Dip. mom.	1.899	5.033	3.938	2.516	1.954

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