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Synthesis and antibacterial evaluation of some new 1,3-benzoxazines

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Abstract

New 2-[(substituted phenyl imino)-methyl]-4,6-diiodo phenols, 2[(substituted phenyl amino)-methyl]-4,6-diiodo phenols and 6,8-diiodo-3-(substituted phenyl)-3,4-dihydro-2*H*-benz-[e]-[1,3]-oxazine were synthesized. Synthesized compounds were screened for antibacterial activity.

Keywords: Synthesis, Schiff bases, substituted amino phenols, substituted 1,3-benzoxazines and antibacterial activity.

Introduction

Benzoxazines have been reported to exhibit diverse biological activities such as sedative[1], hypnotic[2], antifertility[3,4], ovicidal[5], antiangiogenic therapeutic agents [6] ssand anti-inflammatory[7,8] activities. Benzoxazines are also active against broad spectrum gram +ve and gram –ve ocular pathogens, active against[9], *Mycobacterium kansassi*, *M. avium* and *M. bovis*. Some of the benzoxazines have reported to kill *Plasmodium falciparum* in infected human erythrocytes[10]. Benzoxazine derivatives have been reported as the corrosion-protective property as K (+) channel openers[11]. Further benzoxazines are capable of forming a coating film with a high corrosion resistance[12]. Iodoaromatics are versatile synthetic intermediates and used in medicine and biochemistry[13]. Iodo compounds are also reported to possess antifungal and antibacterial activity[14]. considering these features of benzoxazines and iodo compounds, we report in this paper the synthesis and antimicrobial study of 3-(substituted phenyl)-3,4-dihydro-6,8-diiodo benz-[e]-[1,3]-oxazine.

Results and Discussion

The required new Schiff's bases (1,5) 2-[(substituted phenyl imino)-methyl]-4,6-diiodo phenols were prepared by condensing substituted aniline with 3,5-diiodo salicyaldehyde. The compounds (1,5) on reduction with $NaBH_4$ gives 2-[(substituted phenyl amino)-methyl]-4,6-diiodo phenol (6-10). The compounds (6-10) on refluxing with formaldehyde in methanol underwent ring closure to yield 6-8-diiodo-3-(substituted phenyl) -3,4-dihydro-2H-benz-[e]-[1,3]-oxazine (11-15) **(Scheme I)**.

The IR spectra of compounds (1-5) showed peak near at 1613 cm^{-1} due to C=N stretching vibration, a band near at 1586, 1495 due to aromatic stretching and a braod band near at 3495 due to hydroxyl group. The ^1H NMR spectra of compounds (1-5) showed multiplet in the region δ7.2-8.2 due to aromatic protons. A singlet of azomethine was observed near at δ 9 and phenolic hydroxyl group appears as a singlet near at δ 13.

IR spectra of compounds (5-10) showed absence of C=N band which is present in precursor. A band appears at 3350-3450 due to OH. A sharp band appears at 3303 due to NH. Aromatic stretch appears at 1590-1450. ^1H NMR shows absence of singlet due to =CH which is present in Schiff bases. A peak appears at 3.5 due to CH_2 and a broad singlet at 4.5 due to NH proton (D_2O exchangeable).

The IR spectra of compounds (11-15) showed the absence of band due to NH which present in its precursor. ^1H NMR spectra exhibited a peak at δ~4 due to NCH_2 proton and another singlet appears at δ~5 due to NCH_2O.

Melting points, yield, crystal appearance and elemental analysis of compounds 1-15 is given in **table I**.

Materials and Methods

Experimental

Melting points are determined in open capillaries and are uncorrected. IR spectra were recorded on Perkin-Elmer 157 and Shimadzu spectrometer. ^1H NMR was recorded on Aveanue-300 and Brucker WM 400 FT MHZ instrument using TMS as internal standard (chemical shift in δ ppm). The reactions were monitored on TLC and the spots were located in iodine chamber.

General Procedure**:** *Synthesis of 2-[(4-chloro-3-fluoro phenyl imino) methyl]-4,6-diiodo phenol (5)*

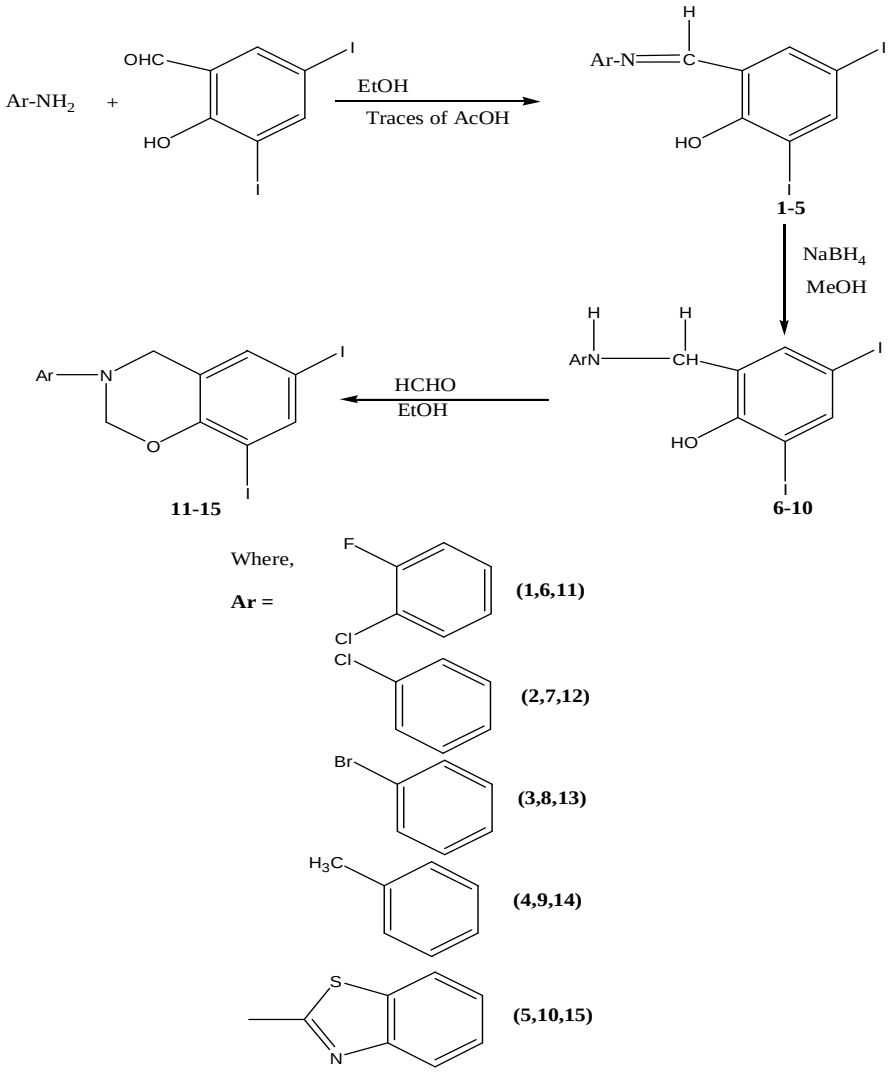
2-hydroxy-3,5-diiodo benzaldehyde (0.01 mol) and 4-chloro-3-fluoro aniline (0.01 mol) was dissolved in methanol (15 ml) and two drops of acetic acid and refluxed for 3 hour. The resulting solution was cooled and poured in cold water. The separated solid was filtered, washed with water and crystallized from ethanol. Other compounds of the series were prepared by same method.

IR ν max cm^{-1} : 3435 (OH), 1613 (C=N), 1586, 1495 (C=C aromatic)
^1H NMR δ : 7.4-8.3 (m, 5H, Ar-H-F), 8.74 (s, 1H, =CH)

MS (M/Z) : 501(M^+)

Synthesis of 2-[(4-chloro-3-fluoro phenyl amino) methyl]-4,6-diiodo phenol (10):-
Compound (0.01 mol) (5) was dissolved in methanol (15 ml) and sodium borohydride (0.015 mol) was added in small protions with stirring within 10 minutes. The reaction mixture was kept at room temperature for 1 hour. The solid separated on evaporation of solvent was filtered, washed with water and crystallized from ethanol. Other compounds of the series were prepared by the same method.
IR ν max cm^{-1} : 3303 (NH), 3455(OH),1610, 1584, 1530 (C=C Aromatic)
^{1}H NMR δ : 4.45 (s, 1H, NH), 3.73 (S, 2H, CH_2), 6.88-7.94(m, 5H, Ar-H+F)
MS (M/Z) : 503.5 (M^+)

Scheme I



Synthesis of 6,8-diiodo-3-(4-chloro-3-fluoro phenyl)-3,4-dihydro-2H-benz [e][1,3]-oxazine (11)
Compound (10) (0.01 mol) and formaldehydes (0.015 mol) were dissolved in ethanol and refluxed in a water bath for 3 hours. The solid separated on cooling was filtered and crystallized from ethanol. Other compounds of the series were prepared by same procedure.
IR ν max cm^{-1} : 3430 (OH), 1622, 1603 (C=C aromatic)
1H NMR δ : 4.5 (s, 1H, NCH_2), 5.38 (s, 1H, OCH_2), 6.94-7.87(m, 5H, Ar-H+F)
MS (M/Z) : 515.5 (M^+)

Table I: Physical and Analytical Data of Compounds (1-15)

Entry	M.P.	Yield	Crystal Appearance	Molecular Formula	Elemental Analysis Found(calculated)		Antibacterial Activity			
					X(Cl,Br,I)	N	Bs	Ec	E. coli	Xc
1	197	76	Yellow orange	$C_{13}H_7ClFI_2NO$	64.15 (64.47)	3.12 (2.79)	18	16	50	43
2	156	81	Orange	$C_{13}H_8Cl_3I_2NO$	59.42 (59.83)	3.31 (2.90)	15	20	30	12
3	138	73	Dark orange	$C_{13}H_8BrI_2NO$	63.58 (63.22)	3.05 (2.65)	12	12	40	32
4	180	69	Pale yellow	$C_{14}H_{11}I_2NO$	52.61 (52.92)	2.61 (2.92)	15	35	40	32
5	192	90	Pale yellow	$C_{14}H_8I_2N_2OS$	49.85 (50.09)	5.21 (5.52)	20	18	62	44
06	190	71	Orange	$C_{13}H_9ONFClI_2$	62.61 (62.22)	3.13 (2.78)	18	16	50	43
7	155	74	Orange	$C_{13}H_{10}ONClI_2$	59.12 (59.58)	2.62 (2.89)	15	20	30	12
8	138	73	Dark orange	$C_{13}H_{10}ONBrI_2$	62.45 (62.97)	2.91 (2.64)	12	12	40	32
9	180	75	Pale yellow	$C_{14}H_{13}ONI_2$	54.23 (54.62)	3.22 (3.01)	15	35	40	32
10	156	72	Yellow	$C_{14}H_{10}ON_2I_2S$	49.57 (49.90)	5.89 (5.50)	19	16	32	28
11	123	70	Pale yellow	$C_{14}H_9ONFClI_2$	59.60 (59.81)	2.35 (2.72)	13	15	62	24
12	132	72	Colorless	$C_{14}H_{10}ONClI_2$	57.88 (58.15)	2.61 (2.82)	12	14	26	18
13	148	74	Pale yellow	$C_{14}H_{10}ONBrI_2$	61.50 (61.57)	2.55 (2.58)	15	11	25	13
14	144	71	Pale yellow	$C_{15}H_{13}ONI_2$	52.95 (53.20)	3.28 (2.94)	10	15	29	12
15	120	72	Pale yellow	$C_{15}H_{10}ON_2I_2S$	48.61 (48.80)	5.30 (5.39)	17	14	67	20
Ampicillin							16	13	30	35

Antibacterial activity

Newly synthesized compounds (1-15) were screened against two plants pathogens *Xanthomonas citri* (Xc) and *Ervinia carotovara* (Ec) and human pathogen *Escherichia coli* (E. coli) and *Bacillus subtilis* (Bs). The activity was studied by using cup plate agar diffusion method[15-17] by measuring diameter of zone of inhibition in mm. The compounds were tested at the concentration of 200 ppm in 5% DMF. The solution was poured in the cup/well of bacteria seeded agar plates. The plates were incubated at 37˚C for 24 hours for E. coli whereas the plates of other three bacteria were incubated at 27±2 ˚C for 24 hours. The activity is reported by measuring the diameter for zone of inhibition in mm. The standard antibiotic used was ampicillin (200 ppm).The results are presented in table I.

Conclusion

Among newly synthesized 1,3-benzoxazines, compounds 1,4,5,6,9,10,11,14 and 15 are more or equally active with that of standard antibiotic used for comparison. Whereas, other compounds were found moderately active. Compound 1,6 and 15 showed significant activity against all bacteria. Considering the significant activity of this compound, further biological testing of the compound on *Xanthomonas citri, Xanthomonas malvecearium* and newly coming insect, Mealybug on cotton is under study.

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