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Synthesis of some novel substituted 5-oxo imidazolines containing azo linkages and their biological screening

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Abstract

5-substituted phenylazo salicyaldehyde derivatives have been prepared by diazotization of aromatic primary amines and condensing them with salicyldehyde on treatment with hydrazine hydrate in ethanol, furnished the 5-substituted phenyl azo salicyldehyde hydrazone. This hydrazone on reaction with 4-benzylidene-2-phenyl oxazolinone in presence of pyridine gives 1-[(2-hydroxy-5-substituted phenyl azo)-benzylidene amino]-2-phenyl-4-benzylidene-5-oxo imidazoline. The newly synthesized compounds were characterized on the basis of elemental analysis and ^{1}H NMR, IR spectral data. The synthesized products have been evaluated for their antimicrobial activity against gram positive and gram negative bacteria. Some of the products exhibited comparable activity with known standard drugs at same concentration.

Keyword: Oxazoline, oxoimidazoline, azosalicyldehyde, antimicrobial activity, antiparkinsonian.

Introduction

Compound bearing azo group exhibit various biological activity [1-4], though vast amount of work has been done on imidazoline, little attention has been created to synthesize imidazoline using azo salicyldehyde hydrazone and oxazolone. Literature survey reveals that imidazoline-5-(4H)-one exhibit promising biological and pharmacological activity. A novel method using microwave induced solvent free synthesis of 1-aryl-2-(1E)-aryl-vinyl-4-arylmethyline-2-imidazoline-5-ones was reported[5]. Recently analysis of imidazoline derivative, its mode of action, their biodegradation and various applications have been studied [6]. Recently pharmaceutical study and particularly leishmanicidal activity of 5- imidazolinone has been carried out[7-9] Now a day an efficient method for the synthesis of long chain dialkyl diamino imidazolines by the reaction of diethylene triamine and several fatty acids under non solvent microwave irradiation using calcium oxide as support is used [10]. Interest in the chemistry of imidazoline continues unabated because of their usefulness as antibacterial [11]

and anti-inflammatory [12] agents. Some of them may be useful in the polymer chemistry. Moreover imidazoline and 5-oxo imidazoline have great therapeutic importance such as anticonvulsant [13], potent CNS depressant [14], sedative and hypnotics [15], hypotensive[16] and potent antiparkinsonian activity[17] promoted by these observations. It was contemplated to synthesize a series of 1-(2-hydroxy-5-(substituted phenyl azo) benzylidene amino]-2-phenyl-4-benzylidene-5oxo imidazolines carrying azo linkages and to study their antimicrobial activity against gram positive and gram negative bacteria.

Salicyldehyde when treated with different diazotized aromatic primary amine yielded 5-substituted phenylazo salicyldehyde (I). This on condensation with hydrazine hydrate gave 5-substituted phenyl azo salicyldehyde hydrazone (II) which on again condensation with 4-substituted benzylidene-2-phenyl-5-oxazolinone (III) [18] in pyridine gave 1-[2-hydroxy-5-(substituted phenylazo) benzylidene amino]-2-phenyl-4-benzylidene-5-oxo imidazoline.

Results and Discussion

Anti-microbial Activity

The newly synthesized compounds were screened for their antimicrobial activities, which were determined using cup-plate method [19] by measuring zone of inhibition in mm. All compounds were screened for their antimicrobial activity against gram positive (*Bacillus magatherium*, *Bacillus subtilis*) and gram negative (*Escherichia coli*, *Protius vulgaris*) bacteria at a concentration of 50 μg/ml. The activity was compared with known antibodies viz. chloramphenacol at same concentration. The results of sensitivity of various pathogenic bacteria to the various newly synthesized compounds are shown in table-1. The title compounds were greaded as highly active, moderately active and poorly active. Majority of compound showed moderate activity against gram positive and gram negative bacteria. Some of them showed poor activity against all the pathogenic bacteria and the other compounds were inactive against *Protius vulgaris*.

Materials and Methods

The melting points were determined in open capillary tube using paraffin bath and are uncorrected. Perkin Elmer-577 spectrophotometer was used to record IR spectra by using KBr disc and PMR spectra were recorded in Bruker AC-300 spectrometer using TMS as an internal standard (Chemical shift in δ ppm) in $CDCl_3$ as solvent

1) 5-substituted phenyl azo salicyldehyde:

p-anisidine (4.04 g, 0.03285M) was dissolved in hydrochloric acid (25ml, 6M) and diazotized using sodium nitrite (4g). A cold solution of salicyldehyde (5g) in aqueous sodium hydroxide (40 ml, 2N) was added slowly with continuous stirring to the diazotized solution. The resulting dark orange solid was washed with water and recrystallized from ethanol-acetic acid mixture (1:1).

Yield : 75%; m.p. 142^{o}C; yield 75%, IR (KBr): 2972 (methoxy C-H asymmetric stretch), 2893 (methoxy C-H symmetric stretch), 1456 (methoxy C-H deformation asymmetric), 1374 (methoxy C-H deformation symmetric), 3068 (C-H aromatic), 1619 (C=C), 1599 (N=N), 1664 (C=O), 1025 (C-O-C), 3181 (aromatic –OH), 2743 (CHO) in conjugation cm^{-1}. ^{1}H NMR: (ppm): δ 11.26 (1H, S, OH), 10.02 (1H, S, CHO), 7.001 – 8.15 (7H, m, Aromatic), 3.89 (3, 3H, OCH_3); % of Nitrogen estimation: a) Calculated – 10.93, b) Found – 10.88

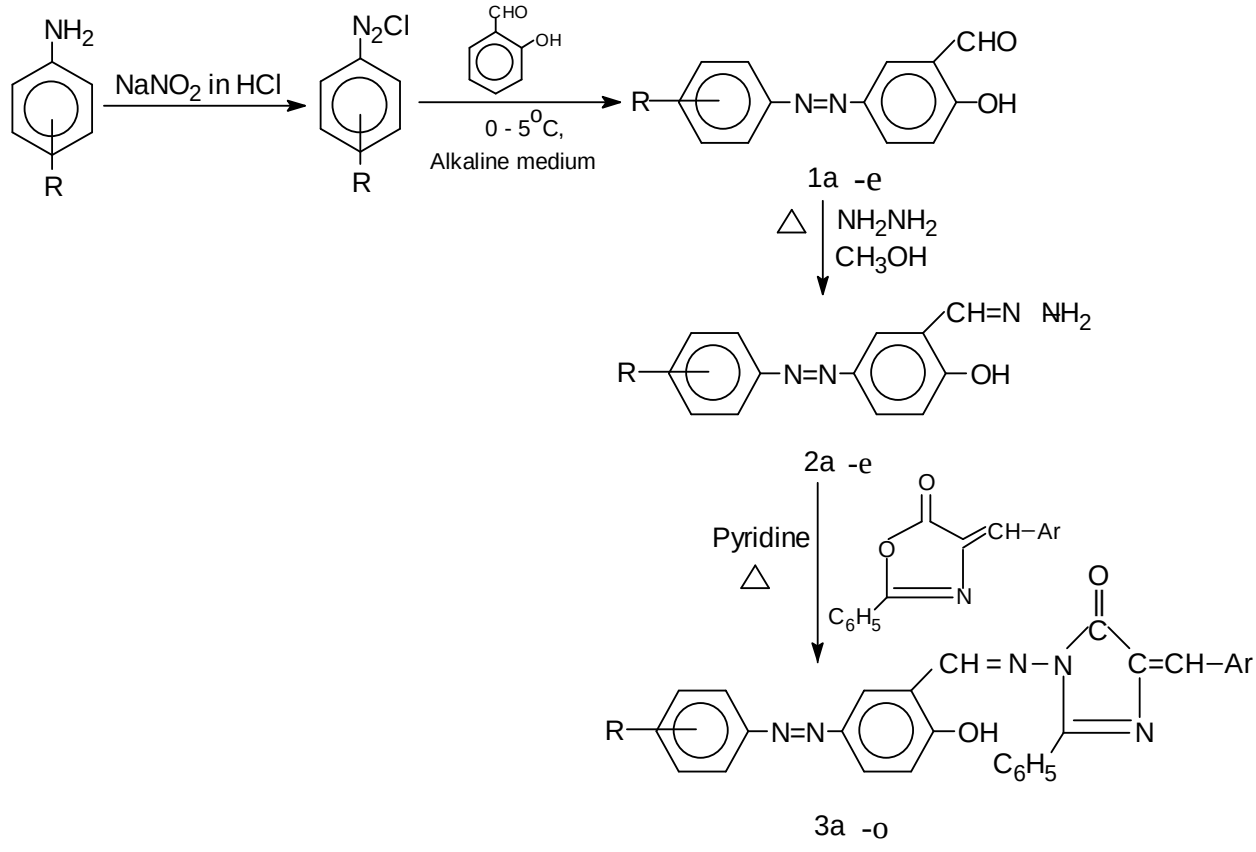
Similarly other members of the series were prepared by adopting same method.

2) 5-substituted phenyl azo salicyldehyde hydrazone:
A mixture of 5-substituted phenyl azo salicyldehyde (0.01 M) in methanol (25 ml) and hydrazine hydrate (0.3 ml, 0.01 M) was refluxed for 2 hrs. The content was poured into crushed ice and excess hydrazine hydrate was neutralized by hydrochloric acid. The product was recrystallized from dioxane.

Yield: 62%; m.p.-181^{o}C, yield 62%, IR(KBr): 2968 (methoxy C-H asymmetric stretch), 2881(methoxy C-H symmetric stretch), 1467 (methoxy C-H deformation asymmetric), 1381 (methoxy C-H deformation symmetric), 3084 (C-H aromatic), 1629 (C=N), 1601 (C=C), 1583 (N=N), 3286 (aromatic O-H), 3379 (–NH_2) cm^{-1}. ^{1}H NMR (ppm): δ 11.4 (1H, s, OH), 8.0 (1H, N=C-H, S), 7-7.95 (7 H, m, aromatic), 5.5 (2H, S, NH_2), 3.95 (3H, S, OCH_3); % of Nitrogen estimation: a) Calculated – 20, b) Found – 19.6.

Similarly other members of the series were prepared by adopting same method.

3) 4-substituted benzylidene-2-phenyl-5-oxazolinone:
4-substituted benzylidene-2-phenyl-5-oxazolinone has been prepared as described by Vogel.
Yield : 68%; M.P. : 178^{o}C



4) 1-[2-hydroxy-5-(substituted phenyl azo) benzylidene amino]-2-phenyl-4-benzylidene-5-oxoimidazoline: To a mixture of 5-substituted phenyl azo salicyldehyde hydrazone (0.01 M) and 4-substituted benzylidene-2-phenyl-5-oxazolinone (0.01 M); 10 ml dry pyridine was added. Contents were refluxed for 8 hrs. Excess of pyridine was removed under reduced

pressure and resulting mass was poured into crushed ice plus hydrochloric acid. The solid product was filtered, washed with water and recrystallized from DMF.

Yield: 70%; M.p.-270^{o}C, yield 70%, IR(KBr): 2965 (methoxy C-H asymmetric stretch), 2838 (methoxy C-H symmetric stretch), 1462 (methoxy C-H deformation asymmetric), 1381 (methoxy C-H deformation symmetric), 3072 (C-H aromatic), 1601 (C=C), 1583 (N=N), 1627 (C=N), 1720 (C=O), 1075 (C-O-C), 3412 (aromatic OH) $cm^{-1.}$; ^{1}H NMR (ppm). δ 11.43 (1H, 3, OH), 7.9 (1H, Sm CH=N), 6.99 – 7.87 (17 H, m, aromatic) 5.52 (1H, S, C=OH), 3.88 (3H, S, OCH_3); % of Nitrogen estimation: a) Calculated – 13.97, b) Found – 13.90.

Similarly other members of the series were prepared by adopting same method.

Table – 1: Physical data of compounds

Compound	R	Ar	Molecular formula	M.W.	% Yield	M. P. ^{o}C	Colour	% of Nitrogen estimation	
								Calculated	Found
3a	4-OCH_3	C_6H_5	$C_{30}H_{23}N_5O_3$	501	70	270	Orange	13.97	13.90
b	OCH_3	C_6H_5	$C_{29}H_{20}N_5O_3Br$	549	78	237	yellow	12.75	12.72
c	4-Br 4-Cl	C_6H_5	$C_{29}H_{20}N_5O_3Cl$	505.5	80	240	Faint yellow	13.84	13.90
d	2-Br	C_6H_5	$C_{29}H_{20}N_5O_3Br$	549	72	220	yellow Sporty	12.75	12.70
e	2-Cl	C_6H_5	$C_{29}H_{20}N_5O_3Cl$	505.5	74	222	yellow Desert	13.84	13.80
f		p-OCH_3-	$C_{31}H_{25}N_5O_4$	531	70	235	charm	13.18	13.10
g	4-OCH_3	C_6H_4	$C_{30}H_{22}N_5O_4Br$	579	75	217	glow Orange	12.08	12.10
h	4-Br	p-OCH_3-C_6H_4	$C_{30}H_{22}N_5O_4Cl$	535.5	75	241	vision	13.07	13.10
I	4-Cl	p-OCH_3-	$C_{30}H_{22}N_5O_4Br$	579	78	247	Yellow charm	12.08	12.00
j	2-Br	C_6H_4	$C_{30}H_{22}N_5O_4Cl$	535.5	80	233	Sunrise	13.07	13.00
k	2-Cl	p-OCH_3-C_6H_4	$C_{30}H_{22}N_5O_4Cl$	535.5	80	227	Faint yellow	13.07	12.98
l	4-OCH_3		$C_{29}H_{19}N_5O_3BrCl$	583.5	72	232	Desert	11.99	12.05
m	4-OCH_3	p-OCH_3-C_6H_4	$C_{29}H_{19}N_5O_3Cl_2$	540	74	242	glow Orange	12.96	12.90
n	4-Br 4-Cl	p-Cl-C_6H_4	$C_{29}H_{19}N_5O_3Br_2$	627	74	253	Sporty yellow	11.16	11.10
o	2-Br 2-Cl	p-Cl-C_6H_4 p-Cl-C_6H_4 p-Cl-C_6H_4 p-Cl-C_6H_4	$C_{29}H_{19}N_5O_3Cl_2$	540	74	259	Sunrise Yellow charm Yellow	12.96	13.00

Table – 2: Anti-microbial activity of synthesized compound: 1 (a – e), 2 (a – e), 3 (a – o)

Compound	Antimicrobial activity zone of inhibition in mm			
	Gram positive		Gram negative	
	Bacillus magatherium	*Bacillus subtilis*	*Escherchia coli*	*Protius vulgaris*
1a	18	10	20	13
b	20	11	19	12
c	17	12	17	18
d	19	15	20	19
e	15	13	23	20
2a	20	14	21	18
b	15	14	20	17
c	19	14	21	17
d	20	12	17	11
e	17	11	17	11
3a	12	14	17	11
b	15	15	20	-
c	16	12	22	-
d	14	12	19	-
e	20	15	19	15
f	18	14	17	12
g	12	11	22	15
h	20	11	18	18
i	15	14	17	-
j	20	10	23	-
k	20	11	23	15
l	12	16	22	12
m	20	18	21	20
n	11	15	20	16
o	17	16	22	16
Chloramphenicol	24	19	26	20

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