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Synthesis and Study of Anti Fungal Activity of 1, 4-Benzothiazines Derivatives

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Abstract: ***Imines forms an important class of heterocyclic compounds such as1,4-Benzothiazine and its derivatives which shows wide range of biological activities such as antimicrobial, antifungal etc. Therefore, some new benzothiazine derivatives were synthesized by using benzalaniline and substituted benzalanilines with sulphene, generated in situ from methane sulphonyl chloride and triethylaminehydroxylchloride, as a starting material. The synthesized 1,4-benzothiazines (Ia -Va) were tested in vitro for their antifungal activity against Alternaria alternate, Curvularialunata, Fusarium oxysporumand Myrothecium roridum by employing the standard technique of spore germination inhibition at various concertation's. Some of the compounds have shown promising antifungal activity against test fungi.***

Keywords: 1, 4- Benzothiazine(1,4-BT), Antifungal activity, Antimicrobial activity, SGI, Benzalaniline's Compound

1. Introduction

Heterocycles having Sulphur or nitrogen atoms or both of them are the general features present in the structure of most of pharmaceutical and natural compounds[1]. Such compounds also act as multidentate ligands[2]. In their connection 1,4- Benzothiazine(1,4-BT) derivatives have been reported to exhibit a wide range of pharmacological properties excluding antifungal, immunostimulant, anti-aldose-reductase, anti-rheumatic, anti-allergic, vasorelaxant, anti-arrhythmic, anti-hypertensive, neuroprotective and cytotoxic activities[3].

1, 4-BT are important pharmacophore to exhibit antitumor activity against the various tumor cell lines[4].

The reaction of benzalaniline and substituted benzalanilines with sulphene gives addition product 1, 4-BT.1,4-Benzothiazine[5], the heterocyclic compounds containing nitrogen and Sulphur in the six membered ring system. It has been reported to possess antifungal activity[6-8]. The Introduction of certain groups/atoms like –OH, -CH_3, -OC_2H_5, -Cl etc. in the phenyl ring increases the activity of parent compound manifold. The present investigation was carried out to study the antifungal activity of different derivatives of 1,4-Benzothiazine because it has been reported that the 1,4-BT and 2-(2-hydroxyphenyl)-6-ethoxy1,4-Benzothiazine are only the compounds possessed fungicidal activity against all the fungi under test[5]. The result of this study is being communicated in this paper.

2. Experimental

The various reactions were carried out by LR grade chemicals unless otherwise stated. The ultraviolet spectra were recorded on a manually operated Hilger-Watt mode H-700 spectrophotometer using silica gel-G in methanol. The IR spectra were recorded in Nujol/KBr, unless otherwise stated. The PMR spectra were recorded by using TMS as standard reference and $CDCl_3$/CCl_4 as solvents. All the compounds gave satisfactory elemental analysis.

Reaction of salicylaldehyde and aniline in methanol was allowed to cool, a solid compound Phenyl-2-hydroxybenzalidene (I) was obtained. Phenyl-2-hydroxybenzalidene (I) (1.97g ,0.01mole) dissolved in ether (25ml) was added slowly and with constant stirring to sulphene generated in situ from methane sulphonyl chloride (1.5ml, 0.01mole) and triethylamine (1.5ml) in dry ether (50ml). The triethylaminehydroxylchloride separated out and filtered. The ether extract was washed with water and dried over anhydrous magnesium sulphate. On evaporation of the solvent, the crude product was filtered and crystallized from petroleum ether to get dark yellow crystals of 2-(2-hydroxyphenyl)-1,4-benzathiazine (Ia), m.p 132^0c yield 45%.

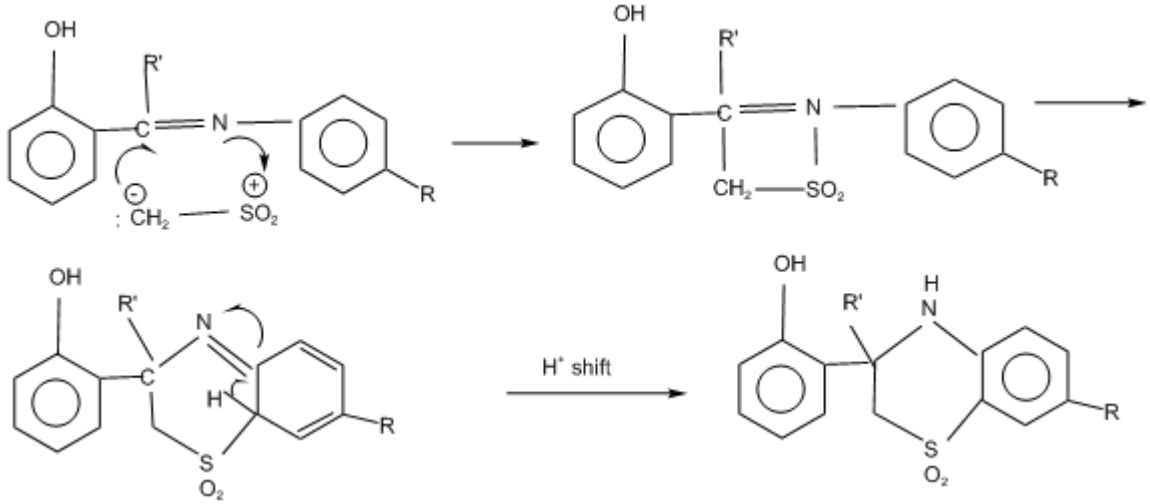
The reaction of Sulphene with 4-Methylphenyl-2-hydroxybenzalidene (II), 4-Methoxy-phenyl-2-hydroxybenzalidene (III), 4-Ethoxyphenyl-2-hydroxybenzaliden (IV) and 4- Chlorophenyl-2-hydroxy-benzalidene(V) was carried out in the similar way to get 1,4-benzothiazine (IIa-Va) respectively.

The stock solution (200ppm) was prepared by dissolving the compound (20mg each) in minimal quantity of ethanol (0.5ml) and volume was made up to 10ml by adding sterilized water. The stock solutions were serially diluted to 1000,500,250,100, 50 and 25ppm.Spore germination (S.G) as defined as those events that result in the loss of the spore-specific properties during biophysical process. The cavity slides[10]were used to study the SGI by these compounds at different concentrations[11. It] needs the presence of O_2 and H_2O.It is characterized by rapid swelling as a result of hydration. The treated spores in cavity slides were kept in

petri plates with moist filter papers disc and incubated at 24°C for 20hrs. The percent spore germination inhibition was recorded by the following formula:

$$\% SGI = \frac{\text{S. G. incontrol} - \text{S. G. in treatment}}{\text{S. G. in control}} X100$$

Compound	R
Ia	H
IIa	CH_3
IIIa	OCH_3
IVa	OC_2H_5



Synthesis of 1, 4-Benzothiazines

Table 1: Characteristics of 1, 4- Benzothiazines

Compound	R	Color	Yield	M.P#	M.F##	Nitrogen%			Sulphur%		
						Found	Cal.	Error	Found	Cal.	Error
Ia	H	Yellow	45	132	$C_{14}H_{13}NO_2S$	5.10	5.09	0.20	11.70	11.64	0.52
IIa	CH_3	Yellow	55	150	$C_{15}H_{15}NO_3S$	4.70	4.84	2.89	11.00	11.07	0.63
IIIa	OCH_3	Orange	52	155	$C_{15}H_{15}NO_4S$	4.68	4.59	1.96	10.29	10.49	1.90
IVa	OC_2H_5	Green	55	168	$C_{16}H_{17}NO_4S$	4.24	4.39	3.42	10.12	10.03	0.90
Va	Cl	Brown	58	180	$C_{14}H_{12}NO_3SCl$	4.46	4.52	1.33	10.40	10.34	0.58

All the melting points are uncorrected.
All the compounds gave satisfactory elemental analysis.

Mathematical interpretation of observation

After inspecting table 1, author found that melting point of compound increased as per quantity of yield except IIa. It is further found that compound having yellow color show melting point slightly less than three times of yield. Quantity and compounds having green and brown color show melting point higher than three times of yield. The variation of collected and calculated values of Sulphur is high for IIIa group- compound compare than other compound.

The variation of observational and calculated values of nitrogen in high for IIa and IV a group compounds compare than other compounds.

The antifungal activity of the synthesized compounds has been expressed in terms of ED50 values (effective dose to inhibit 50 percent germination) and calculated by plotting the spore germination inhibition values against different concentrations of the compounds on the graph paper.

Dithane M-45 and Bavistin were used as standard fungicides to compare the activity of the newly synthesized compounds.

The data in Table (2) shows that some of the compounds have moderate antifungal activity against test fungi. Compound Ia and IVa are best compound against *C.lunata* with ED50 values of 150ppm and 180ppm respectively. The compound Ia and IIa are moderately effective against *F.oxysporium* with ED50 values of 300ppm and 410ppm respectively. The compounds IIa, IIIa and Va has been found to possess ED50 values less than 1000ppm against *C.lunata*. Compound Va has been found to possess ED50 values less than 1000ppm against *A.alternata and F.oxysporum and Myrothecium roridum*.

Table 2: Fungitoxicity of 1, 4 – Benzothiazines

Compound	ED50 values (ppm) against			
	Curvularialunata	*Alternaria alternata*	*Fusarium oxysporium*	*Myrothecium roridum*
Ia	150	700	300	320
IIa	800	680	410	120
IIIa	950	*	*	990
IVa	180	*	*	240
Va	660	990	950	940
Bavistin**	---	---	9	--
Dithane	39	35	---	30

* More than 1000ppm
** Standard fungicide for *Fusarium oxysporium.*
*** Standard fungicide for *Alternaria alternate, Curvularialunata, Myrothecium roridum.*

3. Result and Discussion

Addition of Sulphene, generated in situ from methanesulphonyl chloride and triethylamine, to phenyl-2-hydroxybenzalidene (I) has been found to give 1:1 cycloadduct in good yield. The compound has been formulated as $C_{14}H_{13}NSO_3$ on the basis of elemental analysis. The structural assignment of the compound as Ia is based on spectral studies Infrared spectrum of the product showed band at 3250cm^{-1} indicating the presence of –NH group. IR studies suggest migration of sulphene group from the N-atom of the aniline moiety into the ortho position in the ring and N-atom taking up proton from the benzene ring, there by rearranging the four membered 2-thiazetidine ring into a six membered 1, 4- benzothiazine ring. Further support for the 1, 4-thiazine structure comes from PMR studies. PMR of IVa (R = -OC2H5) indicates two proton quartet at 4.2δ due to –OCH_2- protons, three protons triplet at 1.5δ due to -CH_3- potons, a seven proton multiplet between 6.7 to 7.8δ . The protons of the ring are indicated at 2.1δ (-NH-), 2.5δ (-CH_2-) and 2.8δ (-CH-) all as singlets. The synthesized 1, 4-Benzothiazines along with their characteristics are recorded in Table (1). The synthesized compounds (Ia –Va) were tested in vitro for their antifungal activity against four phytopathogenic fungi viz *Alternaria alternate, urvularia lunata, Fusarium oxysporum and Myrothecium roridum by spore germination method*[12-15].

Declaration Statement: The author declares no competing interest.

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