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RESEARCH ARTICLE

PHASE TRANSFER CATALYTIC SYNTHESIS, SPECTRAL CHARACTERIZATION AND ANTIMICROBIAL EVALUATION OF 2-(PHENYLSELENO) ETHANOIC ACID AND 3-(PHENYL SELENO) PROPANOIC ACID.

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Abstract

2-(phenyl seleno) ethanoicacid (**1**) and 3-(phenyl seleno) propanoicacid (**2**) has been synthesized in more economical and efficient method using phase transfer catalyst, tetraethylammonium bromide. Compound **1** & **2**, has been synthesised by reacting nucleophile, $PhSe^{-}$ (generated *insitu* by borohydride reduction of Ph_2Se_2) with α-chloroacetic acid & 3-chloro propanoicacid via phase transfer catalysis. The presence of catalyst improves the yield of the products and lowers the reaction time, however in absence of the catalyst, yield was very poor. Elemental analysis, IR, ^{1}H, ^{13}C, ^{1}H-^{1}H COSY NMR, ESI mass and molar conductance data has been used to authenticate the new species. The antimicrobial evaluation of both the compound indicates their significant activity at two different concentrations against selected bacterial and fungal strains. These Compound bears an acidic group, showed higher activities due to increase in the lipophilicity and easier penetration of the compounds into the outer cell wall of the microorganisms, which causes death due to cell membrane rupturing thereby boosting their bioactivity.

Introduction:-

The past two decades have witnessed a remarkable growth in the field of organoselenium/tellurium chemistry. It comprises a wide variety of structures that display a remarkable range of properties. During the last few years, a tremendous efforts has been directed towards the synthesis of stable organoselenium compounds. Such compounds have been found to function as antioxidants, chemoprotectors, apoptosis inducers and chemopreventors in several organs such as brain, liver, skin, colon, lung and prostate[1,2].

Besides this organoselenium/tellurium compounds have also showed a great potential for application in biological systems[3], organic synthesis[4], pharmaceutical[5-7], semiconducting material[8-10], ligand chemistry[11], biochemistry[12], spectroscopic studies[13] and have wide applications as homogenous catalyst[14]. Recently a novel organotellurium compound (RT-01), organotellurane, has been identified as a new antileishmanial agent[15] besides this certain selenium derivatives like benzisoselenazolones show antibacterial activities against gram-negative *E-coli* K-12 ROW and gram-positive S.aureus 209P bacteria strains. Even 4H-5,6-dihydro-1,3-selenazine derivatives also shows antibacterial activity against *E.coli* and *S.aureus*[16].

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The phase transfer catalyst like cetyltriethyl ammonium bromide or tetraethyl ammonium bromide is believed to be used in reactions where the two phases are mutually immiscible, the catalyst continuously transfers reacting anions in to the organic phase in form of lipophilic ion pairs and helps in proceeding the reaction, that too at faster rate. Transformations of starting materials into desired final products usually require a number of chemical operations in which additional reagents, catalysts, solvents, etc. are used. Thus in course besides desired products, many waste materials are produced. These wastes should be regenerated, destroyed and disposed consuming much energy and creating heavy burden in the environment. Thus the most general and efficient methodologies that fulfill the requirement is phase transfer catalysis[17]. The methodology is efficiently applicable to a plethora of other base induced reactions of organic anions particularly carbanions.

Prompted by the above reports, herein we report an efficient method for design and synthesis of selenium bearing compound having [Se, O] donor functionalities through phase transfer catalyst. It is worthwhile to mention that use of tetraethyl ammonium bromide as catalyst is especially useful in green chemistry. The newly synthesized compounds have been characterized by various spectroscopic techniques. The antimicrobial activity of the same are also reported in the following pages.

Experimental:-

Diphenyl diselenide[18] was prepared according to the published procedures. α-chloroacetic acid, 3-chloro propanoic acid and tetraethyl ammonium bromide were purchased from CDH (India). Common organic solvents (procured from Qualigens, CDH, Spectrochem and Merck) viz. chloroform, n-hexane, petroleum ether (40-60^{o}C and 60-80^{o}C), ethanol, methanol, dimethyl sulphoxide (DMSO), dimethylformamide (DMF) etc were used after further purification and drying by standard methods[19]. Peptone, beef extract, dextrose, NaCl and agar were purchased from CDH India Ltd. were used as such without any further purification.

The antimicrobial activity has been assessed by using disc diffusion technique for bacterial and fungal strains. Chloramphenicol and fluconazole were used as standard drugs respectively[20-22].

Synthesis of 2 -(phenylseleno) ethanoic acid (1):-

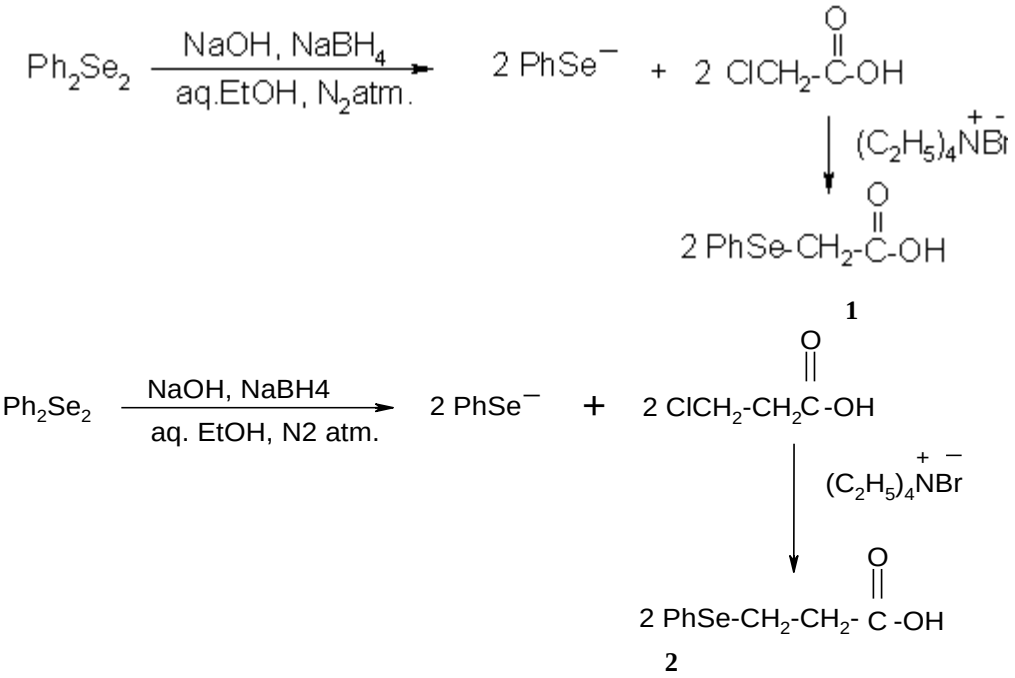
To the solution of diphenyl diselenide (3.12g, 10mmol) in dry ethanol (15mL) under dry nitrogen atmosphere, sodium borohydride (0.74g, 20mmol) in 2 ml of 1M NaOH was added dropwise until the solution become colorless. To this reaction mixture tetraethyl ammonium bromide (2.10g, 10mmol), a phase transfer catalyst was added. The ethanolic solution of α-chloroacetic acid (1.89g, 20mmol) was then added to the mixture dropwise and was allowed to stir overnight. It was washed with 100 mL of dil. HCl solution and extracted into 100 mL (25 x 4) of chloroform. The extract was dried over anhydrous magnesium sulphate and concentrated to 5mL on a rotary evaporator under reduced pressure. It was purified by TLC through a mixture of hexane and chloroform (2:1) to yield 2-(phenylseleno) acetic acid in the form of yellow viscous oil.

Synthesis of 3 -(phenylseleno) propanoic acid (2)

This was synthesized using the above mentioned method except that here 3-chloro propanoic acid was used to produce the compound in form of orange viscous oil.

Results and Discussion:-

Compound **1** and **2**, were synthesized by the interaction of nucleophile, sodium phenylselenolate ($NaPhSe^{-}$) with α-chloroacetic acid & 3-chloropropanoic acid using tetraethylammonium bromide as a phase transfer catalyst[23] in dry ethanol results in the formation of **1** & **2**, as yellow & orange viscous oil in high yield. However in the absence of tetraethyl ammonium bromide the yield was only about 2%.



Scheme 1

Elemental analysis of compounds **1** and **2** provides supporting evidence of their stoichiometry (**Table 1**). The compounds are stable and can be stored under ambient conditions upto six months. They have good solubility in $CHCl_3$, CH_2Cl_2, CH_3OH and C_2H_5OH. The molar conductance data of **1** and **2** have been determined in Dimethyl formamide at ~1Mm concentration level. The conductance value of **1** and **2** have been found to be much lower than the value expected for any electrolyte and hence they may be considered to behave as non electrolyte or non-ionic[24] (**Table 2**).

Various spectroscopic studies reveals the synthesis of said compounds (**Table 3-5**). The assignments have been made on the basis of literature reports of related compounds and additivity principles[25]. The results obtained are reported in the Table which agrees well with the reported values[26].

Antimicrobial activity:-

The antimicrobial activity of compounds **1** and **2** were tested at two different concentrations by disc diffusion method on bacterial and fungal strains namely *Staphylococcus aureus, Bacillus anthracis, Escherchia coli* and *Trichophyton rubrum, Candida tropicalis, Aspergillus niger* respectively. The media used for studies are mentioned in **Table 6.** The compounds show significant activity against all the organisms of bacteria and fungi. However, their activity was found to be minimum against *Aspergillus niger*. It was also concluded that the compounds are slightly more effective against the organism at 40 µg/L then at 20 µg/L (**Table 7 & 8**). It is evident from the data, obtained from antifungal studies that few fungal strains are slightly harder to treat, in comparison to bacteria, because of their cell wall, which is made up of chitin. Thus, the values of the zones of inhibition (**Table 8**) were found to be marginally lower than the values, obtained against bacterial strains, which are easier to penetrate. Both the compound showed minimum activity against *A.Niger*, which may be due to the carboxylic acid group, which are also components of the cell wall of this species. Therefore this makes it difficult for compounds, to easily penetrate into the cell wall of the strain[27].

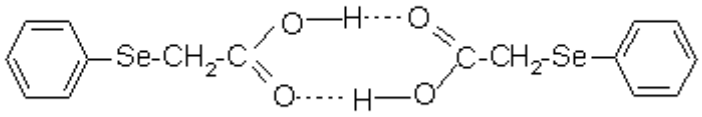
Conclusion:-

2-(phenyl seleno) ethanoic acid (**1)** & 3-(phenyl seleno) propanoic acid (**2)** has been synthesized in high yield (90%) by the reaction of phenylselenolate anions generated *insitu* by borohydride reduction of diphenyldiselenide, with α-chloroacetic acid and 3-chloro propanoic acid using tetraethyl ammonium bromide as phase transfer catalyst. However in the absence of catalyst, the yield of **2** was about 2%. The catalyst is ecofriendly and improves the yield

of the products. The compounds were found to be significantly effective against certain selected bacterial and fungal strains.

Structure:-

From the preceding discussions mainly based on molar conductance, elemental analysis, ESI mass, IR, ^{1}H, $^{13}C\{^{1}H\}$ and support from the previous work, the most possible structure of **1** and **2** have been proposed**.**



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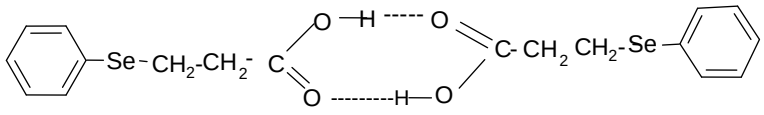

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Table 1:- Physical properties of compounds 1 and 2

S.No.	Compounds	Color	Yield (%)	Solubility	Conductance (ohm^{-1} cm^{2} mol^{-1})
1	**1**	Yellow oil	90	$CHCl_3$, CH_3OH, DMF	4.40
2	**2**	Orange oil	92	$CHCl_3$, CH_3OH, DMF	3.50

Table 2:- Elemental analysis of compounds 1 and 2

S.No.	Compounds	Carbon %		Hydrogen %		Selenium %	
		Calc.	Found	Calc.	Found	Calc.	Found
1	**1**	44.50	44.56	3.71	3.68	36.70	36.76
2	**2**	47.1	47.50	4.30	4.27	34.40	34.70

Table 3:- Important IR bands (cm^{-1}) of compounds 1 and 2

S.No.	Compound	ν (O-H)	ν (C=O)	δ (O-H)	ν (C-O)	ν (Se-C)
1	**1**	3456	1714	1477	1276	468
2	**2**	3400	1710	1470	1275	466

Table 4:- ^{1}H NMR spectral data of compounds 1 and 2

S.No.	Compounds	Aryl Protons (δ ppm)	Se**CH_2**	**OH**	**CH_2** COOH
1.	**1**	7.62-8.04, m, 5H (Se-C_6H_5)	3.02, s, 2H	8.89, s, 1H	-
2.	**2**	7.50-7.90, m, 5H (Se-C_6H_5)	2.90, t, 2H	8.75, s, 1H	4.20, t, 2H

Table 5:- $^{13}C\{^{1}H\}$ NMR spectral data of compounds 1 and 2

S. No.	Compounds	Aryl protons (δ ppm)	Alkyl protons (δ ppm)		
			C=O	Se-CH_2	CH_2- C=O
1	**1**	Se-C_{ipso} 130.32, *o* to Se 131.07, *m* to Se 128.90, *p* to Se 126.85	170.16	29.07	-
2	**2**	Se-C_{ipso} 129.22, *o* to Se 130.07, *m* to Se 127.80, *p* to Se 125.55	170.0	29.00	31.20

Table 6:- List of the used media for the bacterial and fungal studies

S.No.	Media used*		Constituent/l		pH	
	For bacteria	For fungi	For bacteria	For fungi	For bacteria	For fungi
1	NB	SDB	Peptone-10g Beefextract-5g NaCl-5g	Peptone-5g Dextrose-20g	7.2 ± 0.2	5.6 ± 0.2
2	NA	SDA	Peptone-10g Beefextract-5g NaCl-5g Bacteriological agar-16g	Peptone-5g Dextrose-20g Agar-7.5g	7.2 ± 0.2	5.6 ± 0.2

NA- Nutrient agar, NB- Nutrient broth, SDB- Sabouraud dextrose broth, SDA- Sabourauddextrose agar.

Table 7:- Antibacterial activity of compounds 1 & 2

Compounds	Diameter of zone of inhibition (mm)					
	S.aureus (Gram positive)		***B.anthracis (Gram positive)***		***E.coli (Gram negative)***	
	20µg/ml	**40µg/ml**	**20µg/ml**	**40µg/ml**	**20µg/ml**	**40µg/ml**
1	18	22	19	24	20	24
2	32	35	33	38	29	32
STD	-	31	-	31	-	30
Solvent	NA	NA	NA	NA	NA	NA

[Values represent the diameter (mm) of inhibition zone produced around each disc are average of 3 separate experiments, DMSO was used as a control and chloramphenicol as standard drug]

Table 8:- Antifungal activity of compounds 1 & 2

Compounds	Diameter of zone of inhibition (mm)					
	C.tropicalis		***T.rubrum***		***A.niger***	
	20µg/ml	**40µg/ml**	**20µg/ml**	**40µg/ml**	**20µg/ml**	**40µg/ml**
1	21	25	21	22	17	18
2	22	26	22	26	18	19
STD	-	30	-	25	-	30
Solvent	NA	NA	NA	NA	NA	NA

[Values represent the diameter (mm) of inhibition zone produced around each disc are average of 3 separate experiments, DMSO was used as a control and Fluconazole as standard drug]

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