HETEROCYCLIC BENZOTHAIZOLINES AND THEIR GERMANIUM COMPOUNDS

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Abstract : Three heterocyclic benzothiazolines have been prepared by the condensation of 2-furaldehyde, 2-thiophenecarbaldehyde and 2-pyridinecarbaldehyde with 2-mercaptoaniline. These benzothiazolines were reacted with triphenylgermanium chloride and produced compounds of the type $Ph_3Ge(Bzt)$ (where BztH is the benzothiazoline molecule). The heterocyclic benzothiazolines and their germanium compounds were characterized on the basis of elemental analyses, conductance measurements, molecular weight determinations and infrared, proton nuclear magnetic resonance, ultraviolet and 13-carbon nuclear magnetic resonance spectral studies. A trigonal bipyramidal geometry has been proposed for the resulting heterocyclic compounds. To find some practical utility of the synthesized compounds all the benzothiazolines and their compounds have been tested for their fungicidal, bactericidal and antiandrogen activities. The results are in favour of the better activity of the germanium compounds as compared to their parent benzothiazolines.

Introduction

The number and diversity of nitrogen and sulphur donor ligands used to prepare new organometallic compounds has increased rapidly during the recent years. The pronounced biological activity of the metal complexes of thio-ligands has created considerable interest in their coordination chemistry. A variety of diorganogermanium(IV) complexes with thio-ligands and particularly with benzothiazolines have been reported in the current literature but limited reports so far available on triorganogermanium(IV) complexes with these benzothiazolines produced an interest to study such types of complexes with their action as biological and antiandrogen agents.

The heterocyclic benzothiazolines used during these investigations are shown in Figure-1.

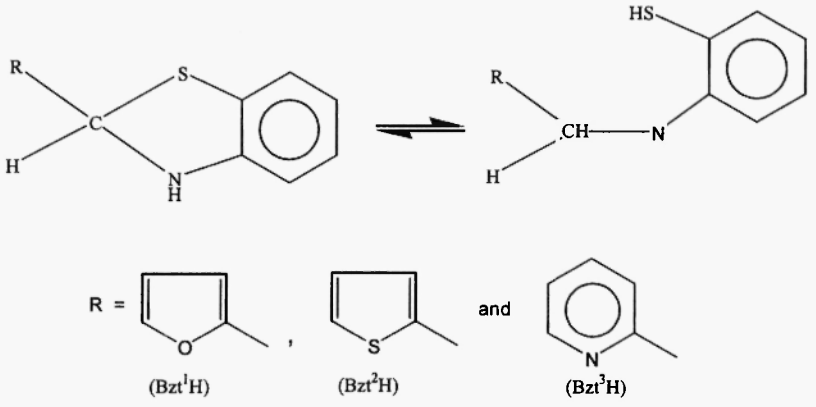

Figure-1

Experimental

All the experimental work and handling of the compounds were carried out in the absence of moisture. Chemicals and solvents were dried and purified by the standard methods. The benzothiazolines were prepared as reported earlier.[1]

Synthesis of Triphenylgermanium(IV) Complexes

To a weighed amount of triphenyl germanium chloride was added the requisite amount of the sodium salt (prepared by reacting the base with freshly cut sodium metal in 20 mL dry methanol) of the ligand in a dry solvent mixture of benzene (2 mL) and methanol (30 mL). The reaction mixture was refluxed

for 8-9 hours during which a white solid (NaCl) separated out. The contents were then cooled and filtered. Benzene (15 mL) was added to the filtrate and it was again refluxed. The process of refluxing and filtration was repeated two or three times until all the sodium chloride had precipitated out. The solvent was then removed by distillation under reduced pressure and the resulting products repeatedly washed with dry *n*-hexane and petroleum ether. It was finally dried in vacuo under reduced pressure. The purity was further checked by TLC using silica gel-G. Correct analyses were obtained that agreed within percentage errors for the following complexes :

Compound	Colour	Yield (%)	Mol. Wt.	
			Found	Calcd.
$Ph_3Ge(Bzt^1)$	Yellow	95	481	506
$Ph_3Ge(Bzt^2)$	Dark yellow	80	502	522
$Ph_3Ge(Bzt^3)$	Light brown	96	498	517

Analytical Methods and Physical Measurements

These are same as reported earlier.[1]

Results and Discussion

The reactions of triphenyl germanium chloride with the sodium salt of the benzothiazolines in the solvent mixture of benzene and methanol proceed smoothly with the precipitation of sodium chloride which was removed by filtration.

$$Ph_3GeCl + N^{\frown}SNA \longrightarrow Ph_3Ge(N^{\frown}S) + NaCl$$

(Where $N^{\frown}SNa$ represents the sodium salt of the benzothiazoline)

All the newly synthesized complexes are coloured solids, soluble in most of the common organic solvents and are non-electrolytes (molar conductivity below 13 $ohm^{-1}cm^2mol^{-1}$). These are monomeric in nature.

Infrared Spectra : The free benzothiazolines show an NH stretching band at 3350 - 3150 cm^{-1}, but no bands of ν(SH) at 2600 - 2500 cm^{-1} and ν(C=N) at 1625 - 1600 cm^{-1}. This is an indicative of the benzothiazoline rather than the Schiff base structure.[3] In the spectra of the germanium complexes, bands due to νNH vibrations disappear indicating the chelation of nitrogen with the germanium atom, and a new band at about 1600 cm^{-1} is observed, which may be assigned to the >C=N vibrations. The appearance of this band suggests that the complexes are germanium - Schiff base derivatives, as the benzothiazoline ring opens to give the Schiff base structure in the presence of the germanium atom. Several new bands in the germanium complexes in the regions, 690 - 670 cm^{-1} and 415 - 425 cm^{-1} are due to the Ge←N[4,5] and Ge-S[4,5] stretching vibrations, respectively and this further lends support to the proposed coordination.

Ultra-Violet Spectra : The ultra-violet spectra of the benzothiazolines consist of two broad and strong bands around 270 and 315 nm, characteristic of the cyclic form of the benzothiazolines. However, an additional band in the organogermanium(IV) complexes is also observed around 400 nm due to the n-π* electronic transitions of the azomethine group. The appearance of this new band in the complexes clearly indicated the formation of the azomethine grouping on complexation and subsequent isomerization of the benzothiazolines into the azomethine form.[3]

^{13}C NMR Spectra : A considerable change in the chemical shift of carbons attached to nitrogen and sulphur is an indication of the role of these elements in coordination.

^1H NMR Spectra : The different signals observed in the proton magnetic resonance spectra of the benzothiazolines and their corresponding organogermanium(IV) complexes have been shown below and which further support the bonding pattern in these complexes.

Compound	NH	H-C-N or H-C=N	Aromatic
Bzt^1H	4.25bs	7.92s	6.60 - 770 m
$Ph_3Ge(Bzt^1)$	-	8.15s	6.80 - 8.00 m
Bzt^2H	4.40 bs	7.84s	6.70 - 7.75 m
$Ph_3Ge(Bzt^2)$	-	8.30s	7.30 - 8.20 m
Bzt^3H	4.60 bs	8.00s	7.00 - 7.95 m
$Ph_3Ge(Bzt^3)$	-	8.90s	7.15 - 8.20 m

Based on these studies the structure for the organogermanium(IV) complexes has been shown in Figure-2.

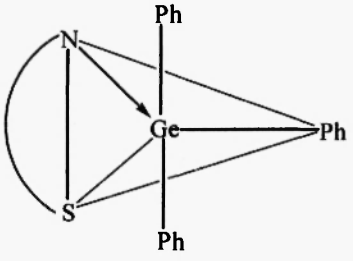

Figure-2

Biological Aspects

Fungicidal and bactericidal activities of the ligands and their corresponding organogermanium(IV) complexes against pathogenic fungi and bacteria are quite promising. The antimicrobial data reveal that the complexes are superior than the free bases. The enhanced activity of the germanium complexes may be ascribed to the increased lipophilic nature of these complexes arising due to the chelation. The activity increased as the concentration was increased. Further, the results of bioactivity were compared with the conventional fungicide *Bavistin* and the conventional bactericide *Sreptomycin*, taken as standards in either case.

Anti-androgen Activity

For checking the efficiency of these compounds as well as the ligands some experiments have been done on male albino rats (*Rattus norvegicus*). The rats selected for these studies were with the weights between 200-250 gms. These rats were regularly checked for any disease and if found infected were isolated and treated. The rats were fed on a diet of rat feed pellets obtained from Hindustan Lever Limited, Mumbai and water was provided *ad libitum*. During, these experiments doses of the bases and their compounds were given orally after mixing in olive oil with the help of hypodermic syringe having pearl point needle for 60 days and withdrawal for 30 days. After the completion of the treatment, the fertility test was done. On the day sixty one, the rats were autopsied and blood was extracted from the heart. The serum was separated and used for serum biochemistry. Reproductive tissues and vital organs were blotted free of blood, weighed and used for the tissue biochemistry observations.

The Body and Organ Weights

The experiments indicated that the body weights of the rats were not much altered after the treatment of the complexes. However, a general decrease in the reproductive organ weights was observed in the weights of the testis, epididymis vas deferens, seminal vesicle and ventral prostate.

Sperm Dynamics and Fertility

A significant decrease in sperm density in testes and cauda epididymis were observed in the benzothiazolines and their germanium complexes. Also, the sperm motility in Cauda epididymis was decreased significantly in the benzothiazolines and their germanium treated rats.

Biochemical Changes

When the results of these investigations were compared with the control, the marked reductions in sialic and protein contents of testes, epedidymis, ventral prostate and seminal vesicle were observed in the benzothiazolines and their organogermanium(IV) complexes treated rats. On the other hand a sharp increase in testicular cholesterol and acid and alkaline phosphatase contents were observed in various treated groups. Seminal vesicular fructose contents were decreased significantly.[4] Thus the present investigations reveal that the benzothiazolines and their organogermanium(IV) complexes altered the reproductive function of male rats and the complexes are more active than the benzothiazolines themselves in inhibiting the fertility in male rats. Thus these compounds may be good antiandrogen agents.

Altered sperm dynamics and fertility after treatment with the benzothiazolines and their germanium complexes.

Group	Compound	Sperm motility *Cauda epididymis*	Sperm density (million/ml)		
			Testes	Epididymis	Fertility test (%)
A	Control	70.0 ± 6.1	1.90 ± 0.20	51.0 ± 1.85	98 +ve
B	Bzt^1H	40.0 ± 3.0	0.62 ± 0.10	23.0 ± 1.70	85 -ve
C	$Ph_3Ge(Bzt^1)$	45.0 ± 4.0	0.60 ± 0.20	20.0 ± 1.20	98 -ve
D	Bzt^2H	55.0 ± 5.0	0.72 ± 0.10	27.0 ± 1.50	75 -ve
E	$Ph_3Ge(Bzt^2)$	40.0 ± 6.0	0.63 ± 0.10	24.0 ± 1.65	88 -ve
F	Bzt^3H	60.0 ± 3.5	0.90 ± 0.10	40.0 ± 1.50	75 -ve
G	$Ph_3Ge(Bzt^3)$	48.0 ± 6.0	0.70 ± 0.10	28.0 ± 1.70	85 -ve

Values are mean ± SEM six determinations
Group A compared with Groups B, D and F
Group C compared with Group B
Group E compared with Group D
Group G compared with Group F

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