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SYNTHESIS AND CHARACTERIZATION OF SOME TETRAORGANOBISMUTH(V) ARYLOXYACETATE FOR THEIR BIOLOGICAL SCREENING

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Abstract- The metal based compounds plays significant role in medical field in treatment of various acute diseases. The present manuscript deals with the synthesis of some tetraorganobismuth (V) aryloxyacetates which are further characterized on the basis of their melting points, elemental analysis along with their spectral analysis to ascertain their structure. The compounds were also tested for their biological studies including antibacterial and antifungal activity in different pathogenic microbial strains and results indicates that these compounds show moderate to higher activity.

Key words- acute disease, elemental analysis, spectral analysis, antibacterial activity, antifungal activity, pathogenic microbial strains

Introduction

Among the pentavalent organobismuth (V) compounds, R_nBiX_{5-x}(n= 1,2,3 and 4) (X = anionic group likes, halide, pseudo halide, nitrate, carboxylates, oximes, amide, imides, etc.), only R_3BiX_2 compounds are well studied and have pentacoordination around the bismuth with a trigonal bipyramidal or square pyramidal configuration [1-5]. The similar structural conclusions have been observed in the case of the corresponding triorganoantimony (V) and arsenic (V) compounds reported earlier [6-10].It is well known that group 15 elements characteristically exhibit structural changes on increasing or decreasing the content and the nature of organic group(s) bound to the central element as well as the anionic group [1]. As a matter of fact this fascinating aspect, apart from other consideration, makes their study rather more interesting. Unlike pentacoordinated covalent R_3BiX_2 compounds R_4BiX are ionic in nature and R_4Bi moiety has a charged tetrahedral configuration $(R_4Bi)^+$ [1, 2, 11] which is especially true in case of halide only. Further studies have shown that R_4BiOR' (R= phenyl) to be covalent molecules with pentacoordination around bismuth, parallel to the observation made in case of R_4SbOR compounds which also has a trigonal bipyramidal configuration. In both cases the oxygen atom occupies an apical position [1, 12].

The present manuscript deals with the systematic study of aryloxyacetates derivatives of bismuth Ph_4BiL (L = $ROCH_2COOH$) and their structural conclusions have been arrived on the basis of molar conductance, molecular weight determination, ultra-violet, infra-red and NMR spectral analysis. The compounds were also tested for their biological studies including antibacterial and antifungal activity in different pathogenic microbial strains.

Experimental

The tetraphenylbismuth (V) chloride Ph_4BiCl was used after dehydration, and aryloxyacetates were used as such. The typical experimental details of the reactions are described below.

Reaction of Tetraphenylbismuth(V)chloride with p-methyl(α-methyl)phenoxy acetic acid(2)

Tetraphenylbismuth(V) chloride (1mmol) and *p*-methyl (α-methyl) phenoxy acetic acid (1mmol) and triethylamine (1ml) were stirred together in benzene for 6h and then refluxed for 2h more to ensure completion of the reaction. A flocculent precipitate of triethylamine hydrochloride (M.P. 240°C) was separated which was removed by filtration. The filtrate on concentration afforded off white crystals, which were recrystalized from pet-ether (40-60°/60-80°C).

Reaction of Tetraphenylbismuth (V) chloride with Sodium salt of phenoxy acetic acid (3)

Tetraphenylbismuth (V) chloride (1mmol) and sodium salt of phenoxy acetic acid (1mmol) was refluxed in benzene for 24h in presence of catalytic amount of 18-crown-6 as phase transfer catalyst. NaCl so formed in the form of white precipitate was filtered off. The filtrate on concentration gives white solid which was recrystalized from pet-ether and hexane mixture.

Reaction of Tetraphenylbismuth (V) chloride with p-chlorophenoxy acetic acid (4)

Tetraphenylbismuth (V) chloride (1mmol) and *p*-chlorophenoxyacetic acid (1mmol) and triethylamine (1ml) were stirred together in benzene for 6h and then refluxed for 2h more to ensure completion of the

reaction. A flocculent precipitate of triethylamine hydrochloride (M.P. 240°C) was separated, which was removed by filtration. The filtrate on concentration afforded off white crystals, which were recrystalized from pet-ether (40-60°/60-80°C).

Antibacterial activity

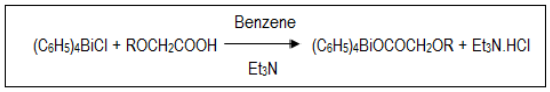
The antibacterial activity of these organobismuth (III) compounds was determined by disc diffusion method [13]. In this technique, the filter paper (Whatman No. 1) sterile discs of 5 mm diameter, impregnated with the test compounds (10 μg/ml of ethanol) were placed on the nutrient agar plate at 37°C for 24 hrs. The inhibition zones around the dried impregnated discs were measured after 24 hrs. The activity was classifieds as 'highly active' (diameter > 14 mm); "moderately active" (diameter = 10-14 mm) and 'slightly active' (diameter = 6-10). The diameter less than 6 mm was regarded as inactive.

Antifungal activity

The antifungal activity of these compounds was tested by agar diffusion method [14] using two concentrations of the test compound, *viz*, 50 and 100 μg/ml against *Aspergillus flavus* and *Aspergillus niger*. The one ml of each organobismuth compound was poured into a petri dish having about 20-25 ml of molten potato dextrose agar medium of. As the medium gets solidify, petri dishes were inoculated separately with the fungal isolates and kept at 26°C for 96 hrs in incubator. All the values (% inhibition) were recorded after 96 hrs and their % inhibition was calculated.

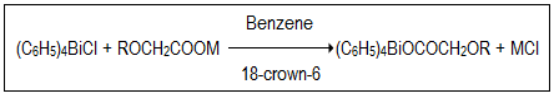
Results and Discussion

Tetraphenylbismuth (V) aryloxyacetates can readily be obtained by the treatment of tetraphenylbismuth (V) chloride with the corresponding aryloxyacids in presence of triethylamine as hydrogen halide acceptor. The reactions were essentially carried out under nitrogen atmosphere to avoid aerial oxygen and moisture. Thus 1:1 reaction of tetraphenylbismuth (V) chloride with an aryloxyacids proceeded in the sense of equation shown below.



[R= $C_6H_3(CH_3)_2$-2, 3; $C_6H_4(CH_3)$-p, C_6H_5, p-ClC_6H_4, o-ClC_6H_4, ß-$C_{10}H_7$, p-$CH_3C_6H_4$(α-methyl)]

These aryloxyacetates can also be obtained by the displacement reaction of tetraphenylbismuth halide with the corresponding metallic salt of acetate in benzene.



[R= $C_6H_3(CH_3)_2$-2, 3; $C_6H_4(CH_3)$-p, C_6H_5, p-ClC_6H_4, o-ClC_6H_4, ß-$C_{10}H_7$,
M= Na/Ag]

The reaction proceeded quite smoothly at room temperature and the products obtained were recrystalized from pet-ether/benzene. Since the newly formed complexes are soluble in organic solvents used in the reaction, their separation from the salt, triethylamine hydrogen chloride ($Et_3N.HCl$) or MCl did not pose any difficulty. The complexes were obtained as white crystalline solids having sharp melting points and fairly stable on air and moisture. The melting points were found in the range 120-200°C and melt without decomposition. The melting point of compound **(1)** $(C_6H_5)_4BiOCOCH_2OC_6H_3(CH_3)_2$2-3 is exceptionally low. The consistency in melting point after repeated crystallization as well as TLC run in chloroform-hexane, with a single spot excluded the presence of mixture of reactants. The molar conductance value of 10^{-3}M solution were recorded in methanol and found in the range 20-30 $Ohm^{-1}mole^{-1}cm^2$ indicating the absence of ionic species in the solution. The molecular weights were taken in nitrobenzene which suggested their monomeric nature. Thus the conductance and molecular weight data coupled with vibrational spectra suggest that these complexes predominantly possess covalent character.

IR Spectra

The infrared spectra of newly synthesized tetraphenylbismuth aryloxyacetates show almost identical absorption bands due to phenyl groups and these bands do not differ significantly from those reported earlier for other bismuth (V) compounds. The absorption spectra of aryloxyacetates derivatives $[(C_6H_5)_4BiOCOCH_2OR]$ were recorded in the solid state in KBr pellets. The $\nu_{asy}CO$ and $\nu_{sym}CO$ stretching mode appearing in the range 1640-1685cm^{-1} and 1290-1385cm^{-1} respectively as strong bands. The $\Delta\nu$ values ($\Delta\nu_{asy}$ CO and $\Delta\nu_{sym}$ CO) of around >300 cm^{-1} indicate unidentate behavior of ligand. The comparison of IR spectra of the compound with the respective ligand in solution did not show any significant shift in $\nu_{asym}OCO$ and $\nu_{sym}OCO$. This indicates the lack of coordination of bismuth through C=O or C-O-Ar centre of the ligand. The Bi-O band appears in the range 610-640 cm^{-1} as a weak band while Bi-C vibration corresponding to y-mode appears in the range 455-475 cm^{-1} as a medium intensity band.

^{1}HNMR Spectra

The ^{1}HNMR spectra of compound $(C_6H_5)_4BiOCOCH_2OC_6H_3(CH_3)_2$2-3**(1)** and compound $(C_6H_5)_4BiOCOCH_2OC_6H_4(CH_3)$-*p***(6)** were obtained at room temperature in $CDCl_3$. For $(C_6H_5)_4BiOCOCH_2OC_6H_3(CH_3)_2$2-3, a multiplet located at δ7.90 ppm (for aromatic protons) and a singlet at δ2.30 ppm corresponding to methyl protons were obtained. The singlet corresponding to $–CH_2$ protons was observed at δ4.10 ppm. Similarly, for compound $(C_6H_5)_4BiOCOCH_2OC_6H_4(CH_3)$-*p* a multiplet centered at δ7.80 ppm corresponds to aromatic protons and a singlet at δ2.30 ppm can be attributed to methyl protons. The singlet for CH_2 protons appears at δ4.50 ppm. The

positions and intensities of the peaks are in good agreement with the proposed formulations of the complexes.

U.V. Spectra

The electronic spectra were obtained in chloroform-hexane mixture in the range 200-400 nm. The UV absorption due to COO group appears at λ 262±4 in all the cases and the absorptions in the range λ296±4 may be attributed to the aryloxy moieties. However, these values are comparable with the absorption peaks of the free ligands i.e. due to C=O and C-O-Ar. Hence, the possibility of coordination through the oxygen of the carbonyl group or through the oxygen of ethereal group can be ruled out. This also gives support to the earlier observation in case of antimony that aryloxyacetates behave as monodentate ligand towards bismuth.

Thus, on the basis of their IR, ^{1}HNMR, UV spectra, molecular weight and conductance measurement data, tetraphenylbismuth aryloxyacetates may be assigned a pentacoordinated trigonal bipyramidal structure with the four phenyl groups occupying the three equatorial positions and one axial position, while the non-phenyl group is at the other axial position. Support for this conclusion comes from the fact that more electronegative group generally occupies axial position.

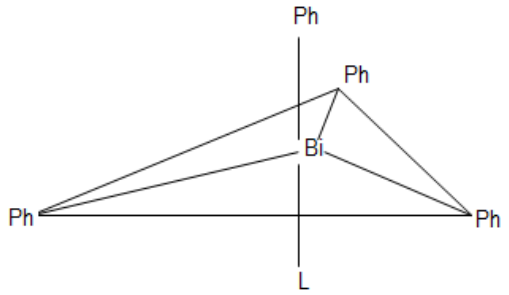


Fig.1- Structure of tetraphenylbismuth (V) aryloxyacetate

Antibacterial activity

All the synthesized compounds were tested for antibacterial activity against three bacterial strains *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Klebsiela pneumoniae* using 10 μg/ml concentration of test compound. The compounds show higher to moderate activity against the bacterial strains. These compounds may react with peptidoglycan layer of bacterial cell wall and damage it by penetrating in such a manner that the phenyl ring gets entered inside the cell by puncturing it followed by death of bacterial cell. Some times these compounds in low concentration may cause bacteriostatic condition by slow down the growth of bacteria.

Antifungal Activity

The antifungal activity of all these compounds was tested against *Aspergillus flavus* and *Aspergillus niger* using 50 and 100 μg/ml concentration. The activity of these compounds was found variable at 50μg/ml concentration but at higher concentration all the compounds show high activity against fungal strains. The role of different aryloxyacetates as ligands was also commendable. These compounds generally damage the fungal strains by puncturing the cell wall similarly as in case of bacteria.

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Table-1 Preparation and properties of tetraphenylbismuth (V) aryloxyacetates

Sr. No.	Complex	Solvent	M.P. (°C)	Colour	Yield (%)	Yield (gm)
1.	$(C_6H_5)_4BiOCOCH_2OC_6H_3(CH_3)_2$2-3	Ether	50	Off-white	61	0.34
2.	$(C_6H_5)_4BiOCOCH_2OC_6H_4(CH_3)$-*p*	Pet-Ether(40-60°/60- 80°)	160	Off-white	72	0.40
3.	$(C_6H_5)_4BiOCOCH_2OC_6H_5$	Pet-Ether (40-60°)	140	white	66	0.35
4.	$(C_6H_5)_4BiOCOCH_2OC_6H_4Cl$-*p*	Hexane	120	white	54	0.31
5.	$(C_6H_5)_4BiOCOCH_2OC_6H_4Cl$-o	Pet-Ether (60-80°)	160	white	57	0.32
6.	$(C_6H_5)_4BiOCOCH_2OC_6H_4CH_3$-*p*	Methanol-benzene	170	white	70	0.38
7.	$(C_6H_5)_4BiOCOCH_2OC_{10}H_7$-ß	Benzene	200	white	69	0.40

Table-2: UV and IR spectral analysis of tetraphenylbismuth (V) aryloxyacetate

Sr. No.	Empirical formula	ν_{asym} (OCO)	ν_{sym} (OCO)	ν(Bi-O)	ν(Bi-C)	UV Absorption, λ(nm)	
						Due to COO (-C=O)	Due to Aryloxy Group (-C-O-Ar)
1.	$C_{34}H_{31}O_3Bi$	1680	1380	610	465	260	272
2.	$C_{34}H_{31}O_3Bi$	1675	1290	620	460	262	274
3.	$C_{32}H_{27}O_3Bi$	1685	1340	635	470	264	280
4.	$C_{32}H_{26}ClO_3Bi$	1678	1385	640	472	260	278
5.	$C_{32}H_{26}ClO_3Bi$	1675	1295	629	475	266	272
6.	$C_{33}H_{29}O_3Bi$	1640	1310	620	455	262	272
7.	$C_{36}H_{29}O_3Bi$	1680	1310	640	450	263	274

Table-3 Anti-bacterial activity of tetraorganobismuth (V) aryloxyacetate

Sr. No.	Compounds	Control	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Klebsiela pneumoniae*
1	$(C_6H_5)_4BiOCOCH_2OC_6H_3(CH_3)_2$2-3	–	+++	+++	++
2	$(C_6H_5)_4BiOCOCH_2OC_6H_4(CH_3)$-*p*	–	++	++	++
3	$(C_6H_5)_4BiOCOCH_2OC_6H_5$	–	+++	++	++
4	$(C_6H_5)_4BiOCOCH_2OC_6H_4Cl$-*p*	–	++	++	++
5	$(C_6H_5)_4BiOCOCH_2OC_6H_4Cl$-o	–	++	++	+++
6	$(C_6H_5)_4BiOCOCH_2OC_6H_4CH_3$-*p*	–	+++	++	++
7	$(C_6H_5)_4BiOCOCH_2OC_{10}H_7$-ß	–	++	++	++

Table-4 Antifungal activity of organobismuth (III) aryloxyacetates at 50 μg/ml concentration

Sr. No.	Compounds	*Aspergillus flavus* Col. Dia. (mm)	% Inhibition	*Aspergillus niger* Col. Dia. (mm)	% Inhibition
1	$(C_6H_5)_4BiOCOCH_2OC_6H_3(CH_3)_2$2-3	0.7	76.6	0.6	70.0
2	$(C_6H_5)_4BiOCOCH_2OC_6H_4(CH_3)$-*p*	0.2	93.3	0.7	65.0
3	$(C_6H_5)_4BiOCOCH_2OC_6H_5$	0.2	93.3	0.7	65.0
4	$(C_6H_5)_4BiOCOCH_2OC_6H_4Cl$-*p*	0.5	83.3	0.4	80.0
5	$(C_6H_5)_4BiOCOCH_2OC_6H_4Cl$-o	0.2	93.3	0.7	65.0
6	$(C_6H_5)_4BiOCOCH_2OC_6H_4CH_3$-*p*	0.2	93.3	0.7	65.0
7	$(C_6H_5)_4BiOCOCH_2OC_{10}H_7$-ß	0.7	76.6	0.7	65.0
8	Control	3.0	–	2.0	–

Table-5 Antifungal activity of organobismuth (III) aryloxyacetates at 100 μg/ml concentration

Sr. No.	Compounds	*Aspergillus flavus* Col. Dia. (mm)	% Inhibition	*Aspergillus niger* Col. Dia.(mm)	% Inhibition
1	$(C_6H_5)_4BiOCOCH_2OC_6H_3(CH_3)_2$2-3	0.1	96.7	0.4	80.0
2	$(C_6H_5)_4BiOCOCH_2OC_6H_4(CH_3)$-*p*	0.2	93.3	0.3	75.0
3	$(C_6H_5)_4BiOCOCH_2OC_6H_5$	0.2	93.3	0.1	95.0
4	$(C_6H_5)_4BiOCOCH_2OC_6H_4Cl$-*p*	0.1	96.7	0.1	95.0
5	$(C_6H_5)_4BiOCOCH_2OC_6H_4Cl$-o	0.4	86.7	0.2	90.0
6	$(C_6H_5)_4BiOCOCH_2OC_6H_4CH_3$-*p*	0.1	96.7	0.3	75.0
7	$(C_6H_5)_4BiOCOCH_2OC_{10}H_7$-ß	0.2	93.3	0.3	75.0
8	Control	3.0	–	2.0	–