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Studies on Diorganoselenium Compounds and their Tellurium Analogs as Potential Acetylcholinesterase Inhibitors

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Few diorganoselenium dihalides and their tellurium analogs have been synthesises. The effect of these compounds on acetylcholinesterase (AChE) activity in rat brain was studies *in vitro* at different concentrations. Both organoselenium as well as organo tellurium compounds inhibited the AChE activity. At a concentration of 10^{-4}M compounds (Ar CO $CH_2)_2$ $SeBr_2$ and (Ar CO_2) Se Cl_2 inhibited the AChE activity by 94.14% and 78.11% while their tellurium analogs at the same concentration exhibited 79.36 and 59.37% inhibition respectively. However, at a lower concentration of 10^{-6}M, no appreciable difference in AChE inhibitory activity of organoselenum compounds and their tellurium analogs was observed.

ORGANOSELENIUM and organotellurium compounds are well known for their antimicrobial[1-4] antiinflammatory[5,6] and biocidal[7] activities. However in the comparative studies, the superiorty of organoselenium compounds as antimicrobial agent over the corresponding tellurium analogs has been reported.[8-9] Our recent studies[10] have shown that some diaryltellurium compounds significantly inhibited the AChE activity. However, whether their organoselenium analogs will also inhibit the AChE is not known, though possibility exists as selenium is an isosteric element. Therefore we synthesised few organotellurium compounds and their selenium analogs of the type (Ar CO)$_2$M X_2 (Type I), (Ar CO $CH_2)_2$ M X_2 (Type II) and (Ar $CH_2)_2$ M X_2 (Type III) **(table 1)**.

EXPERIMENTAL

All the solvents were purified and dried before use by standard methods. The reactions were routinely checked on Silica gel (G) TLC plates. Metal powder (200 mesh) used as such was of the BDH Limited. Absolute dry conditions were maintained during the reaction, using $CaCl_2$ guard tube. Melting points of the compounds were determined in open capillary tubes and are uncorrected. Metals were estimated volumetrically by the method of Vogel.[11] IR Spectra were recorded on a Perkin Elmer-577 spectrophotometer. ^{1}HNMR Spectra were scanned on Varian EM 360 L spectrometer and Mass spectrum was recorded on JEOL Instrument model RJMS-D300.

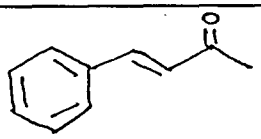
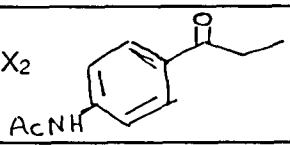
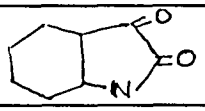
1) α-α' Bis (3 phenyl prop-2- enoyl) Selenium dichloride

Acid chloride of 3 phenyl-2-enoid acid (0.01 mol) was refluxed with (0.04 g.) of Selenium powder in dry benezene for 18 hrs. The reaction mixture was then extracted repeatedly with hot dry beneze. The product obtained after removal of solvent was recrystallised from beneze-pet ether (60-80°C).

m.p. 150°, Yield 60%; Se% Found (calculated): 18.93 (18.97) IR (KBr) cm^{-1}. υC=O, 1690; υC=C

*For Correspondence.

Table - 1

Type of the compound	Ar	M	X	Compound No.
I	$(Ar\,CO)_2\,M\,X_2$ 	Se	Cl	1
		Te	Cl	2
II	$(Ar\,COCH_2)_2\,M\,X_2$ 	Se	Br	3
		Te	Br	4
III	$(Ar\,CH_2)_2\,M\,X_2$ 	Se	Cl	5

(alipathic), 1660; υC=C (aromatic). 1660-1450; υC=Se 460.

Mass spectrum - NO M+ peak was observed. The other peaks were located at m/e 280 (C_6H_5CH=CH-$COSeCl_2$+; 149, 148, 147 ($SeCl_2$)+; 242-244 (C_6H_5CH=$CHCOSeCl$)+; 131 (C_6H_5CH-CHCO)+; 103 (C_6H_5CH=CH)+.

2) Bis (3-phenyl prop-2-eneoyl) tellirum dichloride

It was synthesised using the same method as compound (I), Tellurium powder was used.

m.p. 120°, yield 67%; Te % Found (calculated), 27.72 (27.76)

3) Bis (4-N-acetylamino phenacyl) Selenium dibromide

A solution of w-bromo 4-Nacetylamino acetophenone (2.0 g., 0.01 mol) and Selenium powder (0.4g, 0.005 g atom) in dry beneze was refluxed on water bath for 26 hrs. Then extracted with hot beneze. Crude product obtained after concentration, was recrystallised from beneze-pet ether (bp. 60-80°).

m.p. 117° Yield 60%; Se % Found (calculated),13.15 (13.22) IR (KBr) cm^{-1} : υC-Se, 480; υC=O, 1680; υC=O (amide), 1650; υN-H3300.

^{1}HNMR ($COCl_3$ + DMSO) : 2.1 δ (S, 6H, NH-C(=O)-CH_3); 2.5δ (S, 4H, Ar C-CH_2); 7.97-7.58δ(m, Ar H); 9.5δ NH $COCH_3$)

4) α-α' Bis (4-N acetyl amino pehnacyl) tellurium dibromide

The compound was obtained following the same procedure as in compound (3) except Tellurium metal is used in place of Selenium.

m.p. 170°, Yield 56%; Te % Found (calculated), 20.02 (20.00)

IR (KBr)cm^{-1} :

υ C=O (1690 υC-Te, 500; υ NH, 3300; υ C=O (amide), 1640.

Mass Spectrum : NO M+ peak was observed. Other peaks were located at m\e 292, 256, 254, 200 (base peak), 198, 176, 178, followed by usual fragmentation pattern due to organic moiety.

Table 2: *AChE inhibition by Organoselenium/tellurium compounds

Compound No.	at % Inhibition		
	10^{-4}M	10^{-5}M	10^{-6}M
Physostigmine (Standard)	96.27	94.83	55.25
1.	78.11	67.22	62.71
2.	59.37	57.65	57.37
3.	94.14	70.78	64.36
4.	79.36	74.68	70.71
5.	69.50	54.16	44.81

(*AChE activity observed in control experiment at 10^{-4}, 10^{-5} and 10^{-6} M was 10.68, 12.05 and 12.84 moles of substrate hydrolysed per minute per mg protein.Physostigmine was used as the standard compound under the same experimental conditions).

5) Bis [(2,3 dioxoindol-1-yl)methyl] Selenium dichloride

Three steps were required to synthesised this compound.

(i) N-hydroxy methyl Indoline 2,3 dione (a) was prepared as described in Literature[12] and used in preparation of B.

(ii) N-Chloromethyl Indoline 2,3 dione (b)

Compound (a) (1.7 g. 0.01 ml) was refluxed with $SOCl_2$ (0.02 mol) for 4 hrs. on water bath in absolutely dry condition. The excess of thionyl chloride ($SOCl_2$) was removed by distillation under reduced pressure. Traces of thionylchloride were removed azetropically with dry beneze.

(iii) Compound (b) (2.1g) and Selenium powder (0.4 g) in benzene was refluxed on water bath for 38 hrs. then extracted with methanol. Crude product obtained after removal of solvent was recrystllised with methanol- water.

m.p. 95°C Yield - 56%l; Se % Found (calculated) 16.60 (16.63)

IR(KBr) cm^{-1} : υC=O 1730; υ C-N; 1340; CH aromatic (bending), 740; CH bending (aliphatic), 460; υC-Se ~450.

Mass Spectrum - No M+ peak was observed. Other peaks were located at 149, 177, 107, 146, 91 (base peak), 119, 287, 184.

Acetylcholinesterase Activity

The activity of AChE was assayed by the method of Ellman et al.[13] Briefly, the assay mixture consisting of 2.6 ml. 0f 0.1 M phosphate buffer (pH 8.0,), 0.1 ml of 0.01 M DTNB, 0.02 ml. of enzyme and 0.02 ml of 0.075 M acetylthiocholine iodide was preincubated for 5 minutes followed by addition of substrate. The absorbance was measured per minute for a total of 5 minute at 412 nm. The activity was expressed as n moles of substrate hydrolysed per minute per mg protein.

RESULTS AND DISCUSSIONS

Both organoselenium dihalides and their tellurium analogs appreciably inhibited the AChE activity. The effect was most pronounced for the compounds of the type $(ArCOCH_2)_2$ M X_2 (type II) as compared to $(ArCO)_2$ M X_2 and $(ArCH_2)_2$ M X_2 (type I & III).

As much as 95.1% inhibition of AChE was observed for the compound 3, whereas its tellurium analog (compound 4) was effective in inhibiting the AChE activity by 79.36% at a concentration of 10^{-4} M (**table 2**). On contrary at the lower concentration of 10^{-6} M compound 4 inhibited AChE activity more effectively (inhibition 70.71%) than its Selenium analog, compound 3 (inhibition 64.36%).

Further, the activity of organoselenium compounds is largely concentration dependent. At highest concentration of 10^{-4} M the organoselenium compounds inhibited the AChE activity in the range of 94.14% (compound-3)and 48.80% (compound-4). While on lower concentration (10^{-6}M) the same compounds inhibited AChE activity in the range of 64.36%-33.61%. On the other hand the activity of organotellurium compound is not much affected by concentration. Therefore it can be inferred from the above observations that organotellurium compounds are more effective against AChE than their Selerium analogs.

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