

## SYNTHESIS OF $\alpha, \alpha'$ -BIS(PROPIOPHENONE) TELLURIUM DERIVATIVES AS POTENTIAL BIODYNAMIC AGENTS

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### ABSTRACT

A series of  $\alpha, \alpha'$ -bis(propiofenone) tellurium dihalides, pseudohalides and their adducts with nitrogen donor molecules have been synthesized and evaluated for their antimicrobial activity against various strains of bacteria, fungi and cholinesterase enzyme inhibitory activity on rat brain homogenate. A possible structure-activity co-relationship has been derived.

### INTRODUCTION

ORGANOTELLURIUM compounds have recently been shown to exhibit pharmacological activities like antibacterial<sup>1-4</sup>, antifungal<sup>5,6</sup>, antiinflammatory<sup>7</sup> and germicidal<sup>8,9</sup>. Several complexes of organotellurium compounds<sup>6</sup> with nitrogen, oxygen and sulphur donors were found to be effective as bacteriocides and fungicides. Certain substituted diphenyltellurium dihalides and pseudohalides<sup>10</sup> were active biocides. Cyclic compounds like 2,4-dimethyl cyclotellurapentane-3-5-dione have been successful in the treatment of infective conditions of the eye-like conjunctivities, blepharitis and corneal ulceration on account of its pronounced bacteriostatic activity<sup>8</sup>. It was thought worthwhile to synthesize some newer organotellurium dihalides, pseudohalides and adducts with nitrogen donor molecules in a single framework to exhibit better biological activities.

In the present investigation various  $\alpha, \alpha'$ -bis(propiofenone) tellurium dibromide and diiodide were obtained by heating  $\alpha$ -bromopropiofenone with tellurium metal powder at high temperatures. Adducts were obtained by refluxing  $\alpha, \alpha'$ -bis(propiofenone) tellurium dibromide with donor molecules. Pseudohalides were obtained by halogen exchange reactions. The IR spectra of compounds showed major peaks of  $\nu_{C=O}$  ( $\sim 1680 \text{ cm}^{-1}$ ), tertiary C-H bending ( $\sim 1350 \text{ cm}^{-1}$ ), Te-C<sup>11</sup> bond ( $\sim 500 \text{ cm}^{-1}$ ), Te-N<sup>12</sup> bond ( $\sim 420 \text{ cm}^{-1}$ ) and Te-S<sup>13</sup> bond ( $\sim 280 \text{ cm}^{-1}$ ). PMR signals at 3.1-1.4 $\tau$  for phenyl protons, 8.3-7.4 $\tau$  and 7.6-6.8 $\tau$  for two methyl groups and 6.2-5.5 $\tau$  for tertiary C-H protons agreed with the proposed structures and stereochemistry (table 1).

### EXPERIMENTAL

MP: Open capillaries in sulphuric acid bath (uncorr.)

IR spectra: Perkin-Elmer 577 spectrophotometer. PMR: Varion EM 360L spectrophotometer (chemical shifts in  $\tau$  scale).

MS: Jeol JMS-D 300, TLC on silica gel G plates. Tellurium metal powder (200 mesh) from ASARCO Inc., New York, USA.

1.  $\alpha$ -Bromopropiofenone: It was prepared by the reported method.
2.  $\alpha, \alpha'$ -bis(propiofenone) tellurium dibromide (I), diiodide (II): These were prepared by heating  $\alpha$ -bromopropiofenone with tellurium powder, for II with sodium iodide.
3.  $\alpha, \alpha'$ -bis(propiofenone) tellurium dipseudohalide/amino dithiocarbamate (III-V): These were prepared by refluxing the compound (II) with silver/ammonium salts of pseudohalides/amino dithiocarbamates in a suitable solvent.
4.  $\alpha, \alpha'$ -bis(propiofenone) tellurium diamino dibromide (adducts) (VI-X): These were prepared by refluxing compound (I) with appropriate amines in dichloromethane for  $\sim 6$  h.

IR (CsI,  $\nu_{\text{max}} \text{ cm}^{-1}$ ): C=O ( $\sim 1680$ ): C-H ( $\sim 1350$ ): Te-C ( $\sim 500$ ) Te-N ( $\sim 420$ ) and Te-S ( $\sim 280$ ): PMR ( $\text{CDCl}_3 + \text{DMSO-d}_6$ )  $\tau$ 3.1-1.4 (m, 10H, Ar-H),  $\tau$ 8.3-7.4 (Q, 3H, CH<sub>3</sub>);  $\tau$ 7.6-6.8 (Q, 3H, CH<sub>3</sub>);  $\tau$ 10-9 (S: Te-H). No M<sup>+</sup> was observed. Base peak (100%) for C<sub>6</sub>H<sub>5</sub>CO<sup>+</sup> at m/e 105. Te at m/e 128 (30%). In case of compound IX base peak (100%) for C<sub>4</sub>H<sub>9</sub>NO<sup>+</sup> at 87, m/e 105 (30%); C<sub>6</sub>H<sub>5</sub>CO<sup>+</sup>: m/e 128 (50%) Te and m/e 80 (15%) Br.

### Biological screening

All the compounds have been evaluated for their *in vitro* antibacterial activity against *Bacillus subtilis*, *Bacillus pumilus*, *Staphylococcus aureus*, *Salmonella typhi*, *Escherichia coli* and antifungal activity against *Aspergillus niger* and *Rhizopus nigrican*. Tetracycline HCl and Amphotericin B were used as control in antibacterial and antifungal tests respectively. All

Table 1 Physical constraints of  $\alpha,\alpha'$ -bis(propiofenone) tellurium dihalides, pseudohalides and adducts

Compound No	R	X	m p. °C	Yield %	Molecular formula	Elemental analysis found (calc.) %			
						Te	C	H	N
1	—	Br	110 <sup>a</sup>	45	C <sub>18</sub> H <sub>18</sub> O <sub>2</sub> TeBr <sub>2</sub>	23.00 (23.04)	39.00 (39.01)	3.23 (3.25)	—
2	—	I	180 <sup>b</sup>	60	C <sub>18</sub> H <sub>18</sub> O <sub>2</sub> TeI <sub>2</sub>	19.68 (19.70)	33.32 (33.35)	2.74 (2.77)	—
3	—	NCS	127	60	C <sub>20</sub> H <sub>18</sub> O <sub>2</sub> N <sub>2</sub> TeS <sub>2</sub>	25.01 (25.03)	47.07 (47.09)	3.50 (3.53)	5.45 (5.49)
4	—	Piperidine di-thiocarbamate	134	60	C <sub>30</sub> H <sub>38</sub> O <sub>2</sub> N <sub>2</sub> TeS <sub>4</sub>	17.88 (17.88)	50.40 (50.44)	5.30 (5.32)	3.86 (3.92)
5	—	antinedithiocarbamate	120	60	C <sub>32</sub> H <sub>30</sub> O <sub>2</sub> N <sub>2</sub> TeS <sub>4</sub>	17.45 (17.48)	52.64 (52.63)	4.09 (4.11)	3.81 (3.83)
6	Pyrrolidino-	Br	174	65	C <sub>26</sub> H <sub>36</sub> O <sub>2</sub> N <sub>2</sub> TeBr <sub>2</sub>	18.31 (18.34)	44.82 (44.95)	5.15 (5.17)	4.01 (4.02)
7	Piperidino-	Br	210	67	C <sub>28</sub> H <sub>40</sub> O <sub>2</sub> N <sub>2</sub> TeBr <sub>2</sub>	17.60 (17.63)	46.41 (46.43)	5.50 (5.52)	3.84 (3.86)
8	Morpholino-	Br	183	70	C <sub>26</sub> H <sub>36</sub> O <sub>4</sub> N <sub>2</sub> TeBr <sub>2</sub>	17.51 (17.53)	42.84 (42.88)	4.92 (4.94)	3.81 (3.84)
9	Diethylamino-	Br	207	60	C <sub>26</sub> H <sub>40</sub> O <sub>2</sub> N <sub>2</sub> TeBr <sub>2</sub>	18.19 (18.23)	44.53 (44.59)	5.69 (5.71)	3.96 (4.00)
10	Pyridino-	Br	140	64	C <sub>28</sub> H <sub>28</sub> O <sub>2</sub> N <sub>2</sub> TeBr <sub>2</sub>	17.90 (17.93)	47.19 (47.21)	3.91 (3.93)	3.90 (3.93)

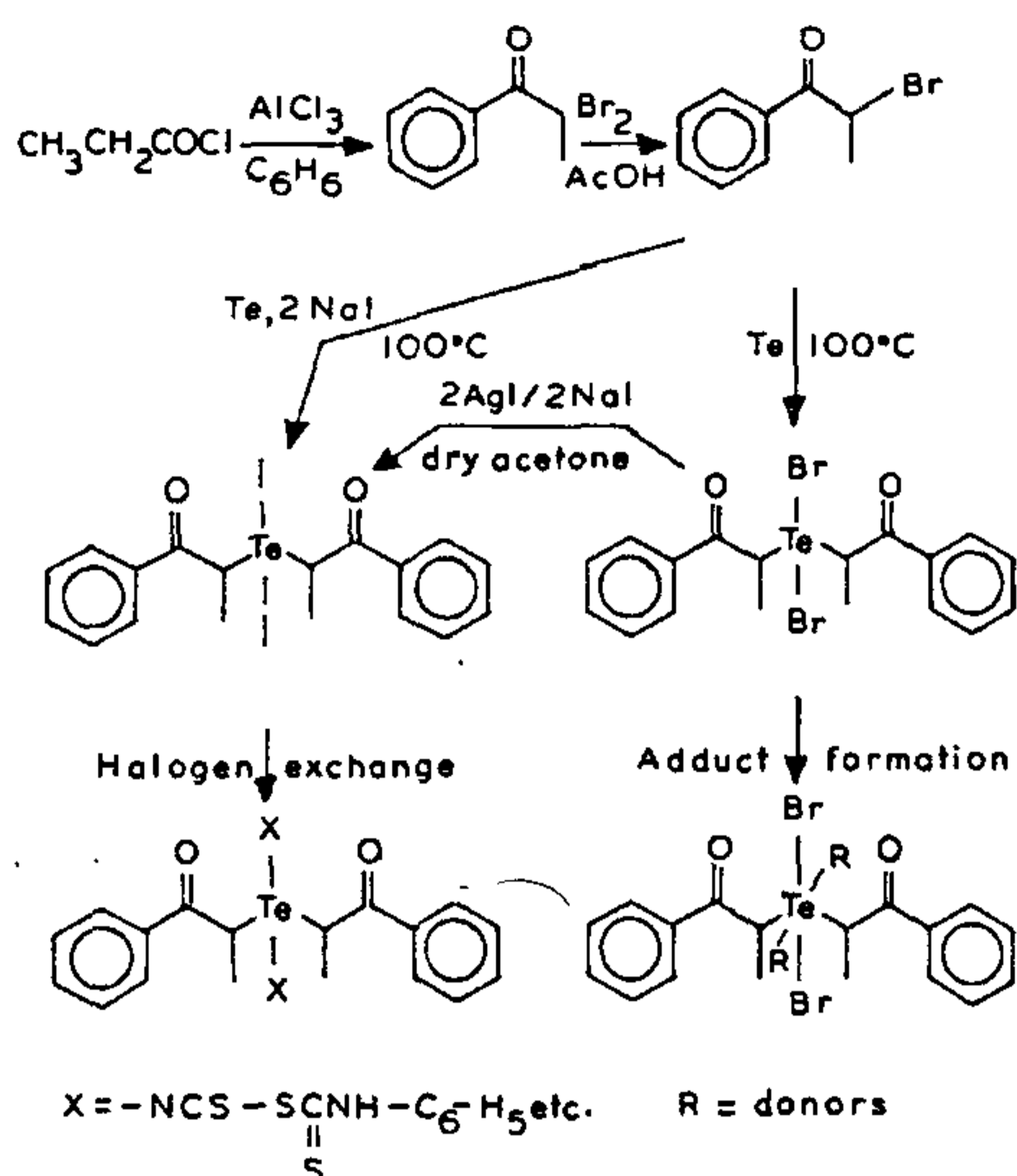
a &amp; b = decomposed.

Table 2 Biological activity data of organotellurium compounds (1-10)

Compound No.	Antibacterial activity					Antifungal activity		AChE activity	
	Mean area inhibition after 24 h					% inhibition of fungus Colony after one week		% inhibition 5 × 10 <sup>-4</sup> M ALD <sub>50</sub> mg/kg (i.p.)	
	<i>B. subtilis</i>	<i>B. pumilus</i>	<i>S. aureus</i>	<i>S. typhi</i>	<i>E. coli</i>	<i>A. niger</i>	<i>R. nigrican</i>		
1	c	c	c	b	d	52	41	78.38	> 1000
2	b	c	d	b	b	48	39	64.85	> 1000
3	a	a	—	—	a	68	25	21.34	464
4	—	—	a	a	—	64	36	33.31	825
5	b	a	a	—	a	59	46	42.21	681
6	c	c	b	c	b	48	35	78.25	1000
7	b	c	b	c	d	36	47	61.28	1000
8	c	b	b	d	c	46	53	77.36	> 1000
9	c	c	d	c	d	39	28	60.45	> 1000
10	b	b	d	b	c	51	38	34.92	> 1000
Tetracycline HCL/Amphotericin B	d	d	d	d	d	(88)	(86)	—	—

Inhibition zone (—) = no inhibition; (a) = Zone size 6–8 mm; (b) = 8–10 mm; (c) = 10–12 mm; (d) = &gt; 12 mm.



$\alpha, \alpha'$ -Bis(propiofenone) tellurium derivatives

these compounds were also evaluated for their cholinesterase enzyme inhibitory activity on rat brain homogenate. The results are summarized in table 2.

*Antibacterial assay*

Agar diffusion techniques<sup>14,15</sup> were employed to determine the antibacterial spectrum. In this method a standard 5 mm diameter sterile filter paper disc impregnated with the compound (10 mg/ml) was placed on agar plate seeded with the test organism. The seeded plates were incubated for 24 h at 37°C and then the zone of inhibition of bacterial growth around the disc was measured. In each case three replications were carried out.

*Antifungal assay*

The antifungal activity was evaluated by agar growth techniques<sup>16</sup> which in brief involves the mixing of the toxicants with synthetic agar medium and allowing the planted fungus to grow on it. The activity was determined at a concentration of 1:1000. The number of replications in each case was three. The average percentage inhibition given by each compound after one week was observed.

Percentage inhibition =  $[(C - T) / C] \times 100$ , where  $C$  is the diameter of fungal colony (in mm) in control petri dish and  $T$  is the diameter of fungal colony (in mm) in test compounds.

*Lethal dose (ALD<sub>50</sub>) in mice*

The method of Horn<sup>17</sup> was used to determine the approximate lethal dose in mice. An initial dose of 464 mg/kg of the compounds (later varied depending on the mortality) was administered i.e. in groups of 4 albino mice each of either sex, each weighing between 16 and 20 g, which were fasted for 24 h. The mortality was recorded at the end of 24 h.

*AChE activity*

This activity was determined according to the method of Parmar *et al*<sup>18</sup>.

## RESULTS AND DISCUSSION

Results indicate that compounds 1, 2, 6, 7, 8, 9 and 10 exhibit considerable activity against bacteria, while the rest show low activity (table 2). The data clearly demonstrated that the parent and the adducts were more toxic to bacteria rather than pseudohalides and dithiocarbamates. The above compounds can probably penetrate the bacterial cell-wall producing degeneration of bacterial cell thus inhibiting the growth of bacteria.

It is likely that the site of interaction responsible for the bacteriocidal properties of the compounds is unaffected by the adducts, hence the adducts and the parent compounds have similar activities.

The antifungal screening results reveal that in general, all the compounds possess marked growth inhibition of the fungal colony at 1000 ppm concentration. The inhibition ranges from 68 to 25% of the different strains used. *A. niger* was more susceptible to almost all the compounds. Compounds 1, 2, 6, 7, 8 and 9 were most active as acetylcholinesterase (AChE) inhibitory agents, while 3, 4, 5 & 10 were moderately active. The results of screening activity showed that as the coordination number of tellurium was increased from +4 to +6, the activity was enhanced quite rapidly. Replacement of halogen atom like Br or I by -CNS or aminodithiocarbamate reduces the activity. There was no definite structure-activity correlation in the fungicidal screening though all the compounds exhibited considerable activity.

AChE results clearly indicated that the presence of halogen group like Br or I with metal increases the activity; on the contrary the pseudohalogen decreases the activity. Adducts were found to be highly active probably due to the donation of electron by the donor atoms to tellurium in the presence of a halogen like bromide but in the case of

adducts with pyridine the activity was reduced due to back bonding through extensive  $\pi$  bonds.

The compounds had high LD<sub>50</sub> values, e.g., > 1000 mg/kg for 1, 2, 8, 9 and 10 indicating that the halides and adducts viz. morpholino, diethylamino and pyridino were non toxic; due to strong biocidal activity, they can be used as effective biocidal agents. Compounds 6 & 7 had an LD<sub>50</sub> of 1000 mg/kg and found to have high bacteriocidal and AChE activity, while compounds 3, 4 & 5 had LD<sub>50</sub> values between 464 and 825 and toxic probably due to the thiocyanate and dithiocarbamate groups.

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## ANNOUNCEMENT

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1988 heralds the silver jubilee year of the Society. The President and the Members of the Society feel that to honour Prof. T. L. Ramachar and his contributions in electrochemistry, it is befitting to create an endowment fund to conduct "T. L. Ramachar Memorial Lecture", from the interest earned out of the endowment fund. The Lecture will be in one of the areas of "Electrochemical Science and Technology" to be organized once a year. For this purpose the Society needs a reserve fund of

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