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Thiopicolinamide Complexes of Selenium and Tellurium: A Structural and Pharmacological Study

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Complexes of selenium(IV) and tellurium(IV) with thiopicolinamide were synthesized and characterized by elemental analyses, conductivity measurements, and infrared and nuclear magnetic resonance spectroscopic data. The complexes were shown to have 1:2 (metal:chelate) stoichiometry with a coordination number of six or eight. These complexes are biologically important as indicated by pharmacological tests.

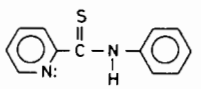
Introduction

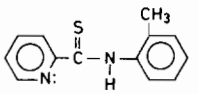
Thiopicolinamides are bidentate ligands exhibiting a variety of biological activities including antibacteriostatic [1, 2], antifungal [3], antitubercular [4, 5] and hypoglycemic [6]. In recent years, several complexes of thiopicolinamides have been investigated [7–10], but no systematic work has been done on the selenium and tellurium complexes.

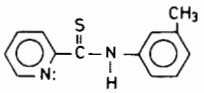
In this study, thiopicolinamide complexes of selenium and tellurium were synthesized, and subsequently characterized by elemental analysis, infrared (IR) and nuclear magnetic resonance (NMR) spectroscopy and conductivity measurements. Pharmacological tests were performed in order to evaluate the hypoglycemic and anti-inflammatory activity of the thiopicolinamides and their selenium and tellurium complexes.

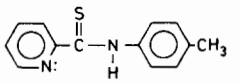
Experimental

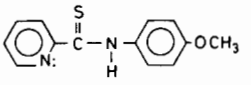
All the chemicals used in this work were of reagent grade. Thiopicolinanilides were prepared according to a procedure described earlier by Porter [11]. 0.020 mol of the corresponding substituted aniline, 0.010 mol of picolinic acid, and 0.015 mol of sulfur were heated in an oil bath maintained at 160–180 °C for 48 hours. Volatile unreacted starting materials were removed by vacuum distillation. The thiopicolinanilide was then dissolved in ethanol and the solvent removed by rotary evaporation. The resulting solid was then recrystallized using a benzene-hexane mixture. An identical procedure was used for the synthesis of the N(α-pyridyl)thiopicolinamide except that 2-amino pyridine was used as a reactant instead of a substituted aniline for the formation of the amide linkage. The following thiopicolinamides were prepared:

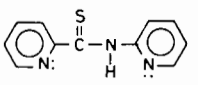
A.  thiopicolinanilide

B.  N-(2-methylphenyl)-thiopicolinamide

C.  N-(3-methylphenyl)-thiopicolinamide

D.  N-(4-methylphenyl)-thiopicolinamide

E.  N-(4-methoxyphenyl)-thiopicolinamide

F.  N-(α-pyridyl)-thiopicolinamide

The selenium(IV) and tellurium(IV) complexes were prepared by mixing the respective metal tetrachloride with the picolinamide in dry benzene in the

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TABLE I. Analytical and Physical Data for Selenium and Tellurium Complexes.[a]

Ligand	Complex Number	Empirical formula of the complex	M.P. °C	%M[b]	%N	%Cl	%S	Molar Cond. (ohm^{-1} cm^2 mol^{-1})
C	I	$(C_{13}H_{11}N_2S)_2SeCl_2$	140	13.02 (13.07)	9.28 (9.27)	11.70 (11.76)	10.59 (10.60)	156.20
D	II	$(C_{13}H_{11}N_2S)_2SeCl_2$	170–75	13.10 (13.07)	9.19 (9.27)	11.73 (11.76)	10.50 (10.60)	156.20
E	III	$(C_{13}H_{11}N_2OS)_2SeCl_2$	90	12.33 (12.42)	8.84 (8.81)	11.21 (11.16)	10.10 (10.06)	150.04
F	IV	$(C_{11}H_8N_3S)_2SeCl_2$	140	13.60 (13.66)	14.57 (14.53)	12.29 (12.28)	11.08 (11.07)	156.60
A	V	$(C_{12}H_{10}N_2S)_2TeCl_4$	227	18.88 (18.84)	8.28 (8.27)	21.00 (20.96)	9.42 (9.45)	153.44
B	VI	$(C_{13}H_{12}N_2S)_2TeCl_4$	77	17.60 (17.59)	7.78 (7.72)	19.59 (19.57)	8.82 (8.82)	175.41
C	VII	$(C_{13}H_{12}N_2S)_2TeCl_4$	88	17.60 (17.59)	7.68 (7.72)	19.52 (19.57)	8.80 (8.82)	176.00
D	VIII	$(C_{13}H_{12}N_2S)_2TeCl_4$	107	17.58 (17.59)	7.83 (7.72)	19.59 (19.57)	8.90 (8.82)	180.42
E	IX	$(C_{13}H_{12}N_2OS)_2TeCl_4$	210	17.76 (17.79)	7.80 (7.81)	19.80 (19.79)	8.90 (8.92)	149.44
F	X	$(C_{11}H_9N_3S)_2TeCl_4$	230	18.19 (18.24)	12.05 (12.01)	20.35 (20.30)	9.09 (9.15)	140.49

[a]Figures in parenthesis are calculated values. [b]M = Se or Te respectively.

molar ratio of 1:2. Table I correlates each ligand A–F with its corresponding selenium(I–IV) or tellurium-(V–X) complex.

The resulting complex was then filtered, washed repeatedly with anhydrous benzene using a Soxhlet extractor, and finally dried under vacuum over P_2O_5.

Elemental analyses were carried out by a procedure discussed elsewhere [12]. Selenium and tellurium were determined as their respective metals. Chlorine was determined as the silver chloride precipitate, while sulfur was determined as the barium sulfate salt. The method of Kjeldahl was used to determine the nitrogen content of the complexes.

Conductivities were measured in dimethylformamide (DMF) using an Elico-CM-82 conductivity bridge with a cell having a cell constant of 0.829 cm^{-1}. All conductivity measurements were performed at room temperature using 10^{-3} *M* solutions of complex.

The infrared spectra (IR) from 4000 to 200 cm^{-1} were obtained using a Perkin-Elmer 180 spectrophotometer. Samples were prepared as KBr pellets. Proton magnetic resonance (PMR) spectra were recorded using a S-60-C PMR instrument. All PMR samples were dissolved in deuterated dimethylsulfoxide (d_6-DMSO), and tetramethylsilane (TMS) was used as the internal standard.

Pharmacological Tests

The hypoglycemic activity tests were carried out using albino rats which had been fasting for 48 hours prior to dosage. 20 mg/kg body weight (selenium complexes) and 100 mg/kg body weight (tellurium complexes) were administered to the rats. Blood samples were retrieved by cardiac puncture four hours after the administration of the test compounds. The sugar content was determined by the Nelson–Somogyi method [13]. Tolbutamide was used as a reference compound in order to assess the pharmacological activity of the thiopicolinamides and their complexes.

The anti-inflammatory activity test was carried out by using the carrageenan induced rat paw edema assay of Winter *et al.* [14]. 20 mg/kg body weight was found to be a safe dose level for thiopicolinamide complexes of selenium(IV) in acute toxicity studies.

Results and Discussion

Analytical Data

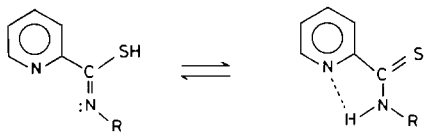
All the complexes are colored and amorphous in nature, and they are soluble in common organic solvents. Except for complex X, all are soluble in DMF and DMSO. The selenium complexes are

hygroscopic. The elemental analyses (see Table I) agree well with 1:2 (metal:chelate) stoichiometry. The molar conductivities are in the range, 140–181 ohm^{-1} cm^2 mol^{-1} suggesting 1:2 electrolyte behavior.

Infrared Spectra

Important infrared frequencies and their assignments are tabulated and available upon request from the author to whom all correspondence should be addressed.

Thiopicolinanilides are capable of exhibiting thiol–thione tautomerism:



I II

Earlier studies with copper–thiopicolinanilide complexes show that the ligand exists as structure II in the complex, and that the pyridyl nitrogen coordinates to the copper [15]. Furthermore, IR and NMR data show that the structure II is more stable than I because of intramolecular hydrogen bonding [16]. Therefore it is presumed that structure II will be the most likely canonical form for coordination to selenium and tellurium.

In the ligands A–F the absorption band observed around 3225–3210 cm^{-1} is assigned to the N–H stretching vibration. The band between 1575 and 1610 cm^{-1} is assigned to the C⁚⁚N stretch of the picolinic moiety [17]. The bands around 1600–1500 cm^{-1} are assigned to a variety of carbon–carbon stretches in the picolinic and anilinic moieties and to the C–N stretch of the thioamide linkage. The C=S stretches of the thioamide group are seen in the regions 1420–1440 cm^{-1} and 1200–1225 cm^{-1}. The peaks in the region 985–990 cm^{-1} are due to a picolinic ring breathing vibration. The peaks appearing between 725 and 790 cm^{-1} are ascribed to out-of-plane C–H bending vibrations [17].

In all of the complexes, a peak appears at 3330 cm^{-1} instead of at 3210 cm^{-1}. This shift to higher frequency indicates that the coordination to the selenium or tellurium takes place through the nitrogen of the thioamide group. The band around 1610 cm^{-1} that has been assigned to the C–N stretch of the picolinic moiety in the ligand shifts to a higher frequency in the complexes indicating coordination has taken place through the picolinic nitrogen. The bands due to C=S stretches do not vary indicating that the sulfur does not participate in chelation.

Proton Magnetic Resonance Spectra

PMR chemical shifts of the ligands and complexes are depicted in Table II. In the ligands, signals observed in the region 7.0 to 9.4 ppm, are due to phenyl and pyridyl ring protons. The signal observed at 3.36 ± 0.01 ppm is due to the proton of the thioamide group. The sharp signal of 2.3–2.4 ppm is due to methyl proton absorptions. The spectra of the complexes show signals in the region 6.70 to 10.00 ppm. There is a variation in the total range assigned to phenyl and pyridyl ring proton absorptions. This supports the infrared data which indicates that the metal ion is coordinated through the pyridyl nitrogen. The signal at 3.36 ppm in the ligand is shifted downfield in all the complexes. This downfield shift is due to the participation of the thioamide nitrogen in the coordination to selenium and tellurium. In some cases, a weak, broad signal is observed around 12.0 ppm in the ligands. This is due to the tautomeric thiol form of the thiopicolinamide.

Pharmacological Tests

The hypoglycemic activity of thiopicolinamides and their corresponding complexes with selenium(IV) and tellurium(IV) are listed in Table III. Tolbutamide at a dosage level of 200 mg/kg of body weight, lowered the blood glucose level in this system to 46.8%. The results were expressed as a percentage difference between the mean change in the control and the mean change in the treated groups, four hours after administration.

TABLE II. Proton Magnetic Resonance Chemical Shifts[a] of Thiopicolinamides and their Selenium(IV) and Tellurium(IV) Complexes.

D	II	VIII	F	IV	X	Assignments
3.35	3.43	3.45	3.37	3.62	4.10	Thioamide proton
7.10 to 8.80	6.70 to 8.83	6.70 to 8.83	7.00 to 9.43	7.67 to 9.00	7.00 to 10.00	Phenyl and pyridyl protons
2.35	2.37	2.30	–	–	–	Methyl protons

[a]In ppm (δ) relative to TMS.

TABLE III. The Effect of Thiopicolinamides and their Corresponding Selenium and Tellurium Complexes on the Blood Glucose Levels of Rats.

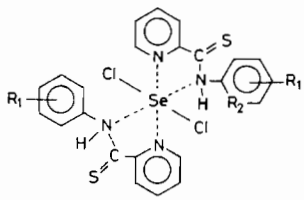
Ligand/Complex	Mg of Glucose per 100 ml of Blood	Percentage Change
A	161.5	+11.6
D	176.9	+22.3
E	192.3	+32.9
F	182.5	+26.1
II	131.1	−09.4
III	38.4	−73.4
IV	100.0	−30.9
V	148.7	+02.8
VIII	243.6	+68.3
IX	123.1	−14.3
X	150.0	+03.7
Tolbutamide (Reference)	76.9	−46.8
Control	144.7	–

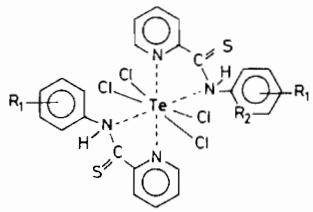
Thiopicolinanilide, N-(4-methylphenyl)thiopicolinamide, N-(4-methoxyphenyl) thiopicolinamide, and N-(α-pyridyl)thiopicolinamide (A,D,E,F) do not exhibit any hypoglycemic activity when compared with tolbutamide. Similarly, the selenium complex of N-(4-methylphenyl)thiopicolinamide (II) and all the tellurium complexes evaluated (V, VIII, IX, X) show limited or no hypoglycemic activity. The selenium complexes formed with N-(4-methoxyphenyl)thiopicolinamide (III) and N-(α-pyridyl)thiopicolinamide (IV) exhibit pronounced hypoglycemic activity when compared with the reference hypoglycemic agent, tolbutamide.

The antiinflammatory activity of the selenium complexes of thiopicolinamides are listed in Table IV, together with the antiinflammatory activity of the phenylbutazone standard. Four percent gumacacia was used to induce edema as described in the procedure of Winter *et al.* The N-(α-pyridyl)thiopicolinamide complex of selenium has significant antiinflammatory activity, whereas the N-(4-methylphenyl)thiopicolinamide and the N-(4-methoxyphenyl)thiopicolinamide complexes of selenium show mild antiinflammatory activity as measured by the inhibition of edema when compared to phenylbutazone.

Conclusions

Some thiopicolinamide complexes of selenium and tellurium have been prepared. The analytical data suggest that the complexes have 1:2 (metal/chelate) stoichiometry. The conductance measurements indicate that the complexes are 1:2 electrolytes. The IR and PMR data indicate that the thioamide nitrogen and the pyridyl nitrogen of the thiopicolinamide chelating agent coordinate with selenium and the tellurium. On the basis of the above information it appears that the selenium complexes are six-coordinate and the tellurium complexes are eight-coordinate. The following tentative structures are proposed:





These structures are similar to those proposed previously for sulfonamide-Schiff bases of selenium and tellurium [18] and aromatic imine complexes of selenium and tellurium [19].

Acknowledgements

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TABLE IV. Antiinflammatory Activity of Thiopicolinamide Complexes of Selenium.

	Complex/Compound	Dose level in mg	Initial reading	Reading after 3 hr	Edema Formed	% Inhibition
1	IV	4.00	6.40	8.48	2.08	40.57
2	II	4.00	6.80	9.44	2.64	24.57
3	III	4.00	7.00	9.62	2.62	25.14
4	Phenylbutazone (standard)	5.00	5.00	5.88	0.83	80.00
5	4% Gumaceria	–	6.20	9.70	3.50	–

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