Pergamon

PII: S0277-5387(97)00107-1

Polyhedron Vol. 16, No. 20, pp. 3625–3633, 1997

0277-5387/97 $17.00+0.00

Palladium(II) complexes of 2-acetylpyridine N(4)-propyl, N(4)-dipropyl- and 3-hexamethyleneiminylthiosemicarbazones with potentially interesting biological activity. Synthesis, spectral properties, antifungal and *in vitro* antitumor activity

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(Received 28 January 1997; accepted 5 March 1997)

Abstract—Some new palladium(II) complexes of 2-acetylpyridine N(4)-propyl- and N(4)dipropyl- and 3-hexamethyleneiminylthiosemicarbazones with potentially interesting biological activity were described. The thiosemicarbazones and their palladium(II) complexes have been characterized by spectroscopic, and electrochemical techniques. The protonation constants of HAc4P K_{a1} and K_{a2}, were determined by spectrophotometry and the pK_{1a} and pK_{a2} values are equal to 12.23 ± 0.02 and 4.11 ± 0.02. The antifungal properties and the effect selected compounds on DNA synthesis of P388 and L1210 cell cultures is reported. © 1997 Elsevier Science Ltd

Keywords: new palladium complexes; 2-acetylpyridine thiosemicarbazones; antitumor activity.

Heterocyclic thiosemicarbazones (TSCs) have aroused considerable interest in chemistry and biology due to their antibacterial, antimalarial, antineoplastic and antiviral activities and represent an important series of compounds because of potentially beneficial, biological activity [1]. In some cases the highest *in vivo* activity is associated with a metal complex rather than the parent TSC [2a]. It is likely that the biological activity is due to the ability to form terdentate chelates with essential heavy metal ions bonding through a sulfur and two nitrogen atoms [2b]. Structural alterations that hinder a TSC's ability to function as a chelating agent with metal ions tend to destroy or reduce its medicinal activity [2c].

We have initiated an investigation on complexes of palladium(II) in an effort to correlate structure with biological activity [3]. This report includes newly prepared palladium(II) complexes of 4N-propyl-2-acetyl pyridine thiosemicarbazone (HAc4P), 4N-dipropyl-2-acetyl pyridine thiosemicarbazone (HAc4DP) and 3-hexamethyleneiminylthiosemicarbazone (HAchexim) (Fig. 1). This work is an extension of previously studied palladium(II) complexes of 2-acetylpyridine TSC [3a] and 2-acetylpyridine N(4)-substituted with smaller substituents [3b], as well as copper(II) [4a], nickel(II) [4b] and cobalt(II) [4c] complexes of these TSCs. Synthetic, spectroscopic, electrochemical and biological studies have been carried out in order to obtain information on structure–activity relationships for systems involving palladium(II) atoms.

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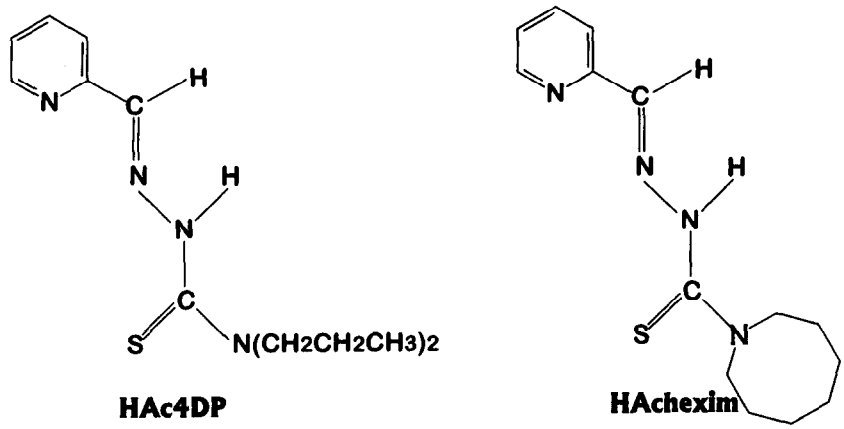


Fig. 1. The tautomeric forms of HAc4P, (R = $NHCH_2CH_2CH_3$), HAc4DP, {R = N $(CH_2CH_2CH_3)_2$} and HAchexim, [R = $N(CH_2)_6$].

RESULTS AND DISCUSSION

The complexes of Pd(II), were prepared according to the reactions (1)-(2), in methanolic or aqueous solutions in the pH range of 1–8.

$$Li_2[PdX_4] + HL \xrightarrow{CH_3OH} Pd(L)X + 2LiX + HX \quad \text{(where X = Cl or Br)} \quad (1)$$

$$Li_2[PdX_4] + 2HL \xrightarrow{CH_3OH/1.5MNH_4OH/H_2OpH=8} Pd(L)_2 + 2LiX + 2HX \quad (2)$$

Attempts to isolate complexes having the stoichiometry $[Pd(HL)_2X_2]$ and $[Pd(HL)X_2]$ were unsuccessful. The stoichiometry of the complexes prepared indicates that palladium(II) is coordinated by the single charged anion HAc4P, HAc4DP, and HAchexim, formed by loss of a proton from the thiol form of the ligands.

Table 1 lists the colors and elemental analyses of the palladium(II) complexes. All are diamagnetic and non-electrolytes, consistent with coordination of the halo ligands.

Spectral studies

Coordinaton of the azomethine nitrogen to palladium(II) is suggested by the shift of the ν(C=N) band to lower frequencies along with the occurrence of the μ(N—N) band to higher frequency in the IR spectra of the complexes compared to that in the ligand. The breathing motion of the pyridine ring is shifted to a higher frequency upon complexation and is consistent with pyridine ring nitrogen coordination.

Table 1. Colors and partial elemental analysis of the palladium(II) complexes of HAc4P, **1**, HAc4DP, **4**, and HAchexim, **8**

No	Compound	Color	Found C	Found H	(Calcd) N	% Pd	X
2	Pd(Ac4P)Cl	yellow	35.0	4.1	15.0	28.3	9.4
			(35.0)	(4.0)	(14.9)	(28.2)	(9.5)
3	(Pd(Ac4P)Br	orange	31.0	3.5	13.4	25.3	19.1
			(31.3)	(3.6)	(13.3)	(25.2)	(19.0)
5	Pd(Ac4DP)Cl	orange	40.2	5.1	13.2	25.5	8.6
			(40.1)	(5.0)	(13.4)	(25.6)	(8.5)
6	(Pd(Ac4DP)Br	orange	36.2	4.5	12.3	23.2	17.2
			(36.3)	(4.6)	(12.1)	(23.1)	(17.2)
7	$Pd(Ac4DP)_2$	red	51.0	6.3	17.0	16.1	0.0
			(50.9)	(6.4)	(17.0)	(16.2)	(0.0)
9	Pd(Achexim)Cl	orange–yellow	40.1	4.8	13.2	25.0	8.6
			(40.3)	(4.7)	(13.4)	(25.5)	(8.5)
10	Pd(Achexim)Br	orange–yellow	36.3	4.3	12.4	22.7	17.0
			(36.4)	(4.2)	(12.1)	(23.0)	(17.3)
11	$Pd(Achexim)_2$	yellow	52.0	5.8	17.2	16.0	0.0
			(51.2)	(5.8)	(17.1)	(16.2)	(0.0)

Table 2. IR spectra assignments of HAc4P, **1** HAc4DP, **4**, and HAchexim, **8** and their palladium(II) complexes

No	ν(CN)	ν(NN)	ν(CS)	ρ(op)	ρ(ip)	ν(PdN)	η(PdS)	ν(PdCl)
1	1582s	1042m	880m	598m	402ms			
2	1560s	1072m	830m	615mw	430m	480w	380w	
3	1560s	1072m	830m	615mw	430m	480w	380w	
4[a]	1613ms	1038m	866m	615m	401ms			
5	1598s	1150s	832m	636ms	422ms	475w	382m	358s
6	1600ms	1080s	835m	635ms	423ms	500ms	400w	
7	1598s	1138s	822mw 780sh	625m	411m	505m	360w	
8[b]	1582ms	1036m	838mw	595mw	402ms			
9	1570ms	1080ms	820m	618mw	420m	501m	390vw	356ms
10	1556ms	1078ms	821m	620mw	418m	500m	390w	
11	1555ms	1082ms	785s 820m	618m	421m	475w	400mw 380w	

[a] Ref. [4a].
[b] Ref. [4b].

The thioamide IV band, which contains considerable ν(CS) character, is less intense in complexes and are found at a lower frequency, suggesting coordination of the metal through sulfur after deprotonation. Table 2 summarizes these bands assignments, as well as ν(PdN, azomethine), ν(PdS), and ν(PdX) [3,4].

The significant electronic absorption bands in the spectra of the complexes are presented in Table 3. The DMF solution spectra of the TSCs and their palladium(II) complexes exhibit a $\pi \rightarrow \pi^*$ band in the 37,000 cm^{-1} region, a pyridyl ring $n \rightarrow \pi^*$ band in the 32,000 cm^{-1} region, and a $n \rightarrow \pi^*$ band in the 25,000 cm^{-1} region due to the thiosemicarbazone moiety; this band is shifted to higher energy in the spectra of the metal complexes. The very intense band at *ca* 22,000 cm^{-1} in the palladium(II) complexes' spectra is reasonably assignable to a combination of sulfur → Pd^{II}, nitrogen (pyridyl) → Pd charge transfer and Pd^{II} d–d bands [3,5].

Results of the ^1H and ^{13}C NMR studies of these palladium(II) complexes are shown in Table 4. The N.M.R. spectra of the TSCs HAc4DP, **3** and Hachexim **8,** in d^6-DMSO confirm that there are two isomers Z and E, the hydrogen bonding Z isomer is present in greater amount; it has the lower field methyl signal (>2.5). The Z:E ratios for HAc4DP, **3** and Hachexim **8,** are *ca* 3:1 in DMSO [6a,b]. Both ^6CH and the acetyl methyl, $(CH_3)C$, are shifted considerably on coordination of TSCs to palladium(II), indicative of variation in the electron density at position 6 and 7. The absence of peaks corresponding to the imino protons, N(3), in these complexes indicates that the ligand is present in the deprotonated form. Of note is that these complexes, **7** and **11** which have two anionic TSCs per palladium(II) center, show a single peak for each of the hydrogens of the coordinated thiosemicarbazones indicating that the tridentate and monodentate ligands are rapidly interchanging in solution. Spectra recorded in $CDCl_3$, at lower temperatures −20°C and −26°C, for $[Pd(Ac4DM)_2]$, where Ac4DM is the monodeprotonated anion of 2-acetylpyridine-N(4)-dimethylthiosemicarbazone, show that a peak at δ 1.841 is assignable to the tridentate ligand and δ 2.069 to the monodentate ligand based on the observation that this peak appears further downfield in the uncomplexed thiosemicarbazone [3b].

Electrochemical studies

Electrochemical oxidation and reduction was studied in DMF solution using cyclic voltammetry (Table 4). Tetrabutylammonium perchlorate (0.1 M) was used as supporting electrolyte in DMF solution and the solutions were 1×10^{-3} M in complex. All potential are relative to the normal hydrogen electrode (NHE) using the reversible ferrocene/ferrocenium couple (+0.400 V *vs* NHE, ΔE_p = 90 mV at 100 mV s^{-1}) as a standard. The reduction and oxidation peaks of the C.V. of TSCs and their Pd^{II} complexes have been identified and denoted by capital letters. The cyclic voltammograms of TSCs show only waves near the more negative margin. This wave may be attributed to the reduction of the conjugated portion of the thiosemicarbazone ligand [7a,b]. The peak C is associated to the reduction of the conjugated portion of the coordinated thiosemicarbazone ligand [7b,c,3b] and is followed by the oxidation peaks D, F and G, which are probably due to coupled chemical oxidations (Fig. 2) [7c,3b]. The main reduction peak B and its counterpart E are reversible for PdL_2 adducts (**7** and **11**) and irreversible for PdLX adduct (**3**). These two peaks are assigned to represent the reduction of Pd^{II}/Pd^{I}, B, and the subsequent oxidation of Pd^{I}, as shown in previous electrochemical studies for similar

Table 3. Electronic spectra (cm^{-1}) of the palladium(II) complexes of HAc4P, HAc4DP, and HAchexim in DMF

Compound	Solution spectra (log ε)	Assignment
2	37.700 (3.98)	$\pi \rightarrow \pi^*$
	32.180 (4.13) 27.650 (4.12) 26.710 (4.12)	$n \rightarrow \pi^*$
	21.520 (3.63)	$d \rightarrow d$ and L $\rightarrow$ MCT
3	37.730 (4.01)	$\pi \rightarrow \pi^*$
	32.200 (4.06) 27.940 (4.07) 26.390 (4.07)	$n \rightarrow \pi^*$
	21.580 (3.45)	$d \rightarrow d$ and L $\rightarrow$ MCT
4	37.860 (3.80)	$\pi \rightarrow \pi^*$
	33.110 (3.93) 27.850 (4.04) 24.720 (4.12)	$n \rightarrow \pi^*$
5	37.700 (3.96)	$\pi \rightarrow \pi^*$
	31.950 (4.07) 27.280 (4.12) 25.920 (4.13)	$n \rightarrow \pi^*$
	22.050 (3.60)	$d \rightarrow d$ and L $\rightarrow$ MCT
6	37.800 (4.02)	$\pi \rightarrow \pi^*$
	31.950 (4.07) 26.740 (4.16) 26.040(4.15)	$n \rightarrow \pi^*$
	22.300 (3.58)	$d \rightarrow d$ and L $\rightarrow$ MCT
7	39.900 (4.11) 34.855 (4.28)	$\pi \rightarrow \pi^*$
	31.075 (4.37) 27.100 (4.38) 26.730 (4.40)	$n \rightarrow \pi^*$
	21.430 (3.71)	$d \rightarrow d$ and L $\rightarrow$ MCT
8	37.800 (3.84)	$\pi \rightarrow \pi^*$
	33.110 (3.95) 28.650 (3.99) 24.720 (3.78)	$n \rightarrow \pi^*$
9	37.680 (3.91)	$\pi \rightarrow \pi^*$
	31.720 (4.01) 27.130 (4.03) 25.900 (4.08)	$n \rightarrow \pi^*$
	21.620 (3.64)	$d \rightarrow d$ and L $\rightarrow$ MCT
10	37.680 (4.01)	$\pi \rightarrow \pi^*$
	31.850 (4.05) 26.920 (4.12) 25.950 (4.13)	$n \rightarrow \pi^*$
	21.520 (3.65)	$d \rightarrow d$ and L $\rightarrow$ MCT
11	36.760 (4.08) 34.840 (4.31)	$\pi \rightarrow \pi^*$
	31.000 (4.37) 24.540 (4.39)	$n \rightarrow \pi^*$
	21.490 (3.71)	$d \rightarrow d$ and L $\rightarrow$ MCT

Table 4. ^1H and ^{13}C NMR spectral assignments for representative diamagnetic palladium(II) complexe (d^6-DMSO and $CDCl_3$)

Compound	$^6CH^a$	$(CH_3)C$	^aCH, ^bCH, ^cCH	^6C	$C{=}N$	$(CH_3)C$	$C{=}S$	^aCH, ^bCH, ^cCH
4[c]		2.53(75)						
		2.38(25)						
7[e]	8.277d	1.868	3.603t,	148.4	158.5	12.80	177.1	53.5
			1.765m					21.6
			0.934t					11.5
8[d]	8.72	2.48(75)	4.08					
		2.37(25)	1.96					
			1.6					
10[b]	7.898d	1.513	2.95br,					
			0.92					
			0.70					
11[c]	8.330d	1.944	3.861t,	148.4	158.6	13.00	182.8	51.4
			1.832					28.4
			1.619					27.1

[a] doublet.
[b] in d^6-DMSO insufficient solubility to record a measurable ^{13}C spectrum.
[c] Ref. [6a].
[d] Ref. [6b].
[e] in $CDCl_3$.

Table 5. Cyclic voltammetry data for the palladium(II) complexes in DMF solution containing 0.1 M tetrabutylammonium perchlorate (100 mV s^{-1})[a]

No	$E_{p,c}$(C)	$E_{p,c}$(B) reduction	$E_{p,a}$(H) oxidation
3	−1.90, −1.73	−1.42	+0.53
7	−1.9	$E^0 = -1.31$	+0.74
10	−1.81	−1.56	+0.71
11	−1.9	$E^0 = -1.45$	+0.66
$[Pd(Ac4DM)_2]$[b]	−1.47	$E^0 = -1.28$	+0.74
$[Pd(Et_2dtc)_2]$[c]		$E^0 = -1.50$	+1.49
$[Pd(Et_2dsc)_2]$[c]		$E^0 = -1.54$	+0.98
$[Pd(pyt)_2]_2$[d]			+0.763

[a] All potentials are relative to NHE.

[b] Where Ac4Dm is 2-Acetylpyridien-N(4)-Dimethylthiosemicarbazone. Ref. [3b].

[c] Where Et_2dtc is diethyldithiocarbamate, and Et_2dsc is diethyldiselenocarbamate Ref. [7d]

[d] Where pyt is pyridine-2-thiole, ref. [7e].

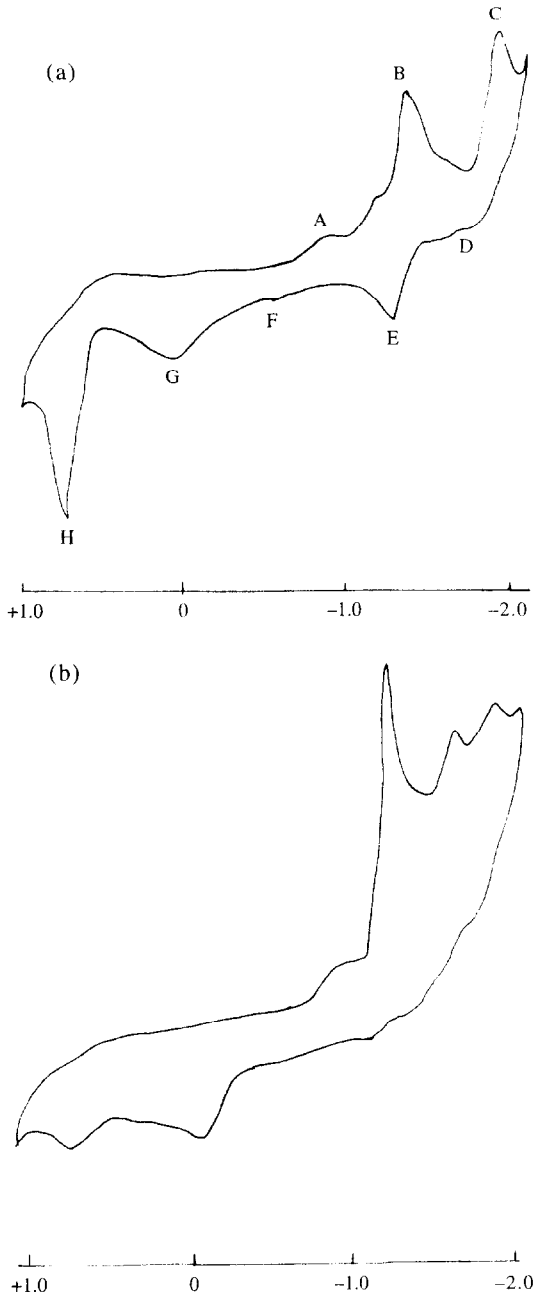


Fig. 2. Cyclic voltammograms (100 mV s^{-1}) (a) of **7** in DMF (1 mM) in the range +1.0 to −2.1 V and (b) **10** in DMF (1 mM) in the range +1.05 to −2.05 V. The quoted potentials are *vs* ferrocene/ferricinium.

complexes [3b,7d]. The separation between peak B and E at a scan rate of 100 mV s^{-1} is characteristic of a quasi-reversible one electron process. The first reversible reduction step, for PdL_2 complexes, requires greater energy as the 4N-substituent becomes bulkier and the approximate order is $Pd(Ac4DM)_2$; $E^0 = 1.28$ [3b] < $Pd(Ac4DP)_2$; $E^0 = -1.31$ < $Pd(Achexim)_2$; $E^0 = -1.45$. The peak H may be assigned to the one electron irreversible oxidation process palladium(II)/palladium(III) (Fig. 2) [7d,e,3b]. Previous electrochemical results indicted that irreversible oxidation of the palladium(II)/palladium(III) occurs in the case of $[Pd(pyt)_2]_2$ [7e] and of $Pd(R_2dtc)_2$ [7d]. It was indicated that the oxidation follows a complex electrode process, in which a rapid decomposition of the oxidation product Pd^{III} occurs [7e,d]. Further investigation is necessary to elucidate the mechanism.

Protonation constants

The protonation constants of HAc4P, K_{a1} and K_{a2} were determined by spectrophotometry, because of its low solubility in water and the high pK value of its first protonation constant (the very low solubility in water prevented the determination of the protonation constants of HAc4DP and HAchexim). HAc4P behaves both as a weak base and a weak acid, and in aqueous solutions there are three independent species. The equilibrium between the species is given from the equations below:

$$L^- + H_3O^+ \overset{K_{a1}}{\rightleftharpoons} HL + H_2O \quad (1)$$

$$HL + H_3O^+ \overset{K_{a2}}{\rightleftharpoons} HL^+ + H_2O \quad (2)$$

The protonation constants of the ligand, HAc4P, K_{a1} and K_{a2} were determined and pK_{a1} and pK_{a2} are equal to 12.23 ± 0.02 and 4.11 ± 0.02, respectively (Fig. 3). The pK_{a2} value is lower than that of pyridine (5.0) and higher than 2-acetylpyridine thiosemicarbazone (3.98). Compared to pyridine the lower value can be attributed to the decrease in electron density on the pyridine nitrogen caused by the electron-withdrawing effect of the thiureide group. The pK_{a2} value is higher than that of thiosemicarbazide (11.45) and 2-acetylpyridine thiosemicarbazone (11.43) and reveals that HAc4P behaves as a weak monoprotic acid. This

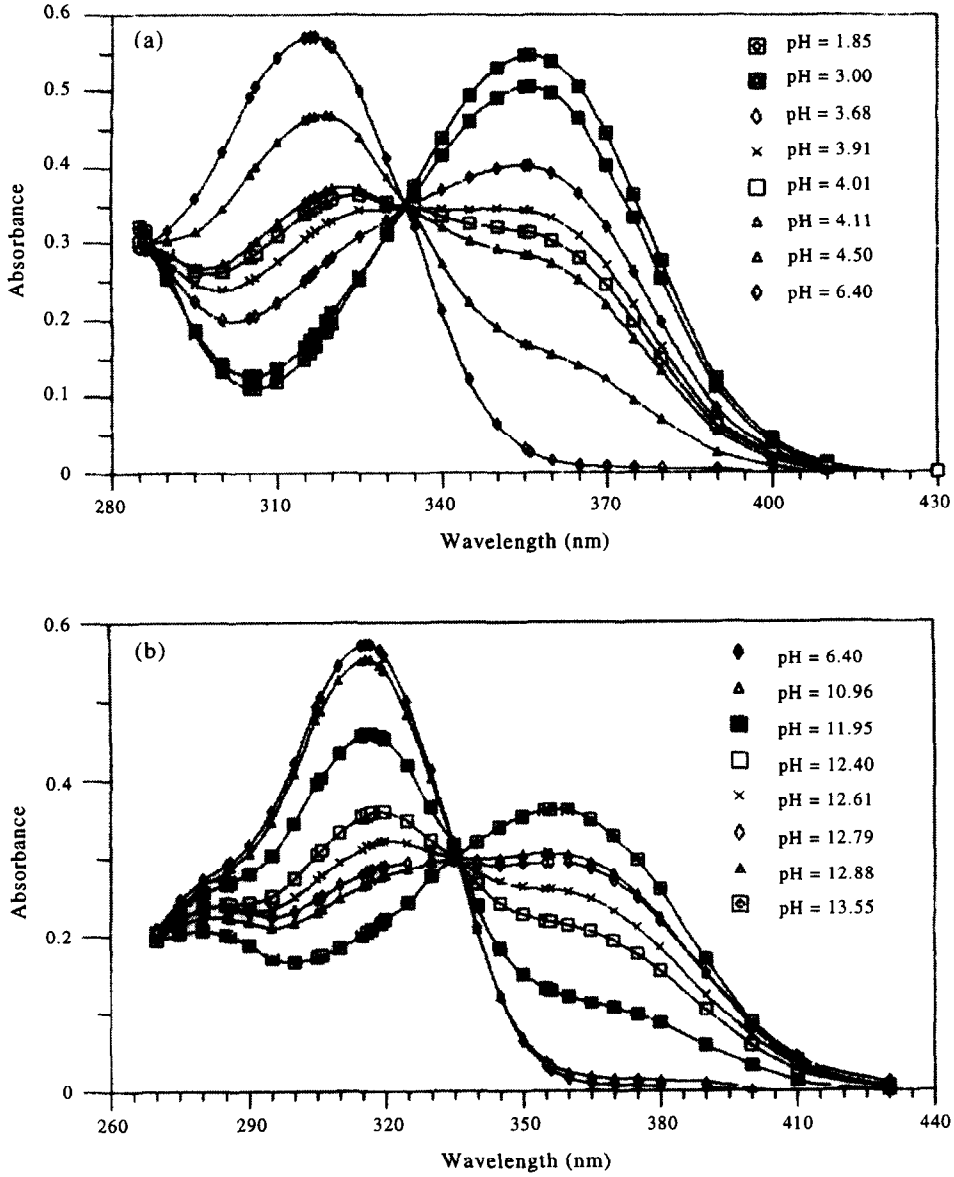
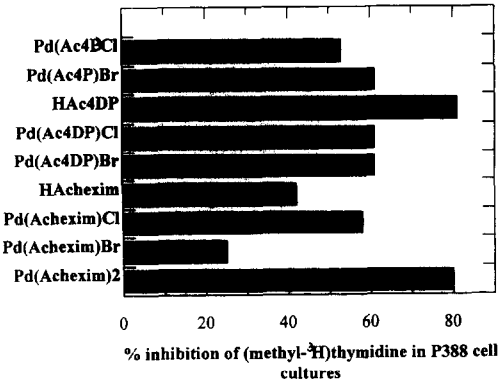


Fig. 3. Absorption spectra of the ligand HAc4P in the low pH region (a), where the species HL and H_2L^+ are present. Absorption spectra of the ligand in the high pH region (b) where the species L^- and HL are present.

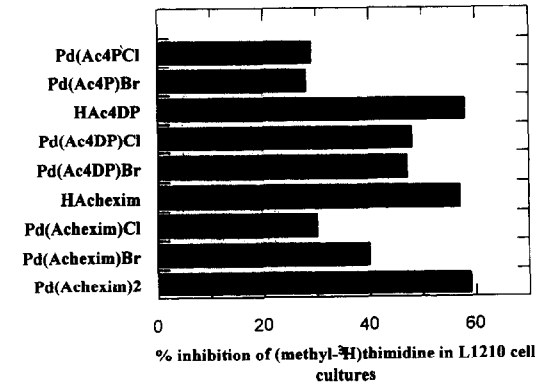
high value may be attributed to the increase in electron density on the thiureide moiety caused by the conjugated system which increases the basicity of N(3) and retards the migration of the hydrogen atom from N(3) to sulfur. The sulfur atom of the deprotonated ligand forms a better electron donor than the pyridine ring nitrogen, which results from the coordination of sulfur by the monodentate anionic heterocyclic TSC in $[PdL_2]$ complexes.

Biological studies

Antitumor screening. The effect of Pd^{II} complexes on DNA synthesis {the mean % inhibition of (methyl-^{3}H) thymidine} of P388 and L1210 cell cultures of eight selected compounds was determined and is shown in Fig. 4. DNA synthesis was determined after 30 min incubation of 10^6 cells in 1 mCi of radioactive precursor in 1 ml medium [8]. The order of their activity in inhibiting incorporation of ^{3}H-thymidine into DNA in L1210 cell cultures is **11 > 4 > 8 > 5 > 6 > 10 > 9 > 2 > 3,** while the order in P388 cell cultures is **11 ≈ 4 > 5 ≈ 6 ≈ 3 > 9 > 2 > 8 > 10.** The highest *in vitro* activity is shown on compounds **11** and **4** on both cell cultures. The palladium(II) compounds were found more sensitive against P388 cell cultures. $Pd(Achexim)_2$, **11,** was found to show the highest *in vitro* and *in vivo* [3c] activity (T/C% = 166 for $Pd(Achexim)_2$, in comparison to T/C% = 112 for the parent ligand, HAchexim) [3c]. This activity is associated with the complex of pal-



(a)



(b)

Fig. 4. The effect of selected palladium(II) complexes on DNA synthesis (a) in P388 and (b) in L1210 cell cultures.

ladium(II) than the parent thiosemicarbazone, HAchexim.

Antifungal screening. Although HAc4DP and HAchexim, as well as their copper(II) and nickel(II) complexes, possess substantial growth inhibition zones at concentrations down to 100 μg/mL [6], none of the present palladium complexes show significant activity against either *Aspergilius niger* or *Paecilomyces varioti.*

Conclusions

The most plausible structure, based on spectroscopic results, for Pd(L)X and $Pd(L)_2$ is square planar as shown in Fig. 5. Anions {loss of N(3) hydrogen} of TSCs coordinate in a planar conformation to a central palladium(II) through the pyridyl N, azomethine N and thiolato S atoms. The fourth coordination site is occupied by either a bromo, chloro or a second ligand bonding *via* only its thiolato S atom. The $[PdL_2]$ complexes, $[Pd(Ac4DP)_2]$ and $[Pd(Achexim)_2]$, seem to be similar to $[Pd(Ac4DM)_2]$, where Ac4DM is the anion of 2-acetylpyridine N(4)-dimethylthiosemicarbazone. The crystal structure determination showed that this complex have one NNS tridentate and a S monodentate ligand [3b].

The *in vitro* and *in vivo* antitumor activities [3c] of Pd^{II} compounds seem promising. The replacement of the group N(4)-propyl or N(4)-dipropyl by a bulkier substituent 3-hexamethyleneiminyl leads to an increase of antineoplastic activity. This activity is inversely related to the ease of reduction.

Among these compounds, the compound $Pd(Achexim)_2$, **11** with *cis*-N_2 and *cis*-S_2 configuration, was found distinctly effective against leukemia [3c] and in inhibiting the incorporation of 3H-thymidine.

EXPERIMENTAL

Materials

Solvents were purified and dried according to standard procedures. Heterocyclic TSCs, were prepared as described by Scovill [7e]. The complexes were analyzed for C, H and N at the European Environmental Research Institute (Ioannina). Analyses of palladium and halogens were performed by gravimetrical and potentiometric techniques. Measurements and instrumentation were performed as reported previously [3].

Preparation of the complexes

Pd(Ac4P)Cl, **2**, *and* Pd(Ac4P)Br, **3**. To a solution of HAc4P (0.185 g, 0.78 mmol) in methanol (9 ml) was added lithium tetrahalogenopalladate(II), Li_2PdX_4, prepared *in situ* from $PdCl_2$ and LiX ($PdCl_2$, 0.192 g, 1.08 mmol, LiCl, 0.173 g, 4.08 mmol or LiBr, 0.354 g, 4.08 mmol, respectively) in methanol (15 ml). The reaction mixture was stirred for 24 h at room temperature and then left in the refrigerator for 1 day. The powders were filtered off, washed with cold methanol and ether and dried *in vacuo* over silica gel, they were redried at 90°C *in vacuo* over P_4O_{10}. Yields 90% and 61% for **2** and **3** respectively.

Pd(Ac4DP)Cl, **5,** *and* Pd(Ac4DP)Br, **6**. To a solution of HAc4DP (0.267 g, 9.96 mmol) in methanol (6 ml) was added lithium tetrahalogenopalladate(II), Li_2PdX_4, prepared *in situ* from $PdCl_2$ and LiX ($PdCl_2$, 0.208 g, 1.17 mmol, LiCl, 0.219 g, 5.16 mmol or LiBr, 0.447 g, 5.16 mmol, respectively) in methanol (15 ml). The same procedure as in preparations **2** and **3** was repeated for isolating and drying the resulting solids. Yields 89% and 76% for **5** and **6** respectively.

Pd(Achexim)Cl, **9,** and Pd(Achexim)Br, **10**. To a solution of HAchexim (0.36 7 g, 1.32 mmol) in methanol (18 ml) was added lithium tetrahalogenopalladate(II), Li_2PdX_4, prepared *in situ* from $PdCl_2$, and LiX ($PdCl_2$, 0.273 g, 1.53 mmol, LiCl, 0.302 g, 7.14 mmol or LiBr, 0.619 g, 714 mmol respectively) in methanol (15 ml). The same procedure as in preparations **2** and **3** was repeated. Yields 92% and 86% for **9** and **10,** respectively.

$Pd(Ac4DP)_2$, **7**. To a solution of HAc4DP (0.352 g, 1.26 mmol) in methanol (6 ml) was added lithium tetrahalogenopalladate(II), Li_2PdX_4, prepared *in situ*

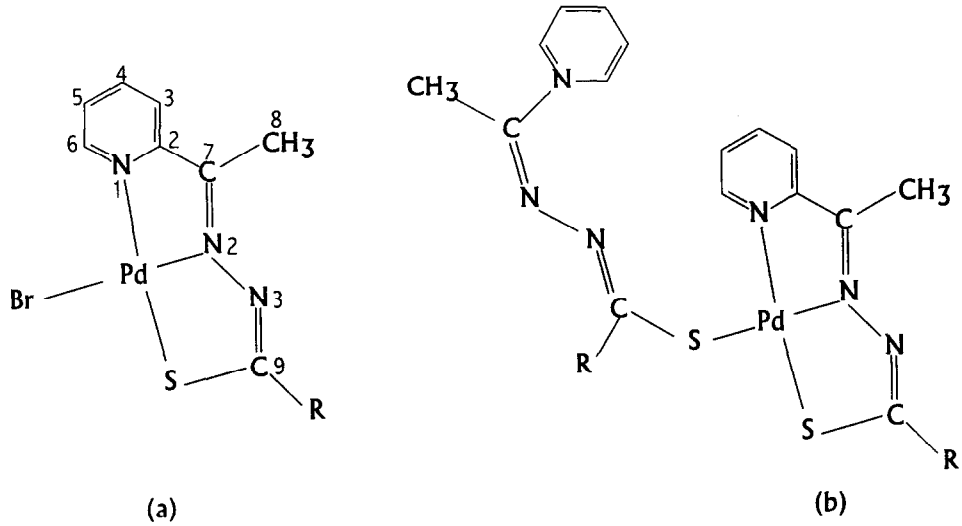


Fig. 5. The proposed geometry (a) for **2, 3, 5, 6, 9, 10** and (b) for **7** and **11**.

from $PdCl_2$ and LiX ($PdCl_2$, 0.112 g, 0.63 mmol, LiCl, 0.122 g, 2.88 mmol) in methanol (15 ml). Immediately, a yellow solid was formed which is dissolved at pH = 8, by the addition of 14–15 ml of aqueous solution 1.5 M NH_3. A red powder was formed and the reaction mixture was stirred for 24 h at room temperature at constant value of pH. The powder was filtered off, washed with cold methanol and ether and dried *in vacuo* over silica gel, it was redried at 70°C *in vacuo* over P_4O_{10}. Yield 90%.

$Pd(Achexim)_2$, **11**. To a solution of HAchexim (0.504 g, 1.83 mmol) in methanol (21 ml) was added lithium tetrahalogenopalladate(II), Li_2PdX_4, prepared *in situ* from $PdCl_2$ and LiX ($PdCl_2$, 0.158 g, 0.90 mmol; LiCl, 0.177 g, 4.17 mmol) in methanol (15 ml). Immediately, a yellow solid was formed which is dissolved at pH = 8, by the addition of 11–12 ml, of aqueous solution 1.5 M NH_3. The reaction mixture was stirred for 24 h at room temperature at constant value of pH. The powder was filtered off, washed with cold methanol and ether and dried *in vacuo* over silica gel, it was redried at 90°C *in vacuo* over P_4O_{10}. Yield 63%.

Incorporation of (methyl-^3H) thymidine

L1210 leucemia cells were grown in RPMI-1640 medium; P388 cells were grown in Dulbecco's medium. All media were supplemented with 10% calf serum, streptomycin penicillin and 42 mM HEPES. DNA synthesis was determined after 30 min incubation of the cells with the (methyl-^{3}H) thymidine precursor of DNA. The cells suspension was placed on Whatman N°41 filters and the wet filters were soaked in 5% cold TCA, twice in 96% alcohol, once in mixture of ether : ethanol (1 : 1) and once in ether. After drying the filters were placed in scintillation fluid and the radioactivity was determined.

Acknowledgements—We thank European Environmental Research Institute (Ioannina) for providing microanalytical service facilities.

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