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Palladium(II) and Platinum(II) Dichloro Complexes Containing Diamine-Estrone Derivatives

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The preparation of *cis*-dichloro Pt(II) and *cis*-dichloro Pd(II) complexes of *N*-[3-hydroxyestra 1:3:5 (10)trien-17β]ethylendiamine, *N*-[3-hydroxyestra 1:3:5 (10)trien-17β]1,3-propylendiamine, and *N*-[3-hydroxyestra 1:3:5 (10)trien-17β]2-aminomethylpyridine is reported. The complexes have been characterized by chemical analysis, infrared spectroscopy and molar conductivity.

[Keywords: Diamine estrogenic complexes; Palladium(II) complexes; Platinum(II) complexes]

Palladium(II)- und Platin(II)dichlorid-Komplexe mit Diamin-Estron-Derivaten

Es wird über die Darstellung von *cis*-Dichlor-Pt(II)- und *cis*-Dichlor-Pd(II)-Komplexen mit *N*-[3-Hydroxyestra 1:3:5 (10)trien-17β]ethylendiamin, *N*-[3-Hydroxyestra 1:3:5 (10) trien-17β]1,3-propylendiamin und *N*-[3-Hydroxyestra 1:3:5 (10)trien-17β]2-aminomethylpyridin berichtet. Die Komplexe wurden mittels chemischer Analyse, IR und Leitfähigkeitsmessungen charakterisiert.

Introduction

The antitumor activity of estrogens against breast and uterus cancer in women and cancer of the prostate in men is well known[1]

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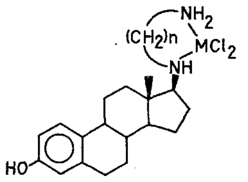
however the disadvantage of this kind of compounds is the large doses required for complete remission of tumors[2].

On the other hand, *cis*-diamine complexes and some related compounds have antitumor properties[3] and *cis*-dichloro-diamine platinum(II) is used in the treatment of male and female genital cancer[4].

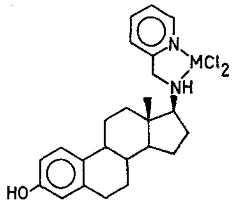
This paper reports on the synthesis and characterization of *cis*-dichloro platinum(II) and *cis*-dichloro palladium(II) of complexes *N*-[3-hydroxyestra 1:3:5 (10)trien-17β]ethylendiamine (*enE*); *N*-[3-hydroxyestra 1:3:5 (10)trien-17β]1,3-propylendiamine (1,3-*pnE*) and *N*-[3-hydroxyestra 1:3:5 (10)trien-17β]2-aminomethylpyridine (2-*pilE*).

It is expected the new platinum(II) complexes will show more activity than estrogens against estrogen dependant mammary tumors. The pharmacological studies of both ligands and platinum complexes are in progress.



n = 2,3

M = Pt(II) or Pd(II)



M = Pt(II) or Pd(II)

Results and Discussion

The ligands used in this study were prepared by reaction of estrone and the corresponding diamine followed by treatment with sodium borohydride by the usual methods[5,6] they were characterized by chemical analysis, mass spectrometry, infrared and ^{1}H-nuclear magnetic resonance spectroscopy.

Metal complexes were obtained by reaction of bis-(benzonitrile) palladium(II) chloride or bis(benzonitrile) platinum(II) chloride with the corresponding diamine[7].

Analytical results, colour, decomposition points and molar conductivities of the synthesized complexes are listed in Table 1.

In general the infrared spectra of ligands and complexes are similar, however, we observe a negative shift[8], of 100 cm^{-1} for the $\nu(NH_2)$

Table 1. *Analytical and physical data for the complexes*

Complex	Decs. point (°C)	Colour	Found (Calcd.) (%) C	H	N	*M*	Cl	Λ^M (27 °C) in *DMF*
*enE*PtCl$_2$	270	yellow	41.39 (41.37)	5.19 (5.17)	4.88 (4.82)	33.60 (33.62)	12.26 (12.24)	36.34
*enE*PdCl$_2$	253	brownish-yellow	48.69 (48.84)	5.99 (6.10)	5,41 (5.69)	21.72 (21.65)	14.35 (14.44)	30.90
1,3*pnE*PtCl$_2$	280	yellow	42.50 (42.42)	5.35 (5.38)	4.76 (4.71)	31.96 (32.82)	11.99 (11.95)	40.62
1,3*pnE*PdCl$_2$	230	brownish-yellow	49.68 (49.86)	6.36 (6.33)	5.43 (5.54)	21.08 (21.05)	14.14 (14.04)	33.59
2-*pilE*PtCl$_2$	262	light yellow	45.88 (45.85)	4.80 (4.77)	4.47 (4.45)	30.60 (31.05)	11.20 (11.30)	37.20
2-*pilE*PdCl$_2$	268	light yellow	53.27 (53.39)	5.52 (5.56)	5.05 (5.19)	20.01 (19.72)	13.12 (13.16)	34.92

vibration of the ligands when they are coordinated. While there is no significant change for the δ(NH_2) band.

Those compounds containing pyridine (2-*pilE* and 2-*pilE*-*M*Cl_2) show clear differences between free and coordinated pyridine[8–10] for example the strong bands at 1 570 and 1 590 cm^{-1} and the medium bands at 400 and 620 in the ligand are shifted in platinum complex to 1 610, 440 and 675 respectively and for the palladium complex the first two strong bands of the ligand are shifted as well to 1 610 and the two medium at 425 and 680 cm^{-1} (Table 2).

Table 2. *Characteristic infrared frequencies (cm*$^{-1}$) of the synthesized compounds

Ligand or complex	ν-OH	ν(NH_2)	δ(NH_2)	ν(*M*-Cl)	ν(*M*-N)	others
enE	3 140	3 310, 3 230	1 605	— —	— —	
*enE*PtCl_2	3 420	3 210	1 610	320, 330	450, 530	
*enE*PdCl_2	3 430	3 220	1 610		445, 515	
1,3*pnE*	3 130	3 320, 3 260	1 605	— —	— —	
1,3*pn*EPtCl_2	3 400	3 220	1 605	315, 325	445, 530	
1,3*pnE*PdCl_2	3 400	3 220	1 608	315, 325	440, 510	
2-*pilE*	3 100	3 320	1 607	— —	— —	1 570, 1 590, 620, 400
2-*pilE*PtCl_2	3 380	3 180	1 610	327, 335	435, 590	
2-*pilE*PdCl_2	3 400	3 230	1 610	325, 335	425, 590	

Ligands and complexes show a broad band due to the phenolic —OH group of the estrone derivatives around 3 100 the former and around 3 400 cm^{-1} the latter (Table 2).

The far infrared spectra of the complexes show the two typical strong bands[11] around 300–340 cm^{-1} due to asymmetric and symmetric *M*-Cl stretching vibrations for a '*cis*' isomer (Table 2).

In the case of the ν(*M*-N) vibration we assign it in agreement with other results[8,10,11] around 440, 530 cm^{-1} (Table 2).

All the complexes have low molar conductivities indicating their non-electrolityc behaviour at 27 °C in dimethylformamide solution ($c \simeq 10^{-3}\,M$).

The ^{1}H-NMR data of the metal derivatives are similar to those of the free ligands (see experimental section) the only differences in the spectra of complexes are a slight shift due to the change of solvent and a small broadening of signals.

Experimental

The solvents used were 'puriss' grade quality. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. IR spectra were recorded on a 283-B Perkin-Elmer spectrometer using hexachloro butadiene mulls (2500-4000 cm^{-1}), Nujol mulls on CsI plates (600-200 cm^{-1}) and KBr wafer (600-4000 cm^{-1}). The mass spectra of ligands were measured on a Hewlett-Packard Mod. 5985 quadropole mass spectrometer. The nmr spectra were recorded on a Varian FT-80A spectrometer ligands in $CDCl_3$ solution and complexes in *DMSO*-d_6 solution. Conductivities of complexes were measured in dimethylformamide solution with specific conductance of 0.017×10^{-4} Ohm^{-1} cm^{-1} at 27 °C on a Beckman Conductivity Bridge Mod. RC-20.

Estrone was a gift from Syntex, SA; diamines were Aldrich products; bis-(benzonitrile)palladium(II) chloride and bis-(benzonitrile)platinum(II)chloride were prepared by the *Kharasch* method[7] using $PdCl_2$ and $PtCl_2$ from Alfa Inorganics. Chemical analyses were determined by Dr. *E. Pascher* in Bonn, Germany. The ligands were prepared according the usual methods[5,6] and the β stereochemistry on C-17 was assigned in accordance with previous results[12].

enE, m.p. 210-212 °C; M^+ 314 *m*/e, 284 *m*/e (base peak); ^{1}H-NMR (ppm): 0.73 s, 1.20-2.37 m, 2.70 m, 6.50 d, 6.60 s, 7.05 d. Anal.: Found C 77.05, H 9.61, N 8.65, O 5.68. Calcd. C 76.43, H 9.55, N 8.91, O 5.10.

1,3-*pnE*, m.p. 153-155 °C; M^+ 328 *m*/e, 270 *m*/e (base peak); H-NMR (ppm): 0.70 s, 1.20-2.40 m, 2.70 m, 3.10 s, 6.55 d, 6.60 d, 7.03 d. Anal.: Found C 76.7, H 9.72, N 8.39, O 5.15. Calcd. C 76.83, H 9.75, N 8.53, O 4.88.

2-*pilE*; m.p. 175-177 °C; M^+ 362 *m*/e, 270 *m*/e (base peak); ^{1}H-NMR (ppm): 0.75 s, 1.5-2.30 m, 2.75 m, 3.40 s, 3.60 s, 3.90 s, 6.47, 6.55 d, 6.62 s, 7.01 d, ca. 7.0, 7.07, 7.18, 7.24, 7.33, 7.50, 7.57, 7.67, 8.46. Anal.: Found C 79.36; H 8.21, N 7.42, O 5.08. Calcd. C 79.55, H 8.28, N 7.73, O 4.42.

Preparation of Complexes

To a solution of 1 mmol of ligand in 250 ml of a solvent mixture benzene-dioxane (2:1) was added a solution of 1 mmole of bis-(benzonitrile) metal derivative in 100 ml of benzene. The reaction mixture was heated at 55 °C for 5 h and after concentration a yellow precipitate is observed which is filtered with suction washed with a mixture benzene-acetone and dried under high vacuum. The yields of the synthesized complexes were:

enE$PtCl_2$ 35%, 1,3-*pnE*$PtCl_2$ 43%, 2-*piLE*$PtCl_2$ 53%, *enEPd*Cl_2 40%, 1,3-*pnE*$PdCl_2$ 49%, 2-*pilE*$PdCl_2$ 58%.

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