# Synthesis and Characterization of Estradiol and Estradienonyl Derivatives of Pentamethylcyclopentadienylruthenium(II)

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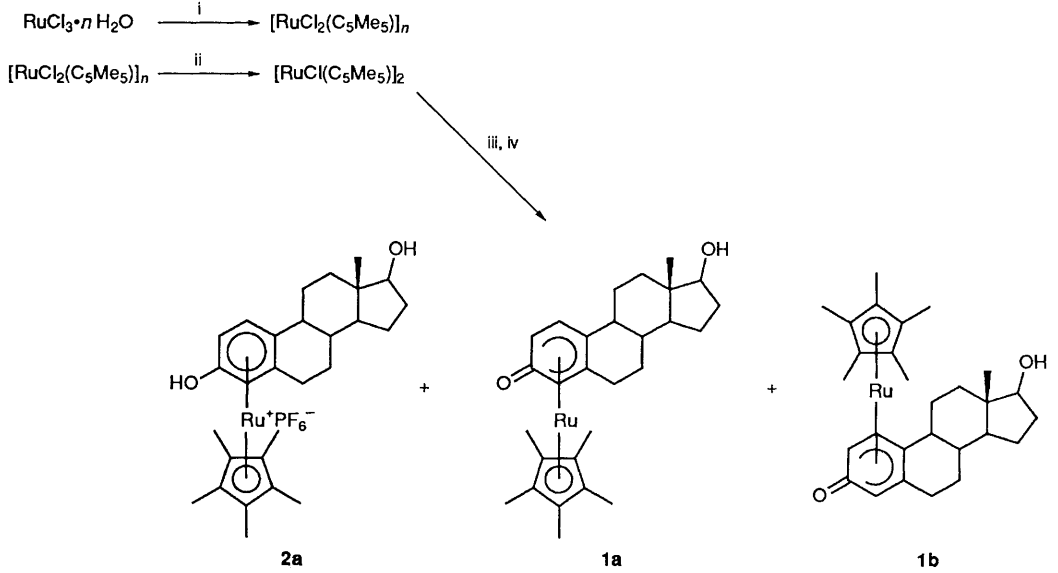
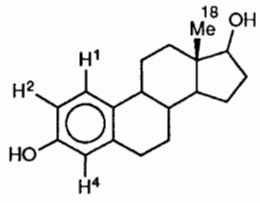
The '$C_5Me_5Ru$' moiety coordinates at the *A* ring of estradiol to give both the α and β isomers of the ketonic form $[Ru(C_5Me_5)(\eta^5\text{-estradienonyl})]$ (**1a** and **1b** respectively) and the α isomer of the phenolic form $[Ru(C_5Me_5)(\eta^6\text{-estradiol})][PF_6]$ **2a**; **1a** reacts with $HPF_6$ to give quantitatively **2a**, but in the presence of $NEt_3$ **1a** was regenerated.

There has been a burgeoning interest in the use of ruthenium derivatives as potential radiopharmaceuticals in nuclear medicine. For example, radiolabelled ruthenocenylalanine has been shown to be a pancreatic imaging agent.[1] Incorporation of a 'CpRu' moiety in biologically active compounds has already been described for complexes such as [Ru(*N*-acetyl-L-phenylalanine)Cp][$PF_6$] and [Ru(*N*-acetyl-L-tyrosine)Cp][$PF_6$].[2] Further this organometallic 'CpRu' fragment has been introduced at the *A* ring of 3-methoxy-estrone.[3] Previously we have reported that the organometallic–hormone species α-[3-*O*-(hydroxypropyl)estradiol]$Cr(CO)_3$ exhibits a good affinity towards the estradiol receptor site;[4a] it is noteworthy that the presence of the hydroxy groups at C-3 and C-17 is essential for the recognition process.[4] Hence we have focused our research




**Scheme 1** *Reagents and conditions*: i, $C_5Me_5H$, MeOH, reflux; ii, Zn, THF, ambient temperature; iii, $KPF_6$ (1 equiv.); iv, estradiol (1 equiv.)

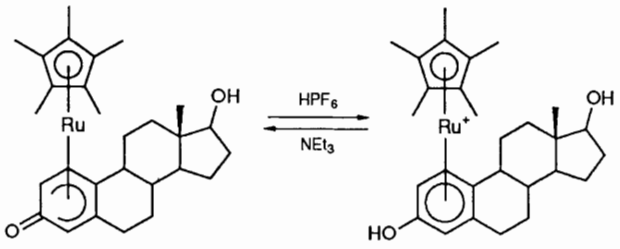



work on preparing such organometallic–hormone compounds using the '$C_5Me_5Ru$' fragment and estradiol without modifications at the C-3 and C-17 position.

Complexation of arenes by the '$C_5Me_5Ru$' fragment has been well documented.[5] The common preparation of such compounds passes *via* the synthesis of $[Ru(C_5Me_5)Cl_2]_n$[6] which can be further converted to coordinatively unsaturated $Ru^{II}$ species, either $[Ru(C_5Me_5)OMe]_2$ or $[Ru(C_5Me_5)Cl]_2$. These latter complexes have proved to be convenient precursors for the preparation of $[Ru(C_5Me_5)(\eta^6\text{-arene})]^+X^-$ derivatives.[7] However the complexation of functionalised aromatic rings by the '$C_5Me_5Ru$' moiety has been less investigated.[8,9]

In this communication we report the synthesis and spectroscopic characterization of the new α,β-$[Ru(C_5Me_5)(\eta^5\text{-estradienonyl})]$ **1a,b** and α-$[Ru(C_5Me_5)(\eta^6\text{-estradiol})][PF_6]$ **2a** species, and show that a rapid interconversion between **1a** and **2a** in solution is taking place at room temperature.

Treatment of a red suspension of $[RuCl(C_5Me_5)]_2$† in tetrahydrofuran (THF) solution with estradiol (1 equiv.) in the presence of $KPF_6$ for two hours gave a white precipitate, while the colour of the supernatant phase changed to brown. The complexation was almost quantitative. The precipitate was separated and analysed by NMR spectroscopy as well as the supernatant phase. The $^1H$ NMR spectrum showed by integration the presence of the α-$[Ru(\eta^5\text{-}C_5Me_5)(\eta^6\text{-estradiol})][PF_6]$ **2a** and (α,β) isomers of $[Ru(\eta^5\text{-}C_5Me_5)(\eta^5\text{-estradienonyl})]$ **1a** and **1b** (Scheme 1) in yields of *ca.* 40, 35 and 25%, respectively. Interestingly the β isomer **2b** was not observed. This is probably due to rapid conversion to give the corresponding **1b**. However **2b** was obtained by direct protonation of **1b** with $H^+PF_6^-$ in dimethyl sulphoxide (DMSO) solution (Scheme 2). It is noteworthy that the course of the reaction is time-dependent. For example after 10 minutes analysis of the reaction mixture by $^1H$ NMR spectroscopy showed the presence of the four products **1a** ⇋ **2a** and **1b** ⇌ **2b** in equilibrium. These complexes were characterized by spectroscopic methods and satisfactory microanalysis was obtained for carbon and hydrogen for the phenolic product **2a**. The $^1H$ NMR spectra of these compounds **1a** and **b** and **2a** and **b** show that on coordination by the '$C_5Me_5Ru$' moiety the aromatic protons H-1, H-2 and H-4 of the *A* ring shift upfield relative to the free ligand.‡ These results are consistent with observations for related rhodium and ruthenium complexes.[9,11] Interestingly the chemical shifts of protons H-2 and H-4 in the α species **1a** and **2a** are in reverse




**1a, b** **2a, b**

**Scheme 2** Interconversion of **1a** and **1b** and **2a** and **2b** by $^1H$ NMR spectroscopy in $[^2H_6]$-DMSO

order relative to those of the β species **1b** and **2b**. This is due to the anisotropic field effect of the '$C_5Me_5Ru$' fragment which operates differently depending whether it is the α or β isomer. This result has been used as an indication of the stereochemistry of the above complexes.‡ Such observation has been reported in the literature for the α,β[RuCp($\eta^6$-estrone 3-methyl ether)][$PF_6$] species and the analogous rhodium compounds.[3,11]

The IR spectrum of α-$[Ru(\eta^5\text{-}C_5Me_5)(\eta^6\text{-estradiol})][PF_6]$ **2a** shows a strong band at ν 830 $cm^{-1}$ (in KBr) corresponding to the counter-ion $PF_6^-$, however this absorption is absent for the corresponding dienonylic complex α-$[Ru(\eta^5\text{-}C_5Me_5)(\eta^5\text{-estradienonyl})]$ **1a** which shows a strong stretching band at 1530 $cm^{-1}$ corresponding to ν(C=O).[12]

The introduction of the '$C_5Me_5Ru$' fragment at the *A*-ring of the estradiol including the modification of the phenol group in the free ligand to give the corresponding ketonic form was confirmed by comparing the $^1H$ NMR spectra of **1a** and **2a**. The $^1H$ NMR spectrum of **1a** shows a further upfield shift relative to that of **2a**. While H-1 appears as a doublet at δ 5.62 (in $[^2H_6]$-DMSO) for **1a**, the resonances for protons H-2 and H-4 are shifted to δ 5.13 and 5.06 with a significant Δδ of 0.40 ppm relative to compound **2a**.‡ We interpret these results as indicative of loss of aromatically in favour of a vinylic description for the arene coordination. Such behaviour was observed in the analogous rhodium series α-$[Rh(C_5Me_5)(\eta^6\text{-estradiol})][2BF_4]$ and α-$[Rh(C_5Me_5)\text{-}(\eta^5\text{-estradienonyl})][BF_4]$ species.[11] Chaudret *et al.* have reported relevant results for the two species $[Ru(C_5Me_5)(\eta^5\text{-PhO})]\cdot 2PhOH$ and $[Ru(C_5Me_5)(\eta^6\text{-PhOH})][CF_3SO_3]$.[9]

We have studied the behaviour of these compounds in solution by treating the zwitterionic forms **1a** and **1b** with $H^+PF_6^-$ in $[^2H_6]$DMSO. Compounds **2a** and **2b** were obtained quantitatively; in the presence of $NEt_3$ the initial products were regenerated (Scheme 2). A mixture of **1a** and **2a** (1 : 1) was dissolved in $CD_3CN$ (0.5 ml) and the $^1H$ NMR spectrum was recorded at various temperatures. An average signal for H-1, H-2 and H-4 was observed at room temperature which coalesces at 243 K; however owing to solubility limitation no further measurement below 233 K was undertaken. These results indicate that exchange is rapid between the two forms; however, the activation energy is higher than that observed for exchange between the compounds $[Ru(C_5Me_5)(\eta^5\text{-PhO})]$–$[Ru(C_5Me_5)(\eta^6\text{-PhOH})]$.[9] For the latter species fast exchange was observed to occur even at 183 K. It is possible that the steric bulk of the steroid ligand β-estradiol in the **1a**–**2a** mixture retards the exchange process relative to that observed between the two species $[Ru(\eta^5\text{-}C_5Me_5)(\eta^5\text{-PhO})]$ and $[Ru(\eta^5\text{-}C_5Me_5)(\eta^6\text{-PhOH})][CF_3SO_3]$.[9] Interestingly, such a conversion phenomenon was not observed for [Ru(*N*-acetyl-L-tyrosine)Cp][$PF_6$] also including a phenolic bioligand.[2]

Our investigations on the reactivity of these complexes $[Ru(C_5Me_5)(\text{steroid})]^{n+}$, $n = 0,1$, with nucleophiles, as well as their biological affinity to the steroidal receptor are in progress.

† $[RuCl(C_5Me_5)]_2$ was obtained by zinc reduction of a suspension of $[RuCl_2(C_5Me_5)]_n$ in THF following Chaudret's procedure.[10]

‡ *Selected $^1H$ NMR data* (250 MHz; $[^2H_6]$-DMSO) for free estradiol: δ 0.66 (s, Me-18), 6.43 (d, $^4J$ 2.5 Hz, H-4), 6.49 (dd, $^3J$ 7.5, $^4J$ 2.5 Hz, H-2) 7.03 (d, $^3J$ 7.5 Hz, H-1).

For **1a**: δ 0.66 (s, Me-18), 1.77 (s, $C_5Me_5$), 5.06 (s, $^4J$ 2.5 Hz, H-4), 5.13 (dd, $^3J$ 6.5, $^4J$ 2.5 Hz, H-2), 5.62 (d, $^3J$ 6.5 Hz, H-1).

For **1b**: δ 0.75 (s, Me-18), 1.81 (s, $C_5Me_5$), 4.90 (dd, $^3J$ 6.5, $^4J$ 2.5 Hz, H-2), 5.00 (s, $^4J$ 2.5 Hz, H-4), 5.51 (d, $^3J$ 6.5 Hz, H-1).

For **2a**: δ 0.66 (s, Me-18), 1.75 (s, $C_5Me_5$), 5.47 (d, $^4J$ 2.5 Hz, H-4), 5.54 (dd, $^3J$ 6.5, $^4J$ 2.5 Hz, H-2), 5.87 (d, $^3J$ 6.5 Hz, H-1).

For **2b**: δ 0.75 (s, Me-18), 1.85 (s, $C_5Me_5$), 5.37 (dd, $^3J$ 6.5, $^4J$ 2.5 Hz, H-2), 5.52 (d, $^4J$ 2.5 Hz, H-4), 5.82 (d, $^3J$ 6.5 Hz, H-1). $^3J$ = *J* (H-1–H-2), $^4J$ = *J*(H-2–H-4).

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