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Synthesis, X-ray structure and chemical properties of 17α-ferrocenylestradiol

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Abstract

The X-ray structure of 17α-ferrocenylestradiol **1a** shows that the ferrocenyl group is at the α position of the steroid, below the plane of the D ring. From acidic medium it is possible to obtain and isolate the derivative with a carbenium ion in 17-α position. This ion is transformed by various nucleophiles into the corresponding olefin **3** with –C=C– at the C16–C17 position. With $NaBH_4$ in acidic medium the reduction leads to a mixture of 17α- and 17β-ferrocenyl $C_{19}H_{26}O$ **4a, 4b** with a predominance of the β product, owing to a more favourable entrance of hydride in the α position. The oxidized derivative 17α-ferriciniumyl-estradiol tetrafluoroborate **5** was prepared and its are properties described.

Keywords: Iron; Ferrocene; X-ray structure; Estradiol derivative; Steroid; Organometallic

1. Introduction

There is increasing interest in the use of ferrocenyl derivatives in medicinal chemistry [1], in therapy [2], and in immunological labelling in particular for assays based on the electrochemical properties of ferrocene [3]. Cais and Wenzel introduced a ferrocenyl fragment into steroidal derivatives, particularly estradiol, for metalloimmunoassay [5] and radioactive labelling [4]. In such compounds the hydroxyl functions were transformed into an ester at the C-3 position [4] or an ether at the C-17α position [5]. No biological studies were pursued with such derivatives. However, the presence of OH groups at both C-3 and C-17 of the steroid molecule are essential for effective binding via hydrogen bonds to a hormone binding site [6]. Our aim was to introduce an organometallic group into estradiol without any protection of the hydroxyl functions in order to preserve the recognition of natural hormonal receptors. We have already described the preliminary results [7]. In particular we synthesised the 17α-ferrocenylestradiol and observed that it binds irreversibly to estradiol receptors [8]. The explanation for this requires more information concerning the reactivity and structure of this compound. In this paper we describe the synthesis, structure, and some features of the chemical reactivity. The synthesis and characterisation of the ferriciniumyl derivative is also reported.

2. Results and discussion

2.1. X-ray structure of 17α-ferrocenylestradiol 1a

Compound **1a** crystallises in the $P2_1$ space group (Table 1) in two forms, **1aA** and **1aB**. An ORTEP view of **1aA** is shown in Fig. 1. Atomic coordinates and se-

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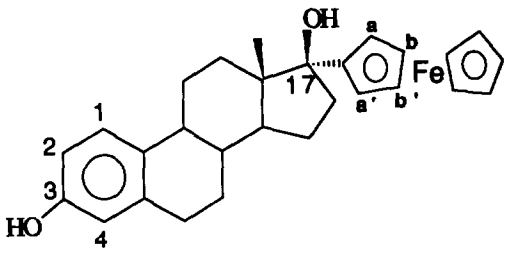
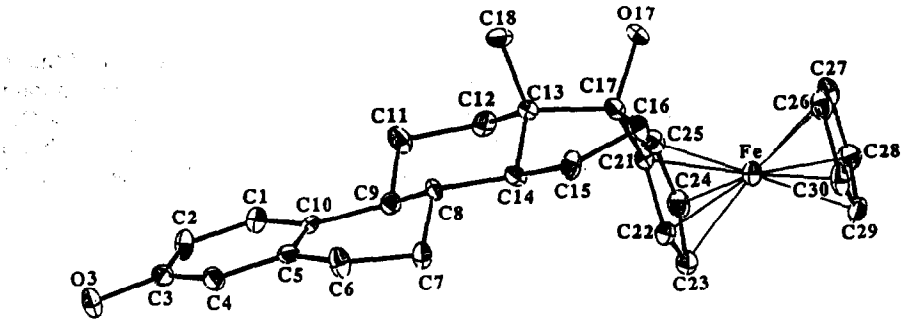
lected bond distances and angles are listed in Table 2 and 3 respectively. In **1a** the ferrocenyl group is below the D ring of the estradiol skeleton. The ORTEP view suggests that the rings of the ferrocenyl substituent are eclipsed. The estrogen derivative forms intermolecular hydrogen bonds and infinite chains, with d(O3–O17) = 2.80 and 2.70 Å. Molecules of ether are included in the structure between these chains. The spacing is very closed to that observed for estradiol hemihydrate itself, where d(O3–O17) = 2.77 Å [9]. Previous studies showed the intermolecular hydrogen bond of the C-3 and C-17 hydroxyl groups is significant in the interaction with the hormonal receptor [10] and is apparently necessary for hormone-receptor binding [6]. The X-ray structure of **1a** shows that even in the presence of a 17α-ferrocenyl substituent the 17β OH is able to hydrogen-bond, consistent with the biochemical properties of **1a** and the estradiol receptor [8].



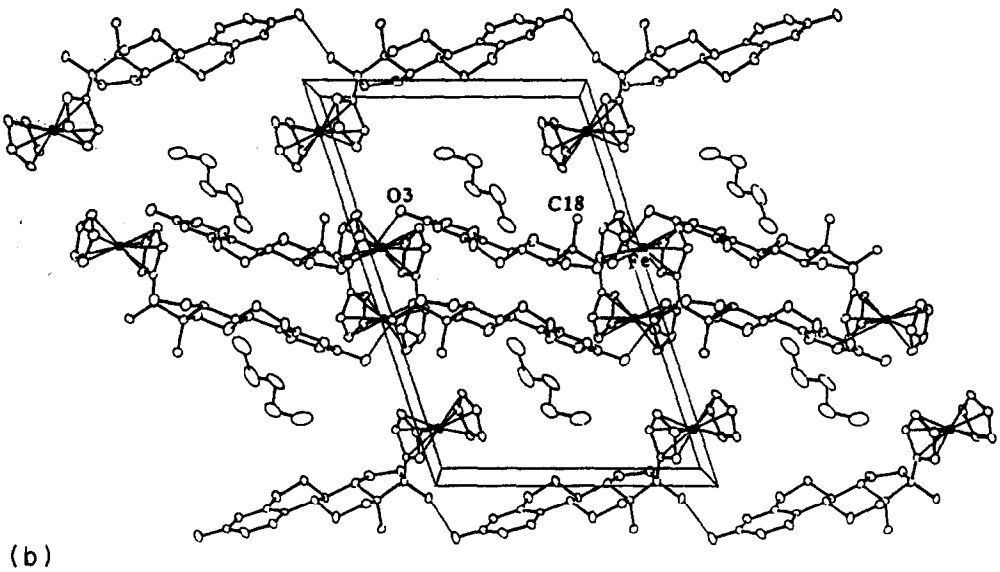
1a

2.2. *Reactivity of 17α-ferrocenylestradiol* **1a**

The reactivity and structure of ferrocenyl alcohols has been well documented in literature [11] and correlated with easy formation of a carbenium ion stabilized by the iron atom. Carbenium ions have proved very useful in asymmetric synthesis [12]. The hypothesis of



(a)



(b)

Fig. 1. Structure of 17α-ferrocenylestradiol **1a**. ORTEP unit cell representation of **1a**. The intermolecular OH...O hydrogen bonds which link the molecule into infinite chains are indicated by thin lines.

Table 1
Crystallographic data

Chemical formula	$C_{28}H_{32}O_2Fe,0.5(C_2H_5)_2O$
Fw	493.48
Crystal system	monoclinic
Space group	$P2_1$
Z	4
a(Å)	11.981(4)
b(Å)	11.945(2)
c(Å)	18.333(3)
β(°)	108.00(2)
V(Å^3)	2495(21)
F(000)	1052
ρ (calcd), g cm^{-3}	1.30
μ (Mo kα)(cm^{-1})	6.28
Cryst. size (mm^3)	0.02×0.42×0.58
Diffractometer	CAD4
Monochromator	graphite
Radiation	Mo kα (0.71070)
Temperature (°C)	20
Scan type	$\omega/2\theta$
Scan range θ, (°)	1.2+0.34 tan θ
2θ range (°)	3–50
Reflctn collected	4596
Reflctn used (criteria)	2484 ($I > 2\sigma(I)$)
R	0.045
R_w [a]	0.050
Absorption correction [b]	Min 0.81 max 1.25
Weighting scheme	Unit weights
Rms (shift/e.s.d) (last ref.)	0.17
I.s. parameters	605

[a] $R_w = [\Sigma_i W_i(F_o - F_c)^2/\Sigma_i W_i F_o^2]^{1/2}$.

prior formation of such a carbenium ion explains the deactivation of the estradiol receptor by 17α-ferrocenylestradiol [13].

The carbenium ion **2** was obtained by addition of $HBF_4 \cdot Et_2O$ in an ethereal solution of **1a**. The cation forms a red-brown microcrystalline fluoroborate. Due to the low solubility of this salt even in CD_2Cl_2 or CD_3CN, and its easy transformation into the corresponding olefin product $C_{29}H_{33}FeO$ **3**, the carbenium ion was identified by comparison of its ^{1}H NMR spectrum with that of **1a** in deuterated trifluoroacetic acid (Fig. 2). The signals of Ha,Ha′ and Hb,Hb′ are shifted from 4.29, 4.02 to 6.18, 5.96 and 4.24, 4.16 to 4.87, 4.78 ppm respectively. The signal of Cp is shifted from 4.23 to 4.70 ppm. Only one signal, at 6.93 ppm, for H1 was observed for the aromatic system: this is due to rapid exchange of H2 and H4 with deuterium in strong acid. The observed deshielding of cyclopentadienyl protons in the alcohol compound compared to the carbenium ion is consistent with previous reports [14].

The salt **2** reacts rapidly with nucleophiles such as water, pyridine, triethylphosphine, ethanethiol, L-cysteine ethylester hydrochlorid, and dimethylsulfide in methylene chloride leading quantitatively to the olefin, as shown in Scheme 1. The formation of other olefinic products resulting from the isomerisation of the carbenium ion was not observed, and this is different from the behaviour of the similar ion stabilized by an acetylene hexacarbonyldicobalt cluster [15]. This may mean that the interaction between the iron atom and C^+ is stronger than that between cobalt and C^+ [16]. Elimination processes from tertiary ferrocenylalcohols in the presence of those nucleophiles have been reported [17]. A similar reactivity was observed directly using the 17α-ferrocenylestradiol under catalytic acidic conditions. With a mixture of both isomers, 17(α, β)-ferrocenylestradiol, and a Lewis acid such as $ZnCl_2$, the olefin was formed, and the α/β ratio in the remaining alcohol dropped from 90/10 to 60/40. That means that the α isomer is more reactive than the β under these conditions.

Ferrocenylcarbenium ions are known to react with a hydride (as sodium tetraborohydride [18] or a silyl hydride [19]) in trifluoroacetic acid. The reaction of 17α-ferrocenylestradiol **1** towards $NaBH_4$ in the presence of trifluoroacetic acid yielded $C_{29}H_{30}FeO$ **3** and $C_{29}H_{32}FeO_2$ **4 (a, b)** (see Scheme 2) resulting from the elimination and reduction respectively. The relative proportions depend on the reaction temperature (Table 4). The reduction by the hydride occurred from the α and β side of the steroid, forming preferentially the β isomer **4b**. Such results are consistent with previous work. In the case of cobalt steroidal derivative, Nicholas et al. [20] showed that the addition of the hydride occurs mostly on the α side of the steroidal skeleton. This might be explained by the structure of the probable transition state. According to Felkin's model [21], the torsional interaction between C13–C18 and C17βH during the bond formation is energetically greater than the C17αH–C16βH interaction.

2.3. Preparation of 17α-[ferriciniumylestradiol tetrafluoroborate 5

Some ferricinium ions, resulting from oxidation of ferrocene compounds, show significant antitumor activity [22]. Therefore we studied the formation of the ferricinium salt **5** resulting from the 17α-ferrocenylestradiol by both electrochemical and chemical synthesis.

The equilibrium between 17α-ferrocenylestradiol and 17α-ferriciniumylestradiol was observed electrochemically and showed a reversible oxidation at 515 mV (vs Ag/AgCl). The oxidation of 17α-ferrocenylestradiol by $AgBF_4$ in diethyl ether led to the ferricinium salt **5** in 39% yield (Fig. 3). The salt crystallised from nitromethane with one equivalent of $AgBF_4$, as suggested by the elemental analysis. The Ag^+ is presumably complexed to the arene.

Table 2
Atomic coordinates for **1a**

	Atom	x	y	z	U_{eq}
Molecule A	Fe(1)	−0.0315(1)	0.6908(2)	0.89724(9)	0.0877
	C(1)	0.7269(9)	0.5592(9)	1.1537(6)	0.0420
	C(2)	0.8460(9)	0.543(1)	1.1760(6)	0.0441
	C(3)	0.9200(9)	0.6262(9)	1.1715(6)	0.0388
	O(3)	1.0379(6)	0.6052(7)	1.1915(4)	0.0477
	C(4)	0.8729(9)	0.7304(9)	1.1461(6)	0.0413
	C(5)	0.7506(9)	0.7473(9)	1.1219(5)	0.0357
	C(6)	0.7070(9)	0.864(1)	1.0937(7)	0.0492
	C(7)	0.5769(8)	0.866(1)	1.0487(6)	0.0402
	C(8)	0.5066(7)	0.7991(9)	1.0912(6)	0.0305
	C(9)	0.5434(8)	0.6747(9)	1.0950(6)	0.0373
	C(10)	0.6758(8)	0.6615(8)	1.1256(5)	0.0306
	C(11)	0.4474(9)	0.605(1)	1.1367(7)	0.0452
	C(12)	0.342(1)	0.619(1)	1.0993(6)	0.0435
	C(13)	0.3045(8)	0.7411(9)	1.0954(6)	0.0379
	C(14)	0.3749(9)	0.8048(9)	1.0531(6)	0.0377
	C(15)	0.316(1)	0.9213(9)	1.0376(6)	0.0418
	C(16)	0.1842(9)	0.8945(9)	1.0242(6)	0.0429
	C(17)	0.1760(8)	0.7698(9)	1.0452(6)	0.0387
	O(17)	0.0985(6)	0.7568(7)	1.0911(4)	0.0432
	C(18)	0.3255(9)	0.783(1)	1.1778(6)	0.0620
	C(21)	0.1317(7)	0.694(1)	0.9767(5)	0.0355
	C(22)	0.1381(8)	0.7088(9)	0.9006(6)	0.0369
	C(23)	0.091(1)	0.615(1)	0.8554(6)	0.0478
	C(24)	0.052(1)	0.541(1)	0.9032(7)	0.0484
	C(25)	0.0758(9)	0.5861(9)	0.9760(6)	0.0444
	C(26)	−0.1387(9)	0.809(1)	0.9224(7)	0.0473
	C(27)	−0.1886(8)	0.701(1)	0.9203(6)	0.0399
	C(28)	−0.2028(9)	0.654(1)	0.8473(7)	0.0490
	C(29)	−0.1665(9)	0.734(1)	0.8039(6)	0.0480
	C(30)	−0.1272(9)	0.827(1)	0.8497(7)	0.0452
Molecule B	Fe(1)	0.0522(1)	0.8737(2)	0.59785(8)	0.0354
	C(1)	0.586(1)	1.032(1)	0.3545(7)	0.0569
	C(2)	0.684(1)	1.042(1)	0.3280(7)	0.0499
	C(3)	0.749(1)	0.955(1)	0.3224(6)	0.0488
	O(3)	0.8418(7)	0.9711(8)	0.2939(5)	0.0628
	C(4)	0.7183(9)	0.850(1)	0.3428(7)	0.0517
	C(5)	0.6253(9)	0.8358(9)	0.3713(6)	0.0408
	C(6)	0.5994(9)	0.717(1)	0.3927(7)	0.0518
	C(7)	0.5155(9)	0.717(1)	0.4402(6)	0.0464
	C(8)	0.4120(9)	0.7929(9)	0.4037(6)	0.0397
	C(9)	0.4554(9)	0.9123(8)	0.4106(6)	0.0338
	C(10)	0.5573(9)	0.9275(9)	0.3776(5)	0.0361
	C(11)	0.355(1)	0.995(1)	0.3762(8)	0.0392
	C(12)	0.253(1)	0.978(1)	0.4109(6)	0.0527
	C(13)	0.2085(9)	0.859(1)	0.4020(6)	0.0449
	C(14)	0.3127(9)	0.781(1)	0.4400(6)	0.0379
	C(15)	0.257(1)	0.669(1)	0.4425(7)	0.0558
	C(16)	0.141(1)	0.694(1)	0.4558(7)	0.0501
	C(17)	0.1219(9)	0.824(1)	0.4465(6)	0.0437
	O(17)	0.0032(6)	0.851(1)	0.4031(4)	0.0581
	C(18)	0.150(1)	0.833(1)	0.3172(7)	0.0639
	C(21)	0.1474(8)	0.883(1)	0.5228(5)	0.0391
	C(22)	0.100(1)	0.992(1)	0.5332(6)	0.0417
	C(23)	0.145(1)	1.019(1)	0.6118(7)	0.0507
	C(24)	0.218(1)	0.931(1)	0.6495(7)	0.0524
	C(25)	0.2191(9)	0.848(1)	0.5949(6)	0.0511
	C(26)	−0.003(1)	0.809(1)	0.6824(6)	0.0465
	C(27)	−0.012(1)	0.7277(9)	0.6245(7)	0.0457
	C(28)	−0.088(1)	0.769(1)	0.5552(7)	0.0514
	C(29)	−0.1261(8)	0.876(1)	0.5715(6)	0.0483
	C(30)	−0.072(1)	0.899(1)	0.6495(7)	0.0444

Table 2 (continued).

	Atom	x	y	z	U_{eq}
Solvent	O(30)	0.5301	0.307	0.2501	0.1201
	C(31)	0.491	0.256	0.1789	0.1187
	C(32)	0.591	0.205	0.1591	0.1501
	C(33)	0.444	0.375	0.2620	0.1406
	C(34)	0.445	0.366	0.342	0.1824

2.4. Circular dichroism spectra

Usually ferrocene compounds exhibit Cotton effects (CE) in the region of "metallocene" band (350–500 nm) depending on the specific substituents [12b], whereas ferricinium salts may show less intensive CEs corresponding to a metal–ligand charge-transfer (600–700 nm) [3].

In the CD spectrum of **1** in CF_3COOH, that is of cation **2**, two CEs of equal intensity, (+) at 355 nm and (−) at 320 nm were observed, whereas for **1** itself in CH_3OH there is no observable CE other than a very intensive positive band at 300 nm, possibly of arene origin. Presumably, CEs in the ferrocene band are of very low intensity.

For a ferricinium salt **5** in CH_3NO_2 an intensive (−) CE at 480 nm was seen with a hint of a (+) CE around 620 nm.

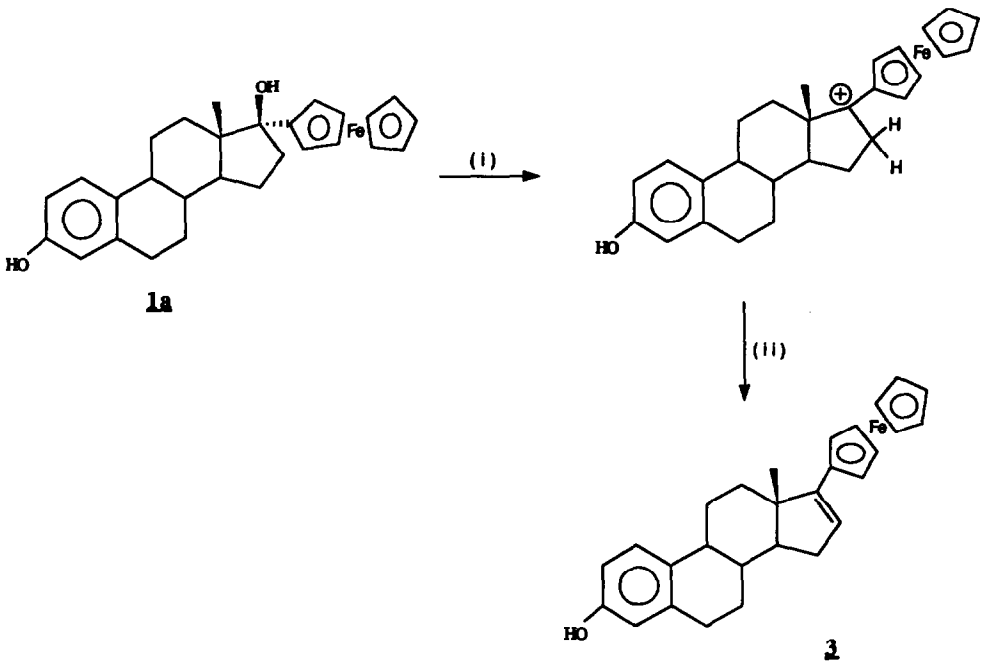
3. Conclusion

The synthesis and X-ray structure demonstrates the ability of 17α-ferrocenylestradiol to hydrogen-bond between the phenolic 3 and hydroxyl 17 (OH) groups. That may explain why the 17α-ferrocenylestradiol derivative retains a good affinity for the estradiol receptor even with a bulky organometallic group at the 17 α position. The chemical reactivity of 17-ferrocenylestradiol is related to the existence of a tertiary carbenium ion stabilized by the iron atom.

4. Experimental section

4.1. Synthesis of 17(α, β)-ferrocenylestradiol 1a,1b

To a solution of bromoferrocene (580 mg, 2.9 mmol) in ether were added dropwise 1.6 ml of a solution of butyllithium in ether (2.75 M). The solution turned red and the mixture was cooled to −50°C. A solution of 840 mg (2.18 mmol) of 3-O-[dimethyl(*tert*butyl) silyl]estrone in 50 ml of THF was then added dropwise. The mixture went yellow. The reaction was allowed to warm to room temperature and concentrated under reduced pressure. The mixture was hydrolysed with water (100 ml) and extracted with ether. The solution



1a 3

Scheme 1. (i) acid medium; (ii) nucleophile: water, pyridine, triethylphosphine, ethanethiol, dimethylsulfide.

was evaporated to dryness and the residue dissolved and stirred 15 min in 1 ml of (^{t}Bu$_4$N)F in THF. The product was washed with water, extracted with ether, and chromatographed on silica (eluant: ether/pentane 1/1 $R_f = 0.5$) yielding 450 mg of 17(α, β)-ferrocenylestradiol **1a,1b** (yield: 44%; α/β 90/10).

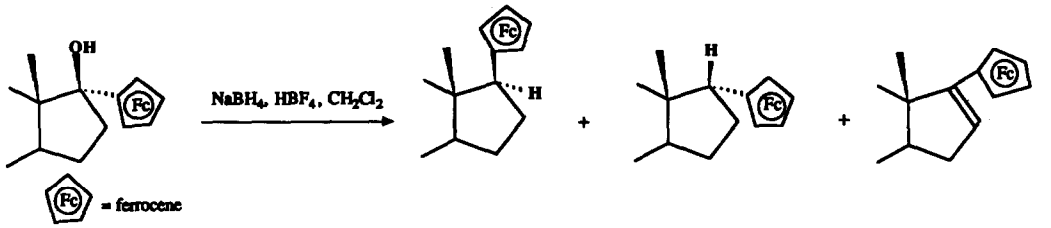
Anal. calcd. for $C_{28}H_{32}FeO_2$: C, 73.68; H, 7.02. Found: C, 73.75; H, 7.11%.

^{1}H NMR (δ, ppm, $CDCl_3$): 7.05 (d, 8.5 Hz, H1), 6.56 (dd, 8.5 et 2.5 Hz, H2), 6.53 (d, 2.5 Hz, H4), 4.23 (s, Cp), 4.29–4.24–4.16–4.02 (m, Cp substituted), 2.80 (m, H6a,b), 1.00 (s, Me18). ^{13}C NMR (δ, ppm, benzene d_6): 126.41 (C1), 115.19–112.63 (C2–C4), 153.31 (C3), 138.24–133.00 (C5–C10), 97.30 (C17), 77.20 (C21), 68.26–67.82–67.16–65.80 (C22–C23–C24–C25), 68.59 (C26–C27–C28–C29–C30), 45.88 (C13), 48.21–43.49–39.30 (C9–C8–C14), 23.67–26.31–27.35–29.65–33.48–38.62 (C6–C7–C11–C12–C15–C16), 14.48 (C18). Mass spectroscopy: 186 (100%): $Fe(C_5H_5)^{2+}$; 456 M^+, 438 (M^+, H_2O); 121 $FeC_5H_5^+$, 57 FeH^+, 43 C_3H_7. UV in ethanol: 231 nm/ε 6840; 278 nm/ε 3126. IR (in KBr): 3348 (broad), 2929–2873(s), 1610–1502–1453(m), 1003, 817 cm^{-1}. HPLC: Column inverse phase C18-flow 1 ml min^{-1} solvent: MeOH/H_2O 95/5, λ 254 nm $t = 3.6$ min. Circular dichroïsm [CH_3OH]: λ max 300 nm (+) Relative Intensity 4.5 not Cotton effect.

4.2. X-ray structure of 17α-ferrocenylestradiol 1a

1a crystallises on slow evaporation of a CH_2Cl_2/ether solution leading to crystals suitable for X-ray diffraction.

Crystal data for **1a**: intensity data were collected at room temperature. The accurate cell dimensions and orientation matrix were obtained from least squares refinements of the setting angles of 25 well defined reflections. No decay in the intensities of two standard reflections was observed during the course of data



1 4a 4b 3

Scheme 2.

Table 3
Main interatomic distances (Å) and bond angles (°) for **1a**

	Molecule A	Molecule B
C(1)–C(2)	1.37(1)	1.40(2)
C(2)–C(3)	1.35(2)	1.33(2)
C(3)–C(4)	1.39(1)	1.39(2)
C(4)–C(5)	1.41(1)	1.38(1)
C(5)–C(10)	1.38(1)	1.39(1)
C(10)–C(1)	1.39(1)	1.39(2)
C(3)–O(3)	1.37(1)	1.37(1)
C(17)–O(17)	1.44(1)	1.43(1)
C(17)–C(21)	1.51(1)	1.51(1)
C(21)–C(25)	1.45(2)	1.40(1)
C(25)–C(24)	1.38(1)	1.42(2)
C(24)–C(23)	1.42(2)	1.41(2)
C(23)–C(22)	1.40(2)	1.41(1)
C(22)–C(21)	1.43(1)	1.45(2)
C(26)–C(27)	1.42(2)	1.42(2)
C(27)–C(28)	1.41(1)	1.40(2)
C(28)–C(29)	1.40(2)	1.42(2)
C(29)–C(30)	1.39(2)	1.40(1)
C(30)–C(26)	1.40(2)	1.39(2)
Fe(1)–C(21)	2.046(9)	2.044(9)
Fe(1)–C(22)	2.025(9)	2.03(1)
Fe(1)–C(23)	2.06(1)	2.04(1)
Fe(1)–C(24)	2.04(1)	2.04(1)
Fe(1)–C(25)	2.04(1)	2.04(1)
Fe(1)–C(26)	2.06(1)	2.01(1)
Fe(1)–C(27)	2.056(9)	2.03(1)
Fe(1)–C(28)	2.02(1)	2.05(1)
Fe(1)–C(29)	2.02(1)	2.04(1)
Fe(1)–C(30)	2.03(1)	2.02(1)
C(3)–C(2)–C(1)	121.0(11)	122.1(11)
O(3)–C(3)–C(2)	119.3(10)	119.1(12)
O(17)–C(17)–C(13)	109.0(9)	110.8(9)
O(17)–C(17)–C(16)	110.5(8)	111.5(10)
C(21)–C(17)–C(13)	112.7(8)	112.4(9)
C(21)–C(17)–C(16)	113.9(9)	112.3(10)
C(21)–C(17)–O(17)	107.3(8)	107.0(8)
C(17)–C(21)–Fe(1)	128.1(7)	127.1(8)
C(22)–C(21)–C(17)	128.7(10)	124.2(10)
C(21)–C(22)–Fe(1)	70.2(5)	69.5(6)
C(30)–C(26)–C(27)	106.3(10)	108.0(10)

collection. Complete crystal data and crystal data parameters are listed in Table 1. The usual corrections for Lorentz and polarization effects were applied. An empirical absorption correction DIFABS [24] was applied (maximum correction 1.25, minimum correction 0.81).

Computations were performed by using CRYSTALS [25] adapted to a Microvax II computer. Scattering factors and corrections for anomalous dispersion were from Ref. [26]. The structure was solved by direct methods and refined with anisotropic thermal parameters for all non-hydrogen atoms [27]. Because of the poor data-to-variables ratio, hydrogen atoms were included as fixed contributions except for the hydroxyl hydrogen atoms which were located on a difference Fourier map. The asymmetric entity contains two independent $C_{28}H_{32}FeO_2$ molecules and one solvent (diethyl ether) molecule.

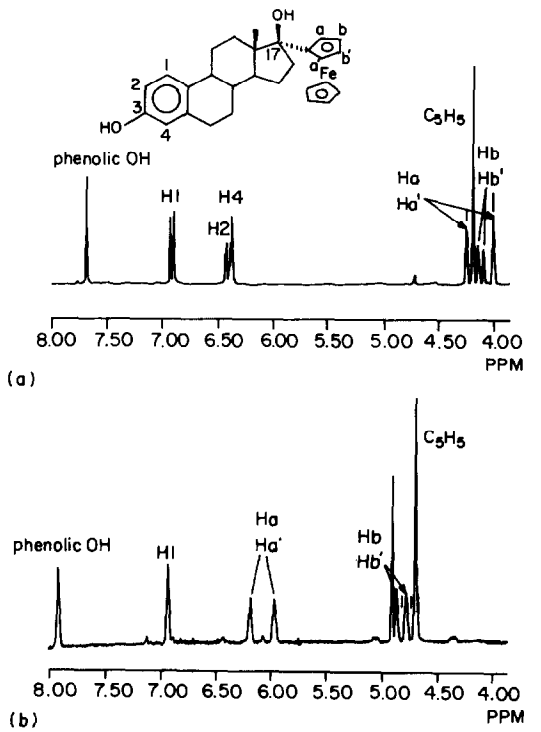


Fig. 2. (a) ^{1}H NMR spectrum of 17α-ferrocenylestradiol **1a**, recorded in THF-d_4; (b) ^{1}H NMR spectrum of cation 17-[(C_5H_5)-$Fe(C_5H_4)C_{19}H_{25}O$][CF_3COO] recorded in trifluoroacetic acid-d.

Full lists of structural parameters have been deposited at the Cambridge Crystallographic Data Centre.

4.3. Reaction of 17α-ferrocenylestradiol 1a with L-cysteine ethylester hydrochloride in the presence of acid

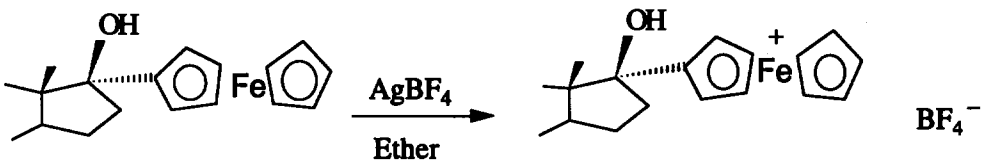
To a solution of **1a** (50 mg, 0.11 mmol) in THF (6 ml) was added 75 mg of L-cysteine ethyl ester hydrochloride (0.44 mmol) and 4-toluenesulfonic acid (17 mg, 0.028 mmol). The solution was stirred for 12 h and the solvent then removed under reduced pressure. The residue was chromatographed on silica gel (eluent: ether/pentane 1/3) yielding 40 mg of $C_{29}H_{30}FeO$ **3**.

A similar reaction in refluxing THF with a mixture of 17(α, β)-ferrocenylestradiol (90/10) (50 mg, 0.11

Table 4
Relative proportions of the isomers

	Temperature (°C)		
	20	0	−20
5	50 [a]	65	75
4a	40	25	15
4b	10	10	10
4a/4b	4	2.5	1.5

[a] Relative amount of **3**, **4a**, **4b**



1a **5**

Fig. 3. Oxidation of 17α-ferrocenylestradiol by $AgBF_4$ to give **5**.

mmol) in the presence of 20 mg of $ZnCl_2$ (0.15 mmol) gave a similar result.

4.4. Reaction of 1a with $NaBH_4$

To a solution of 17α-ferrocenylestradiol (50 mg, 0.11 mmol) in 5 ml of CH_2Cl_2 were added 80 mg of $NaBH_4$ (2.1 mmol) and 0.1 ml of $HBF_4 \cdot Et_2O$. Gas was evolved and the solution became first violet and then yellow after 30 min. The reaction led to different proportions of reduction and elimination products $C_{29}H_{32}FeO_2$ **4(a, b)** and $C_{29}H_{30}FeO$ **3**, respectively depending on temperature 20°C, 0°C and −20°C.

^1H NMR (δ, ppm, CD_2Cl_2): **4a** 7.11 (d, 8.5 Hz, H1), 6.52 (dd, 8.5 et 2.5 Hz, H2), 6.55 (d, 2.5 Hz, H4), 4.10 (s, Cp), 4.05–4.07 (m, Cp substituted), 0.37 (s, Me18) **4b** 7.04 (d, 8.5Hz, H1), 6.55 (dd, 8.5 et 2.5 Hz, H2), 6.50 (d, 2.5 Hz, H4), 4.05 (s, Cp), 3.92 (m, Cp substituted), 0.86 (s, Me18).

4.5. Synthesis of 2

17α-Ferrocenylestradiol **1a** (100 mg, mmol) was dissolved in 10 ml of ether. 0.3 ml of $HBF_4 \cdot Et_2O$ was added at room temperature. A brown-violet product precipitated, which was washed with ether until the washings were neutral, and dried under vacuum. The product is slightly soluble in CH_2Cl_2.

^1H NMR (δ, ppm, deuterated trifluoroacetic acid): 7.93 (OH phenolic), 6.93 (s, H1), 6.18–5.96 (s, broad, Haa'), 4.87–4.78 (s broad, Hbb'), 4.70 (s, Cp), 0.89 (s, Me 18).

Circular dichroism (CF_3CO_2H): λ max 355 nm (+) relative intensity 1; 320 nm (−) relative intensity 1.

4.6. Synthesis of 17α-ferriciniumylestradiol tetrafluoroborate-nitromethane (1 / 1) 5

To 82 mg of 17α-ferrocenylestradiol (0.17 mol) in diethyl ether was added an etheral solution of 100 mg of silver fluoroborate (0.5 mmol). A bluish-grey precipitate appeared immediately. This was separated, washed with diethyl ether, and dissolved in 5 ml of nitromethane. The blue-green solution was siphoned through a compact thick paper filter to remove finely divided metallic silver. The treatment was repeated until the nitromethane was colourless. Combined nitromethane extracts were evaporated at 1 mmHg, and the solid left was dried *in vacuo*. The yield was 56 mg (39%).

Circular dichroïsm: λ max 480 nm (+) relative intensity 1 with Cotton effect.

Anal. calcd. for $C_{29}H_{35}AgB_2F_8Fe$: C, 43.6; H, 4.4; Fe, 7.0; B, 2.7; F, 19.0. Found: C, 42.8; H, 4.4; Fe, 8.5; B, 2.7; F, 18.1%.

By X-fluorescence analysis the ratio Fe:Ag was found as 1:1. Additional treatment with ether or nitromethane does not effect the composition.

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