SYNTHESIS OF NEW ESTRONE DERIVATIVES USING EXCESS OXALYL CHLORIDE

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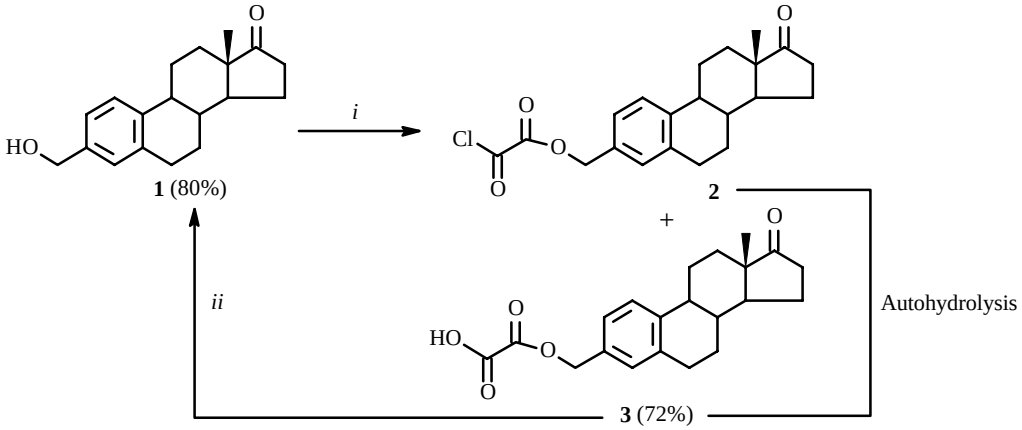
*The synthesis and structure elucidation of three new estrone derivatives chloro-oxo-acetic acid (estra-1,3,5(10)-trien-17-on-3-yl methyl) ester (**2**), oxalic acid mono (estra-1,3,5(10)-trien-17-on-3-yl methyl) ester (**3**), and ethyl (3-methoxyestra-1,3,5(10)-trien)-17β-yl oxalate (**5**) have been described.*

Key words: steroids, estrone, esterification, oxalyl chloride, NMR.

Estrone, one of the three naturally occurring estrogens, the others being estradiol and estriol, belongs to the group of female steroidal sex hormones. It is produced primarily from androstenedione originating from the gonads, adrenal cortex, and ovary. Estrone is a primary estrogenic component of several pharmaceutical preparations, including those containing conjugated and esterified estrogens, which are used to treat estrogen deficiency. There is also significant interest in the potential application of estrogen and its derivatives for the treatment and prevention of breast cancer [1, 2]. Modification of estrone structure, especially in the A and D rings, can bring about remarkable changes in the pharmacological activity of estrone [3]. As part of our on-going studies on the synthesis of new monomeric and dimeric steroid derivatives [4–6], we now report the synthesis and structure elucidation of three new estrone derivatives.



i: oxalyl chloride, DCM, 24 h, r.t.; *ii*: AcCl, EtOH, MeCN, 24 h, r.t.

Scheme 1

Chloro-oxo-acetic acid (estra-1,3,5(10)-trien-17-on-3-yl methyl) ester (**2**) and oxalic acid mono (estra-1,3,5(10)-trien-17-on-3-yl methyl) ester (**3**) were obtained from 3-methylhydroxyestra-1,3,5-trien-17-one (**1**) using excess oxalyl chloride under

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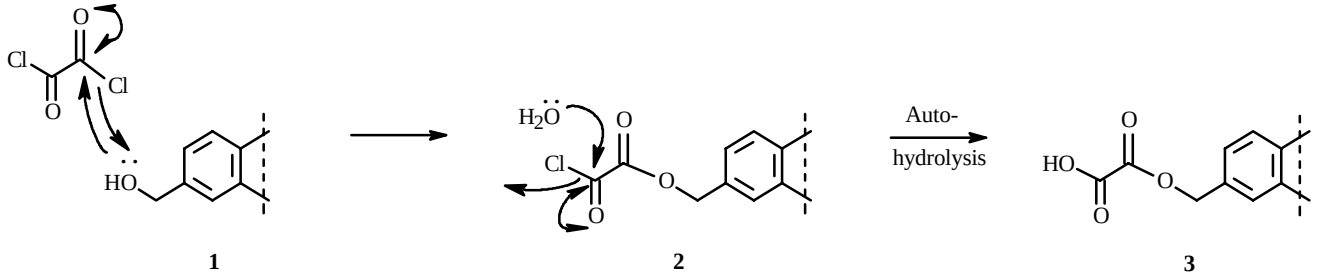
N_2 at r.t. (Scheme 1). The reaction between **1** and oxalyl chloride in pyridine afforded **3** in good yield (72%) via a reactive intermediate chloro-oxo-acetic acid (3-hydroxymethylestra-1,3,5(10)-trien-17-on)-3-yl ester (**2**). Presence of two compounds **2** and **3** (almost 1:1) was evident from the TLC analysis (Silica gel analytical plate, solvent system 10% EtOAc in petroleum-ether, visualized with I_2 vapour). The ^{1}H NMR and ^{13}C NMR spectra of the mixture of **2** and **3**, obtained immediately after the reaction was complete, showed clearly the presence of these compounds. When this mixture had been left in the NMR tube in $CDCl_3$ for **2** days, and the ^{1}H and ^{13}C NMR spectra were obtained again, it was found that this mixture turned into one compound, and it was **3**. The possible reaction mechanism is shown in Scheme 2. It has been observed previously that the use of excess oxalyl chloride generally leads to the formation of the respective chloro-oxo compounds which are rather labile to further nucleophilic reactions [7]. The IR spectrum of **3** revealed absorption bands at 1767 and 1739 cm^{-1} for the oxalate C=O and 1710 cm^{-1} for the ketonic C=O.



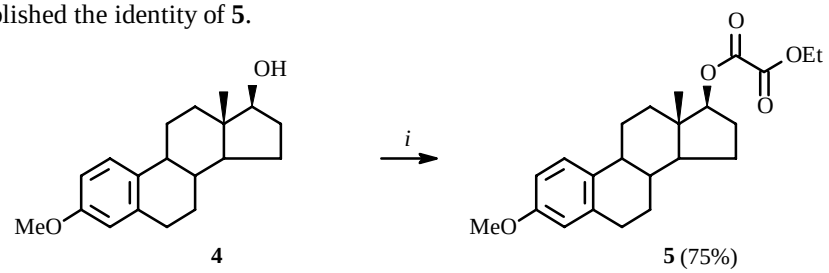
1 **2** **3**

Scheme 2. Possible reaction mechanism of compound 3 via compound 2 by auto-hydrolysis.

The ^{1}H NMR spectrum of **3** showed all signals associated with the starting material (**1**). However, the signal for the oxymethylene protons (3-methylhydroxy) was much deshielded (δ 5.27) compared to that of **1** (δ 4.63). This significant deshielding effect on the oxymethylene protons is contributed by the oxalate carbonyl forming an ester linkage with the 3-methylhydroxy moiety of **1**. The presence of a free acid group in the oxalate moiety was evident from the 1H broad singlet at δ 7.45. The ^{13}C NMR spectrum re-confirmed the structure of **3** by displaying signals at δ 158.0 and 157.4 for two carbonyls of the oxalate moiety and at δ 69.3 for the oxymethylene carbon (as opposed to δ 65.2 for **1**). The HRESIMS spectrum of **3** confirmed the structure by exhibiting the $[M+H]^+$ 357.17021 for $C_{21}H_{25}O_5$.

An attempt for esterification of estra-1,3,5-trien-17-on-3-yl methyl oxalic acid (**3**) led to the formation of 3-methylhydroxyestra-1,3,5-trien-17-one (**1**) instead of the expected ethyl ester of **3** (Scheme 1). Since HCl was produced *in situ*, instead of esterification, **3** was readily hydrolyzed back to **1**. Compound **1** was readily characterized by comparison of its mp, IR and ^{1}H NMR data with the literature data [8] and also by MS and ^{13}C NMR data analyses.

Synthesis of another estrone derivative, ethyl (3-methoxyestra-1,3,5(10)-trien)-17β-yl oxalate (**5**), was achieved in a similar fashion. Possibly the use of excess oxalyl chloride resulted in the formation of the intermediate chloro-oxo-acetic acid which reacted with EtOH to yield 5. In the HREIMS spectrum of **5**, the molecular ion was observed at *m/z* 386.20932, which corresponds to the molecular formula $C_{23}H_{30}O_5$. A characteristic doublet at 1759 and 1742 cm^{-1} in the IR spectrum suggested the presence of oxalate ester carbonyls and the ethyl ester carbonyl at 1742 cm^{-1} in **5**. This was supported by ^{1}H NMR signals at δ 1.42 (t, J = 6.7, 3H) for $OCH_2\mathbf{CH_3}$, 4.35 (q, J = 6.7 Hz, 2H) for $O\mathbf{CH_2}CH_3$ and 4.85 (m, 1H) for 17α-CH-O. In its ^{13}C NMR spectrum, the signals for a deshielded oxymethine (δ 85.6) for C-17, an oxymethylene (δ 63.0) for $O\mathbf{CH_2}CH_3$ and a methyl carbon (δ 14.0) for $OCH_2\mathbf{CH_3}$ and two carbonyl carbons for the oxalate moiety (δ 157.5 and 158.1, respectively, for **CO**-CO-OEt and CO-**CO**-OEt) established the identity of **5**.



4 **5** (75%)

i: oxalyl chloride, DCM, 24 h, r.t.

Scheme 3

EXPERIMENTAL

The steroid starting material (3-methylhydroxyestra-1,3,5-trien-17-one, **1**) was synthesized and identified previously in one of our labs [8]. All chemicals and solvents were used throughout without further purification. The reactions were monitored and the purity of the products was assessed by thin-layer chromatography (TLC) performed on silica gel (Merck type 60) and visualized under UV illumination and/or by I_2 vapour. Melting points of the products were determined on a Gallenkamp melting point apparatus. Infrared spectra (wave numbers in cm^{-1}) were recorded on an ATI Mattson Genesis FTIR spectrophotometer as KBr pellets. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Unity INOVA 400 MHz NMR spectrometer. Chemical shifts are reported in ppm downfield from TMS, using the middle resonance of $CDCl_3$ (7.25 ppm for ^1H and 77.23 ppm for ^{13}C) as an internal standard and coupling constants (J) in Hz. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, m = multiplet) coupling constant (s), integration and peak assignment. MS were recorded at the EPSRC Mass Spectrometry Service at Swansea.

Chloro-oxo-acetic Acid (Estra-1,3,5(10)-trien-17-on-3-yl methyl) ester (2) and Oxalic Acid Mono (estra-1,3,5(10)-trien-17-on-3-yl methyl) ester (3). A stirred solution of 3-methylhydroxyestra-1,3,5(10)-trien-17-one (**1**, 10 mg, 0.035 mmol) in dichlomethane (DCM) (3 ml) was treated with excess oxalyl chloride (~2 drops) under N_2 at r.t. After 24 h, the resulting mixture was evaporated to obtain a mixture of **2** and **3** as an oil (10 mg, 76%). When this mixture had been left in chloroform for 2 days it was found that this mixture turned into **3** (Scheme 1).

Compound 2. IR ($\nu_{max}CHCl_3$, cm^{-1}): 3026w (C-H), 2959s (C-H), 2932s (C-H), 2857s (C-H), 1767s (oxalate C=O), 1739s (oxalate C=O), 1710s (ketonic C=O), 1608w (C=C), 1598w (C=C), 1457m, 1310m, 1259m, 1176s (C-O), 1084m, 1009m and 623s (C-Cl). ^1H NMR (400 MHz, $CDCl_3$, δ, J/Hz): 0.89 (s, 3H, 18-Me), 5.29 (s, 2H, Ph-**CH_2**-O), 7.15 (d, J = 1.8, 1H, Ph H-4), 7.21 (dd, J = 1.8 and 8.2, 1H, Ph H-2), 6.22 (d, J = 8.2, 1H, Ph H-1). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 129.8 (C-1), 125.9 (C-2), 141.2 (C-3), 126.8 (C-4), 137.3 (C-5), 29.3 (C-6), 26.4 (C-7), 38.0 (C-8), 44.4 (C-9), 130.7 (C-10), 25.7 (C-11), 31.5 (C-12), 48.1 (C-13), 50.5 (C-14), 21.6 (C-15), 35.9 (C-16), 221.8 (C-17), 13.9 (C-18), 70.4 (O-CH_2), 157.2 (-CO-O), 158.1 (-CO-OH).

Compound 3. Colorless oil, 9 mg, 72%. IR ($\nu_{max}CHCl_3$, cm^{-1}): 3026w (C-H), 2959s (C-H), 2932s (C-H), 2857s (C-H), 1767s (oxalate C=O), 1739s (oxalate C=O), 1710s (ketonic C=O), 1608w (C=C), 1598w (C=C), 1457m, 1310m, 1259m, 1176s (C-O), 1084m, 1009m. ^1H NMR (400 MHz, $CDCl_3$, δ, J/Hz): 0.89 (s, 3H, 18-Me), 5.27 (s, 2H, Ph-**CH_2**-O), 6.22 (d, J = 8.2, 1H, Ph H-1), 7.15 (d, J = 1.8, 1H, Ph H-4), 7.21 (dd, J = 1.8 and 8.2, 1H, Ph H-2), 7.45 (br s, 1H, -COOH). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 129.7 (C-1), 125.8 (C-2), 140.8 (C-3), 126.4 (C-4), 137.1 (C-5), 29.2 (C-6), 26.3 (C-7), 38.0 (C-8), 44.3 (C-9), 130.7 (C-10), 25.6 (C-11), 31.5 (C-12), 48.1 (C-13), 50.5 (C-14), 21.6 (C-15), 35.9 (C-16), 222.1 (C-17), 13.8 (C-18), 69.3 (O-CH_2), 157.4 (-CO-O), 158.0 (-CO-OH). ESIMS: *m/z* 357 $[M+H]^+$, 379 $[M+Na]^+$. HRESIMS: *m/z* Found: 357.17021. $C_{21}H_{25}O_5$ requires 357.17019.

3-Methylhydroxyestra-1,3,5(10)-trien-17-one (1). An attempt for esterification of **3** (8 mg, 0.022 mmol) in MeCN (1 ml) was carried out using AcCl (1 drop) and EtOH (2 ml) at r.t. (Scheme 1). After 24 h, the resulting mixture was rotary evaporated to obtain **1** (white solid, 5 mg, 80%), mp: 153–154°C (*lit.* mp: 156–158°C, IR and ^1H NMR) [8]. ^{13}C NMR (100 MHz, $CDCl_3$): δ 127.7 (C-1), 124.5 (C-2), 139.2 (C-3), 125.6 (C-4), 138.3 (C-5), 29.3 (C-6), 26.3 (C-7), 38.0 (C-8), 44.3 (C-9), 136.8 (C-10), 25.6 (C-11), 31.5 (C-12), 48.1 (C-13), 50.4 (C-14), 21.6 (C-15), 35.9 (C-16), 222.1 (C-17), 13.8 (C-18), 68.9 (O-CH_2). ESIMS: *m/z* 285 $[M+H]^+$, 307 $[M+Na]^+$.

Ethyl (3-methoxyestra-1,3,5(10)-trien)-17b-yl Oxalate (5). A stirred solution of estradiol-3-methyl ether (**4**, 50 mg, 0.18 mmol) in dry DCM (6 ml) was treated with oxalyl chloride (1 drop) in DCM under N_2 (Scheme 3). After standing 24 h at r.t., the yellow solution was quenched with $CHCl_3$ (1% EtOH) and rotary evaporated at 40°C. The crude gummy product was purified by recrystallization from a mixture (2:1) of $CHCl_3$ and EtOAc and a colorless solid was obtained as compound **5** (white amorphous solid, 52 mg, 75%), mp: 82–84°C. IR ($\nu_{max}CHCl_3$, cm^{-1}): 3026w (C-H), 2954s (C-H), 2923s (C-H), 2856s (C-H), 1759s (oxalate C=O), 1742s (oxalate and ethyl ester C=O), 1608w (C=C), 1598w (C=C), 1492s, 1453m, 1310m, 1260m, 1158s (C-O), 1084m, 1008m, 911m and 732m. ^1H NMR (400 MHz, $CDCl_3$, δ, J/Hz): 0.91 (s, 3H, 18-Me), 1.42 (t, J = 6.7, 3H, -OCH_2CH_3), 3.78 (-OMe), 4.35 (q, J = 6.7, 2H, 24-OCH_2CH_3), 4.85 (m, 1H, 17α-CH-O), 6.71 (d, J = 1.8, 1H, H-4), 6.68 (dd, J = 1.8 and 8.2, 1H, H-2), 7.19 (d, J = 8.2, 1H, H-1). ^{13}C NMR (100 MHz, $CDCl_3$): δ 126.4 (C-1), 113.9 (C-2), 158.2 (C-3), 113.9 (C-4), 137.9 (C-5), 29.8 (C-6), 26.2 (C-7), 38.6 (C-8), 43.8 (C-9), 132.3 (C-10), 25.7 (C-11), 36.8 (C-12), 43.4 (C-13), 49.7 (C-14), 23.3 (C-15), 27.3 (C-16), 85.6 (C-17), 12.1 (C-18), 55.3 (-OMe), 14.0 (-OCH_2CH_3), 63.0 (-OCH_2CH_3), 157.5

(-CO-CO-OEt), 158.1 (-CO-CO-OEt). HREIMS: *m/z* Found: 386.20932. $C_{23}H_{30}O_5$ requires 386.20931. EIMS *m/z* (rel. int.): 386 $[M]^+$ (100), 358 (3), 269 (21), 186 (11) and 173 (19).

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