Short communication

Synthesis of 17β-Hydroxy Steroidal Oxalate Dimers from Naturally Occurring Steroids

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Abstract

Three new symmetrical steroidal oxalate dimers (**2**, **4** and **6**) were synthesised from naturally occurring 17β-hydroxysteroids, namely, testosterone (**1**), 5α-androst-2-en-17β-ol (**3**) and 3-oxo-5α-androstan-17β-ol (**5**), using oxalyl chloride in the presence of pyridine.

Keywords: Steroid, oxalyl chloride, esterification, oxalate dimers, NMR.

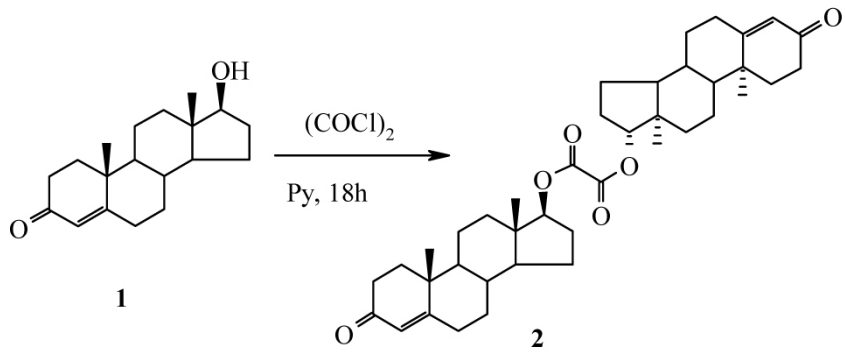
1. Introduction

Steroid-based dimers are an important group of biologically active organic molecules. They were initially isolated as synthetic by-products[1,2] and are also found in nature.[3,4] Dimeric steroids exhibit micellar, detergent, and liquid crystal behaviour[5] and are pharmaceutically important[6]. They have been utilised as catalysts for certain organic reactions[7] and can be used to develop new pharmacologically active steroids.[6] As part of our on going studies on the synthesis of steroidal dimers and monomers,[8–10] we now report here the synthesis of three new steroidal dimers which contain an oxalate ester linkage between the C-17 positions of two molecules.

2. Results and Discussion

Three symmetrical steroidal 17β-oxalate dimers (**2**, **4** and **6**) were synthesised from their respective alcohols using oxalyl chloride in presence of pyridine as a base. Generally, oxalyl chloride with pyridine gives esters of oxalic acid with various types of alcohols.[11] Because of the presence of secondary alcohol functionality at C-17, testosterone (**1**) which is a natural steroid hormone, was an ideal starting material for the synthesis of a ring D-ring D dimer via oxalic acid spacer. The treatment of **1** with oxalyl chloride in presence of pyridine for 18 h resulted in the synthesis of bis (androst-5-en-3-on)-17β-yl oxalate (**2**) in a yield of 51% (Scheme 1). The IR absorption bands at 1763 and 1741 cm^{-1} were for the oxalate carbonyls, and that at 1712 cm^{-1} was for the ketone carbonyl functionality at C-3. In the ^1H NMR spectrum, the signal for the oxymethine proton at C-17 and C-17' showed a deshielded triplet at δ 4.68 as opposed to δ 3.66 of the starting material. The ^{13}C chemical shift of C-17 and C-17' oxymethine carbons (Table 1) was also deshielded further (δ 85.1 as opposed to δ 81.6 of **1**) as a result of the oxalate ester formation at C-17 and C-17'. The presence of oxalate functionality was confirmed further from a ^1H–^{13}C long-range (^3J) correlation from the oxymethine protons (δ_H 4.68) to the oxalate carbonyls (δ_C 158.1) observed in the HMBC spectrum.

The IR spectra of oxalate dimers **4** and **6** showed two characteristic absorption bands, similar to those observed in case of **2**, in the region of 1768–1738 cm^{-1}. The ^1H and ^{13}C NMR spectra of these dimers demonstrated signals similar to those of respective starting materials (**1**, **3** and **5**) with the exception that significant downfield shifts of the signals for the protons and carbons adjacent to the oxalate group were observed. The ^{13}C NMR spectra (Table 1) displayed a signal at δ 157.6 or 158.1 characteristics for the oxalate carbonyls.



Scheme 1

Table 1: ^{13}C NMR ($CDCl_3$, 100 MHz) data of dimers **2**, **4** and **6**

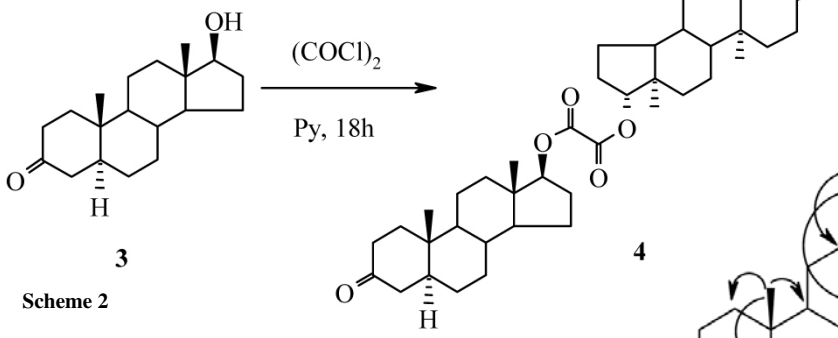
Carbon no.	Chemical shifts (δ) in ppm		
	2	**4**	**6**
1 and 1'	35.7	38.5	39.6
2 and 2'	33.9	38.1	125.6
3 and 3'	199.4	211.7	125.6
4 and 4'	124.0	44.6	30.1
5 and 5'	170.7	46.6	41.3
6 and 6'	32.7	28.7	28.4
7 and 7'	31.4	31.2	31.2
8 and 8'	35.3	35.2	35.2
9 and 9'	53.9	53.6	53.8
10 and 10'	38.6	35.7	34.5
11 and 11'	20.5	20.9	20.2
12 and 12'	36.5	36.7	36.7
13 and 13'	42.3	43.0	42.8
14 and 14'	50.1	50.4	50.5
15 and 15'	23.5	23.5	23.4
16 and 16'	27.3	27.3	27.2
17 and 17'	85.1	85.3	85.3
18 and 18'	12.0	11.4	11.6
19 and 19'	17.4	12.2	11.9
2 × CO	158.1	157.6	158.1

a yield of 47% (Scheme 2). In the ^{1}H NMR spectrum of **4**, the signal for the oxymethine proton at C-17 and C-17' showed a deshielded triplet at δ 4.67 as opposed to δ 3.71 of the starting material. The ^{13}C chemical shift of C-17 and C-17' oxymethine carbons (Table 1) was also deshielded further (δ 85.3 as opposed to δ 81.8 of **3**) as a result of the oxalate ester formation at C-17 and C-17'. The presence of oxalate functionality was confirmed further from a ^{1}H–^{13}C long-range (^3J) correlation from the oxymethine protons (δ 4.67) to the oxalate carbonyls (δ 157.6) observed in the HMBC spectrum (Figure 1).

Another oxalate dimer, bis (5α-androst-2-en)-17β-yl oxalate (**6**), connected by ring D-ring D via oxalic acid spacer, was synthesised from another androgen derivative, 5α-androst-2-en-17β-ol (**5**) in a yield of 54% (Scheme 3).

3. Experimental

The steroid starting materials [testosterone (**1**), 5α-androst-2-en-17β-ol (**3**) and 3-oxo-5α-androstan-17β-ol (**5**)] and oxalyl chloride were purchased from Aldrich and



Scheme 2

Similar reaction protocol was adopted to synthesise a ring D-ring D dimer via an oxalic acid spacer. A 5α-testosterone derivative, 3-oxo-5α-androstan-17β-ol (**3**) was treated with oxalyl chloride in presence of pyridine for 18h to yield bis (5α-androstan-3-on)-17β-yl oxalate (**4**) in

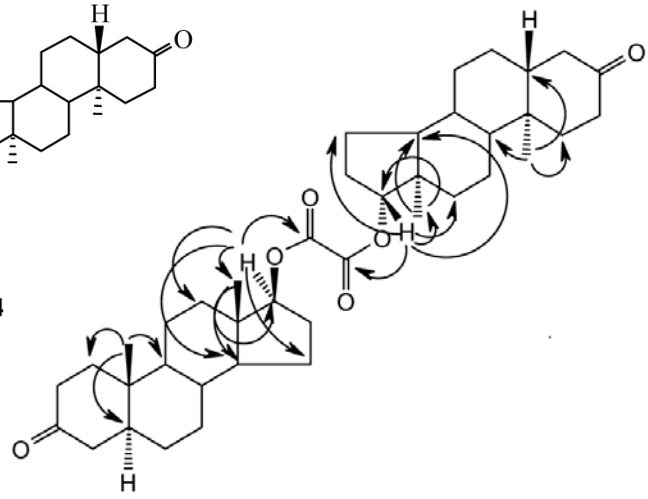
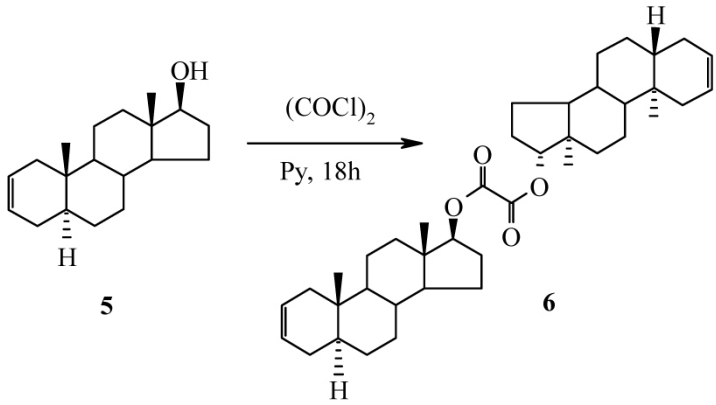


Figure 1: Key ^{1}H–^{13}C long-range correlations observed in the HMBC spectrum of **4**



Scheme 3

used as received. All chemicals and solvents were used 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 visualised under UV illumination and/or by I_2 vapour. Melting points of the products were determined on a Gallen-kamp 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. NMR spectra were obtained in $CDCl_3$. Chemical shifts (δ) are reported in ppm downfield from TMS, using the residual solvent peak (7.25 ppm for ^1H and 77.23 ppm for ^{13}C) as an internal standard and coupling constants (*J*) in Hz. Mass spectroscopic analyses were performed at the EPSRC Mass Spectrometry Service at Swansea.

Each individual stirred solution of testosterone (**1**, 600 mg, 2.08 mmol), 3-oxo-5α-androstan-17β-ol (**3**, 3.82 g, 13.15 mmol) and 5α-androst-2-en-17β-ol (**5**, 200 mg, 0.73 mmol) in dry pyridine (10, 15 and 6 ml, respectively) was treated dropwise with oxalyl chloride (132 mg, 1.04 mmol; 835 mg, 6.58 mmol; 47 mg, 0.37 mmol, respectively) over 5 min under N_2 (strongly exothermic reaction and white fumes evolved). After standing 18h at r.t., each product was treated as follows.

Bis (androst-4-en-3-on)-17β-yl oxalate (2): The resulting yellow solution was evaporated at reduced pressure. The crude solid was purified by recrystallisation from a mixture (2 : 1) of $CHCl_3$ and EtOAc. The title compound **2** (335 mg, 51%) was found as an off-white powder, mp: 256–257 °C. IR ($CHCl_3$; ν_{max}, cm^{-1}): 2943 (C–H), 2858 (C–H), 1763 (oxalate C=O), 1741 (oxalate C=O), 1675 (ketonic C=O), 1613 (C=C), 1433, 1318, 1190 (C–O), 912 and 755. ^1H NMR (400 MHz, $CDCl_3$): δ 0.86 (s, 6H, 18-Me and 18'-Me), 1.15 (s, 6H, 19-Me and 19'-Me), 4.68 (t, *J* = 7.9 Hz, 2H, 17-CH-O and 17'-CH-O), 5.69 (m, 2H, 4-CH and 4'-CH); ^{13}C NMR (Table 1). FABMS: *m/z*: 631 $[M + H]^+$. HRFABMS: Found: 631.39986; calc. 631.39984 for $C_{40}H_{55}O_6$.

Bis (5α-androstan-3-on)-17β-yl oxalate (4): Water (2 ml) was cautiously added, and the slurry was diluted with more H_2O (20 ml). The colourless precipitate was collected, washed with H_2O and dried over H_2O pump. The crude solid was purified by recrystallisation from a mixture (2:1) of $CHCl_3$ and EtOAc. The title compound **4** (1.98 g, 47%) was obtained as a white amorphous, mp: 283–284 °C (decomp.). IR ($CHCl_3$; ν_{max}, cm^{-1}): 2929 (C–H), 2854 (C–H), 1762 (oxalate C=O), 1740 (oxalate C=O), 1712 (ketonic C=O), 1446, 1314, 1182 (C–O), 996 and 755. ^1H NMR (400 MHz, $CDCl_3$): δ 0.83 (s, 6H, 18-Me and 18'-Me), 0.97 (s, 6H, 19-Me and 19'-Me), 4.67 (t, *J* = 7.5 Hz, 2H, 17-CH-O and 17'-CH-O), ^{13}C NMR (Table 1). FABMS: *m/z*: 635 $[M + H]^+$. HRFABMS: Found: 635.4313; calc. 635.4311 for $C_{40}H_{59}O_6$.

Bis (5α-androst-2-en)-17β-yl oxalate (6): The resulting solution was rotary evaporated at reduced pressure. The solid was dissolved in DCM and washed with H_2O to remove pyridine. The crude was purified by recrystallisation from a mixture (2:1) of $CHCl_3$ and EtOAc. The title compound **6** (121 mg, 54%) was found as a white powder**,** mp: 182–183 °C. IR ($CHCl_3$; ν_{max} cm^{-1}): 2963 (C–H), 2848 (C–H), 1768 (oxalate C=O), 1738 (oxalate C=O), 1655 (C=C), 1445, 1379, 1314, 1180 (C–O), 908 and 736. ^1H NMR (400 MHz, $CDCl_3$): δ 0.74 (s, 6H, 18-Me and 18'-Me), 0.84 (s, 6H, 19-Me and 19'-Me), 5.56 (br m, 4H, 2-CH, 2'-CH, 3-CH and 3'-CH), 4.69 (t, *J* = 7.9 Hz, 2H, 17-CH-O and 17'-CH-O); ^{13}C NMR (Table 1). FABMS: *m/z* 603 $[M + H]^+$, 625 $[M + Na]^+$. HRFABMS: Found: 603.44131; calc. 603.44130 for $C_{40}H_{59}O_4$.

4. Conclusions

Three new 17β-steroidal oxalate dimers (**2**, **4** and **6**) were synthesised from readily available steroid, testosterone (**1**), 5α-androst-2-en-17β-ol (**3**) and 3-oxo-5α-androstan-17β-ol (**5**). All three dimers were identified by comprehensive spectroscopic data analyses.

5. Acknowledgements

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6. References

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Povzetek

V prispevku je opisana priprava treh novih simetričnih steroidnih dimerov (**2, 4** in **6**) iz naravnih 17β-hidroksisteroidov, t.j. testosterona (**1**), 5α-androst-2-en-17β-ola (**3**) in 3-okso-5α-androstan-17β-ola (**5**), z uporabo oksalil klorida in piridina.