

Short communication

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

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Received: 01-08-2006

Abstract

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

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

1. Introduction

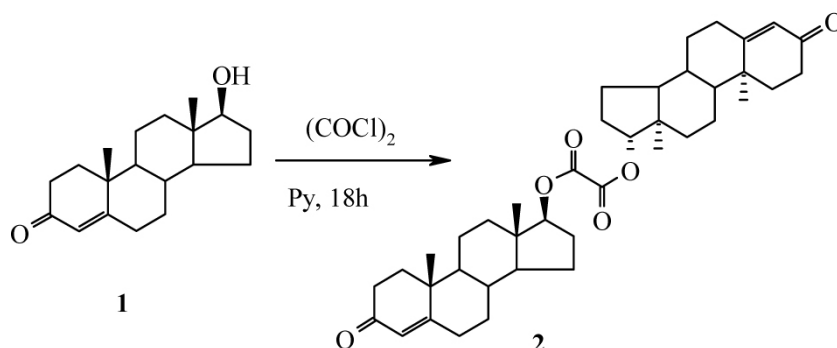
Steroid-based dimers are an important group of biologically active organic molecules. They were initially isolated as synthetic by-products^{1,2} and are also found in nature.^{3,4} Dimeric steroids exhibit micellar, detergent, and liquid crystal behaviour⁵ and are pharmaceutically important⁶. They have been utilised as catalysts for certain organic reactions⁷ 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 17 β -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)-17 β -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 ¹³C 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–¹³C 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 ¹³C 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 ¹³C 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

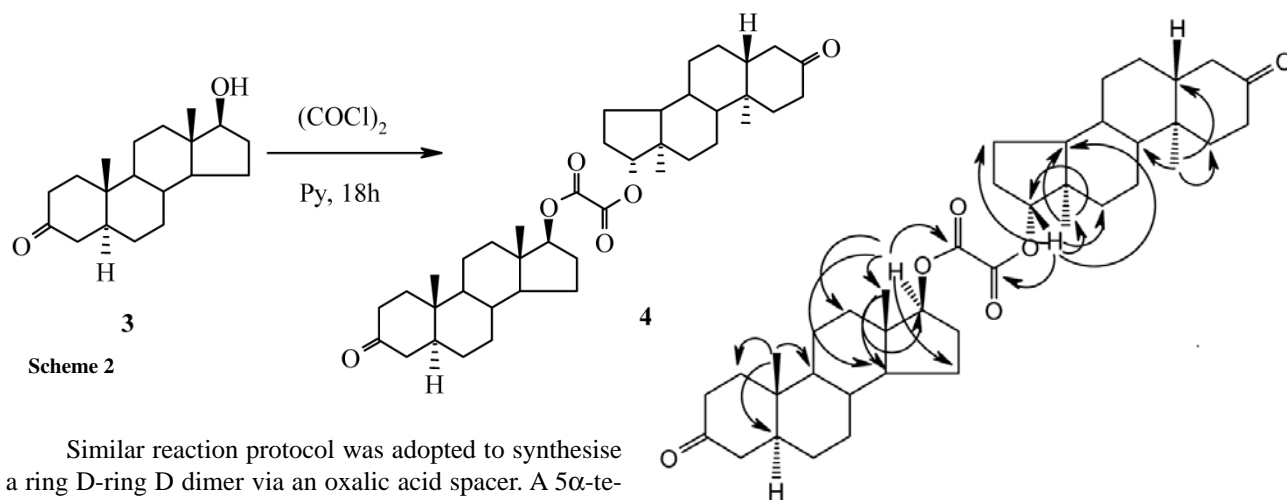
Carbon no.	Chemical shifts (δ) in ppm		
	2	4	6
1 and 1'	35.7	38.5	39.6
2 and 2'	33.9	38.1	125.6
3 and 3'	199.4	211.7	125.6
4 and 4'	124.0	44.6	30.1
5 and 5'	170.7	46.6	41.3
6 and 6'	32.7	28.7	28.4
7 and 7'	31.4	31.2	31.2
8 and 8'	35.3	35.2	35.2
9 and 9'	53.9	53.6	53.8
10 and 10'	38.6	35.7	34.5
11 and 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 \times CO	158.1	157.6	158.1

a yield of 47% (Scheme 2). In the ^1H 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 ^1H - ^{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 (5 α -androst-2-en)-17 β -yl oxalate (6), connected by ring D-ring D via oxalic acid spacer, was synthesised from another androgen derivative, 5 α -androst-2-en-17 β -ol (5) in a yield of 54% (Scheme 3).

3. Experimental

The steroid starting materials [testosterone (1), 5 α -androst-2-en-17 β -ol (3) and 3-oxo-5 α -androstan-17 β -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 5 α -testosterone derivative, 3-oxo-5 α -androstan-17 β -ol (3) was treated with oxalyl chloride in presence of pyridine for 18h to yield bis (5 α -androstan-3-on)-17 β -yl oxalate (4) in

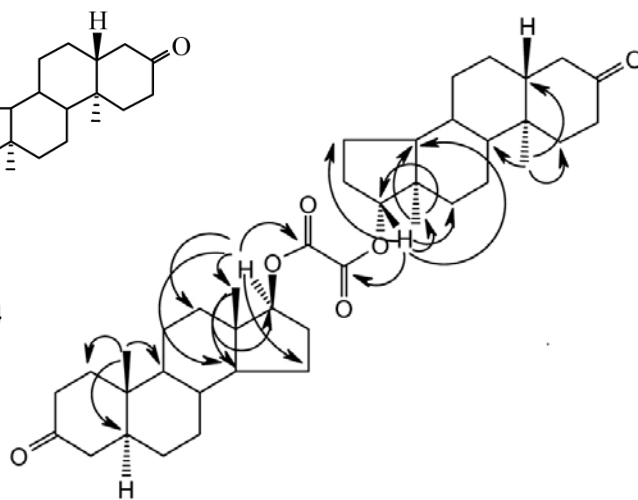
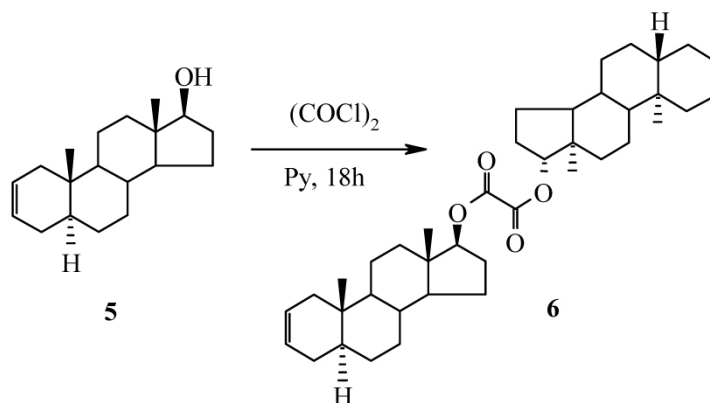


Figure 1: Key ^1H - ^{13}C long-range correlations observed in the HMBC spectrum of 4



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 I₂ 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 CDCl₃. 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 ¹³C) 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 N₂ (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 CHCl₃ and EtOAc. The title compound **2** (335 mg, 51%) was found as an off-white powder, mp: 256–257 °C. IR (CHCl₃; 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, CDCl₃): 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); ¹³C NMR (Table 1). FABMS: *m/z*: 631 [M + H]⁺. HRFABMS: Found: 631.39986; calc. 631.39984 for C₄₀H₅₅O₆.

Bis (5α-androstan-3-on)-17β-yl oxalate (4): Water (2 ml) was cautiously added, and the slurry was diluted with more H₂O (20 ml). The colourless precipitate was collected, washed with H₂O and dried over H₂O pump. The crude solid was purified by recrystallisation from a mixture (2:1) of CHCl₃ and EtOAc. The title compound **4** (1.98 g, 47%) was obtained as a white amorphous, mp: 283–284 °C (decomp.). IR (CHCl₃; 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, CDCl₃): 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), ¹³C NMR (Table 1). FABMS: *m/z*: 635 [M + H]⁺. HRFABMS: Found: 635.4313; calc. 635.4311 for C₄₀H₅₉O₆.

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 H₂O to remove pyridine. The crude was purified by recrystallisation from a mixture (2:1) of CHCl₃ and EtOAc. The title compound **6** (121 mg, 54%) was found as a white powder, mp: 182–183 °C. IR (CHCl₃; 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, CDCl₃): 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); ¹³C NMR (Table 1). FABMS: *m/z*: 603 [M + H]⁺, 625 [M + Na]⁺. HRFABMS: Found: 603.44131; calc. 603.44130 for C₄₀H₅₉O₄.

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

The authors thank the funding body for the development trust fund for a PhD studentship (LN) and EPSRC National Mass Spectrometry Service Centre (Department of Chemistry, University of Wales Swansea, Swansea, UK) for MS analysis.

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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.