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Synthesis and X-ray crystal structure of ethyl (5β-cholan-24-oic acid ethyl ester) -3α-yl oxalate

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An unexpected product, ethyl (5β-cholan-24-oic acid ethyl ester)-3α-yl oxalate, has been obtained during dimer formation studies from lithocholic acid and its molecular and crystal structure has been determined.

Keywords: steroids, X-ray crystallography, esters

Previously, four lithocholic acid dimers have been formed via esterification reactions.[1] During attempts to optimise the yield of one of these oxalate dimers using an excess of oxalyl chloride in chloroform, an oxalate ester was obtained which appeared to contain only a single steroid nucleus. We have characterised this steroidal ester by spectroscopic and crystallographic analyses.

Discussion

Ethyl (5β-cholan-24-oic acid ethyl ester)-3α-yl oxalate (**2**) was prepared from lithocholic acid as shown in the scheme.

A plot of the molecule is shown in Fig.1.

Mechanism of reaction

The origin of the two ester groups can be explained by the reaction of the acid chloride intermediates with ethanol. Thus, the initial reaction of the steroid alcohol with the excess of oxalyl chloride gives the half ester quantitatively, with concomitant conversion of the carboxyl group of the steroid to its acid chloride, again as a result of the excess of oxalyl chloride.[2] Ethyl esters are formed during the work-up procedure upon contact with the alcohol.

Crystallography

The bond lengths and angles are normal for this type of molecule. As no heavy atom is present the absolute stereochemistry of the molecule has not been determined by the X-ray study and is assumed to correspond to that of lithocholic acid. The chiral centres in the molecule (Fig.1) then become R at C3, C5, C17 and C20 and S at C8, C9, C10, C13 and C14. Ring conformations are: A (chair), B (chair), C (distorted chair), D (distorted C13 envelope).

A weak, non-classical, intermolecular hydrogen bond C25–H25A...O3^{I} (I=symmetry operation 1.5–*x*, 1–*y*,0.5+*z*) is also present. Here C25–H25A = 0.99Å, C25...O3^{I} = 3.152(7)Å, H25A...O3^{I} = 2.56Å and C25–H25A...O3^{I} = 119°. The length of the molecule is indicated by the separation between C26 and C30 = 21.910(8)Å. The pseudo torsion angle C19–C10...C13–C18 is 1.59(5)°.

Experimental

Synthesis of ethyl (5β-cholan-24-oic acid ethyl ester)-3α-yl oxalate (**2**): Lithocholic acid (**1**), oxalyl chloride and dichloromethane were purchased from Aldrich and used as received. The purity of the product was supported by Thin-Layer Chromatography (TLC) performed on silica gel (Merck type 60) and visualised under UV illumination and/or by I_2 vapour. The compound was purified by Vacuum Liquid Chromatography (VLC) using TLC grade silica (Kiselgel 60 PF_{254}). The melting point of the product was 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 CD_3OD (3.30 ppm for ^{1}H and 49.15 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 (*J*), integration and peak assignment.

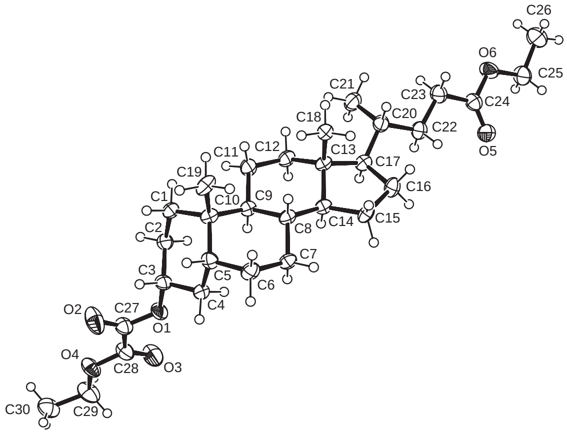
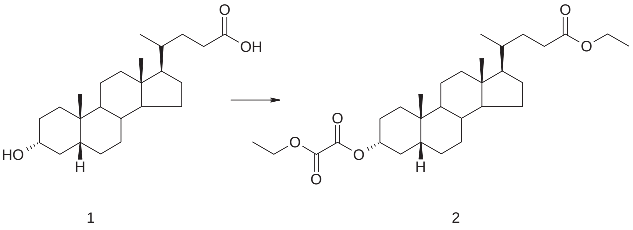


Fig.1. The atomic arrangement in the molecule. Ellipsoids are shown at the 50% probability level.



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Scheme 1

A stirred solution of lithocholic acid (300 mg) in dichloromethane (10 ml) was treated drop wise with oxalyl chloride (521 mg) under nitrogen at room temperature. After 24 h, chloroform (10 ml), containing 0.5–1% of ethanol was added, and the mixture was evaporated *in vacuo*. The crude product was purified by preparative TLC (EtOAc/hexane 3:7) to give the diester as a colourless solid (336 mg, 83%), recrystallised from $CHCl_3$/EtOH (2:1), m.p. 96^{o} C, ν_{max} 2934, 2862, 1765 (oxalate C=O), 1739 (ester C=O), 1453, 1378, 1304, 1260, 1193 (ester C-O), 1023, 973 and 760 cm^{-1}. ^{1}H NMR (400 MHz): δ 0.59 (s, 3H, 18-Me), 0.86 (d, *J* = 6.2 Hz, 3H, 21-Me), 0.89 (s, 3H, 19-Me). ^{13}C NMR (100 MHz): δ 34.9 (C1), 26.2 (C2), 77.9 (C3), 31.8 (C4), 41.9 (C5), 27.0 (C6), 26.3 (C7), 35.8 (C8), 40.3 (C9), 34.6 (C10), 20.8 (C11), 40.1 (C12), 42.7 (C13), 56.4 (C14), 24.2 (C15), 28.2 (C16), 56.0 (C17), 12.0 (C18), 23.2 (C19), 35.3 (C20), 18.3 (C21), 31.3 (C22), 31.0 (C23), 174.3 (C24), 60.2 (C25), 14.3 (C26), 157.4 (C27), 158.2 (C28), 63.1 (C29) and 14.0 (C30). The FABMS spectrum of the compound revealed the $[M+H]^+$ and $[M+Na]^+$ ions at *m/z* 505 and 527, respectively, indicating the molecular formula, $C_{30}H_{48}O_6$.

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X-ray crystallography

All crystallographic measurements were performed with a Bruker KappaCCD diffractometer using graphite-monochromated Mo-Kα radiation. A rotating anode source, an area detector and ϕ and ω scans were used with a detector-to-crystal distance of 35 mm. The programs DENZO[3] and COLLECT[4] were used in data collection and cell refinement. The structure was solved with SIR-97[5] and refined with SHELX-97.[6] Details of the crystal data and refinement are given in Table 1.

Table 1 Crystal data and structure refinement for $C_{30}H_{48}O_6$

Molecular formula	$C_{30}H_{48}O_6$
Formula weight	504.68
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 7.4550(2) Å, α= 90°.
	b = 11.1580(3) Å, β= 90°.
	c = 33.9840(11) Å, γ = 90°.
Volume	2826.89() 14Å^3
Z	4
Density (calculated)	1.186 Mg/m^3
Absorption coefficient	0.081 mm^{-1}
F(000)	1104
Crystal size	0.18 × 0.10 × 0.01 mm^3
Theta range for data collection	2.98 to 27.42°.
Index ranges	$-9<=h<=9$, $-14<=k<=14$, $-43<=l<=43$
Reflections collected	18195
Independent reflections	3447 [R(int) = 0.0947]
Completeness to theta = 27.42°	93.5 %
Max. and min. transmission	0.9992 and 0.9856
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3447 / 0 / 328
Goodness-of-fit on F^2	1.145
Final R indices [I>2σ(I)]	$R1$ = 0.0637, $wR2$ = 0.1177
R indices (all data)	$R1$ = 0.1586, $wR2$ = 0.1526
Final weighting scheme	calc $w=1/\sigma^2(Fo^2)+(0.0294P)^2+2.4251P]$ where: $P=(Fo^2+2Fc^2)/3$
Extinction coefficient	0.0026(6)
Largest diff. peak and hole	0.293 and –0.330 e Å^{-3}

All non-hydrogen atoms were allowed to refine with anisotropic displacement parameters. The hydrogen atoms were located geometrically and allowed to ride with isotropic temperature factors constrained to be 1.2 U_{eq} (non-methyl hydrogens) or 1.3 U_{eq} (methyl hydrogens) of the attached atom. Plots and molecular geometries were obtained with PLATON.[7] Full crystallographic data, excluding structure factors, have been deposited at the Cambridge Crystallographic Data Centre (CCDC) (number 254356). Issue 1. Any request to the CCDC should quote the full literature citation and the reference number.

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