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## The crystal structure of 14-oxo-13,14-seco-5 $\alpha$ -cholest-13(18)-en-3 $\beta$ -yl acetate and the assignment of the configuration of its acetoxy derivatives

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The crystal structure of 14-oxo-13,14-seco-5 $\alpha$ -cholest-13(18)-en-3 $\beta$ -yl acetate (**2**), obtained (in addition to the (*E*)- $\Delta^{12}$ -isomer **3**) by oxidative fragmentation of the C(13)-C(14) bond of 14 $\alpha$ -hydroxy-5 $\alpha$ -cholestan-3 $\beta$ -yl acetate (**1**), was determined by X-ray analysis. In addition, the configurations of the acetoxy derivatives **4-6**, formed by the thermal lead tetraacetate oxidation of **1**, were deduced from the relevant <sup>1</sup>H-NMR parameters.

**Keywords:** X-ray analysis, 14-oxo-13,14-seco-5 $\alpha$ -cholest-13(18)-en-3 $\beta$ -yl acetate, acetoxy derivatives of, <sup>1</sup>H-NMR.

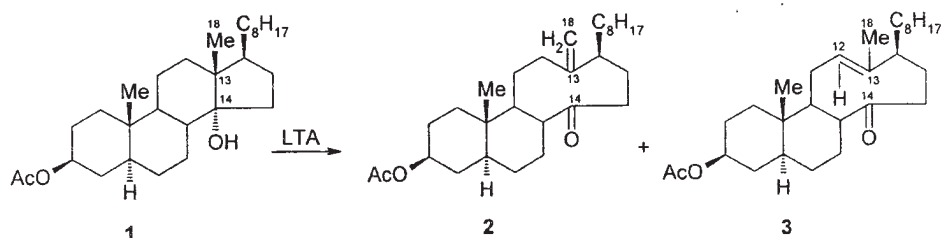
### INTRODUCTION

In a recent publication<sup>1</sup> we reported that the lead tetraacetate (LTA) oxidation of 14 $\alpha$ -hydroxy-5 $\alpha$ -cholestan-3 $\beta$ -yl acetate (**1**)<sup>2</sup> proceeds (exclusively with LTA/ $\Delta$  or LTA/I<sub>2</sub> and preferentially with LTA/h $\nu$ ) by fragmentation of its C(13)-C(14) bond to give a new type of modified 13,14-secosteroids containing a nine-membered ring instead of the steroid rings C and D, *i.e.*, the 13(18)-didehydro-13,14-seco derivative **2** and the isomeric (*E*)- $\Delta^{12}$ -13,14-seco ketone **3** (Scheme 1).

It was found that the seco ketone **2**, when formed by thermal LTA oxidation, reacts further with the oxidant undergoing the known allylic and  $\alpha$ -acetoxylation,<sup>3</sup> to give derivatives **4-6** (Scheme 2). Although the positions of acetoxylation of **2** have been well established, the stereochemistry of the introduced acetoxy groups in compounds **4-6** has remained undefined.\*\*

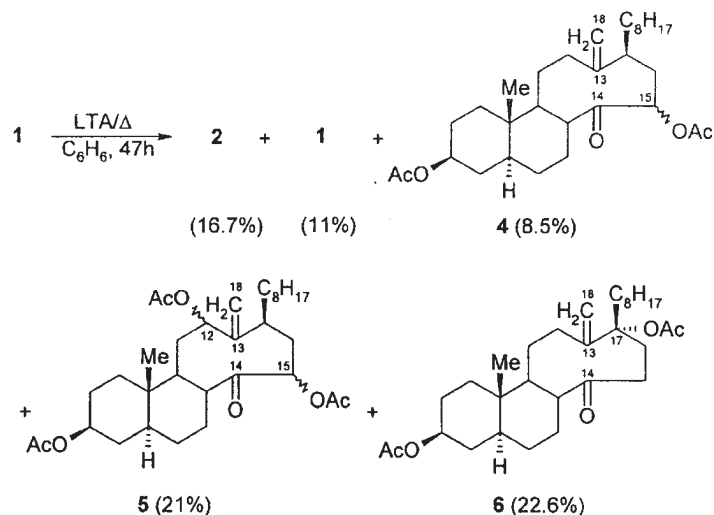
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\*\* The 17 $\alpha$ -position of the acetoxy group in compound **6** was only suggested in the previous paper.



Scheme 1.

Therefore, in order to obtain additional information concerning the structural characteristics of the seco ketone **2** and its acetoxy derivatives, in the present paper the solid state conformation of the seco ketone **2** was determined by X-ray analysis and the configuration of the introduced acetoxy groups deduced from the relevant  $^1\text{H-NMR}$  parameters.



Scheme 2.

## RESULTS AND DISCUSSION

### *X-Ray crystal structure analysis of the seco ketone 2*

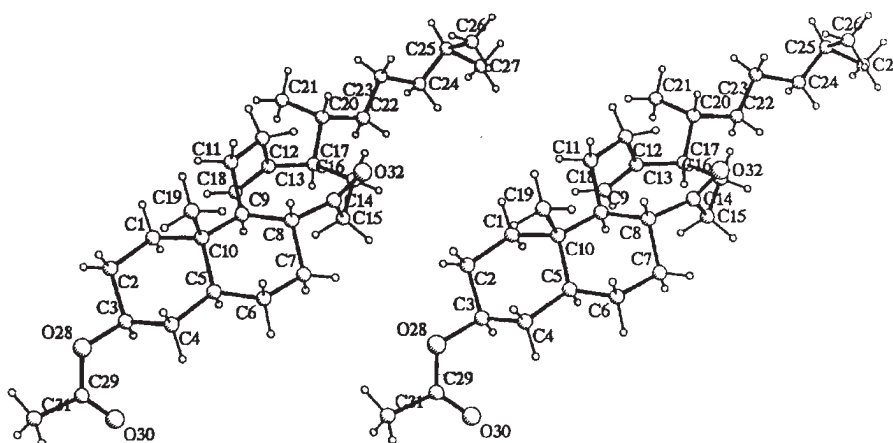
X-Ray analysis of compound **2** confirmed the proposed structure to be 14-oxo-13,14-seco-5 $\alpha$ -cholest-13(18)-en-3 $\beta$ -yl acetate (**2**) (*cf.* Table I).

The results show that there are two independent molecules in the asymmetric part of the unit cell of **2**.<sup>\*</sup> These two molecules seem to have very similar conformations. (The stereoscopic view is given in Fig. 1).

<sup>\*</sup> The crystals used for the analysis were of poor quality which explains the rather low  $2\theta_{\text{max}}$  and the high standard deviations of the geometrical parameters.

TABLE I. Crystal data and structure refinement for **2**

Empirical formula	$C_{29}H_{48}O_3$
Formula weight	444.67
Temperature	293(2) K
Wavelength	1.54178 Å
Crystal system	orthorhombic
Space group	$P21212$
Unit cell dimensions	$a = 34.43(2)$ Å $\alpha = 90^\circ$ $b = 21.55(12)$ Å $\beta = 90^\circ$ $c = 7.509(3)$ Å $\gamma = 90^\circ$
Volume	$5571(31)$ Å <sup>3</sup>
<i>Z</i>	8
Density (calc.)	1.060 Mg/m <sup>3</sup>
Absorption coefficient	0.510 mm <sup>-1</sup>
<i>F</i> (000)	1968
Crystal size	0.36 × 0.1 × 0.08 mm
Θ range for data collection	3 – 50°
Index ranges	$0 \leq h \leq 36, 0 \leq k \leq 21, 0 \leq l \leq 7$
Reflections collected	3331
Independent reflections	3331 [R(int) = 0.0000]
Refinement method	full-matrix least squares of Fsqd
Data/restraints/parameters	3331/244/579
Goodness-of-fit (all data)	0.858 (1.379)
Final <i>R</i> indices [ <i>I</i> > 2σ( <i>I</i> )]	<i>R</i> 1 = 0.0765, <i>wR</i> 2 = 0.1676
<i>R</i> indices (all data)	<i>R</i> 1 = 0.1655, <i>wR</i> 2 = 0.1990
Absolute structure parameter	1.1 (10)
Extinction coefficient	0.0008 (2)
Largest diff. peak and hole	0.159 and -0.186 e·Å <sup>-3</sup>

Fig. 1. Stereoscopic view of the seco ketone **2** in its solid state conformation.

H-Atom positions were calculated with the assumption of normal geometry. A list of the fractional atomic coordinates, isotropic thermal parameters and bond lengths and angles has been deposited at the *Cambridge Crystallographic Data Centre* as the supplementary publication No. 102112.

#### Assignment of the configuration of the acetoxy derivatives 4-6

An inspection of molecular models indicated that the mobility of the nine-membered ring of ketone **2** in solution is restricted by the presence of the rings A and B and the 17 $\beta$ -sidechain. However, its 14-oxo and 13-methylidene groups are flexible and can be either „ $\alpha$ -oriented“ (*i.e.*, below the general plane of the 9-membered ring) or „ $\beta$ -oriented“ (*i.e.*, above the general plane of the ring).

It can be safely assumed that the stereochemistry of acetoxylation should depend upon the orientation of these groups, since, for steric reasons, the acetoxy functions introduced into the 9-membered ring of the seco ketone **2** are expected to occupy equatorial (or pseudoequatorial) positions.

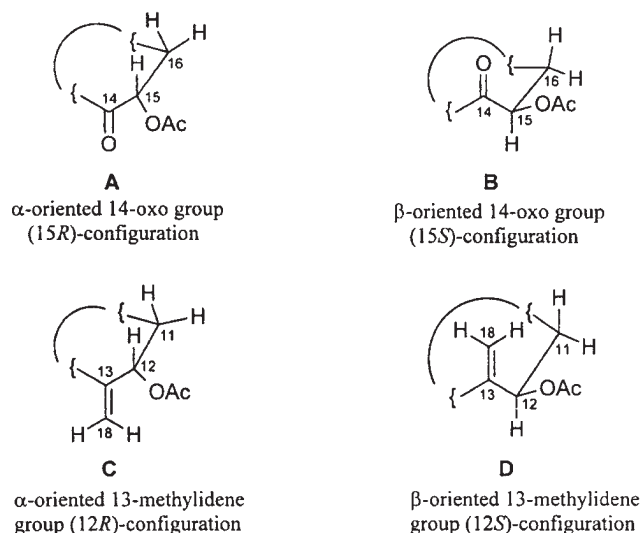


Fig. 2. Partial structure of the nine-membered ring in compounds **4** and **5** with possible orientation of the 14-oxo (**A** and **B**) and 13-methylidene group (**C** and **D**).

In the case of 15-acetoxylation, the equatorial 15-acetoxy group in conformation with the  $\alpha$ -oriented 14-oxo group has the (15*R*)-configuration (Fig. 2, **A**), while the equatorial isomer with a  $\beta$ -oriented 14-oxo group, has the (15*S*)-configuration (Fig. 2, **B**). The fact that compounds **4** and **5** have the (15*S*)-configuration was deduced from their  $^1\text{H-NMR}$  spectral data (Table II).

The H-C(15) signal in compounds **4** and **5** appears as a *dd* at  $\delta$  5.41 and 5.39 ppm, respectively.\* The coupling parameters of these resonances are  $J = 6.9$  and 2.8 Hz for the former and  $J = 5.1$  and  $\approx 2.5$  Hz for the latter compound (Table II), sug-

\* The calculated value for O=C-CH(OAc);  $\delta$  5.40 ppm.<sup>4</sup>

gesting, in accordance with the (15*S*)-configuration, an unequal dihedral angle (of about 60° and 180°)<sup>5</sup> between the H-C(15) and H<sub>2</sub>C(16) methylene group. In the (15*R*)-isomer the H-C(15) signal, due to the nearly equal dihedral angle between the H-C(15) and H<sub>2</sub>C(16) protons, would appear as a triplet.

A similar reasoning can also be applied when the configuration at C(12) in compound **5** is considered. The H-C(12) resonance in **5** appears at δ 5.26 ppm as a *t*, *J* = 6.7 Hz, which is consistent with the (12*R*)-configuration (see Fig. 2, C). For the (12*S*)-configuration a *dd* multiplicity for this proton would be expected (Fig. 2, D).

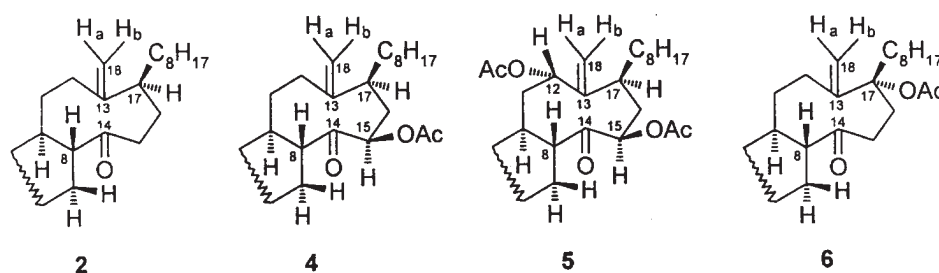


Fig. 3. The nine-membered ring of **2** and its acetoxyated derivatives **4-6**.

The latter data imply that the 13-methylidene group in the (12*R*)-acetoxy derivative **5** is  $\alpha$ -oriented. The same orientation in the 17 $\alpha$ -acetoxy derivative **6** can be deduced from the strong deshielding effect which the AcO group exerts on the methylidene protons (see Table II). The deduced configurations of the acetoxyated compounds **4-6** are presented in Fig. 3.

TABLE II. Selected <sup>1</sup>H-NMR spectral data\* of the seco ketone **2** and its ecetoxyated products **4-6**

	<b>2</b>	<b>4</b>	<b>5</b>	<b>6</b>
H <sub><math>\alpha</math></sub> -C(3)	4.72 <i>m</i>	4.72 <i>m</i>	4.70 <i>m</i>	4.71 <i>m</i>
H <sub><math>\beta</math></sub> -C(8)	2.41 <i>br.t</i>	2.63 <i>dt</i>	2.77 <i>dt</i>	2.58 <i>dq</i>
	<i>J</i> = 11.6	<i>J</i> = 11.7, 4, 6	<i>J</i> = 11.4, 5.4	<i>J</i> = 11.0, 4, 6
H <sub><math>\beta</math></sub> -C(12)	—	—	5.26 <i>t</i>	—
			<i>J</i> = 6.7	
H <sub><math>\alpha</math></sub> -C(15)	—	5.41, <i>dd</i>	5.39, <i>dd</i>	—
		<i>J</i> = 6.9, 2.8	<i>J</i> = 5.1, $\approx$ 2.5	
H <sub><math>\alpha</math></sub> -C(17)	2.65, <i>br.d</i>	$\approx$ 2.30 <i>m</i>	2.30, <i>dd</i>	—
	<i>J</i> = 13.6		<i>J</i> = 16.0, 7.2	
H <sub><math>\beta</math></sub> 18	5.00	5.10	5.09	5.25
H <sub><math>\alpha</math></sub> C=C(13)	4.84	4.91	5.20	5.23

\*Chemical shifts are in  $\delta$  values, *J* in Hz.

The above results also indicated that conformations of the nine-membered ring of the acetoxy derivatives **4-6** in solution (the computed C-skeleton of which is shown in Fig. 4) and the solid-state conformation of the seco ketone **2**, determined by the X-ray analysis (Fig. 1), contain the 14-oxo and 13-methylidene groups ori-

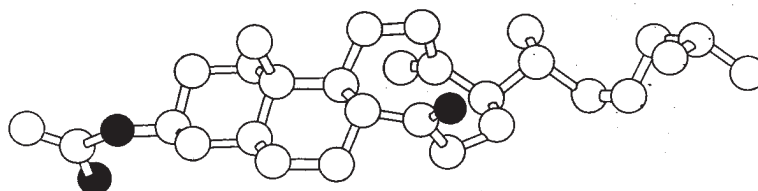


Fig. 4. The computed C-skeleton of compounds 4-6.

ented in the same manner, *i.e.*, in all compounds the 14-oxo function is  $\beta$ -oriented and the 13-methylidene group is  $\alpha$ -oriented.

#### EXPERIMENTAL

##### *Thermal LTA oxidation of 14 $\alpha$ -hydroxy-5 $\alpha$ -cholestan-3 $\beta$ -yl acetate (1)*

A suspension of diol acetate **1** (500 mg, 1.12 mmol), LTA (730 mg, 1.65 mmol) and CaCO<sub>3</sub> (165 mg, 1.65 mmol) in dry benzene (45 ml) was heated at reflux with stirring for 20 h, after which time the starch-iodide test was negative. Additional amounts of LTA (500 mg, 1.13 mmol) and of CaCO<sub>3</sub> (113 mg, 1.13 mmol) were added, and the heating at reflux continued for an additional 27 h. The mixture was cooled to r.t., diluted with Et<sub>2</sub>O, the insoluble precipitate filtered off through Celite and washed with Et<sub>2</sub>O. The organic solution was washed successively with aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> soln., aq. NaHCO<sub>3</sub> soln. and water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated. The resulting mixture (590 mg) was separated by chromatography on a SiO<sub>2</sub> column (150 g). Elution with toluene/EtOAc (96:4) afforded **2** (83 mg, 16.7%), **4** (48 mg, 8.5%), starting 14 $\alpha$ -ol **1** (55 mg, 11%), **5** (132 mg, 21.0%) and **6** (127 mg, 22.6%). Identification of the products and their spectral characteristics are given in Ref. 1.

<sup>1</sup>H-NMR Spectra were recorded at 250 MHz (Bruker AM-250) in CDCl<sub>3</sub> solution at room temperature using SiMe<sub>4</sub> as the internal standard. Selected data are given in Table II.

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#### ИЗВОД

##### КРИСТАЛНА СТРУКТУРА 14-ОКСО-13,14-СЕКО-5 $\alpha$ -ХОЛЕСТ-13(18)-ЕН-3 $\beta$ -ИЛ-АЦЕТАТА И ОДРЕЂИВАЊЕ КОНФИГУРАЦИЈЕ ЊЕГОВИХ АЦЕТОКСИ ДЕРИВАТА

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Кристална структура 14-оксо-13,14-секо-5 $\alpha$ -холест-13(18)-ен-13 $\beta$ -ил-ацетата (**2**), који се добива (поред (*E*)- $\Delta^{12}$ -изомера **3**) оксидативном фрагментацијом C(13)-C(14) везе 14 $\alpha$ -хидрокси-5 $\alpha$ -холестан-3 $\beta$ -ил-ацетата (**1**) одређена је анализом X-зрака. Поред тога, конфигурације његових ацетокси деривата **4-6**, који се граде при термичкој олово-тетраацетатној оксидацији, изведене су на основу одговарајућих <sup>1</sup>H-NMR параметара.

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