

THE FORMATION OF 8,14-SECO-STEROID SYSTEMS:
 $3\beta,5,17\beta$ -TRIHYDROXY-8,14-SECO-5 α -ANDROSTAN-8-ONE
AND ITS 3,17-DIACETATE ESTER

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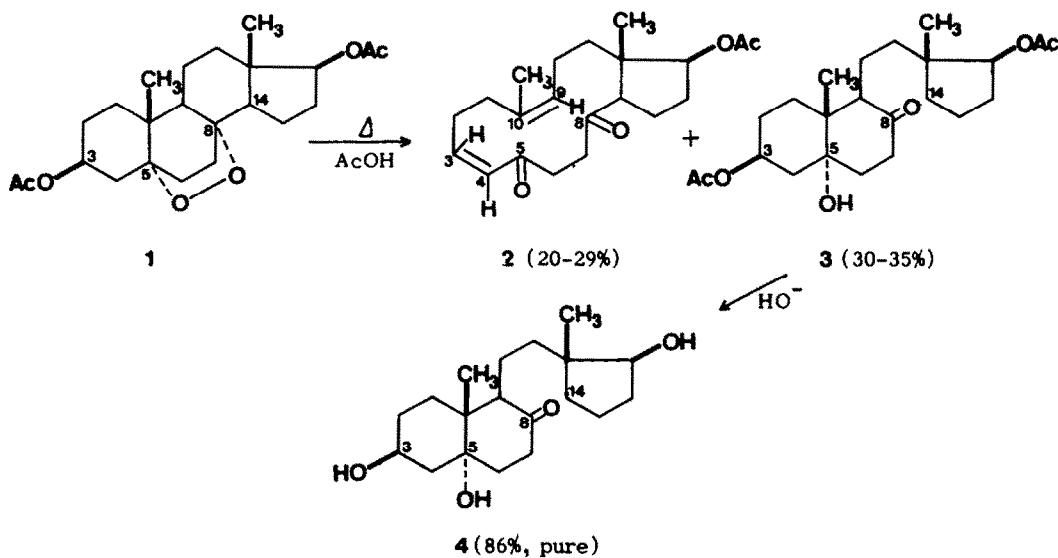
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Abstract - When subjected to thermolysis under acidic conditions, the steroidal 5 α ,8 α -peroxide 1 afforded, in addition to the 5,10;8,9-diseco derivative 2, a monofragmentation compound, i.e. the 8,14-seco-steroid 3, the structure of which was determined by X-ray analysis of its hydrolysis product 4.

In the course of our study concerning the possibility to synthesize 5,10;8,9-diseco-steroids, i.e. modified steroid derivatives containing a 14-membered ring, we have also investigated the thermolysis of 5,8 α -peroxy-5 α -androstane- $3\beta,17\beta$ -diol diacetate (1)¹ in acetic acid. Under these conditions, two major products were obtained (Scheme): as already reported,¹ the desired (E,E)- 17β -hydroxy-5,10;8,9-diseco-3,9-androstadiene-5,8-dione acetate (2), in 20-29% yield, and an oily trihydroxy-ketone diacetate, in 30-35% yield, which could



Scheme

be hydrolyzed to a crystalline keto-triol, $C_{19}H_{32}O_4$, m.p. $141-2^\circ$. The structure of this latter compound, as determined by X-ray analysis (see below), was shown to be 4, i.e. to correspond to $3\beta,5,17\beta$ -trihydroxy-8,14-seco- 5α -androstan-8-one (for the conformation in the solid state see Figure), and that, therefore, the diacetate precursor, formed in the thermolysis reaction of 1, is product 3.

X-Ray analysis and structure determination. - Crystal data of $3\beta,5,17\beta$ -trihydroxy-8,14-seco- 5α -androstan-8-one (4) are as follows: $C_{19}H_{32}O_4$, monoclinic, space group $P2_1$ with $a = 12.158(16)$, $b = 6.233(4)$, $c = 12.783(13)$ Å, $\beta = 105.66(8)^\circ$; $V = 932.7(16)$ Å³. Two molecules per unit cell ($Z = 2$) gave $D_x = 1.16$ g cm⁻³. The intensity data were recorded on a Syntax P2, diffractometer, using graphite monochromatized MoK α radiation ($\lambda = 0.71069$ Å). 1519 independent reflections were measured, of which 931, with $I > 2.5\sigma$ (I), were used in the structure determination. The structure was solved by tangent refinement of random phases, and refined first with isotropic and then anisotropic temperature factors using SHELX 76.² Hydrogen atoms positions (except H of methyl C(18), calculated) were found on a Fourier difference and introduced in the refinement process. The final R value is 0.055. The list of atomic coordinates and molecular dimensions has been deposited with the Cambridge Crystallographic Data Center.

The Figure is a stereoscopic view, showing the numbering of the atoms (programme PLUTO³).

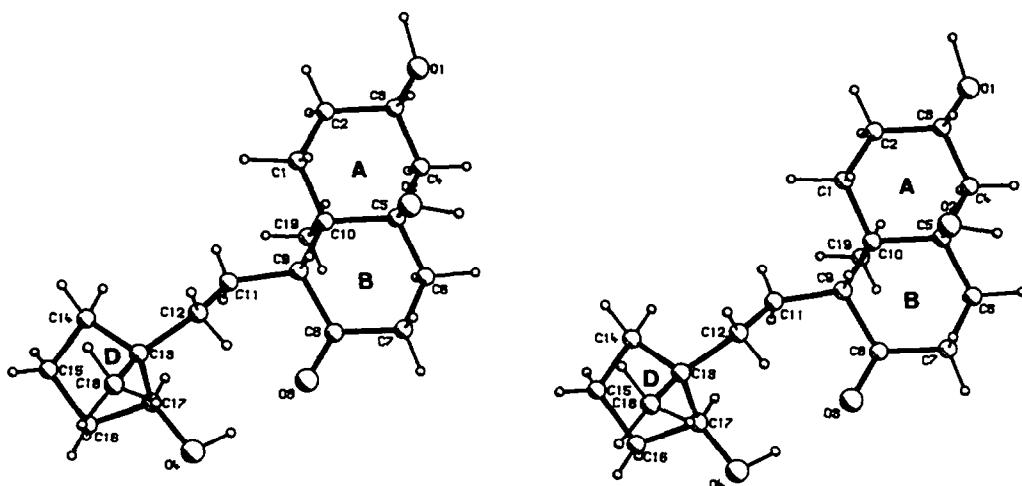


Figure. Structure and solid-state conformation of $3\beta,5,17\beta$ -trihydroxy-8,14-seco- 5α -androstan-8-one (4)

The two six-membered rings A and B are in parallel chair conformations with an approximate local mirror plane containing C(5) and C(10). The pentagonal cycle D exhibits a half-chair conformation, the twofold symmetry axis passing through C(15) and the middle point of the C(13)-C(17) bond.

Intermolecular hydrogen bonds exist between O(4)-O(1) = 2.78 Å ($x-1, y, z$) and between O(2)-O(1) = 2.79 Å ($1-x, 0.5+y, 1-z$).

Further work is in progress in order to elucidate the mechanism of formation of 3 β ,5,17 β -trihydroxy-8,14-seco-5 α -androstan-8-one 3,17-diacetate (3) from the 5 α ,8 α -peroxide 1, and to examine the synthetic possibilities of these new and interesting seco-steroids (3 and 4).

EXPERIMENTAL[†]

M.ps are uncorrected. IR spectra were measured on a Perkin-Elmer Spectrophotometer, Model 337. $^1\text{H-NMR}$ spectra were recorded at 360 MHz on a Bruker HX-360 spectrometer, and $^{13}\text{C-NMR}$ spectra at 20.1 MHz on the same apparatus; solvent - CDCl_3 , internal standard - TMS, room temp; chemical shifts are reported in ppm as δ values. Mass spectra were obtained on a Mass Spectrometer Varian CH7. Silica gel of 0.063-0.200 mm size was used for preparative column chromatography. The separation of products was monitored by thin-layer chromatography on silica gel G (Stahl) with benzene-ethyl acetate (7:3), detection being effected with 50% aqueous sulphuric acid.

Thermolysis of 5,8 α -peroxy-5 α -androstan-3 β ,17 β -diol diacetate (1). - A solution of the peroxy-diacetate 1^4 (5.0 g, 12.3 mmol) in acetic acid (400 ml) and water (4 ml) was refluxed with stirring under nitrogen for 28 hours, when practically all starting material was consumed. The solvent was evaporated *in vacuo*, leaving an oily residue (about 5 g) which was chromatographed on silica gel (200 g). Elution with benzene-diethyl ether (9:1) gave the 5,10;8,9-diseco-compound 2^1 (1.25 g, 29.3%), whereas benzene-diethyl ether 7:3 eluted 3 β ,5,17 β -trihydroxy-8,14-seco-5 α -androstan-8-one 3,17-diacetate (3) (1.705 g, 34%), as on oil: $[\alpha]_D^{20} = -19.9^\circ$ ($c = 1.0$, CHCl_3); IR (neat): $\nu_{\text{max}} = 3460, 1740, 1700, 1240 \text{ cm}^{-1}$; $^1\text{H-NMR}$: 0.82 (s, $\text{H}_3\text{C}-18$), 0.94 (s, $\text{H}_3\text{C}-19$), 2.04 (s, AcO-3 and AcO-17), 2.23 (d x d, $J_1 = \sim 15 \text{ Hz}$, $J_2 = \sim 4 \text{ Hz}$, one H) and 2.72 (m, two H) ($= \text{H}_2\text{C}-7 + \text{HC}-9$), 4.75 (q, HC-17), 5.15 (m, HC-3); $^{13}\text{C-NMR}$ (selected data): 70.6 (d, C-3), 74.0 (s, C-5), 36.4 (t, C-7), 212.4 (s, C-8), 55.1 (d, C-9), 44.3 (s, C-10), 45.0 (s, C-13), 39.5 (t, C-14), 82.0 (d, C-17); MS: $m/z = 408$ (M^+). (Found: C, 67.32; H, 9.10. Calc. for $\text{C}_{23}\text{H}_{36}\text{O}_6$ (408.52): C, 67.62; H, 8.88%).

Alkaline hydrolysis of 3 β ,5,17 β -trihydroxy-8,14-seco-5 α -androstan-8-one 3,17-diacetate (3). - A solution of the seco-diacetate 3 (500 ml, 1.22 mmol) in 5% methanolic potassium hydroxide (50 ml) was left overnight at room temperature. The mixture was neutralized with acetic acid, diluted with water and extracted with diethyl ether. The organic layer was washed with water, aqueous NaHCO_3 and water, dried over Na_2SO_4 (anh.) and evaporated to dryness under reduced pressure, to give 3 β ,5,17 β -trihydroxy-8,14-seco-5 α -androstan-8-one (4) (397 mg, ~100%), which was recrystallized from acetone-methanol (342 mg, 86%), m.p. 141-142 $^\circ$: $[\alpha]_D^{20} = -21.1^\circ$ ($c = 1.0$, CHCl_3); IR (KBr): $\nu_{\text{max}} = 3460, 3340, 1680 \text{ cm}^{-1}$; $^1\text{H-NMR}$: 0.82 (s, $\text{H}_3\text{C}-18$), 0.89 (s, $\text{H}_3\text{C}-19$), 2.24 (d x d, $J_1 = \sim 15 \text{ Hz}$, $J_2 = \sim 4 \text{ Hz}$, one H) and 2.72 (m, two H) ($= \text{H}_2\text{C}-7 + \text{HC}-9$), 3.78 (t, HC-17), 4.10 (m, HC-3); $^{13}\text{C-NMR}$ (selected data): 67.2 (d,

[†] IR (and some ^1H 80 MHz NMR) measurements (Prof. D. Jeremic) and elemental microanalyses (Dr. R. Tasovac) were carried out at the Department of Chemistry in Belgrade. $^1\text{H-NMR}$ (at 360 MHz) and $^{13}\text{C-NMR}$ measurements (Dr. H. Fuhrer) and the recording of mass spectra were performed at Ciba-Geigy Ltd. in Basle (Switzerland).

C-3), 74.5 (s, C-5), 36.5 (t, C-7), 212.4 (s, C-8), 55.4 (d, C-9), 44.3 (s, C-10), 44.7 (s, C-13), 39.7 (t, C-14), 79.9 (d, C-17); MS: m/z = 324 (M^+). (Found: C, 70.60; H, 9.72. Calc. for $C_{19}H_{32}O_4$ (324.45): C, 70.34; H, 9.94%).

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