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Structure elucidation of new compounds from acidic treatment of the progestins gestodene and drospirenone

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ABSTRACT

Gestodene acidic treatment afforded a single rearrangement product, namely 13-β-ethyl-18,19-dinorpregna-4,14,16-trien-3,20-dione **3**, which was originated through HCl-catalyzed Rupe rearrangement. Drospirenone acidic treatment yielded two epimeric lactones by addition of HCl to the 6β,7β-cyclopropane ring, namely 7β-(chloromethyl)-15β,16β-methylene-3-oxo-17β-pregn-4-ene-21,17-carbolactone **4** and 7β-(chloromethyl)-15β,16β-methylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone **5**. The structure of the compounds was assessed by spectroscopic and crystallographic methods.

1. Introduction

Examining degradation products of drug substances under stress conditions is useful in establishing the intrinsic stability of the molecule, identifying degradation products and developing and validating suitable analytical procedures. During the stability testing recommended for drug substances and products by the International Conference on Harmonisation [1,2] gestodene **1**, a potent synthetic 19-nortestosterone progestin widely used in the third-generation contraceptive pills [3], and the progestin spironolactone derivative drospirenone **2** [4], were submitted to acidic treatment in order to evaluate their susceptibility to acids. Interestingly, in the applied conditions new compounds were isolated in significant yields. As the progestogenic activity of steroids may be often accompanied by other side biological effects depending also on their metabolic conversion products [3,4], we decided to deepen the knowledge of gestodene and drospirenone fate in acidic conditions. So in this paper we describe the identification of the gestodene and drospirenone transformation products under acidic conditions through spectroscopic characterisation and X-ray crystallography.

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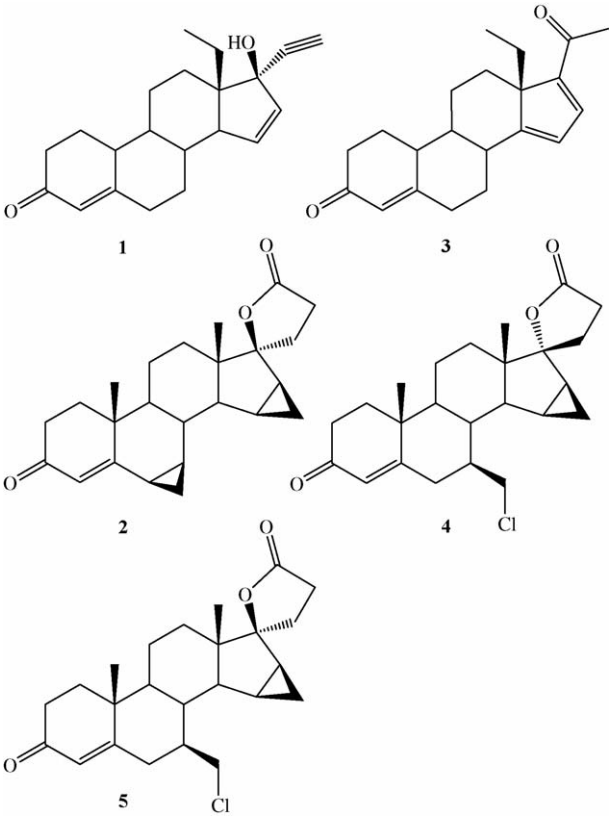

2. Experimental

2.1. General

Uncorrected melting points were determined on a Büchi apparatus. Optical rotations were determined on a Perkin-Elmer 241 polarimeter in a 1 dm cell at 20 °C using chloroform solutions. Gestodene [5] and drospirenone [6] were a generous gift of Industriale Chimica s.r.l. Saronno, Italy and all reagents were purchased from Aldrich. Reactions were monitored by TLC on Silica Gel 60 F-254 plates (Merck) with detection by spraying with cerium based reagent solution and heating to 110 °C. Column chromatography was performed on Silica Gel 60 (70-230 mesh, Merck). Mass spectrometry was performed on a Thermo Electron TRACE DSQ™ spectrometer through the rapid heating filament Direct-Exposure Probe (DEP) insertion mode. The mass spectrometric analyses were performed in electron impact (EI-MS) ionization at an electron energy of 70 eV with a source temperature of 250 °C. All NMR spectra were recorded at 298 K with a Bruker FT-NMR AVANCE™ DRX500 spectrometer operating at 500.13 and 125.76 MHz for ^{1}H and ^{13}C respectively, in $CDCl_3$ solutions at 298 K. Chemical shifts are reported as δ (ppm) relative to $CHCl_3$ fixed at 7.24 ppm for ^{1}H NMR spectra and relative to $CDCl_3$ fixed at 76.95 ppm (central line) for ^{13}C NMR spectra. A combination of 1D and 2D COSY, HMQC and NOESY experiments, using standard Bruker pulse programs, was used for the assignment of compounds **3**–**5** resonances.

2.2. Chemistry

2.2.1. Acidic treatment of gestodene (1)

Gestodene (1.90 g, 6.13 mmol), was suspended in 1 M hydrochloric acid (380 mL) at 80 °C. After 2 h gestodene was almost completely converted in one more polar compound as resulted by TLC analysis (ethyl acetate–petroleum ether 1:1). The mixture was cooled and, after adding 1 M NaOH (380 mL), extracted with two volumes of dichloromethane (190 mL). The organic layers were dried over sodium sulphate, and the organic solvent was removed under reduced pressure affording a yellow solid residue (1.80 g). Flash chromatography (ethyl acetate–petroleum ether 3:7) of the crude reaction product yielded *13-β-ethyl-18,19-dinorpregna-4,14,16-trien-3,20-dione* **3** (1.55 g, 5.00 mmol) that showed: mp 206–207 °C (dec) (from dichloromethane–hexane); $[\alpha]_D = +580.5^\circ$ ($c = 1$); ^{1}H NMR ($CDCl_3$): $\delta = 0.28$ (t, $J = 7.0$ Hz, 3 H, CH_3), 0.86–0.94 (m, 2 H, H9 and H12α), 1.48 (m, 1 H, H11β), 1.54 (m, 1 H, H1α), 1.62 (m, 1 H, H7α), 1.78–1.86 (m, 2 H, H11α and C*H*aH18), 2.11–2.70 (m, 3 H, H7β, H8 and CH*H*$_b$18), 2.23–2.33 (m, 6 H, H1β, H2α or β, H10 and $CH_3$21), 2.36–2.45 (m, 2 H, H2α or β and H6β), 2.53 (m, 1 H, H12β), 2.58 (m, 1 H, H6α), 5.86 (br s, 1 H, H4), 6.04 (br dd, $J = 2.0$ and 2.5 Hz, 1 H, H15), 7.25 ppm (dd, $J = 2.5$ Hz, 1 H, H16); ^{13}C NMR ($CDCl_3$): $\delta = 7.43$ (CH_3CH_2), 25.24 (CH_3CH_2), 25.96 (C11), 26.53 (C21), 26.80 (C1), 28.53 (C7), 34.97 (C6), 36.38 (C2), 36.78 (C12), 40.78 (C8), 42.75 (C10), 53.37 (C9), 58.07 (C13), 119.91 (C15), 125.02 (C4), 143.36 (C16), 152.68 (C═), 165.12 (C═), 169.21 (C═), 192.77 (C20), 199.56 ppm (C3); EI-MS: *m/z* 310 $[M]^+$; Anal. calcd. for $C_{21}H_{26}O_2$: C 81.25, H 8.44; found: C 80.97, H 8.48.

2.2.2. Acidic treatment of drospirenone (2)

Drospirenone (2.00 g, 5.46 mmol), was treated with acetone (30 mL) and 36% hydrochloric acid (0.75 mL) under reflux for 2 h. This treatment caused complete disappearing of the starting material and formation of two main compounds (TLC, ethyl acetate 100%) together with tars not further identified. After cooling the mixture was neutralized with a saturated $NaHCO_3$ solution, water was added and acetone was removed under reduced pressure. The residue was extracted twice with ethyl acetate, and the organic layers were washed with brine and dried over sodium sulphate. The solvent was removed under reduced pressure affording a semi-solid residue (1.50 g). Flash chromatography (hexane–ethyl acetate from 50:50 to 30:70) of the crude reaction product yielded compound **4** (0.70 g, 1.74 mmol), and compound **5** (0.10 g, 0.25 mmol) in the order.

7β-Chloromethyl-15β,16β-methylene-3-oxo-17β-pregn-4-ene-21,17-carbolactone **4** showed: mp 198 °C (from methanol), $[\alpha]_D = +19.0^\circ$ ($c = 1$); ^{1}H NMR ($CDCl_3$): $\delta = 0.56$ (m, 1 H, H15′α), 0.87 (s, 3 H, H18), 0.95 (m, 1 H, H15′β), 1.12 (m, 1 H, H9), 1.16 (s, 3 H, H19), 1.25 (m, 1 H, H12 β), 1.38 (m, 1 H, H11β), 1.45 (m, 1 H, H16), 1.49 (m, 1 H, H15), 1.62–1.74 (m, 3 H, H12α, H11α and H1α), 1.86–2.00 (m, 3 H, H8, H7 and 1β), 2.10 (m, 1 H, H14), 2.16 (m, 1 H, H20β), 2.23 (m, 1 H, H20α), 2.28–2.42 (m, 3 H, H2α, H2β and H6α), 2.51 (m, 1 H, H21β), 2.61 (m, 1 H, H6β), 2.69 (m, 1 H, H21α), 3.80 (dd, $J_{7'a,7} = 1.70$ and $J_{7'a,7'b} = 11.2$ Hz, 1 H, H7′a), 4.10 (dd, $J_{7'b,7} = 4.5$ Hz, 1 H, H7′b), 5.76 ppm (d, $J = 2.1$ Hz, 1 H, H4); ^{13}C NMR ($CDCl_3$): $\delta = 9.71$ (C15′), 17.23 (C19), 19.52 (C15), 20.26 (C18), 20.83 (C11), 25.48 (C16), 26.87 (C20), 29.46 (C21),

33.90 (C2), 34.37 (C12), 35.25 (C8), 35.47 (C1), 36.40 (C6), 38.17 (C10), 42.47 (C7), 43.70 (C13), 49.97 (C7′), 53.00 (C14), 53.48 (C9), 96.72 (C17), 124.06 (C4), 168.91 (C5), 176.48 (C22), 198.94 ppm (C3). EI-MS: *m/z* 402 $[M]^+$(100), 404 $[M+2]^+$(30); Anal. calcd. for $C_{24}H_{31}ClO_3$: C, 71.54; H, 7.75; found: C 71.78, H 7.77.

7β-(Chloromethyl)-15β,16β-methylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone (**5**) showed: mp 214–215 °C (dec) (from methanol); $[\alpha]_D = +53.0°$ ($c = 1$); ^{1}H NMR ($CDCl_3$): $\delta = 0.57$ (m, 1 H, H15′α), 1.03 (s, 3 H, H18), 1.08 (m, 1 H, H9), 1.17 (s, 3 H, H19), 1.29 (m, 1 H, H15′β), 1.37 (m, 1 H, H16), 1.40–1.48 (m, 3 H, 2 H12 and H15), 1.64 (m, 1 H, H1α), 1.66–1.72 (m, 2 H, 2 H11), 1.77 (m, 1 H, H14), 1.89 (m, 1 H, H7), 1.92–2.00 (m, 2 H, H8 and H1β), 2.05 (m, 1 H, H20β), 2.31 (m, 1 H, H2α), 2.36–2.44 (m, 2 H, H6α and H20α), 2.51 (m, 1 H, H21α), 2.58 (m, 1 H, H6β), 2.62 (m, 1 H, H21β), 3.87 (dd, $J_{7'a,7} = 1.70$ and $J_{7'a,7'b} = 11.2$ Hz, 1 H, H7′a), 3.98 (dd, $J_{7'b,7} = 4.5$ Hz, 1H, H7′b), 5.77 ppm (d, $J = 2.1$ Hz, 1 H, H4); ^{13}C NMR ($CDCl_3$): $\delta = 10.09$ (C15′), 17.20 (C19), 19.30 (C15), 19.88 (C18), 21.34 (C11), 26.11 (C16), 29.35 (C21), 31.07 (C20), 33.94 (C2), 35.51 (C1 and C8), 36.51 (C6), 36.51, (C12), 38.19 (C10), 42.59 (C7), 42.76 (C13), 49.70 (C7′), 52.00 (C14), 53.69 (C9), 95.40 (C17), 123.99 (C4), 168.68 (C5), 176.49 (C22), 198.94 ppm (C3); EI-MS: *m/z* 402 $[M]^+$(100), 404 $[M+2]^+$(30); Anal. calcd. for $C_{24}H_{31}ClO_3$: C, 71.54; H, 7.75; found: C 71.71, H 7.78.

2.3. *X-ray crystal studies of compounds 3 and 4*

The crystals of $C_{21}H_{26}O_2$ (**3**) and $C_{24}H_{31}ClO_3$ (**4**) were obtained by recrystallization from methanol as colorless prisms. A summary of the crystal data, data collection, and structure refinement is presented in Table 1. The intensity data were collected with a CAD4 diffractometer with graphite monochromated Mo Kα radiation (λ = 0.71073 Å). The cell parameters were determined and refined by least-squares fit of 20 high angle reflections. The structures were solved by direct methods [7] and conventional Fourier synthesis [8]. The refinement of the structures was made by full matrix least-squares on F^2. All non-H-atoms were refined anisotropically. The H-atoms positions were detected in a difference Fourier synthesis and refined with isotropic thermal factors, while some of them were introduced at calculated positions in their described geometries and allowed to ride on the attached carbon atom with fixed isotropic thermal parameters ($1.2U_{eq}$ of the parent carbon atom). Selected bond distances and angles are reported in Table 2. The supplementary crystallographic data have been deposited with the Cambridge Crystallographic Data Center (CCDC deposition numbers 299001, 299002. Copies can be obtained, free of charge, from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Table 1 – Crystal data and structure refinement for 3 and 4

Compound	3	4
Empirical formula	$C_{21}H_{26}O_2$	$C_{24}H_{31}ClO_3$
Formula weight	310.42	402.94
Temperature (K)	293(2)	293(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Orthorhombic	Tetragonal
Space group	$P2_12_12_1$	$P4_32_12$
Unit cell dimensions(Å)	$a = 7.037(3)$ $b = 12.172(2)$ $c = 20.024(6)$	$a = 9.479(2)$ $c = 44.963(1)$
Volume (Å^3)	1715.1(9)	4040(1)
Z	4	8
Calculated density (Mg/m^3)	1.202	1.325
Absorption coefficient (mm^{-1})	0.075	0.212
F(0 0 0)	672	1728
Crystal size (mm)	0.9 × 0.4 × 0.6	0.3 × 0.28 × 0.7
θ range (°)	2.03–24.99	3.47–25.86
Limiting indices	$-1 \le h \le 8$ $0 \le k \le 14$ $0 \le l \le 22$	$-10 \le h \le 11$ $0 \le k \le 11$ $0 \le l \le 53$
Reflections collected/unique	2037/2001 [$R_{(int)} = 0.0851$]	3791/3407 [$R_{(int)} = 0.0592$]
Completeness to θ	24.99 99.4%	25.86 90.8%
Refinement method		Full-matrix least-squares on F^2
Data/restraints/parameters	2001/0/312	3407/0/370
Goodness-of-fit	1.008	1.188
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0443 wR2 = 0.1111	R1 = 0.0782 wR2 = 0.1710
Largest diff. peak and hole (Å^3)	0.182; −0.239	0.251, −0.238

3. Results and discussion

3.1. *Chemistry*

When treated with 1 M hydrochloric acid at 80 °C, gestodene (**1**) was converted in a slightly more polar compound as observed by TLC in more than 80% yield after 2 h. The purified reaction product was then submitted to spectroscopic analyses to clarify its structure. EI-mass spectrometry showed the same 310 molecular ion of gestodene for the new compound. However ^{1}H and ^{13}C NMR analysis revealed both the absence of the hydroxy and ethynyl group of gestodene. In fact neither exchangeable protons were observed in the ^{1}H NMR spectrum nor resonances accounting for acetylenic and alcoholic carbons were present in the 70–90 ppm range of the ^{13}C NMR spectrum. On the contrary, a sharp methyl singlet at 2.30 ppm and an additional carbonylic carbon (192.77) with respect to gestodene indicated the presence of an acetyl group. Finally the existence of three double bonds was established by six olefinic carbons at 169.21, 165.12, 152.68, 143.36, 125.02 and 119.91 ppm, the last three linking a proton as resulted from the HMQC experiment which correlated these ^{13}C resonances to the three olefinic protons, respectively at 7.25, 5.86 and 6.04 ppm, in the ^{1}H NMR spectrum. In particular, the coupling (2.5 Hz) between the 7.25 and 6.04 ppm resonances indicated two conjugated double bonds. Basing on these data, it was assumed that gestodene underwent the Rupe rearrangement [9], which consists in the acid-catalyzed rearrangement of tertiary α-acetylenic alcohols to yield α,β-unsaturated ketones, in our case affording the α,β-unsaturated dienone **3**. A similar rearrangement was also reported for a series of steroidal propargylic alcohols in the presence of acid ion exchangers [10,11]. The obtained 14,16-diene-steroids, used as intermediates in the synthesis of pharmacologically active molecules [11,12], to best of our knowl-

Table 2 – Selected bond lengths [Å] and angles [°] for 3 and 4

Compound	3	4
Cl–C(C7′)		1.741(6)
O(3)–C(3)	1.221(6)	1.224(6)
O(17)–C(17)		1.446(6)
O(17)–C(22)		1.271(7)
O(20)–C(20)	1.221(7)	
O(22)–C(22)		1.163(7)
C(1)–C(2)	1.519(8)	1.523(9)
C(1)–C(10)	1.500(8)	1.505(7)
C(2)–C(3)	1.485(9)	1.426(8)
C(3)–C(4)	1.443(9)	1.443(7)
C(4)–C(5)	1.338(8)	1.324(7)
C(5)–C(6)	1.511(8)	1.487(7)
C(5)–C(10)	1.510(8)	1.457(7)
C(6)–C(7)	1.510(8)	1.498(7)
C(7)–C(8)	1.518(7)	1.501(7)
C(7)–C(7′)		1.507(7)
C(8)–C(9)	1.556(7)	1.549(6)
C(8)–C(14)	1.493(7)	1.492(7)
C(9)–C(10)	1.549(7)	1.545(7)
C(9)–C(11)	1.522(7)	1.474(8)
C(11)–C(12)	1.524(8)	1.501(8)
C(12)–C(13)	1.530(7)	1.505(7)
C(13)–C(14)	1.497(7)	1.510(7)
C(13)–C(17)	1.522(7)	1.513(7)
C(14)–C(15)	1.335(7)	1.506(7)
C(15)–C(16)	1.443(8)	1.480(8)
C(15)–C(15′)		1.514(8)
C(16)–C(17)	1.351(8)	1.468(8)
C(16)–C(15′)		1.479(9)
C(17)–C(20)	1.463(8)	1.523(7)
C(20)–C(21)	1.484(9)	1.405(10)
C(21)–C(22)		1.471(9)
C(7)–C(C7′)–Cl		110.9(4)
O(3)–C(3)–C(2)	121.3(7)	122.1(5)
O(3)–C(3)–C(4)	122.1(7)	122.7(5)
O(17)–C(17)–C(13)		106.4(4)
O(17)–C(17)–C(16)		104.7(5)
O(17)–C(17)–C(20)		104.2(5)
O(17)–C(22)–C(21)		109.3(6)
C(22)–O(17)–C(17)		112.7(4)
O(20)–C(20)–C(17)	120.8(6)	
O(20)–C(20)–C(21)	120.7(6)	
O(22)–C(22)–O(17)		121.3(6)
O(22)–C(22)–C(21)		129.3(7)

edge have not been yet tested for their biological activities or toxicities.

When refluxed for 2 h with 36% aq. HCl in acetone [13], drospirenone **2** was completely converted (TLC) into a complex mixture of decomposition products from which two main compounds were recovered over the tars in about 40% yields. The products, isolated in a 70:10 relative ratio, were submitted to spectroscopic analyses to clarify their structures. EI-mass spectrometry of both compounds showed a 402 molecular ion and an isotopic $[M+2]^+$ 404 ion in a 3/1 relative ratio accounting for two isomeric drospirenone monochloro-derivatives, 366 being drospirenone molecular mass. In particular 6,7-cyclopropane ring opening of drospirenone by HCl addition, with formation of a structure in which a chloromethyl is bounded to the C-7 of drospirenone in a β-orientation, was demonstrated by ^{1}H NMR analysis for both the obtained compounds. In fact, starting from the characteristic vinylic H-4 proton (5.76 ppm) the H-6 (2.35 and 2.61 ppm) and H-7 (1.92 ppm) resonances of the most abundant compound **4** were assigned because of a cross peak between H-4 and one H-6 (2.35 ppm) in its NOESY spectrum. Finally, vicinal coupling of the characteristic chloromethyl group (two protons at 3.80 and 4.10 ppm) with H-7 confirmed that it was bound to C-7. The α-orientation of the C-7 proton, demonstrated by its correlation with H-9 (1.12 ppm) in the NOESY spectrum, accounted for the β-orientation of the chloromethyl group at C-7. Analogously a NOESY cross peak between H-4 (5.77 ppm) and H-6 at (2.38 ppm) allowed to establish the resonance of H-7 (1.89 ppm) and consequently the binding of the choromethyl group (two protons at 3.87 and 3.98 ppm) at C-7 of the less abundant compound **5**. Also in this case a NOESY cross peak between H-7 and H-9 (1.08 ppm) confirmed the chloromethyl β-binding. Complete ^{1}H and ^{13}C NMR signal assignments of the NMR spectra of compounds **4** and **5** were achieved using a combination of 1D and 2D (COSY, HMQC and NOESY) experiments (see experimental). Basing on these data it was possible to demonstrate that compounds **4** and **5** were two epimeric lactones at C-17. In fact, whereas the NOESY spectrum of compound **4** showed strong nOe contacts between the two H-20 protons of the lactonic ring at 2.16 and 2.23 ppm and the C-18 methyl protons at 0.87 ppm, accounting for the R configuration of C-17 of **4**, namely 7β-(chloromethyl)-15β,16β-methylene-3-oxo-17β-pregn-4-ene-21,17-carbolactone, the NOESY spectrum of **5** did not show these correlations supporting the structure of 7β-(chloromethyl)-15β,16β-methylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone for **5**, with the same 17S configuration of drospirenone. A 6,7-cyclopropane ring opening of drospirenone by HCl addition was already described but the formation of compound **5** only was reported without any characterisation of the obtained product [13].

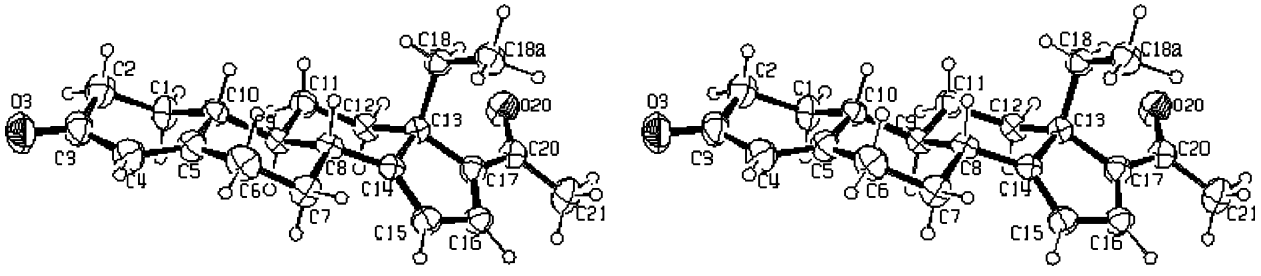

Fig. 1 – ORTEP stereoviews of 3 (50% probability level, H atoms of arbitrary sizes).

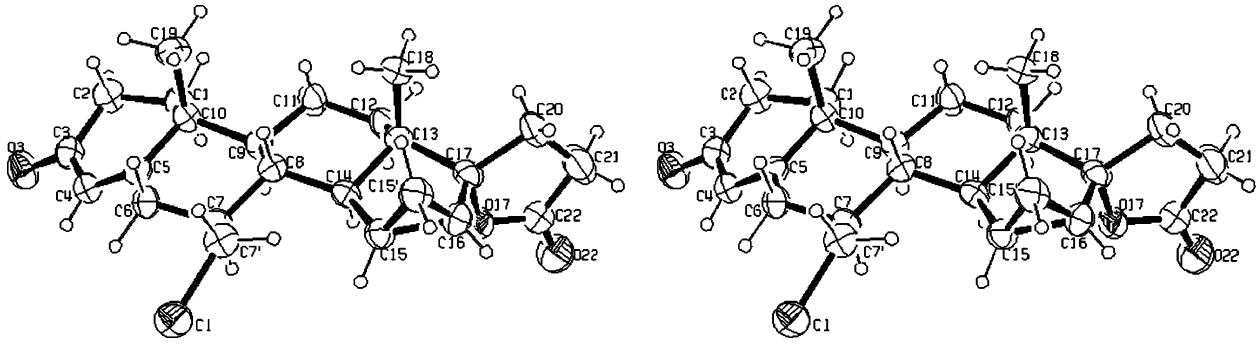

Fig. 2 – ORTEP stereoviews of 4 (50% probability level, H atoms of arbitrary sizes).

3.2. *Crystallographic studies*

The definitive assessment of the structures of the new compounds **3** and **4** was realized through X-ray crystallographic studies. Compound **3** had its stereogenic centers unchanged with respect to its precursor, while compound **4** showed an inverted 17R configuration referring to drospirenone **2**. The molecular structure of **3**, derived by acidic rearrangement of gestodene **1**, is shown in Fig. 1 as ORTEP stereoviews with the relative atom numbering scheme.

The conformation of the **A/B/C** ring system is characterized as follows: ring **A** 1α,2β-half chair, ring **B** 5α,8β-chair, ring **C** 8β,12α-chair. The presence of the two double bonds C14–C15 (1.335(7) Å) and C16–C17 (1.351(8) Å) renders the ring **D** nearly planar, with deviations from its mean plane ranging between −0.011(5) and 0.016(6) Å and about coplanar to the acetyl moiety at C17. The 13β-ethyl group is in a *gauche* conformation with respect to the **C/D** ring junction as shown by the value of the torsion angle C14–C13–C18–C18a of 56.9(6)°. Theoretical studies [14] indicate that also in the case of gestodene (**1**), in which a C15–C16 unsaturation is present in the **D** ring, the *gauche* conformation is slightly preferred over the *trans* one. The molecular structure of **4**, originating from drospirenone (**2**), is shown in Fig. 2 as ORTEP stereoviews with the relative atom numbering scheme.

The conformation of the **A/B/C** ring system is similar to the one of **3**. The C10 and C7 substituents cause some distortion at the torsion angle C4–C5–C10–C1 (−15.4(7)°) as well in the torsion angle C6–C5–C10–C9 (49.5(6)°). The orientation of the spirolactone ring is defined by the torsion angle C18–C13–C17–O17 of −160.5(5)° confirming the spectroscopic results indicating a *trans* orientation of the lactonic oxygen with respect to the methyl at C13, inverted referring to drospirenone (**2**). The saturated ring **D** presents an envelope conformation with C13 0.531(5) Å out of the plane of the remaining four atoms. The fused 15β,16β-cyclopropane ring is inclined to ring **D** with a dihedral angle of 62.3(4)° The spirolactone ring is rather twisted with deviations from the mean plane in the interval −0.065(7) to 0.074(9) Å and forms an angle of 74.9(2)° with the **D** ring. Finally, the 7-clorometyl group is β-oriented, with the chlorine atom in a *trans* arrangement with respect to C8. In Table 2, selected bond lengths and significant torsion angles, that define the conformation of the two compounds, are reported.

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