

## Oxidation Reactions in $9\alpha$ -Halosteroids by Jones Reagent

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Recibido el 30 de agosto de 2007; aceptado el 7 de diciembre de 2007

**Abstract.** Current investigations guided to searching androstane derivatives with potential anabolic activity, weakly androgenic one directed us to synthesize  $3\beta,11\beta$ -dihydroxy- $9\alpha$ -halo- $5\alpha$ -androstane-17-ones (**4a-c**). These compounds were oxidized by Jones' Reagent at 0°C obtaining a selective oxidation of the equatorial  $3\beta$ -hydroxyl group. This behaviour could be explained by the high steric hindrance at the  $11\beta$ -position, increased by the strong inductive effect of the halogen atom at C- $9\alpha$  over the electronic density of the H- $11\alpha$ .

**Key words:** Oxidation, androstane, anabolic activity, stereochemistry.

**Resumen.** Investigaciones recientes dirigidas a encontrar derivados androstánicos con potencial actividad anabólica y débil carácter androgénico nos llevó a sintetizar  $3\beta,11\beta$ -dihidroxi- $9\alpha$ -halo- $5\alpha$ -androstan-17-onas (**4a-c**). Estos compuestos fueron oxidados con el reactivo de Jones a 0°C obteniendo una oxidación selectiva del grupo equatorial  $3\beta$ -hidroxilo. Este comportamiento puede ser explicado por el elevado impedimento estérico en la posición  $11\beta$ , incrementado por el fuerte efecto inductivo en el C- $9\alpha$  sobre la densidad electrónica de H- $11\alpha$ .

**Palabras clave:** Oxidación, androstano, actividad anabólica, estereoquímica.

## Introduction

The different methods for alcohol oxidation in the steroid field have a significant importance due to the different reactivity of the secondary hydroxyl groups in dependence of its position and stereochemistry [1-3]. Among those methods, the oxidation by means of chromium (VI) derivatives is commonly chosen because a high selectivity is frequently observed, and among these last, the Jones' reagent ( $\text{CrO}_3$ ,  $\text{H}_2\text{SO}_4$ , Acetone/ $\text{H}_2\text{O}$ ), is the most common used [4-6].

The relative rates of oxidation of a series of steroidal alcohols reveal a markedly greater rate for the axial alcohol *versus* the equatorial isomer at each skeletal position, as well as a pronounced trend to faster reactions as the hydroxyl group becomes more sterically hindered. Thus, the decreasing observed reactivity [7] among axial alcohols is:  $11\beta > 2\beta, 4\beta > 6\beta > 1\alpha > 7\alpha > 3\alpha$ .

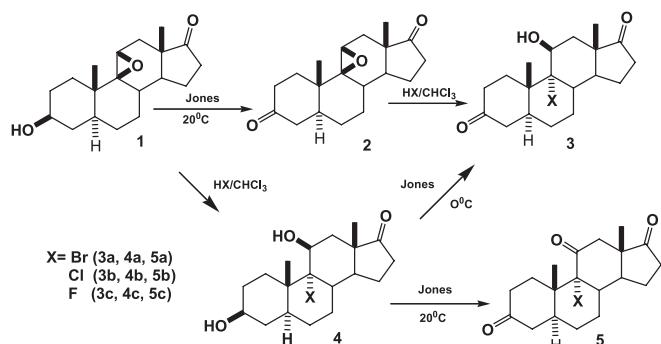
Schreiber and Eschenmoser [7] suggested that this acceleration is steric in origin. Any strain in an axial alcohol or its intermediate chromate ester, is relieved in forming the corresponding ketone, when the hybridisation is changed from  $sp^3$  to  $sp^2$ . The greater accessibility of the equatorial hydrogen in an axial alcohol has also been suggested as a factor in determining the rate of decomposition of the chromate.

The chromic oxidation of a molecule possessing axial and equatorial hydroxyl groups in different skeletal position could direct to selective oxidation of the equatorial one depending on their steric hindrance. No data of selective oxidation of one hydroxyl group present in an androstane- $3\beta,11\beta$ -diol was found in the literature. The aim of this work focuses on the

effect of the temperature on the oxidation of several halo-androstanediol derivatives by Jones' reagent.

## Results and Discussion

In current searching guided to obtain potential anabolic derivatives, we have prepared the  $9\alpha$ -haloandrostanes **3a-c**, **4a-c**, and **5a-c**, oxygenated at positions 3, 11, and 17, as shown in Scheme 1.



**Scheme 1:** General scheme of synthesis of  $9\alpha$ -haloandrostanes.

The synthetic pathway started from the well known epoxide **1** [8,9]; and when this compound was oxidized by Jones' reagent at room temperature, the epoxydiketone **2** was obtained in 63%. In the  $^1\text{H}$  NMR spectrum of **2** the characteristic signal

for 3 $\alpha$ -H is absent indicating that the 3 $\beta$ -hydroxyl group was oxidized ( $^{13}\text{C}$  NMR for C-3  $\delta$  210.4); the proton 11 $\alpha$  of the epoxy moiety is still present at 3.5 ppm as a wide singlet ( $^1\text{H}$  NMR for C-11  $\delta$  60.9). The regioselective opening of **2** by anhydrous HCl, HBr, and HF using standard conditions, provided the three first desired androstanes, the diketohalohydrins **3a-c** in 75%, 78% and 70% respectively. In the  $^1\text{H}$  NMR spectra of these compounds H-11 appears in the range 4.28-4.70 ppm, deshielded in comparison to the chemical shift in the starting material (3.50 ppm) [9]. In the  $^{13}\text{C}$  NMR spectra, C-11 in **3a-c** is shown in the range 70.2-74.1  $\delta$ , while in the non-halogenated compound appears at 60.9 ppm. This effect is certainly caused by the presence of the halogen atoms at position 9 $\alpha$ .

The ring opening of the epoxy **1** under the same reaction conditions, directed to the halohydrins **4a-c** in 80%, 76% and 80% yield, better results than that obtained in the epoxide opening **2**. In this way three other potential anabolic steroids were obtained. Characteristic signals in  $^1\text{H}$  NMR for **4a-c** are those of H-3a at 3.50-3.62 ppm (typical for this proton, base of an equatorial hydroxyl group) and H-11 $\alpha$  at 4.13-4.68 ppm. The signal for C-3 is slightly influenced by the halogen atom at position 9: in **4a-c** appears at 69.8-70.1 ppm while in 5 $\alpha$ -androstane-3 $\beta$ -ol C-3 is shown down-field: 71.2 ppm. [10]

The oxidation of **4a-c** by Jones' reagent, at room temperature, afforded the 9 $\alpha$ -halogenated triketones **5a-c** in 80%, 85% and 81% yield. The  $^1\text{H}$  NMR spectra do not show the protons 3 $\alpha$ , and 11 $\alpha$ , base of the hydroxyl groups confirming the oxidation of the alcohols. In  $^{13}\text{C}$  NMR the three carbonyl groups are clearly observed: **5a**; 210.3, 201.2, and 216.3 ppm for compound **5b**; and 210.3, 215.9 and 224.2 ppm for compound **5c**.

In another hand, when the oxidation step was carried out at 0°C, a selective oxidation of the 3 $\beta$ -hydroxyl group was obtained generating the diketohalohydrins **3a-c** in better yields (78%, 74% and 80% respectively). The typical signals for the alcohol group at C-11 are visualized in a very close range (4.28-4.70 ppm) as starting material (4.13-4.68 ppm). The selective oxidation of **4a-c** could be explained by the high steric hindrance at the 11 $\beta$ -position that causes difficulties for the formation of the chromate ester. Additionally, the strong inductive effect due to the 9 $\alpha$ -halogen atom increases the selectivity of the oxidation step.

To support the observed results we realized theoretical studies of selected bond lengths (Å) and Mulliken charges in steroids **4** and **4a-c** (Table 1).

According these calculations, the halogen atom at C-11 slightly diminishes carbon-hydrogen bonds in C-3 but strongly for C-11 ones, and in both cases in the sense Br > Cl > F. Additionally, the presence of the halogen atom diminishes the C<sub>11</sub>-H<sub>11</sub> bond length; therefore, the abstraction of proton H<sub>11</sub> in the oxidation step is much more difficult and that's why the oxidation of the hydroxyl group at C-3 occurs preferably than that placed in C-11. The variation of the Mulliken charges over the hydroxyl group at C-11 reveals that the electronic density is directly dependant on the halogen electronegativity. The electrostatic potential maps for **4** and **4c** (X=H and X=F) are shown in figure 1.

**Table 1.** Selected bond lengths (Å) and Mulliken charges in steroids **4** and **4a-c**.

Parameters	X=H ( <b>4</b> )	X=F ( <b>4a</b> )	X=Cl ( <b>4b</b> )	X=Br ( <b>4c</b> )
H-C <sub>3</sub>	1.10532	1.10480	1.10463	1.10452
H-C <sub>11</sub>	1.10028	1.09835	1.09703	1.09676
$q_{O_3}$	-0.556	-0.557	-0.557	-0.557
$q_{O_{11}}$	-0.542	-0.546	-0.548	-0.550
$q_{H_3}$	0.063	0.067	0.070	0.071
$q_{H_{11}}$	0.078	0.093	0.104	0.105



**Figure 1.** Variation of the electronic density of the hydroxyl group at C-11.

## Conclusion

The oxidation of different axial and equatorial alcohol groups, by Jones' reagent, in steroid frameworks is still a helpful reaction and selective behaviour can be obtained modifying certain parameters, in this manuscript we present a selective oxidation in dependence of the reaction temperature. The strong inductive effect of the halogen in the 9 $\alpha$ -position over the electronic density of the 11 $\beta$ -hydroxyl group permitted selective oxidation of a 3 $\beta$ -hydroxyl group.

## Experimental

Data of the starting material 9 $\beta$ ,11 $\beta$ -epoxy-5 $\alpha$ -androstane-3 $\beta$ -ol-17-one (**1**), has been previously reported by Ruiz and co-workers [8,9]. Melting points were measured on an Electrothermal melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was carried out on silica gel (Merck, Kieselgel 60 GF254). Yields are reported as weight rate. Nuclear Magnetic Resonance (NMR) experiments were done on a Mercury-300 spectrometer operating at 300 ( $^1\text{H}$ ) and 75.5 MHz ( $^{13}\text{C}$ ). The NMR spectra were measured at 25°C in  $\text{CDCl}_3$  solutions and referenced to internal TMS ( $\delta = 0$  ppm) and  $\text{CDCl}_3$  ( $\delta = 77.0$  ppm) for  $^1\text{H}$  and  $^{13}\text{C}$  NMR, respectively. 2D H,H-COSY spectra were recorded according to a standard pulse program. The heteronuclear shift correlated 2D NMR was performed with the standard Bruker pulse program XHCORR. Fixed delays were adjusted to  $^1J(\text{C},\text{H}) = 135$  Hz.

These methods were carried out on Bruker-500 instrument. In the case of the  $^{13}\text{C}$  NMR the allocations were made by comparison with tables reported by Blunt and Stothers [11], as well as later works of Römer and co workers [12]; Ruiz and Vélez [13,14]. Experimental  $^1\text{H}$ -NMR chemical shifts are in agreement with those calculated using reference of Bhacca, N.S. and Williams, D. H. [15]. Mass spectra (MS) were recorded on a TRIO 1000 Fisons Instruments spectrometer at 12 and 70 eV. The absolute configuration of epoxy **1** and chloroderivative **4b** was determined by X Ray [16,17].

Selected bond lengths ( $\text{\AA}$ ) and Mulliken charges for steroids **4** and **4a-c** (Table 1) were calculated according the Density Functional Theory of Kohn-Sham [18], by means of the Hybrid Interchange Functional of Becke with only 3 parameters[19] and correlation functional Lee-Yang-Parr (B3LYP) [20]. Calculations were run using the Gaussian program 03W Revision D.01 [21] in a PC Dell Precision 690, possessing 2 Intel Xeon Dual Core (1.6 MHz) processors and 4 Gb of RAM. The geometries of **4** and 4-haloandrostanes **4a-c** were fully optimized using the 6-31G(d,p) basis set followed by a calculus of frequencies to make sure the existence of stationaries points in both method and basis set. The requested convergence on the density matrix was  $10^{-7}$  and a 0.00045 and 0.0018 thresholds for maximum force and maximum displacement, respectively.

The electrostatic potential was calculated over the previously optimized structures using B3LYP/6-31G\*\* level. The surface of the electrostatic potential was generated through the same methodology, mapping the electrostatic potential over a surface of electronic density of 0.0004 electron/ $\text{\AA}^3$ . The red colour signals a potential maximum negative value and the blue one, the potential maximum positive. These calculations were carried out using the Gaussview software [22].

**9 $\beta$ ,11 $\beta$ -Epoxy-5 $\alpha$ -androstane-3,17-dione (2).** Jones' reagent (6.6 ml) was added slowly to a solution of **1** (5 g) in acetone (100 mL) at 20°C. The progress of reaction was followed by TLC (chloroform / methanol 9.8/0.2). The reaction was worked up to give **2** (3.15 g, 63%).

mp 130–133°C.  $^1\text{H}$  NMR,  $\delta$  3.5 (1H, s, H-11), 1.06 (3H, s,  $\text{CH}_3$ -18), 1.23 (3H, s,  $\text{CH}_3$ -19);  $^{13}\text{C}$  NMR  $\delta$ : 32.1 (C-1), 37.3 (C-2), 210.4 (C-3), 44.3 (C-4), 43.3 (C-5), 32.7 (C-6), 26.8 (C-7), 33.8 (C-8), 66.5 (C-9), 37.3 (C-10), 60.9 (C-11), 34.1 (C-12), 45.8 (C-13), 52.2 (C-14), 22.5 (C-15), 34.8 (C-16), 219.2 (C-17), 16.4 (C-18), 14.4 (C-19); MS  $m/z$ : 302 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{19}\text{H}_{26}\text{O}_3$ : C, 75.45; H, 8.67; Found: C, 75.62; H, 8.82.

**9 $\alpha$ -Bromo-11 $\beta$ -hydroxy-5 $\alpha$ -androstane-3,17-dione (3a):** Preparation of this compound was carried out by two methods: a) 1.0 g of **2** was dissolved in 12 mL of acetic acid and cooled to 10°C. A solution of hydrogen bromide 10% in acetic acid (3.15 mL) was slowly dropped. The reaction mixture was stirred for 30 min and the progress of the reaction was followed by TLC (chloroform: methanol 9.8:0.2). When the reaction was completed, water (15 mL) was added and the result-

ing mixture was stirred for 5 min. The solid was filtered and washed with water until neutral pH. The crude product was crystallised from methanol. Yield 75%.

b) A solution of Jones' reagent (0.9 mL) was added slowly to a solution of 0.5 g of **4a** in 30 mL of cooled acetone (0°C), during 10 min, taking care not to exceed 2°C. The progress of the reaction was followed by TLC (cyclohexane / ethyl acetate 1/1). The reaction was worked up to give 0.39 g of **3a** (Yield 78 %). mp 82–86°C.  $^1\text{H}$  NMR  $\delta$ : 4.70 (1H, t,  $J$  = 1.7 Hz, H-11), 1.11 (3H, s,  $\text{CH}_3$ -18), 1.58 (3H, s,  $\text{CH}_3$ -19);  $^{13}\text{C}$  NMR  $\delta$ : 37.7 (C-1), 37.2 (C-2), 211.5 (C-3), 44.3 (C-4), 41.4 (C-5), 27.6 (C-6), 26.5 (C-7), 36.0 (C-8), 98.0 (C-9), 46.9 (C-10), 74.1 (C-11), 34.2 (C-12), 41.9 (C-13), 46.0 (C-14), 21.0 (C-15), 35.2 (C-16), 218.9 (C-17), 16.0 (C-18), 18.0 (C-19). MS  $m/z$ : 364/366 ( $\text{M}^+$ -18). Anal. Calcd for  $\text{C}_{19}\text{H}_{27}\text{O}_3\text{Br}$ : C, 59.67; H, 7.12; Found: C, 59.80; H, 7.28.

**9 $\alpha$ -Chloro-11 $\beta$ -hydroxy-5 $\alpha$ -androstane-3,17-dione (3b).** Preparation of this compound was carried out by two methods: a) A solution of **2** (0.8 g) in chloroform (40 mL) was cooled at 5°C and added by 16 mL of a 0.54 M solution of hydrogen chloride in chloroform. The reaction mixture was stirred for 30 min and the progress of the reaction was followed by TLC (chloroform / methanol 9.8/0.2). When the reaction was completed water (15 mL) was added and the resulting mixture was stirred for 5 min. The organic layer was washed with 10% aqueous sodium bicarbonate and water until neutral pH. The organic layer was dried over anhydrous sodium sulphate and concentrated to dryness. The crude product was crystallised from methanol to give **3b**. Yield 78%.

b) Using the method b for **3a**, yielded **3b** in 74% from **4b**. mp 185–187°C.  $^1\text{H}$  NMR  $\delta$ : 4.48 (1H, t,  $J$  = 1.7 Hz, H-11), 1.14 (3H, s,  $\text{CH}_3$ -18), 1.53 (3H, s,  $\text{CH}_3$ -19);  $^{13}\text{C}$  NMR  $\delta$ : 37.6 (C-1), 36.9 (C-2), 211.3 (C-3), 44.0 (C-4), 39.8 (C-5), 27.5 (C-6), 25.0 (C-7), 32.3 (C-8), 89.8 (C-9), 46.8 (C-10), 73.9 (C-11), 32.5 (C-12), 41.8 (C-13), 44.9 (C-14), 21.2 (C-15), 35.2 (C-16), 218.7 (C-17), 15.8 (C-18), 17.2 (C-19); MS  $m/z$ : 338/340 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{19}\text{H}_{27}\text{O}_3\text{Cl}$ : C, 67.42; H, 8.05; Found: C, 67.55; H, 8.86.

**9 $\alpha$ -Fluoro-11 $\beta$ -hydroxy-5 $\alpha$ -androstane-3,17-dione (3c).** Preparation of this compound was carried out by two methods: a) In a polyethylene reactor of 150 mL provided with magnetic stirring were placed 25 ml of pyridine HF to 65%, cooled to 0°C, and slowly added by 5 g of **2** dissolved in 75 ml of chloroform. The progress of the reaction was followed by TLC (chloroform / methanol 9.8/0.2). After 30 min, the reaction mixture was poured over a 10% solution of  $\text{K}_2\text{CO}_3$  (1.5 L). The organic phase was extracted with chloroform ( $4 \times 50$  mL); the organic extracts were washed with brine to neutral pH. The organic phase was dried with anhydrous sodium sulphate, and evaporated to dryness. Yield 70%.

b) Using the method b for **3a**, yielded **3c** in 80% from **4c**. mp 234–236 °C  $^1\text{H}$  NMR  $\delta$ : 4.28 (1H, dt,  $J_{11-12a} = J_{11-12e} = 2.7$  Hz,  $J_{11-F} = 9.1$  Hz, H-11), 1,11 (3H, s,  $\text{CH}_3$ -18), 1,37 (3H, s,  $\text{CH}_3$ -19);  $^{13}\text{C}$  NMR d: 31.5 (C-1), 37.5 (C-2), 211.2 (C-3), 43.7 (C-

4), 39.2 (C-5), 27.3 (C-6), 24.9 (C-7), 33.8 (C-8), 99.3 (C-9), 40.0 (C-10), 70.2 (C-11), 37.3 (C-12), 46.3 (C-13), 45.2 (C-14), 21.4 (C-15), 35.3 (C-16), 219.0 (C-17), 15.3 (C-18), 14.6 (C-19); MS  $m/z$ : 322 [M $^+$ ].

**9 $\alpha$ -Bromo-3 $\beta$ ,11 $\beta$ -dihydroxy-5 $\alpha$ -androstane-17-one (4a):** A mixture of **1** (1.0 g) and acetic acid (12 mL) was cooled at 10°C and a solution of hydrogen bromide 10% in acetic acid (3.15 ml) was added. The reaction mixture was stirred for 30 min and the progress of the reaction was followed by TLC (chloroform: methanol 9.8:0.2).

When the reaction was completed water (15 mL) was added and the resulting mixture was stirred for 5 min. The solid was filtered and washed with water until neutral pH. The crude product was crystallised from methanol to give **3a**. Yield (0.8 g, 80%). mp 189–91°C.  $^1$ H NMR  $\delta$ : 3.62 (1H, m, H-3), 4.68 (1H, t,  $J$ =4.3 Hz, H-11), 1.17 (3H, s, CH<sub>3</sub>-18), 1.38 (3H, s, CH<sub>3</sub>-19);  $^{13}$ C NMR  $\delta$ : 36.5 (C-1), 30.3 (C-2), 69.8 (C-3), 37.3 (C-4), 39.2 (C-5), 27.1 (C-6), 26.6 (C-7), 36.1 (C-8), 100.6 (C-9), 47.2 (C-10), 73.6 (C-11), 32.5 (C-12), 42.1 (C-13), 46.1 (C-14), 20.9 (C-15), 35.2 (C-16), 220.8 (C-17), 15.6 (C-18), 18.8 (C-19); MS  $m/z$ : 366/368 (M $^+$ -18). Anal. Calcd for C<sub>19</sub>H<sub>29</sub>O<sub>3</sub>Br: C, 59.35; H, 7.61; Found: C, 59.55; H, 7.75.

**9 $\alpha$ -Chloro-3 $\beta$ ,11 $\beta$ -dihydroxy-5 $\alpha$ -androstane-17-one (4b):** A mixture of **1** (0.8 g) and chloroform (40 mL) was cooled at 5°C and a solution of hydrogen chloride (0.54 M) in chloroform (16 mL) was added. The reaction mixture was stirred for 30 min and the progress of the reaction was followed by TLC (chloroform: methanol 9.8:0.2). When the reaction was completed water (15 mL) was added and the resulting mixture was stirred for 5 min. The organic layer was washed with 10% aqueous sodium bicarbonate and water until neutral pH. The organic layer was dried over anhydrous sodium sulphate and concentrated to dryness. The crude product was crystallised from methanol to give **3b**. Yield (0.61 g, 76%). mp 125–128°C.  $^1$ H NMR  $\delta$ : 3.57 (1H, m, H-3), 4.41 (1H, t,  $J$ =4.3 Hz, H-11), 1.10 (3H, s, CH<sub>3</sub>-18), 1.30 (3H, s, CH<sub>3</sub>-19);  $^{13}$ C NMR  $\delta$ : 36.2 (C-1), 30.3 (C-2), 69.9 (C-3), 37.2 (C-4), 37.5 (C-5), 27.2 (C-6), 25.2 (C-7), 35.2 (C-8), 91.2 (C-9), 47.0 (C-10), 73.3 (C-11), 30.9 (C-12), 41.8 (C-13), 45.0 (C-14), 21.0 (C-15), 35.3 (C-16), 220.7 (C-17), 15.5 (C-18), 18.2 (C-19); MS  $m/z$ : 340/342 (M $^+$ ); Anal. Calcd for C<sub>19</sub>H<sub>29</sub>O<sub>3</sub>Cl: C, 67.02; H, 8.59; Found: C, 67.09; H, 8.77.

**9 $\alpha$ -Fluoro-3 $\beta$ ,11 $\beta$ -dihydroxy-5 $\alpha$ -androstane-17-one (4c)** In a polyethylene reactor of 150 mL provided with magnetic agitation, were placed 25 mL of pyridine HF to 65% and cooled off to 0 °C. Later, it was added, slowly, 5 g of **1** dissolved in 75 mL of chloroform. The progress of the reaction was followed by TLC (chloroform: methanol 9.8:0.2). Finalized the reaction (30 min), the reaction mixture was poured over 1500 mL of a strongly shaken solution of K<sub>2</sub>CO<sub>3</sub> (10%). Extracted with 4 × 50 mL of chloroform each one; the organic extracts were washed finally with a hydrochloride acid solution 6N and

with water, until pH neutral. The organic phase was dried with anhydrous sodium sulphate, it filtered and it evaporated until dryness. Yield (4 g, 80%), crystallize from methanol. mp 208–210°C.  $^1$ H NMR  $\delta$ : 3.5 (1H, m, H-3), 4.13 (1H, d, H-11), 1.01 (3H, s, CH<sub>3</sub>-18), 1.09 (3H, s, CH<sub>3</sub>-19);  $^{13}$ C NMR  $\delta$ : 29.7 (C-1), 30.4 (C-2), 70.1 (C-3), 36.6 (C-4), 36.8 (C-5), 27.0 (C-6), 25.2 (C-7), 33.5 (C-8), 99.6 (C-9), 39.7 (C-10), 69.5 (C-11), 36.9 (C-12), 46.5 (C-13), 45.3 (C-14), 21.3 (C-15), 35.4 (C-16), 220.9 (C-17), 15.1 (C-18), 15.4 (C-19); MS  $m/z$ : 324 [M $^+$ ].

**9 $\alpha$ -Bromo-5 $\alpha$ -androstane-3,11,17-trione (5a):** Jones' reagent (7.8 mL) was added slowly to a solution of **4a** (2 g) in acetone (280 mL) at 20°C. The progress of the reaction was followed by TLC (chloroform: methanol 9.8 / 0.2). When the reaction was completed, the oxidant excess was eliminated with methanol (2.5 mL). The acetone was evaporated and water (100 mL) was added. The precipitate was collected by filtration, washed with water until neutral pH and dried. The crude product was crystallised from methanol to give **5a**. Yield (1.4 g, 80%). mp 163–165°C.  $^1$ H NMR  $\delta$ : 1.38 (3H, s, CH<sub>3</sub>-19), 0.87 (3H, s, CH<sub>3</sub>-18);  $^{13}$ C NMR  $\delta$ : 37.8 (C-1), 35.6 (C-2), 210.3 (C-3), 44.4 (C-4), 40.7 (C-5), 28.2 (C-6), 25.0 (C-7), 39.3 (C-8), 87.6 (C-9), 49.4 (C-10), 200.7 (C-11), 45.5 (C-12), 41.5 (C-13), 44.2 (C-14), 21.2 (C-15), 34.0 (C-16), 216.4 (C-17), 13.9 (C-18), 14.8 (C-19); MS  $m/z$ : 301 (M $^+$ -79). Anal. Calcd for C<sub>19</sub>H<sub>25</sub>O<sub>3</sub>Br: C, 59.98; H, 6.63; Found: C, 60.15; H, 6.81.

**9 $\alpha$ -Chloro-5 $\alpha$ -androstane-3,11,17-trione (5b):** Preparation of this compound was carried out by a similar method described for compound **5a**. Yield (1.7 g, 85%). mp 208–210°C.  $^1$ H NMR  $\delta$ : 0.88 (3H, s, CH<sub>3</sub>-18), 1.38 (3H, s, CH<sub>3</sub>-19);  $^{13}$ C NMR  $\delta$ : 37.6 (C-1), 35.5 (C-2), 210.3 (C-3), 44.1 (C-4), 39.7 (C-5), 27.9 (C-6), 23.6 (C-7), 39.1 (C-8), 84.0 (C-9), 49.3 (C-10), 201.2 (C-11), 45.4 (C-12), 41.1 (C-13), 43.2 (C-14), 21.1 (C-15), 31.9 (C-16), 216.3 (C-17), 13.6 (C-18), 14.5 (C-19); MS  $m/z$ : 336/338 (M $^+$ ). Anal. Calcd for C<sub>19</sub>H<sub>25</sub>O<sub>3</sub>Cl: C, 67.83; H, 7.50; Found: C, 67.91; H, 7.63.

**9 $\alpha$ -Fluoro-5 $\alpha$ -androstane-3,11,17-trione (5c):** Preparation of this compound was carried out by a similar method described for compound **5a**. Yield (1.62 g, 81%) mp: 165 – 167°C.

$^1$ H NMR  $\delta$ : 0.84 (3H, s, CH<sub>3</sub>-18), 1.29 (3H, s, CH<sub>3</sub>-19);  $^{13}$ C NMR  $\delta$ : 30.2 (C-1), 37.4 (C-2), 210.2 (C-3), 43.7 (C-4), 39.8 (C-5), 27.3 (C-6), 24.5 (C-7), 38.3 (C-8), 99.0 (C-9), 38.8 (C-10), 204.2 (C-11), 47.1 (C-12), 49.9 (C-13), 44.2 (C-14), 21.2 (C-15), 35.9 (C-16), 215.9 (C-17), 14.0 (C-18), 12.4 (C-19); MS  $m/z$ : 320 [M $^+$ ]

## Acknowledgments

The authors thank CONACYT for financial support (Grant 47632Q) and to Dr. Francisco J. Meléndez-Bustamante (Laboratorio de Química Teórica, BUAP) for theoretical studies.

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