Synthesis of 9α-chloro and bromo-androstane derivatives

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New steroids derivatives having a chlorine and a bromine atom at 9α-position were obtained from a key intermediate 5α-9(11),16-pregnadien-3β-ol-20-one acetate. These steroids have potential anabolic/androgenic activity.

Keywords: anabolic/androgenic, 9α-chloro-5α-androstane, 9α-bromo-5α-androstane, androstane

Anabolic steroids are compounds that produce retention of nitrogen, calcium, potassium, chloride, phosphate and water, and the growth of bones.[1] These drugs are used in facilitating recovery from protein-wasting disorders. In HIV patients, anabolic steroids are used to recover lean muscle mass, organ failure and secondary immune dysfunction.[2] They are indicated in the treatment of anemia caused by deficient red cell production in aplastic congenital, myelofibrosis, hypoplastic and acquired anemia. They are indicated in the treatment of chronic obstructive pulmonary disease, hypogonadism, impotence and metastatic cancer.[3] Testosterone is the most potent natural androgen. Anabolic and androgenic steroids are synthetic that are derived from testosterone which is secreted by the testicles and in a small quantity by the ovaries and the suprarenal cortex. The goal of researchers in the anabolic steroid golden age (1935–65) was to synthesise a compound which retained a high degree of anabolic activity coupled with a vastly diminished androgenic activity. This property was quantified using the anabolic/androgenic ratio (A/A ratio). At present, most commercially available anabolic steroids were synthesised in the course of the work done during the 30 years of anabolic steroid research. However it is not possible to establish what chemical modification will reinforce the anabolic activity with a simultaneous decrease of the androgenic activity.[4,5]

Substitutions at 9α-H by halogen and 11β-H by hydroxyl group has a positive effect[6-8] on the anabolic/androgenic ratio. We have commenced research for new compounds from accessible raw materials with a better anabolic/androgenic ratio.

The present paper describes the preparation steroids containing chlorine and bromine with potential anabolic/androgenic activity.

The key intermediate, 9β,11β-epoxy-5α-androstan-3β-ol-17-one **(1)** was synthesized from hecogenin according to a method that described by Ruiz.[9] Oxidation of **1** with Jones' reagent in acetone produced 9β,11β-epoxy-5α-androstan-3,17-dione (**2**) (63 % yield). Attention was then directed to the preparation of 9α-chloro-3β,11β-dihydroxy-5α-androstan-17-one (**3**), 9α-bromo-3β,11β-dihydroxy-5α-androstan-17-one (**4**), 9α-chloro-5α-androstan-3,11,17-trione (**5**), 9α-bromo-5α-androstan-3,11,17-trione (**6**), 9α-chloro-11β-hydroxy-5α-androstan-3,17-dione (**7**) and 9α-bromo-11β-hydroxy-5α-androstan-3,17-dione (**8**).

For the preparation of **3** (76 % yield) and **7** (78 % yield), **1** and **2** were respectively treated with hydrogen chloride in chloroform. On the same way for preparation of **4** (80 %) and **8** (75 %), **1** and **2** were respectively treated with hydrogen bromide in acetic acid. The oxidation of hydroxyl groups in compounds **3** and **4** with Jones´ reagent in acetone at room temperature gave **(5)** (85 % yield) and **(6)** (80 % yield), respectively.[10,11]

The structures of the products were supported by spectroscopic analysis (see Experimental).[12-15]

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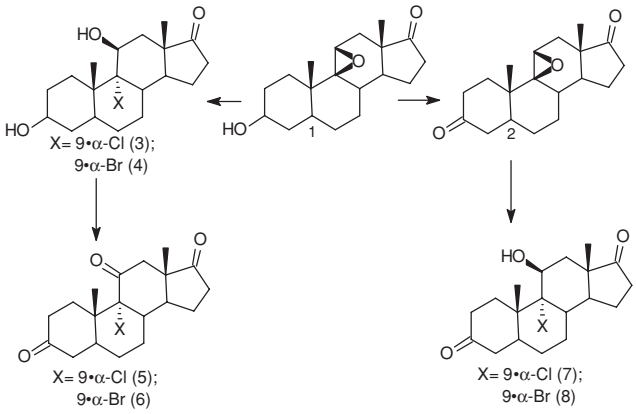

Scheme 1

Table 1 ^{13}C NMR chemical shifts of synthesised compounds (δ in ppm)

	2	3	4	5	6	7	8
C1	32.1	36.2	36.5	37.6	37.8	37.6	37.7
C2	37.3	30.3	30.3	35.5	35.6	36.9	37.2
C3	210.4	69.9	69.8	210.3	210.3	211.3	211.5
C4	44.3	37.2	37.3	44.1	44.4	44.0	44.3
C5	43.3	37.5	39.2	39.7	40.7	39.8	41.4
C6	32.7	27.2	27.1	27.9	28.2	27.5	27.6
C7	26.8	25.2	26.6	23.6	25.0	25.0	26.5
C8	33.8	35.2	36.1	39.1	39.3	35.3	36.0
C9	66.5	91.2	100.6	84.0	87.6	89.8	98.0
C10	37.3	47.0	47.2	49.3	49.4	46.8	46.9
C11	60.9	73.3	73.6	201.2	200.7	73.9	74.1
C12	34.1	30.9	32.5	45.4	45.5	32.5	34.2
C13	45.8	41.8	42.1	41.1	41.5	41.8	41.9
C14	52.2	45.0	46.1	43.2	44.2	44.9	46.0
C15	22.5	21.0	20.9	21.1	21.2	21.2	21.0
C16	34.8	35.3	35.2	31.9	34.0	35.2	35.2
C17	219.2	220.7	220.8	216.3	216.4	218.7	218.9
C18	16.4	15.5	15.6	13.6	13.9	15.8	16.0
C19	14.4	18.2	18.8	14.5	14.8	17.2	18.0

Table 1 contains the complete ^{13}C NMR assignment for synthesised compounds showing changes in the chemical shift of the adjacent to atoms of the introduced groups.

Experimental

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 GF_{254}). Nuclear Magnetic Resonance (NMR) experiments were done on a Mercury-400 spectrometer operating at 300 (^{1}H) and 75.5 MHz (^{13}C). The NMR spectra were measured at 25 °C in $CDCl_3$ solutions and referenced to internal TMS (δ = 0 ppm) and $CDCl_3$ (δ = 77.0 ppm) for ^{1}H and ^{13}C NMR, respectively. 2D ^{1}H,^{1}H-COSY spectra were recorded according to standard pulse programs. The heteronuclear shift correlated 2D NMR via ^1J(C,H) was performed with the standard Bruker pulse program XHCORRD. Fixed delays were adjusted to ^1J(C,H) = 135 Hz. These methods were carried out variously on Bruker Avance-300 and Bruker-500 instruments. Mass spectra (MS) were recorded on a TRIO 1000 Fisons Instruments spectrometer at 12 and 70 eV.

9β,11β-epoxy-5α-androstan-3,17-dione (**2**): Jones´ reagent (6.6 ml) was added slowly to a solution of **1** (5 g) in acetone (1000 ml) at 10–15 °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 %). m.p. 130–133 °C. Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.45; H, 8.67. Found: C, 75.62; H, 8.82. ^{1}H NMR ($CDCl_3$) δ: 3.5 (1H,s, H-11); 1.23 (3H,s,CH_3-19); 1.06 (3H,s,CH_3-18). MS *m/z*: 302 (M^+).

9α-chloro-3β,11β-dihydroxy-5α-androstan-17-one (**3**): 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 sulfate and concentrated to dryness. The crude product was crystallised from methanol to give **3** (0.61 g, 76 %). m.p. 125–128 °C. Anal. Calcd for $C_{19}H_{29}O_3Cl$: C, 67.02; H, 8.59. Found: C, 67.09; H, 8.77. ^{1}H NMR ($CDCl_3$) δ: 4.41 (1H,t, *J*=4.3 Hz,H-11), 3.57 (1H,m,H-3), 1.30 (3H,s,CH_3-19) and 1.10 (3H,s,CH_3-18). MS *m/z*: 340/342 (M^+).

9α-bromo-3β,11β-dihydroxy-5α-androstan-17-one (**4**): 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 **4** (0.8 g, 80 %). m.p. 189–191 °C. Anal. Calcd for $C_{19}H_{29}O_3Br$: C, 59.35; H, 7.61. Found: C, 59.55; H, 7.75. ^{1}H NMR ($CDCl_3$) δ: 4.68 (1H,t,*J*=4.3 Hz, H-11), 3.62 (1H,m, H-3), 1.38 (3H,s,CH_3-19) and 1.17 (3H,s,CH_3-18). MS *m/z*: 366/368 (M^+-18).

9α-chloro-5α-androstan-3,11,17-trione (**5**): Jones´ reagent (7.8 ml) was added slowly to a solution of **3** (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 yield **5** (1.7 g, 85 %). m.p. 208–210 °C. Anal. Calcd for $C_{19}H_{25}O_3Cl$: C, 67.83; H, 7.50. Found: C, 67.91; H, 7.63. ^{1}H NMR ($CDCl_3$) δ: 1.38 (3H,s,CH_3-19); 0.88 (3H,s,CH_3-18). MS *m/z*: 336/338 (M^+).

9α-bromo-5α-androstan-3,11,17-trione (**6**): Preparation of this compound was carried out by a similar method to described for compound **5**. (1.4 g, 80 %). m.p. 163–165 °C. Anal. Calcd for $C_{19}H_{25}O_3Br$: C, 59.98; H, 6.63. Found: C, 60.15; H, 6.81. ^{1}H NMR ($CDCl_3$) δ: 1.38 (3H,s,CH_3-19); 0.87 (3H,s,CH_3-18). MS *m/z*: 301 (M^+-79).

9α-chloro-11β-hydroxy-5α-androstan-3,17-dione (**7**): Preparation of this compound was carried out by a similar method to described for compound **3**. Yield (1.56 g, 78 %). m.p. 185–187 °C. Anal. Calcd for $C_{19}H_{27}O_3Cl$: C, 67.42; H, 8.05. Found: C, 67.55; H, 8.86. ^{1}H NMR ($CDCl_3$) δ: 4.48 (1H, t, *J*=4.3 Hz, H-11); 1.53 (3H, s, CH_3-19); 1.14 (3H, s, CH_3-18). MS *m/z*: 338/340 (M^+).

9α-bromo-11β-hydroxy-5α-androstan-3,17-dione (**8**): Preparation of this compound was carried out by a similar method to described for compound **4**. Yield (1.5 g, 75 %). m.p. 82–86 °C. Anal. Calcd for $C_{19}H_{27}O_3Br$: C, 59.67; H, 7.12. Found: C, 59.80; H, 7.28. ^{1}H NMR ($CDCl_3$) δ: 4.70 (1H, t, *J*=4.3 Hz, H-11); 1.58 (3H, s, CH_3-19); 1.11 (3H, s, CH_3-18). MS *m/z*: 364/366 (M^+-18).

Dr H. Vélez-Castro is most grateful to Deutscher Akademischer Austauschsdienst (DAAD) for the possibility to record many ^{1}H and ^{13}C NMR spectra during his stage at the Humboldt University to Berlin, Germany.

Received 20 January 2005; accepted 10 April 2005
Paper 05/3014

References

1 Anabolic A14. Pharmaprojects Copyright © 2001. PJB Publications Ltd. *Clin. J. Nutrit*., 1996, **75**, 129.
2 M. Bowers, *Bull. of Exp. Treat. AIDS*. No.30, (1996), Sept.
3 W.N. Phillips. *Anabolic Reference Guide.* Mile High Publishing, Golden, CO. 1991.
4 F. Murad, C. Robert and Jr. Haynes, *Andrógenos y Esteroides Anabólicos*. Las Bases Farmacológicas de la Terapéutica. 1984**, III**, 1413.
5 W. Llewellyn. Anabolics 2004. *Molec. Nutri.:* Jupiter, 2004.
6 J.A. Vida. *Androgens and Anabolic Agents*, Academic Press, New York, 1969, p.24.
7 C.H. Robinson, L.E. Finckenor, R. Tiberi, M. Eisler, R. Neri, A. Watnick, P.L. Perlman, P. Holroyd, W. Charney and E.P. Oliveto. *J. Am. Chem. Soc.*, 1960, **82**, 4611.
8 L. Herr, U.S. Pat., 2,813,881, to Upjohn, (1957), CA 52:2952i.
9 J.A. Ruiz, Tesis en Opción al titulo de Doctor en Ciencias Químico Farmacéutica, 1999.
10 M. Reyes, Y.Ma. Álvarez, J.A. Ruiz and H. Vélez. *Revista CENIC de Ciencias Químicas 2000*, 31, 127.
11 J.A. Ruiz, Rev. *CENIC Cienc. Quím*. 2001, 32, 164.
12 H. Novoa, O.M. Peeters, N.M. Blaton, C.J. Ranter J.A. Ruíz, M. Reyes and Y. Ma. Álvarez, *Acta Crystallogr., 2000*, C56, 582.
13 H. Novoa, O.M. Peeters, N.M. Blaton, C.J. Ranter J.A. Ruíz, M. Reyes and Y. Alvarez, *Acta Crystallogr*, 2001, **E57**, 39.
14 H. Novoa, O.M. Peeters, N.M. Blaton, C.J. Ranter, J.A. Ruíz, M. Reyes and Y. Alvarez, *Acta Crystallogr*., 2001, **E57**, 166.
15 J.A Ruiz, M. Reyes, Y.M. Alvarez, H. Vélez, G. García, A.M. Piloto, A. Valdivielso and M.I. Domínguez. CU. Pat. 22 840, CQF (2002).