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Synthesis of Novel 17-Oxo-17a-Aza-D-Homo-3, 5-Seco-Steroids as Potential 5α-Reductase Inhibitors

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Abstract

Benign prostatic hyperplasia (BPH) is a non-malignant enlargement of the prostate gland. It is a leading disorder of the elderly male population. Excessive production of dihydrotestosterone has been implicated in this pathological condition. Steroidal 5α-reductase is a membrane bound NADPH dependent enzyme which is responsible for the conversion of testosterone (T) to dihydrotestosterone (DHT). Therefore, inhibition of production of DHT by 5α-reductase inhibitors is an important approach for the treatment of BPH. The proposed 17-oxo-17a-aza-D-homo-3,5-seco-steroids **(17-20)** have been synthesized using diosgenin as the starting material. Diosgenin was converted to 17-oxo-3, 5-seco-4-nor-androstan-3-oic acid following six steps: Oppenauer oxidation, Lemieux-von Rudloff oxidation, Wolff-Kishner reduction, Marker degradation, oximation and Beckmann rearrangement. 17-Oxo-3, 5- seco-keto acid was then converted to 17-oxo-17a-aza-D-homo-3, 5-seco-4-nor-androstan-3-oic acid by oximation followed by Beckmann rearrangement. The resulted seco-keto acid was then treated with thionyl chloride and the respective amines and phenols to get the desired 3, 5-seco-steroidal amides **(17-18)** and esters **(19-20)** respectively.

Keywords: BPH; DHT; Diosgenin; 5α-Reductase; Seco-steroids.

1. Introduction

Benign prostatic hyperplasia (BPH) is a non-malignant enlargement of the prostate gland. It is caused by increase in the number of stromal and epithelial cells, resulting in the obstruction of proximal urethra, thus causing urinary flow disturbances [1]. It is a leading disorder of the elderly male population. Testosterone (T), an androgen plays a major role in prostate growth. Within the prostate, testosterone gets converted to a more powerful androgen, dihydrotestosterone (DHT). DHT stimulates cell growth in the tissue (the glandular epithelium) that lines the prostate gland and is the major cause of the rapid prostate enlargement that occurs between puberty and young adulthood. DHT is a prime suspect in prostate enlargement in later adulthood [2]. 5α-Reductase is a membrane bound NADPH enzyme which is responsible for the conversion of testicular T to DHT. Thus 5α-reductase dictates the cellular availability of DHT to

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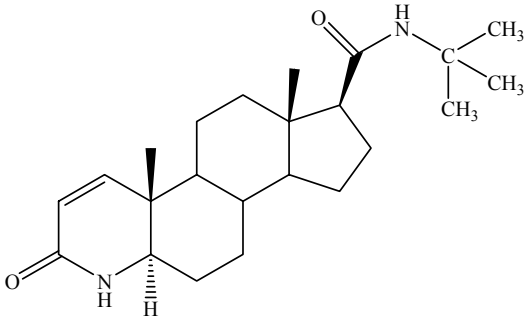
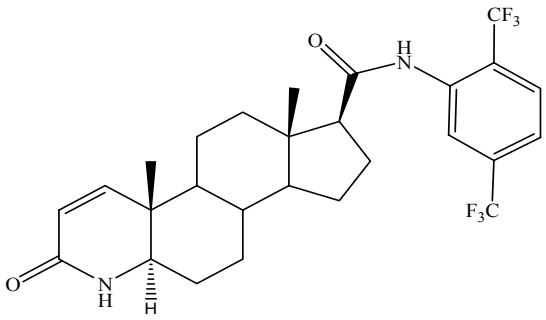
prostatic epithelial cells and consequently modulates its growth. Therefore, inhibition of 5α-reductase is a logical treatment of 5α-reductase activity disorder i.e. BPH [3].

5α-Reductase inhibitors suppresses the DHT concentration by blocking the enzyme and thus shrink the size of prostate and ultimately provides relief from the symptoms related to the static mechanical obstruction caused by BPH. Further, the rationale for use of 5α-reductase inhibitors is rooted in the observation that these are more specific to DHT androgens action without affecting / lowering testosterone level, thus capable of decreasing long term side effect of castration due to loss of testosterone without compromising the efficacy of hormonal therapy [4, 5].

During last two decades, continuous search for potent and selective 5α-reductase inhibitors have resulted into the development of several steroidal and non-steroidal compounds, but steroidal derivatives attracted more attention, as these are highly active and small changes in the steroid nucleus may result into significant alteration in biological activity. Finasteride [6] **(1)** and Dutasteride [7] **(2)** are two clinically used steroidal drugs having lactam in ring A of the steroidal nucleus. Their 5α-reductase inhibitory activity is considered to be attributed by the lactam that mimics intermediate transition state.

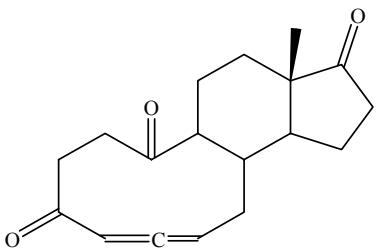


(1)



(2)

Zerhouni *et al.* found that (4*R*)-5,10-secoestra-4,5-diene-3,10,17-trione **(3)** and (4*R*)-5,10-seco-19-norpregna-4,5-diene-3,10,20-trione **(4)** were noncompetitive and possibly irreversible inhibitors of epididymal 5α-reductase [8].



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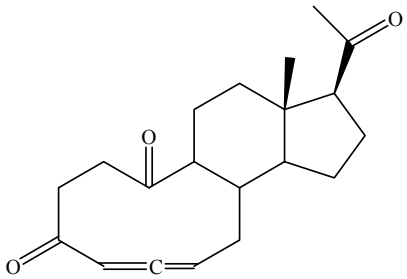


(4)

Therefore, it was considered of interest to synthesize analogues related to Finasteride **(1)** and Dutasteride **(2)** having a lactam in ring D of the steroid nucleus instead of ring A and N-alkylcarbamoyl moiety at the position 3 instead of position 17. In addition, the related analogues will have steroidal ring A open, having various conformations on account of free rotation between positions 1 and 10 and other between positions 1 and 3, thus more flexibility and freedom for interaction at the receptor site. Such compounds are expected to have 5α-reductase inhibitory activity.

Moreover, esters of progesterone exhibited anti-androgenic activity due to the formation of covalent linkage with the target enzyme, in addition to competing, thus irreversibly inhibiting the enzyme activity [9]. Therefore, it was also envisaged to prepare ester analogues of 17-oxo-17a-

aza-D-homo-3,5-seco-4-nor-androstan-3-oic acid with the aim that these analogues may have 5α-reductase inhibitory activity.

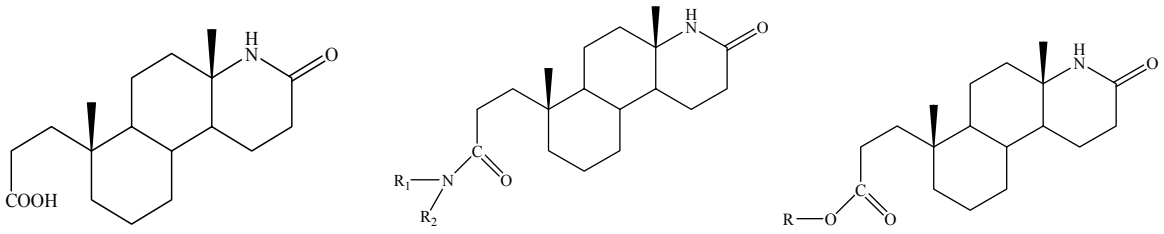
2. Experimental

2.1. Chemicals and Reagents

All chemicals and reagents were obtained from S. D. Fine-Chem. Limited, E. Merck (India) Limited, Sigma-Aldrich and Loba Chemie. Plates for thin layer chromatography (TLC) were prepared with silica gel G (E. Merck) and activated at 110°C for 30 min. Melting points were determined on Veego make silicone oil bath type melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained with Perkin Elmer RXI, FTIR model using potassium bromide pellets. Elemental analyses were carried out on a Perkin-Elmer 2400 CHN elemental analyzer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded with FT-NMR Avance-II Brucker AC-400F (400 MHz) spectrometer at Sophisticated Analytical Instrumentation Facility (SAIF), Panjab University, Chandigarh using tetramethylsilane (TMS) as internal standard. The spin multiplicities are indicated by the symbols: s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), m (multiplet), bs (broad singlet) and bd (broad doublet).

2.2. Chemistry

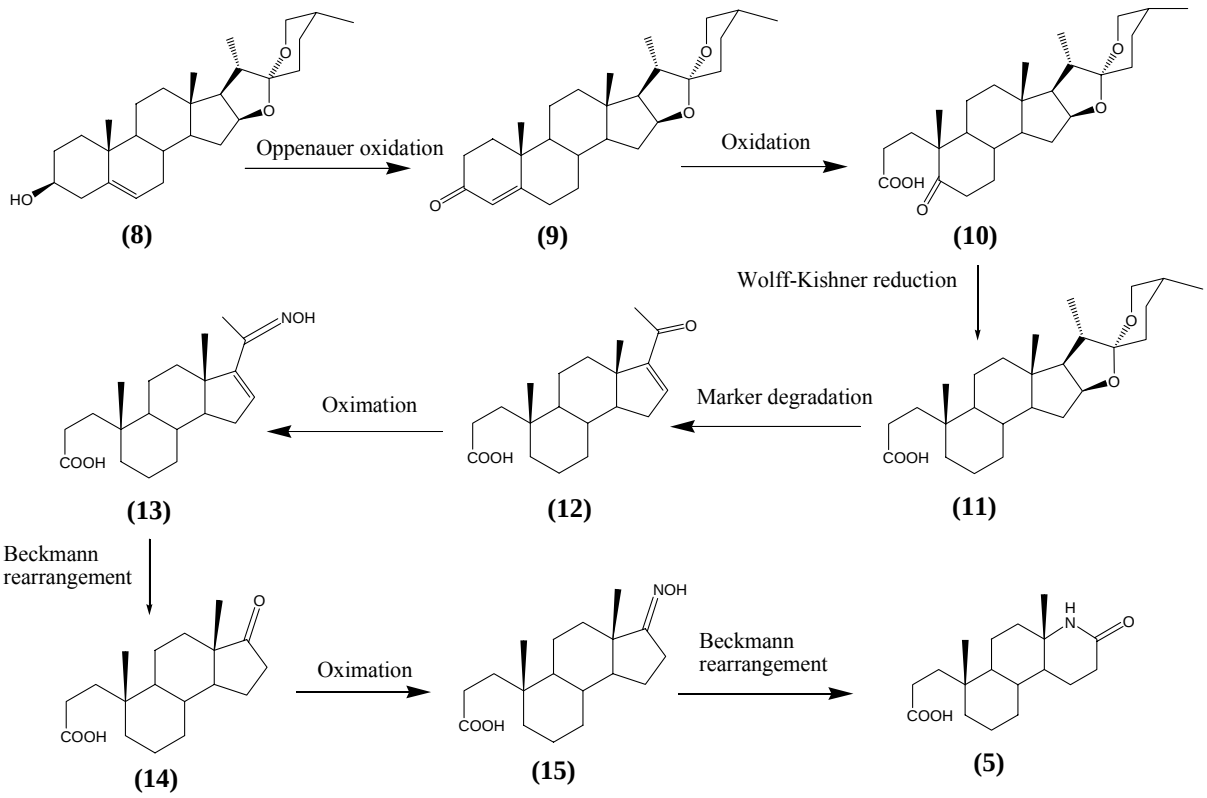
The work carried out is described under the heads : Synthesis of 17-oxo-17a-aza-D-homo-3,5-seco-4-nor-androstan-3-oic acid **(5)**; Synthesis of 3-N-(alkylamino)-17-oxo-17a-aza-D-homo-3,5-seco-4-nor-androstane-3,17-diones **(6)** and Synthesis of aryl 17-oxo-17a-aza-D-homo-3,5-seco-4-nor-androstan-3-oates **(7)**.



(5) **(6)** **(7)**

2.3. *Synthesis of 17-Oxo-17a-aza-D-homo-3, 5-seco-4-nor-androstan-3-oic acid* **(5)** (Scheme -1)
(25R)-4-Spirosten-3-one **(9)**

(25*R*)-5-Spirosten-3*β*-ol **(8)** (3.0 g, 7.0 mmol) was dissolved in a mixture of cyclohexanone (30 ml), dry dioxan (110 ml) and dry toluene (180 ml). Traces of moisture were removed by azeotropic distillation of toluene (15 ml). The distillation was continued at a slow rate while adding a solution of aluminium isopropoxide (2.5 g) in dry toluene (25 ml) drop wise [10]. The reaction mixture was refluxed for 5 hr, allowed to stand overnight at room temperature, filtered at the pump and the residue was washed with dry toluene (25 ml). The combined filtrate and the washings were steam distilled until the complete removal of organic solvent was affected. The reaction mixture was then allowed to cool and extracted with chloroform (4 x 100 ml). The chloroform extract was washed with water, dried and solvent removed under reduced pressure. The residue was crystallized from ethyl acetate to yield (25*R*)-4-spirosten-3-one **(9)** (2.25 g, 75.0%), mp 184-185°C (lit. [11] 186-188°C).



Scheme 1

Spectral data

UV_{max} (MeOH): 240 nm (log ε 4.94),IR (KBr): 2940, 1675, 1054, 920, 899, 864 and 799 cm^{-1}, ^{1}H-NMR ($CDCl_3$): δ 0.80 (d, 3H, 27-*CH₃*), 0.82 (s, 3H, 18-*CH₃*), 0.97 (d, 3H 21- *CH₃*), 1.2 (s, 3H, 19-*CH₃*), 3.4-3.5 (dd, 2H, 26-*CH₂*), 4.4 (m, 1H, 16-*CH*) and 5.6 ppm (s, 1H, 4-*vinylic*). Anal.Calcd for $C_{27}H_{40}O_3$: C, 78.60; H, 9.77. Found: C, 77.97; H, 10.49.

2.4. (25R)-5-Oxo-3, 5-seco-4-nor-spirostan-3-oic acid **(10)**

A solution of potassium carbonate (1.4 g) in water (40 ml) was added to a stirred solution of (25*R*)-4-spirosten-3-one **(9)** (2.5 g, 6.0 mmol) in *t*-butanol-water (9:1) azeotrope (150 ml), followed by 25 ml solution of sodium metaperiodate (10.0 g in 125 ml water) and 0.8% aqueous solution of potassium permanganate (2.5 ml). The remaining sodium metaperiodate solution was introduced at a rate of 6.0 ml/ min over 10 min and then 1.5 ml/ min over the next 30 min. The permanganate solution was added whenever necessary to maintain the permanganate colour. After 5 hr the excess of permanganate was destroyed with sodium metabisulphite and the resulting iodine coloured solution was concentrated under reduced pressure to around 200 ml, cooled to 4°C, acidified with ice-cold sulphuric acid (50.0%) and extracted with solvent ether (3 x 20 ml) .The ether extract was washed free of iodine with aqueous sodium metabisulphite (5.0%) followed by water, dried and the solvent removed under reduced pressure to leave a white solid which was crystallized from acetone to obtain (25*R*)-5-oxo-3, 5-seco-4-nor-spirostan-3-oic acid **(10)** (1.95 g, 78.0%), mp 212-213°C (lit. [12-14] 210-213°C).

Spectrl data

IR (KBr): 2937, 1720, 1660, 1052, 980, 919, 897 and 865 cm^{-1},^{1}H-NMR ($CDCl_3$): δ 0.75 (d, 3H, 27-*CH₃)*, 0.80 (s, 3H, 18-*CH₃*), 0.97 (d, 3H, 21-*CH₃*), 1.12 (s, 3H, 19-*CH₃*), 3.30-3.50

(dd, 2H, 26-*CH*$_2$) and 4.40 ppm (m, 1H, 16-*CH*),[13] C-NMR ($CDCl_3$): δ 215 (C-5 of C=O), 179 (C-3 of COOH), 109.42 (C-22), 80.5 (C-16), 66.87 (C-26), 61.9 (C-17), 20.50 (C-19), 17.22 (C-27) and 16.18 ppm (C-18).

2.5. (25R)-3, 5-Seco-4-nor-spirostan-3-oic acid **(11)**

(25*R*)-5-Oxo-3, 5-seco-4-nor-spirostan-3-oic acid **(10)** (2.0 g, 4.0 mmol), hydrazine hydrate (98.0%, 80 ml), sodium hydroxide (6.0 g) and diethylene glycol (200 ml) were refluxed for 3 hr under nitrogen atmosphere. Excess of hydrazine hydrate was removed by distillation under reduced pressure until the internal temperature of the reaction mixture was 190°C. It was further refluxed for 4 hr under nitrogen atmosphere, cooled and poured into ice-cold water (500 ml). The diluted reaction mixture was acidified with concentrated hydrochloric acid and the precipitated material was filtered at the pump and crystallized from methanol to yield the (25*R*)-3, 5-seco-4-nor-spirostan-3-oic acid **(11)** (1.0 g, 50.0%), mp 140-142°C.

Spectral data

IR (KBr): 2927, 1710, 1242, 1055, 980, 925, 899 and 863 cm^{-1},[1]H-NMR ($CDCl_3$): δ 0.77 (s, 3H, 18-*CH*$_3$), 0.78 (d, 3H, 27-*CH*$_3$), 0.89 (s, 3H, 19- *CH*$_3$), 0.95 (d, 3H, 21-*CH*$_3$), 3.3-3.5 (dd, 2H, 26-*CH*$_2$) and 4.4 ppm (m, 1H, 16-CH).[13]C-NMR ($CDCl_3$): δ 179 (C-3 of COOH), 109.35 (C-22), 80.90 (C-16), 66.80 (C-26), 62.18 (C-17), 21.60 (C-19) and 17.19 (C-27) 16.15 ppm (C-18).

2.6. 20-Oxo-3, 5-seco-4-nor-16-pregnen-3-oic acid ***(12)***

(25R)-3, 5-Seco-4-nor-spirostan-3-oic acid **(11)** (5.0 g, 12.0 mmol), methyl ammonium chloride (5.0 g), acetic anhydride (25 ml) and pyridine (25 ml) were refluxed for 8 hr. The reaction mixture was then cooled and poured into ice-cold water (500 ml). The residue was then filtered, washed repeatedly with dilute hydrochloric acid to remove pyridine, dried and dissolved in dichloromethane (60 ml) and glacial acetic acid (30 ml). The solution was then cooled to -5°C, stirred and to this was added dropwise cold solution of chromium trioxide (2.0 g) in acetic acid (90.0%, 40 ml). The reaction mixture was stirred for further 1 hr at -5°C. Excess of chromium trioxide was destroyed by adding sodium metabisulphite solution (10.0%, 40 ml) at 0°C. After separating the organic layer, the aqueous layer was extracted with chloroform (5 x 50 ml). The combined organic layer was washed with water, sodium bicarbonate (5.0%) and water. The extract was dried, filtered and solvent removed under reduced pressure [15, 16]. The oily residue so obtained was refluxed with glacial acetic acid (60.0ml), for 3 hr, cooled and poured into water (500 ml). It was extracted with chloroform (3 x 50 ml), washed with water, aqueous sodium bicarbonate (5.0%) and water. The extract was dried, filtered and the solvent removed under reduced pressure to give a residue which was crystallized from methanol to yield 20-oxo-3, 5-seco-4-nor-16-pregnen-3-oic acid **(12)** (2.5g, 50.0%), mp 115-117°C.

Spectral data

UV_{max} (MeOH): 236.8 nm (log ε 4.95), IR (KBr): 2930, 1735, 1665, 1240 and 1040 cm^{-1},[1]H NMR ($CDCl_3$): δ 0.75 (s, 3H, 19-*CH*$_3$), 0.85 (s, 3H, 18-*CH*$_3$), 2.10 (s, 3H, 21-*CH*$_3$) and 6.75 ppm (br, 1H, 16- *vinylic*).

2.7. 20-Oximino-3, 5-seco-4-nor-16-pregnen-3-oic acid **(13)**

A solution of 20-oxo-3, 5-seco-4-nor-16-pregnen-3-oic acid (**12)** (4.0 g, 12.0 mmol) and hydroxylamine hydrochloride (2.0 g, 28.0 mmol) in pyridine (50 ml) was heated on steam bath for 1 hr [17]. The reaction mixture was poured with stirring into ice-cold water (500 ml). The

precipitated material was filtered, washed repeatedly to remove pyridine, dried and crystallized from acetone to yield 20-oximino-3,5-seco-4-nor-16-pregnen-3-oic acid **(13)** (3.6 g, 90.0%) mp 121-124°C.

Spectral data

IR (KBr): 3346, 2940, 1725 and 1245 cm^{-1},^{1}H-NMR ($CDCl_3$): δ 0.90 (s, 3H, 18-*CH_3*), 1.2 (s, 3H, 19-*CH_3*), 2.15 (s, 3H, 21- *CH_3*) and 6.00 ppm (br, 1H, 16-*vinylic*), Anal.Calcd for $C_{20}H_{31}NO_3$: N, 4.20. Found: N, 4.31.

2.8. 17-Oxo-3, 5-seco-4-nor-androstan-3-oic acid **(14)**

A cold solution of phosphorus oxychloride (8 ml) in dry pyridine (24 ml) was added drop wise to a stirred solution of 20-oximino-3, 5-seco-4-nor-16-pregnen-3-oic acid **(13)** (2.0 g, 6.0 mmol) in pyridine (20 ml) below 0°C. The reaction mixture was occasionally shaken further for 3 hr at 0°C and poured into a mixture of crushed ice (50 g) and hydrochloric acid (60 ml) [18]. The resulting suspension was then allowed to stand for 30 min at room temperature and diluted with water (100 ml). The precipitated material was filtered, washed repeatedly with water, dried and crystallized from acetone to yield 17-oxo-3,5-seco-4-nor-androstan-3-oic acid **(14)** (1.44 g,72.0%) , mp 172-174**°**C.(lit. [19] 175-177°C).

Spectral data

IR (KBr): 3347, 2928, 1735, 1646, 1245 and 1040 cm^{-1},^{1}H-NMR ($CDCl_3$): δ 0.96 (s, 3H, 18-*CH_3*) and 1.4 ppm (s, 3H, 19-*CH_3*).

2.9. 17-Oximino-3, 5-seco-4-nor-androstan-3-oic acid **(15)**

17-Oxo-3, 5-seco-4-nor-androstan-3-oic acid **(14)** **(**2.0 g, 6.0 mmol) was dissolved in 95.0% ethanol (40.0 ml) and refluxed. To this was added aqueous solution of hydroxylamine hydrochloride (1.0 g, 14.0 mmol) and sodium acetate trihydrate (2.6 g, 20.0 mmol) in water (60 ml) and the reaction mixture was refluxed further for 4 hr [20]. The solvent was partially removed by distillation and the reaction mixture was poured into ice-cold water (400 ml). The precipitated material was filtered, washed with water, dried and crystallized from methanol to give 17-oximino-3,5-seco-4-nor-androstan-3-oic acid **(15)** (1.86g, 93.0%) mp 221-223°C.

Spectral data

IR (KBr): 3350, 2940, 1730, 1650, 1245 and 1050 cm^{-1},^{1}H-NMR ($CDCl_3$): δ 0.96 (s, 3H, 18-*CH_3*) and 1.4 ppm (s, 3H, 19-*CH_3*), Anal.Calcd for $C_{18}H_{29}NO_3$: N, 4.56. Found: N, 4.77.

2.10. 17-Oxo-17a-aza-D-homo-3, 5-seco-4-nor-androstan-3-oic acid **(5)**

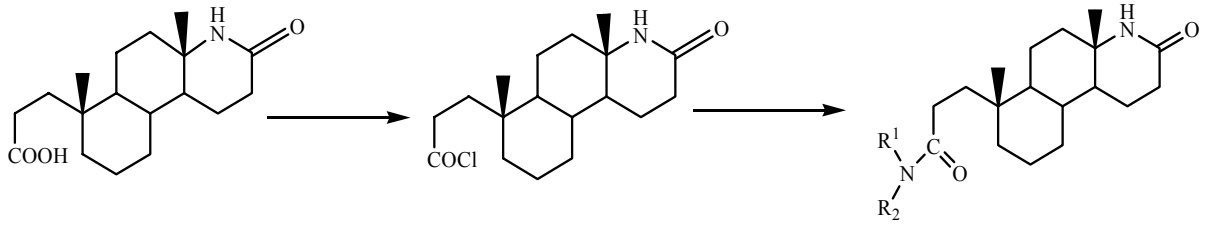
A solution of thionyl chloride (1 ml) in dioxan (2 ml) was added while stirring to a solution of 17-oximino-3, 5-seco-4-nor-androsten-3-oic acid **(15)** (1.0 g, 6.0 mmol) in benzene (32 ml) cooled to 15°C. The reaction mixture was kept at 20°C for 17 min, cooled in an ice bath and water (25 ml) was added. The solution was made alkaline with ammonia. The upper benzene layer was separated and the aqueous layer was extracted with chloroform (4 x 25 ml) [21]. The combined organic portion was washed with water (2 x 20 ml) and the solvent was removed under vacuum to obtain brownish residue which was crystallized from methanol to yield 17-oxo-17a-aza–D-homo-3, 5-seco-4-nor-androstan-3-oic acid **(5)** (0.5 g, 50.0%) mp 220-223°C.

Spectral data

IR *(KBr):* 3400, 2930, 1735, 1665, 1245 and 1054 cm^{-1},^{1}H-NMR ($CDCl_3$): δ 0.95 (s, 3H, 18-*CH_3*) and 1.2 ppm (s, 3H, 19-*CH_3*),Anal.Calcd for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51; N, 4.56. Found: C, 70.20; H, 10.30; N, 4.35.

2.11. Synthesis of 3-N-(alkylamino)-17a-aza–D-homo-3, 5-seco-4-nor-androstane-3,17-diones **(6)**

17-Oxo-17a-aza-D-homo-3, 5-seco-4-nor-androstan-3-oic acid (0.5 g, 16.0 mmol) **(5)** was taken in a round bottom flask and freshly distilled thionyl chloride (5 ml) was added. The reaction mixture was stirred at room temperature for 18 hr. The unreacted thionyl chloride was distilled off and the residue was dried under vacuum to get the acid chloride **(16)**. The acid chloride **16** was dissolved in dichloromethane and added dropwise to the solution of desired amine (8 ml) in dicholoromethane at 0°C. The reaction mixture was stirred for 1 hr. Solvent was removed under reduced pressure to get 3-N-amino-17a-aza-D-homo-3, 5-seco-4-nor- androstane-3, 17-dione [22] (**Scheme 2**).



(5) **(16)** **(17) R_1= H; R_2 = -$CH_2CH_2CH_3$**
(18) R_1= H; R_2 = -CH $(CH_3)_2$

Scheme 2

Spectral data of compound **(17)**

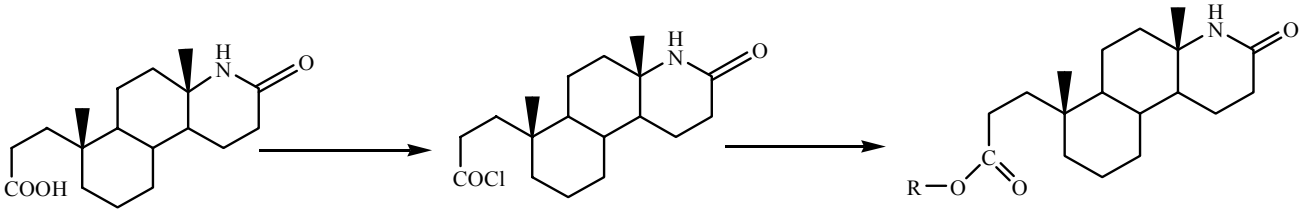
Yield: (0.28 g, 56.0%); mp 125-127°C, IR (KBr): 3413, 2935, 1650, 1640 and 1025 cm^{-1},^{1}H-NMR ($CDCl_3$): δ 0.85 (s, 3H, 18-*CH_3*), 1.1 (s, 3H, 19-*CH_3*), 0.84 (t, 3H, -CH_2CH_2*CH_3*), 1.60 (m, 2H, -CH_2*CH_2*CH_3) and 3.12 ppm (t, 2H, -*CH_2*CH_2CH_3).

Spectral data of compound **(18)**

Yield: (0.3 g, 60.0%); mp 163-165°C, IR (KBr): 3250, 2935, 1680, 1630 and 1025 cm^{-1},^{1}H-NMR ($CDCl_3$): δ 0.85 (s, 3H, 18-*CH_3*), 1.1 (s, 3H, 19-*CH_3*), 2.30 (*m*, 1H, -C*H*(*CH_3*)$_2$), 1.45 (d, 6H, -*CH*(CH_3)$_2$).

2.12. Synthesis of aryl 17-oxo-17a-aza-D-homo-3, 5-seco-4-nor- androstan-3-oates **(7)**

17-Oxo-17a-aza-D-homo-3, 5-seco-4-nor-androstan-3-oic acid **(5)** (0.5 g, 14.0 mmol) was taken in a round bottom flask and freshly distilled thionyl chloride (5 ml) was added. The reaction mixture was stirred at room temperature for 18 hr. The unreacted thionyl chloride was distilled off and the residue dried under vacuum to get the acid chloride **(16)**. The acid chloride was dissolved in acetone and added dropwise to the solution of phenol (8 ml) at 0°C. The reaction mixture was stirred for 1 hr. Solvent was removed under reduced pressure to get aryl 17-oxo-17a-aza-D-homo-3, 5-seco-4-nor-androstan-3-oate (**Scheme 3**).



(5) **(16)** **(19) R= C_6H_5-**
(20)R=4-NO_2-C_6H_4-

Scheme 3

Spectral data of compound **(19)**

Yield: (0.3 g, 48.3%); mp 195-198°C, IR (KBr): 3340, 2940, 1720, 1670 and 1275 cm^{-1},^{1}H-NMR ($CDCl_3$): δ 0.85 (s, 3H, 18-*CH_3*), 1.1 (s, 3H, 19-*CH_3*), 7.4 (t, 2H, 3-*CH* and 5-*CH* aromatic), 7.6 (t, 1H, 4-*CH* aromatic) and 8.1 ppm (d, 2H, 2-*CH* and 6-*CH*).

Spectral data of compound **(20)**

Yield: (0.3 g, 43.5%); mp 120-122°C, IR (KBr): 3340, 2940, 1720, 1670 and 1275 cm^{-1},^{1}H-NMR ($CDCl_3$): δ 0.70 (s, 3H, 18-*CH_3*), 0.9 (s, 3H, 19-*CH_3*), 6.9 (d, 2H, 2-*CH* and 6-*CH* aromatic) and 8.2 ppm (d, 2H, 3-*CH* and 5-*CH*).

3. Results and Discussion

The proposed 17-oxo-17a-aza-D-homo-3,5-seco-steroids were synthesized using diosgenin as the starting material. Oppenauer oxidation of the diosgenin using cyclohexanone -toluene system followed by oxidation of the α,β-unsaturated ketone with periodate-permanganate reagent of Lemieux-von Rudloff gave the 3,5-seco-keto acid. The seco-keto acid was subjected to Wolff-Kishner reduction using mixture of hydrazine hydrate, sodium hydroxide and diethylene glycol followed by Marker degradation with acetic anhydride and pyridine in presence of methylamine hydrochloride and oxidation with chromium trioxide gave 20-oxo-3,5-seco-4-nor-pregn-16-en-3-oic acid.

It was converted to oxime (hydroxylamine hydrochloride in pyridine) which on Beckmann rearrangement using phosphorus oxychloride-pyridine followed by acid hydrolysis gave 17-oxo-3, 5-seco-4-nor-androstan-3-oic acid. 17-Oxo-3, 5-seco-acid was converted to oxime and subjected to Beckmann rearrangement using thionyl chloride to get the desired 17-oxo-17a-aza-D-homo-3, 5-seco-4-nor-androstan-3-oic acid. The lactam so obtained was converted to acid chloride by treating with thionyl chloride and reacted with the respective amines and phenols to get the proposed amides and esters respectively.

4. Conclusion

We have successfully synthesized the novel 17-oxo-17a-aza-D-homo-3,5-seco-steroidal derivatives from commercially available diosgenin which are related to Finasteride **(1)** having lactam in ring D of the steroidal nucleus instead of ring A and N-alkylcarbamoyl or ester moiety at position 3, an important aspects of this protocol. This work can prove to be a guideline for the synthesis of steroidal compounds related to Finasteride **(1)** and Dutasteride **(2)** with invert configuration for the treatment of BPH.

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References

[1] T.L. Bullock, G.L. Andriole, Expert Opin. Emerg. Drugs 11 (2006) 111-123.
[2] G. Andriole, N. Bruchovsky, L.W. Chung, A. M. Matsumoto, R. Rittmaster, C. Roehrborn, D. Russell, D. Tindall, J. Urol. 172 (2004) 1399-1403.
[3] S.A. Kaplan, Urology 58 (2001) 65-70.
[4] A. Kurup, R. Garg, C. Hansch, Chem. Rev. 100 (2000) 909-924.
[5] P. Sanchez, J.M. Torres, E. Ortega, Neurochem. Res. 30 (2005) 577-581.
[6] F.C. Lowe, J.D. McConnell, P.B. Hudson, N.A. Romas, R. Boake, M. Lieber, M. Elhilali, J. Geller, J. Imperto-McGinely, G. Andriole, R.C. Bruskewitz, P.C. Walsh, G. Bartsch, J.N. Nacey, S. Shah, F. Pappas, A. Ko, T. Cook, E. Stoner, J. Waldstreicher, Urology 61 (2003) 791-796.
[7] B. Djavan, S. Milani, Y.K. Fong, Expert Opin. Pharma. 6 (2005) 311-317.
[8] N.A. Zerhouni, M. Maes, C. Sultan, S. Rothwell, C.J. Mlgeon, Steroids 33 (1979) 277-285.
[9] M. Cabeza, I. Heuze, E. Bratoeff, E. Murillo, E. Ramirez, A. Lira, Chem. Pharm. Bull. 49 (2001) 1081-1084.
[10] H. Singh, R.K. Gupta, T.R. Bhardwaj, Indian J. Chem. 27B (1988) 508-512.
[11] R.E. Marker, T. Tsukamoto, D.L. Turner, J. Am. Chem. Soc. 62 (1940) 2525-2531.
[12] H. Singh, P.P. Sharma, R.B. Mathur, Indian J. Chem. 11 (1973) 1254-1256.
[13] R.U. Lemieux, E.V. Rudloff, Can. J. Chem. 33 (1955) 1701-1709.
[14] E.V. Rudloff, Can .J. Chem. 43 (1965) 1784-1791.
[15] R.E. Marker, H. Rohrmann, J. Am. Chem. Soc. 61 (1939) 3592-3593.
[16] R.E. Marker, E. Rohrmann, J. Am. Chem. Soc. 62 (1940) 518-520.
[17] G.H. Posner, B.A. Halford, S. Peleg, P. Dolan, T.W. Kensler, J. Med. Chem. 45 (2002) 1723-1730.
[18] M. Kumar, A.K. Rungta, T.R .Bhardwaj, H. Singh, Indian J. Chem. 29B (1990) 611-614.
[19] A. Kasal, Collect. Czech. Chem. Commun. 45 (1980) 2541-2549.
[20] E.B. Hershberg, J. Org. Chem.13 (1948) 542-546.
[21] M.R. Yadav, M.M. Ganesh, R .Giridhar, M. Kumar, Asian J. Chem. 16 (2004) 1027-1033.
[22] C.A.G.N. Montalbetti, V. Falque, Tetrahedron 61 (2005) 10827-10852.