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Original research paper

New steroidal derivatives synthesized using 3β-hydroxyandrosten-17-one as starting material

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In this study, we synthesized some new substituted steroidal derivatives using 3β-hydroxyandrosten-17-one (dehydroepiandrosterone) as starting material. The synthesized steroidal derivatives **1-11** were evaluated for their androgenic-anabolic activities compared to testosterone as positive control. Details of the synthesis, spectroscopic data and toxicity (LD_{50}) of synthesized compounds are reported.

Keywords: dehydroepiandrosterone, steroidal derivatives, androgenic-anabolic agents

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Natural steroids and their synthetic congeners were extensively studied during the last decade (1, 2). In a previous work, some new heterocyclic compounds showing anti-parkinsonian (3), antitumor (4–6), antimicrobial (7–10) and anti-inflammatory (11) activity were synthesized. We found that certain substituted steroidal derivatives showed androgenic, anabolic and anti-inflammatory activities (12). Steroidal pyrazolines are an interesting group of compounds, many of which possess wide spread pharmacological properties such as analgesic, antipyretic and antiandrogenic activities (13, 14). These derivatives are also well known for their pronounced anti-inflammatory (15) activity and are used as potent antidiabetic agents (16). In addition, the pharmacological and antitumor activities of many heterocyclic compounds have been reviewed (17–19). Recently, nitrogenous derivatives exhibited a general ionophoric potency for divalent cations (20) and are used as novel thiocyanate-selective membrane sensors (21). In view of these reports and in continuation of our previous work in heterocyclic chemistry, we have herein synthesized some new compounds containing steroidal structure for the evaluation of androgenic-anabolic activity as compared to testosterone as standard drug (Fig. 1).

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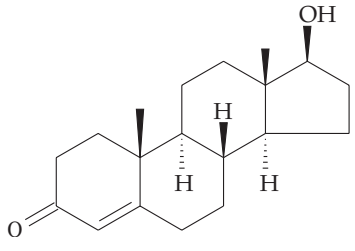


Fig. 1. Testosterone structural formula.

EXPERIMENTAL

Melting points were determined on an Electrothermal IA 9000 apparatus (Electrothermal, UK) and are uncorrected. Elemental analyses for the final compounds were performed on Elementar, Vario EL (USA) at the Microanalytical Unit, National Research Centre, Cairo Egypt, and were found within ± 0.4% of the theoretical values. The IR spectra (KBr) were recorded on an FT IR-8201 PC Spectrophotometer (Shimadzu, Japan). The ^{1}H NMR spectra were measured with Jeol 270 MHz (Japan) in DMSO-d_6 and the chemical shifts were recorded in (δ, ppm) relative to TMS. Mass spectra were run at 70 eV with a Finnigan SSQ 7000 (thermo-instrument system incorporation, USA) spectrometer using EI. The reactions were followed by TLC (silica gel, aluminum sheets 60 F_{254}, Merck, Germany). Testosterone and dehydroepiandrosterone were purchased from Aldrich (Germany).

Physicochemical and spectral data for the synthesized compounds are given in Tables I and II, respectively.

*Synthesis of 17β-cyano-17α-methylamino-androst-5-en-3β-ol (**1a**) and 17β-cyano-17α-phenylamino-androst-5-en-3β-ol (**1b**)*

To a stirred solution of dehydroepiandrosterone (0.29 g, 1 mmol) in absolute ethanol (25 mL), the appropriate primary amine, namely, methylamine or aniline (1 mmol) in ethanol (5 mL) was added dropwise. Hydrochloric acid (5 mL, 10%) was added to the reaction mixture; then, potassium cyanide (0.1g, ~1 mmol) in water (10 mL) was added dropwise. The reaction mixture was stirred at room temperature for 96 hours, diluted with water (100 mL) and neutralized with sodium bicarbonate (10%). The resulting mixture was extracted with chloroform, washed with water, dried over anhydrous sodium sulphate and evaporated under reduced pressure. The obtained residue was solidified with diethyl ether, the obtained solid was filtered off, dried and crystallized from the proper solvent to give the corresponding carbonitriles **1a,b**, respectively (Scheme 1).

*Synthesis of 17β-cyano-17α-[N-methyl-N-(1,1-diaminoethyl)]androst-5-en-3β-ol **(2a)** and 17β-cyano-17α-[N-phenyl-N-(1,1-diaminoethyl)]androst-5-en-3β-ol (**2b**)*

A mixture of **1a,b** (1 mmol) and dimethylamino-2-chloroethane (0.17 g, 1.2 mmol) was refluxed for 7 hours in the presence of triethylamine (0.2 mL) as a catalyst in benzene. The reaction mixture was washed with water, 10% sodium bicarbonate, then with

Table I. Physical and analytical data of newly synthesized compounds

Compd. No.	R	Yield (%)	M.p. (°C)	$[\alpha]_D^{25}$ (*c* 1, MeOH)	Color (solvent for crystallization)	Mol. formula (M_r)[a]
1a	CH_3	98	281	+91	White powder (MeOH)	$C_{21}H_{32}N_2O$ (328.49)
1b	C_6H_5	84	316	+76	Pale yellow powder (AcOEt)	$C_{26}H_{34}N_2O$ (390.56)
2a	CH_3	81	217	+79	White powder (AcOMe)	$C_{25}H_{41}N_3O$ (399.62)
2b	C_6H_5	76	271	+94	White powder (MeOH)	$C_{30}H_{43}N_3O$ (461.69)
3a	CH_3	68	235	+88	White powder (EtOH)	$C_{27}H_{43}N_3O$ (425.65)
3b	C_6H_5	77	286	+96	White powder (EtOH)	$C_{32}H_{45}N_3O$ (487.72)
4a	CH_3	64	196	+66	White powder (AcOH)	$C_{25}H_{36}N_2O_3$ (412.57)
4b	C_6H_5	72	216	+86	White powder (AcOH)	$C_{30}H_{38}N_2O_3$ (474.64)
5a	CH_3	65	288	+69	White powder (MeOH)	$C_{25}H_{30}F_6N_2O_3$ (520.51)
5b	C_6H_5	68	249	+79	Pale yellow powder (MeOH)	$C_{30}H_{32}F_6N_2O_3$ (582.58)
6a	CH_3	55	211	+92	White (MeOH)	$C_{21}H_{38}N_2O$ (334.54)
6b	C_6H_5	65	218	+76	White powder (AcOEt)	$C_{26}H_{40}N_2O$ (396.61)
7a	CH_3	67	199	+96	White (AcOMe)	$C_{21}H_{36}N_2O$ (332.52)
7b	C_6H_5	72	148	+79	White powder (MeOH)	$C_{26}H_{38}N_2O$ (394.60)
8a	CH_3	55	188	+89	White powder (EtOH)	$C_{21}H_{34}N_2O_2$ (346.51)
8b	C_6H_5	49	198	+77	Orange powder (EtOH)	$C_{26}H_{36}N_2O_2$ (408.58)
9a	CH_3	60	252	+95	White powder (AcOH)	$C_{21}H_{33}NO_3$ (347.49)
9b	C_6H_5	62	249	+75	White powder (AcOH)	$C_{26}H_{35}NO_3$ (409.56)
10a	CH_3	69	207	+93	White powder (MeOH)	$C_{21}H_{31}NO_3$ (345.48)
10b	C_6H_5	78	187	+76	White powder (MeOH)	$C_{26}H_{33}NO_3$ (407.55)
11a	CH_3	80	178	+88	Pale yellow powder (AcOH)	$C_{23}H_{37}N_3O$ (371.56)
11b	C_6H_5	76	213	+79	White powder (MeOH)	$C_{28}H_{39}N_3O$ (433.63)

[a] Confirmed by elemental analysis showing values within ± 0.4% of the theoretical values unless otherwise stated.

water and dried over anhydrous sodium sulphate. The benzene part was evaporated under reduced pressure and the residue obtained was solidified with *n*-hexane. The obtained solid was filtered off, dried and crystallized from the proper solvent to give the derivatives **2a,b**, respectively (Scheme 1).

*Synthesis of 17β-cyano-17α-[N-methyl-N-(piperidin-1-ylmethyl)amino]androst-5-en-3β-ol (**3a**) and 17β-cyano-17α-[N-phenyl-N-(piperidin-1-ylmethyl)amino]androst-5-en-3β-ol (**3b**)*

A mixture of carbonitrile derivatives **1a**,**b** (1 mmol) and piperidine (4 mmol) was refluxed for 2 hours in the presence of powdered paraformaldehyde (12 mg) in 1% hydrochloric acid in ethanol (15 mL). The reaction mixture was concentrated under reduced pressure to dryness; the solid formed was collected by filtration, washed with ethanol, dried and crystallized from the proper solvent to afford the corresponding piperidenyl derivatives **3a**,**b**, respectively (Scheme 1).

Table II. Spectral data of newly synthesized compounds

Compd. No.	Mass (m/z, %)	IR (ν, cm^{-1})	^1H NMR (δ, ppm)
1a	328.49 (M^+] (32), 254 (100)	3448–3378 (OH, NH), 2224 (C≡N), 1634 (C=C)	0.76 (s, 3H, CH_3, C-19), 0.88 (s, 3H, CH_3, C-18), 0.96–1.04 (m, 1H, CH), 1.15–1.25 (m, 4H, $2CH_2$), 1.42–1.56 (m, 6H, $3CH_2$), 1.60–1.80 (m, 4H, $2CH_2$), 1.94–1.98 (m, 1H, CH), 2.38 (s, 3H, N-CH_3), 2.42–2.48 (m, 2H, CH_2), 2.56–2.59 (m, 1H, CH), 3.55–3.60 (m, 1H, 3α-CH), 3.92 (s, 1H, NH, exchangeable with D_2O), 5.58–5.64 (m, 1H, CH, C-6), 10.00 (s, 1H, OH, exchangeable with D_2O)
1b	390 [M^+] (12), 274 (100)	3448–3378 (broad band, OH, NH), 2224 (C≡N), 1634 (C=C)	0.78 (s, 3H, CH_3, C-19), 0.87 (s, 3H, CH_3, C-18), 0.95–1.05 (m, 1H, CH), 1.10–1.24 (m, 4H, $2CH_2$), 1.43–1.55 (m, 6H, $3CH_2$), 1.62–1.79 (m, 4H, $2CH_2$), 1.97–2.04 (m, 1H, CH), 2.44–2.50 (m, 2H, CH_2), 2.58–2.62 (m, 1H, CH), 3.56–3.64 (m, 1H, 3α-CH), 4.05 (s, 1H, NH, exchangeable with D_2O), 5.55–5.65 (m, 1H, CH, C-6), 7.23–7.50 (m, 5H, Ar-H), 10.05 (s, 1H, OH, exchangeable with D_2O)
2a	399 [M^+] (22), 301 (100)	3451–3391 (OH), 2227 (C≡N), 1632 (C=C)	0.78 (s, 3H, CH_3, C-19), 0.94 (s, 3H, CH_3, C-18), 0.96–1.00 (m, 1H, CH), 1.10–1.23 (m, 4H, $2CH_2$), 1.38–1.55 (m, 6H, $3CH_2$), 1.62–1.79 (m, 4H, $2CH_2$), 1.82–1.85 (m, 4H, 2 CH_2), 1.97–2.00 (m, 1H, CH), 2.32, 2.36, 2.39 (3s, 9H, 3 × N-CH_3), 2.44–2.48 (m, 2H, CH_2), 2.55–2.60 (m, 1H, CH), 3.54–3.61 (m, 1H, 3α-CH), 5.60-5.65 (m, 1H, CH, C-6), 9.98 (s, 1H, OH, exchangeable with D_2O)
2b	461 [M^+] 28), 363 (100)	3444–3386 (OH), 2223 (C≡N), 1630 (C=C)	0.74 (s, 3H, CH_3, C-19), 0.89 (s, 3H, CH_3, C-18), 0.98–1.05 (m, 1H, CH), 1.16–1.25 (m, 4H, $2CH_2$), 1.41–1.57 (m, 6H, $3CH_2$), 1.64–1.80 (m, 4H, $2CH_2$), 1.85–1.88 (m, 4H, 2 CH_2), 1.96–2.05 (m, 1H, CH), 2.34, 2.36 (2s, 6H, 2 × N-CH_3), 2.45–2.50 (m, 2H, CH_2), 2.56–2.60 (m, 1H, CH), 3.57–3.64 (m, 1H, 3α-CH), 5.58–5.66 (m, 1H, CH, C-6), 7.18–7.46 (m, 5H, Ar-H), 9.96 (s, 1H, OH, exchangeable with D_2O)
3a	425 [M^+] (33), 260 (100)	3458–3377 (OH), 2226 (C≡N), 1634 (C=C)	0.75 (s, 3H, CH_3, C-19), 0.91 (s, 3H, CH_3, C-18), 0.96–1.00 (m, 1H, CH), 1.10–1.23 (m, 4H, $2CH_2$), 1.38–1.55 (m, 6H, $3CH_2$), 1.58–1.62 (m, 6H, $3CH_2$), 1.65–1.79 (m, 4H, $2CH_2$), 1.97–2.00 (m, 1H, CH), 2.20–2.26 (m, 4H, $2CH_2$), 2.36 (s, 3H, N-CH_3), 2.44–2.48 (m, 2H, CH_2), 2.55–2.60 (m, 1H, CH), 3.42 (s, 2H, N-CH_2-N), 3.54–3.61 (m, 1H, 3α-CH), 5.60–5.65 (m, 1H, CH, C-6), 10.03 (s, 1H, OH, exchangeable with D_2O)
3b	487 [M^+] (8), 345 (100)	3455–3396 (OH), 2225 (C≡N), 1635 (C=C)	0.79 (s, 3H, CH_3, C-19), 0.95 (s, 3H, CH_3, C-18), 0.98–1.02 (m, 1H, CH), 1.10–1.23 (m, 4H, $2CH_2$), 1.38–1.55 (m, 6H, $3CH_2$), 1.56–1.60 (m, 6H, $3CH_2$), 1.66–1.79 (m, 4H, $2CH_2$), 1.95–2.05 (m, 1H, CH), 2.24–2.28 (m, 4H, $2CH_2$), 2.42–2.46 (m, 2H, CH_2), 2.53–2.62 (m, 1H, CH), 3.40 (s, 2H, N-CH_2-N), 3.52–3.64 (m, 1H, 3α-CH), 5.56–5.61 (m, 1H, CH, C-6), 7.18–7.46 (m, 5H, Ar-H), 10.02 (s, 1H, OH, exchangeable with D_2O)

4a	412 [M^+] (32), 260 (100)	2224 (C≡N), 1742 (CO, ester), 1728 ($COCH_3$), 1632 (C=C)	0.77 (s, 3H, CH_3, C-19), 0.92 (s, 3H, CH_3, C-18), 1.00–1.05 (m, 1H, CH), 1.18–1.26 (m, 4H, $2CH_2$), 1.40–1.55 (m, 6H, $3CH_2$), 1.63–1.78 (m, 4H, $2CH_2$), 1.95–2.00 (m, 1H, CH), 2.23 (s, 3H, CO-CH_3), 2.34 (s, 3H, N-CH_3), 2.40–2.50 (m, 2H, CH_2), 3.65 (s, 3H, COO-CH_3), 2.56–2.62 (m, 1H, CH), 3.54–3.62 (m, 1H, 3α-CH), 5.57–5.64 (m, 1H, CH, C-6)
4b	474 [M^+] (42), 345 (100)	2223 (C≡N), 1739 (CO, ester), 1725 ($COCH_3$), 1634 (C=C)	0.79 (s, 3H, CH_3, C-19), 0.90 (s, 3H, CH_3, C-18), 0.99–1.04 (m, 1H, CH), 1.16–1.24 (m, 4H, $2CH_2$), 1.43–1.53 (m, 6H, $3CH_2$), 1.62–1.80 (m, 4H, $2CH_2$), 1.98–2.04 (m, 1H, CH), 2.25 (s, 3H, CO-CH_3), 2.41–2.53 (m, 2H, CH_2), 3.66 (s, 3H, COO-CH_3), 2.58–2.62 (m, 1H, CH), 3.52–3.56 (m, 1H, 3α-CH), 5.52–5.60 (m, 1H, CH, C-6), 7.20–7.34 (m, 5H, Ar-H)
5a	520 [M^+] (16), 244 (100)	2226 (C≡N), 1748 (CO, ester), 1732 (CO, $COCF_3$), 1635 (C=C)	0.79 (s, 3H, CH_3, C-19), 0.98 (s, 3H, CH_3, C-18), 1.05–1.10 (m, 1H, CH), 1.20–1.27 (m, 4H, $2CH_2$), 1.45–1.54 (m, 6H, $3CH_2$), 1.65–1.82 (m, 4H, $2CH_2$), 1.96–2.05 (m, 1H, CH), 2.35 (s, 3H, N-CH_3), 2.44–2.48 (m, 2H, CH_2), 2.53–2.61 (m, 1H, CH), 3.53–3.64 (m, 1H, 3α-CH), 5.54–5.63 (m, 1H, CH, C-6)
5b	582 [M^+] (9), 363 (100)	2228 (C≡N), 1747 (CO, ester), 1734 (CO, $COCF_3$), 1636 (C=C)	0.79 (s, 3H, CH_3, C-19), 0.92 (s, 3H, CH_3, C-18), 0.98–1.06 (m, 1H, CH), 1.14–1.25 (m, 4H, $2CH_2$), 1.45–1.56 (m, 6H, $3CH_2$), 1.60–1.81 (m, 4H, $2CH_2$), 1.96–2.00 (m, 1H, CH), 2.43–2.52 (m, 2H, CH_2), 2.59–2.64 (m, 1H, CH), 3.54–3.58 (m, 1H, 3α-CH), 5.52–5.59 (m, 1H, CH, C-6), 7.22–7.35 (m, 5H, Ar-H)
6a	332 [M^+] (52), 244 (100)	3580–3490 (OH), 3448–3376 (NH_2, NH), 1634 (C=C)	0.81 (s, 3H, CH_3, C-19), 0.96 (s, 3H, CH_3, C-18), 0.99–1.08 (m, 1H, CH), 1.22–1.26 (m, 4H, $2CH_2$), 1.41–1.55 (m, 6H, $3CH_2$), 1.62–1.79 (m, 4H, $2CH_2$), 1.98–2.02 (m, 1H, CH), 2.36 (s, 3H, N-CH_3), 2.40–2.45 (m, 2H, CH_2), 2.52–2.57 (m, 1H, CH), 3.39 (s, 2H, CH_2-N), 3.50–3.61 (m, 1H, 3α-CH), 3.75 (s, 2H, NH_2, exchangeable with D_2O), 3.98 (s, 1H, NH, exchangeable with D_2O), 5.58–5.62 (m, 1H, CH, C-6), 9.99 (s, 1H, OH, exchangeable with D_2O)
6b	394 [M^+] (14), 274 (100)	3560–3474 (OH), 3442–3388 (NH_2, NH), 1635 (C=C)	0.79 (s, 3H, CH_3, C-19), 0.94 (s, 3H, CH_3, C-18), 0.98–1.05 (m, 1H, CH), 1.24–1.28 (m, 4H, $2CH_2$), 1.42–1.58 (m, 6H, $3CH_2$), 1.64–1.83 (m, 4H, $2CH_2$), 1.96–2.04 (m, 1H, CH), 2.41–2.47 (m, 2H, CH_2), 2.54–2.59 (m, 1H, CH), 3.38 (s, 2H, CH_2-N), 3.53–3.64 (m, 1H, 3α-CH), 3.76 (s, 2H, NH_2, exchangeable with D_2O), 3.99 (s, 1H, NH, exchangeable with D_2O), 5.56–5.63 (m, 1H, CH, C-6), 7.21–7.36 (m, 5H, Ar-H), 9.98 (s, 1H, OH, exchangeable with D_2O)
7a	MS *m/z* (%): 334 [M^+] (26), 260 (100)	3560–3480 (OH), 3440–3388 (NH_2, NH)	0.80 (s, 3H, CH_3, C-19), 0.92 (s, 3H, CH_3, C-18), 0.99–1.02 (m, 1H, CH), 1.16–1.27 (m, 4H, $2CH_2$), 1.39–1.57 (m, 6H, $3CH_2$), 1.63–1.81 (m, 6H, $3CH_2$), 1.97–2.05 (m, 1H, CH), 2.34 (s, 3H, N-CH_3), 2.44–2.48 (m, 2H, CH_2), 2.56–2.65 (m, 1H, CH), 3.00–3.10 (m, 1H, 5δ-CH), 3.37 (s, 2H, CH_2-N), 3.53–3.60 (m, 1H, 3α-CH), 3.80 (s, 2H, NH_2, exchangeable with D_2O), 4.02 (s, 1H, NH, exchangeable with D_2O), 9.98 (s, 1H, OH, exchangeable with D_2O)

7b	396 [M^+] (33), 256 (100)	3566–3477 (OH), 3443–3386 (NH_2, NH)	0.79 (s, 3H, CH_3, C-19), 0.88 (s, 3H, CH_3, C-18), 0.97–1.00 (m, 1H, CH), 1.15–1.25 (m, 4H, $2CH_2$), 1.42–1.56 (m, 6H, $3CH_2$), 1.61–1.80 (m, 6H, $3CH_2$), 1.99–2.06 (m, 1H, CH), 2.43–2.49 (m, 2H, CH_2), 2.57–2.64 (m, 1H, CH), 3.05–3.15 (m, 1H, 5δ-CH), 3.35 (s, 2H, CH_2-N), 3.54–3.62 (m, 1H, 3α-CH), 3.78 (s, 2H, NH_2, exchangeable with D_2O), 4.00 (s, 1H, NH, exchangeable with D_2O), 7.22–7.35 (m, 5H, Ar-H), 10.00 (s, 1H, OH, exchangeable with D_2O)
8a	346 [M^+] (10), 244 (100)	3560–3474 (OH), 3442–3388 (NH_2, NH), 1660 (C=O, amide), 1636 (C=C)	0.79 (s, 3H, CH_3, C-19), 0.94 (s, 3H, CH_3, C-18), 0.95–1.05 (m, 1H, CH), 1.16–1.25 (m, 4H, $2CH_2$), 1.44–1.54 (m, 6H, $3CH_2$), 1.61–1.82 (m, 4H, $2CH_2$), 1.96–2.05 (m, 1H, CH), 2.33 (s, 3H, N-CH_3), 2.42–2.49 (m, 2H, CH_2), 2.57–2.64 (m, 1H, CH), 3.52–3.63 (m, 1H, 3α-CH), 3.74 (s, 2H, NH_2, exchangeable with D_2O), 3.98 (s, 1H, NH, exchangeable with D_2O), 5.56–5.61 (m, 1H, CH, C-6), 9.86 (s, 1H, OH, exchangeable with D_2O)
8b	408 [M^+] (18), 256 (100)	3569–3480 (OH), 3439–3392 (NH_2, NH), 1662 (C=O, amide), 1635 (C=C)	0.81 (s, 3H, CH_3, C-19), 0.93 (s, 3H, CH_3, C-18), 0.99–1.05 (m, 1H, CH), 1.15–1.24 (m, 4H, $2CH_2$), 1.43–1.57 (m, 6H, $3CH_2$), 1.65–1.80 (m, 4H, $2CH_2$), 1.98–2.02 (m, 1H, CH), 2.40–2.48 (m, 2H, CH_2), 2.54–2.61 (m, 1H, CH), 3.50–3.64 (m, 1H, 3α-CH), 3.86 (s, 2H, NH_2, exchangeable with D_2O), 3.97 (s, 1H, NH, exchangeable with D_2O), 5.53–5.60 (m, 1H, CH, C-6), 7.18–7.38 (m, 5H, Ar-H), 9.98 (s, 1H, OH, exchangeable with D_2O)
9a	347 [M^+] (14), 301 (100)	3472–3396 (OH, NH), 1718 (CO, acid), 1634 (C=C)	0.78 (s, 3H, CH_3, C-19), 0.92 (s, 3H, CH_3, C-18), 0.97–1.06 (m, 1H, CH), 1.18–1.26 (m, 4H, $2CH_2$), 1.43–1.57 (m, 6H, $3CH_2$), 1.60–1.80 (m, 4H, $2CH_2$), 1.95–2.00 (m, 1H, CH), 2.32 (s, 3H, N-CH_3), 2.40–2.47 (m, 2H, CH_2), 2.55–2.62 (m, 1H, CH), 3.53–3.62 (m, 1H, 3α-CH), 4.02 (s, 1H, NH, exchangeable with D_2O), 5.55–5.60 (m, 1H, CH, C-6), 9.86–10.56 (br. s, 2H, 2 x OH, exchangeable with D_2O)
9b	409 [M^+] (8), 345 (100)	3444–3387 (OH, NH), 1723 (CO, acid), 1630 (C=C)	0.81 (s, 3H, CH_3, C-19), 0.97 (s, 3H, CH_3, C-18), 0.99–1.04 (m, 1H, CH), 1.20–1.25 (m, 4H, $2CH_2$), 1.42–1.56 (m, 6H, $3CH_2$), 1.61–1.79 (m, 4H, $2CH_2$), 1.96–2.02 (m, 1H, CH), 2.39–2.46 (m, 2H, CH_2), 2.53–2.60 (m, 1H, CH), 3.54–3.60 (m, 1H, 3α-CH), 4.15 (s, 1H, NH, exchangeable with D_2O), 5.52–5.58 (m, 1H, CH, C-6), 7.19–7.36 (m, 5H, Ar-H), 9.88–10.60 (br. s, 2H, 2 x OH, exchangeable with D_2O)
10a	345 [M^+] (100)	3505–3410 (OH, NH), 1735 (CO, enone), 1719 (CO, acid), 1636 (C=C)	0.80 (s, 3H, CH_3, C-19), 0.94 (s, 3H, CH_3, C-18), 0.99–1.06 (m, 1H, CH), 1.21–1.27 (m, 4H, $2CH_2$), 1.41–1.59 (m, 6H, $3CH_2$), 1.62–1.81 (m, 4H, $2CH_2$), 1.98–2.04 (m, 1H, CH), 2.35 (s, 3H, N-CH_3), 2.42–2.49 (m, 2H, CH_2), 2.54–2.60 (m, 1H, CH), 4.00 (s, 1H, NH, exchangeable with D_2O), 5.52–5.61 (m, 1H, CH, C-6), 10.86 (br. s, 1H, OH, exchangeable with D_2O)

10b	407 [M^+] (15), 407 (100)	3448–3386 (OH, NH), 1734 (CO, enone), 1721 (CO, acid), 1635 (C=C)	0.83 (s, 3H, CH_3, C-19), 0.95 (s, 3H, CH_3, C-18), 1.00–1.05 (m, 1H, CH), 1.21–1.27 (m, 4H, $2CH_2$), 1.39–1.58 (m, 6H, $3CH_2$), 1.63–1.82 (m, 4H, $2CH_2$), 1.96–2.05 (m, 1H, CH), 2.40–2.46 (m, 2H, CH_2), 2.51–2.59 (m, 1H, CH), 3.98 (s, 1H, NH, exchangeable with D_2O), 5.50–5.60 (m, 1H, CH, C-6), 7.21–7.35 (m, 5H, Ar-H), 10.68 (br. s, 1H, OH, exchangeable with D_2O)
11a	371 [M^+] (16), 299 (100)	3454–3378 (OH, NH), 1633 (C=C), 1610 (C=N)	0.77 (s, 3H, CH_3, C-19), 0.94 (s, 3H, CH_3, C-18), 0.99–1.06 (m, 1H, CH), 1.19–1.25 (m, 4H, $2CH_2$), 1.40–1.56 (m, 6H, $3CH_2$), 1.61–1.83 (m, 4H, $2CH_2$), 1.97–2.00 (m, 1H, CH), 2.38 (s, 3H, N-CH_3), 2.41–2.48 (m, 2H, CH_2), 2.54–2.58 (m, 1H, CH), 3.52–3.60 (m, 1H, 3α-CH), 3.64–3.68 (m, 4H, $2CH_2$), 3.98 (s, 1H, NH, exchangeable with D_2O), 5.55–5.65 (m, 1H, CH, C-6), 8.40 (s, 1H, NH, exchangeable with D_2O), 10.06 (s, 1H, OH, exchangeable with D_2O)
11b	433 [M^+] (26), 274 (100)	3462–3386 (OH, NH), 1636 (C=C), 1605 (C=N)	0.79 (s, 3H, CH_3, C-19), 0.87 (s, 3H, CH_3, C-18), 0.97–1.04 (m, 1H, CH), 1.16–1.25 (m, 4H, $2CH_2$), 1.40–1.54 (m, 6H, $3CH_2$), 1.60–1.80 (m, 4H, $2CH_2$), 1.98–2.03 (m, 1H, CH), 2.42–2.50 (m, 2H, CH_2), 2.58–2.64 (m, 1H, CH), 3.55–3.61 (m, 1H, 3α-CH), 3.66–3.69 (m, 4H, $2CH_2$), 4.00 (s, 1H, NH, exchangeable with D_2O), 5.51–5.62 (m, 1H, CH, C-6), 7.19–7.38 (m, 5H, Ar-H), 8.32 (s, 1H, NH, exchangeable with D_2O), 10.00 (s, 1H, OH, exchangeable with D_2O)

*Synthesis of 17*β*-cyano-17*α*-(*N*-methylacetamido)-androst-5-en-3*β*-acetate* ***(4a)****,*
*17*β*-cyano-17*α*-(*N*-phenylacetamido)-androst-5-en-3*β*-acetate (****4b****),*
*17*β*-cyano-17*α*-(*N*-methyl-trifluoroacetamido)-androst-5-en-3*β*-trifluoroacetate* ***(5a)***
*and 17*β*-cyano-17*α*-(*N*-phenyl-trifluoroacetamido)-androst-5-en-3*β*-trifluoroacetate (****5b****)*

A solution of compounds **1a,b** (150 mg) in acetyl chloride or trifluoroacetic anhydride (5 mL) was stirred at room temperature for 24 hours. The reaction mixture was poured into ice-water, the separated solid was filtered off, dried and crystallized from the proper solvent to yield the compounds **4a,b** and **5a,b**, respectively (Scheme 2).

*Synthesis of 17*β*-aminomethyl-17*α*-(*N*-methyl)-androst-5-en-3*β*-ol* ***(6a)****,*
*17*β*-aminomethyl- 17*α*-(*N*-phenyl)-androst-5-en-3*β*-ol (****6b****),*
*17*β*-aminomethyl-17*α*-(*N*-methyl)-androstan-3*β*-ol (****7a****)*
*and 17*β*-aminomethyl-17*α*-(*N*-phenyl)-androstan-3*β*-ol (****7b****)*

A mixture of compounds **1a,b** (5 mmol) and catalytic reagents, namely, palladium--charcoal or platinum oxide-charcoal (Adam's catalyst) (50 mg) in absolute ethanol (25 mL) was shaken at 75 °C under hydrogen (5×10^5 Pa) for 7 hours and filtered. The filtrate was evaporated under reduced pressure, the residue was solidified with ether, the separated solid was filtered off, dried and crystallized from the proper solvent to yield the compounds **6a,b** and **7a,b**, respectively (Scheme 2).

Synthesis of 3β-hydroxy-17α-methyl amino-androst-5-ene-17β-carboxamide ***(8a)*** *and 3β-hydroxy-17α-phenyl amino-androst-5-ene-17β-carboxamide* ***(8b)***

A solution of compounds **1a,b** (1 mmol) in sulphuric acid (0.5 mol L^{-1}, 10 mL) was heated at 50 °C for 5 hours, then left overnight at room temperature. The reaction mixture was poured into ice water, the separated product was filtered off, washed with water, dried and crystallized from the proper solvent to give the corresponding carboxamide derivatives **8a,b**, respectively (Scheme 3).

Synthesis of 3β-hydroxy-17α-methyl amino-androst-5-ene-17β-carboxylic acid ***(9a)*** *and 3β-hydroxy-17α-phenyl amino-androst-5-ene-17β-carboxylic acid* ***(9b)***

A mixture of compounds **1a,b** (1 mmol) in alcoholic sodium hydroxide (25 mL, 10%) was refluxed for 7 hours. The reaction mixture was acidified with 1 mol L^{-1} hydrochloric acid (pH ~ 3). The separated product was filtered off, washed with water, dried and crystallized from the proper solvent to give the corresponding acid derivatives **9a,b**, respectively (Scheme 3).

*Synthesis of 3-oxo-17α-methyl amino-androst-5-ene-17β-carboxylic acid (****10a****) and 3-oxo-17α-phenyl amino-androst-5-ene-17β-carboxylic acid (****10b****)*

A mixture of compounds **1a,b** (2 mmol) and Killian reagent (6 mL) [prepared from potassium dichromate (6 g) and concentrated sulfuric acid (8 mL) in water (27 mL)] in glacial acetic acid (15 mL) was stirred at room temperature for 1.5 hours. The reaction mixture was warmed with methanol (15 mL) to destroy excess chromic acid, then it was poured into ice-water; the solid formed was filtered off, washed with water, dried and crystallized from the proper solvent to give 3-oxo-17-substituted amino-androst-5-ene-17-carboxylic acids **10a,b**, respectively (Scheme 3).

*Synthesis of 17α-(2-imidazolyl)-17β-methyl amino-androst-5-ene-3β-ol (****11a****) and 17α-(2-imidazolyl)-17β-phenyl amino-androst-5-en-3β-ol (****11b****)*

A mixture of compounds **1a,b** (1 mmol) in ethylene diamine (15 mL) was refluxed for 3 hours. The reaction mixture was poured into water, the formed solid was filtered off and crystallized from the proper solvent to give the corresponding imidazole derivatives **11a,b**, respectively (Scheme 3).

Biological screening

Animals. – Biological experiments were made according to the ethical rules and animals were obtained from the animal house colony of the National Research Center, Cairo, Egypt. All animals were allowed free access to water and were kept on a constant standard diet. Prepubertal Sprague-Dawley male albino rats 21 day old (45–50 g), were used to investigate the effect of the tested compounds on the development of male sex organs. Adult male albino rats (150 days) weighting (150–200 g) were used in the present work to evaluate the androgenic-anabolic activity of all newly synthesized derivatives.

Acute toxicity (LD_{50})

Male rats were used to determine intraperitoneal LD_{50} of the tested compounds. Prior to determination of the LD_{50} value, a range finding screen was conducted using 20 rats each treat with a tested compound at a dose ranging from 3–2000 mg kg^{-1}. Based on the mortality observed within 14 days, the doses used for the LD_{50} determination were 3, 10, 30, 100, 300, 1000, 2000 mg kg^{-1} for compounds administered by intraperitoneal injection as a 10% solution in dimethyl sulphoxide (DMSO). Control animals received intraperitoneal injections of DMSO. For each concentration and control, ten male rats were injected with the tested compounds twice daily for two weeks to kill any swirved animals. From the mortality data of all tested animals, the intraperitoneal LD_{50} values for each agent were determined according to Austen *et al*. (22) (Table III).

Table III. Evaluation of LD_{50} *of the synthesized compounds*

Compound	LD_{50} (mg kg^{-1})[a]
Testosterone	2751 ± 5
Dehydroepiandrosterone	3411 ± 4
1a	3211 ± 8
1b	2561 ± 5
2a	2818 ± 5
2b	2913 ± 6
3a	2781 ± 4
3b	2750 ± 6
4a	2713 ± 6
4b	2514 ± 6
5a	3164 ± 8
5b	3000 ± 7
6a	2634 ± 8
6b	2894 ± 7
7a	2856 ± 7
7b	2646 ± 7
8a	2895 ± 7
8b	2648 ± 7
9a	2865 ± 6
9b	2743 ± 5
10a	2891 ± 5
10b	2914 ± 4
11a	2988 ± 5
11b	2755 ± 3

[a] Mean ± SD, $n = 24$.

Androgenic-anabolic activity

Groups of immature male albino rats (each group contains 8 animals), 21 days old, received subcutaneously particular target compounds and testosterone as reference standard at a total dose of 0.7 mg kg^{-1} according to the following design: group 1 received the vehicle (DMSO); group 2 received the testosterone reference standard in vehicle (DMSO) (at a dose of 0.1 mg kg^{-1} daily for 7 days); group 3 was subdivided into 22 subgroups, each received individually one of the tested compounds (at a dose of 0.1 mg kg^{-1} daily for 7 days).

Androgenic-anabolic activity of all newly synthesized compounds was measured according to the reported procedure (23, 24) (Tables IV and V).

Table IV. Androgenic-anabolic activity of newly synthesized compounds

Compound	Mass of prostate gland (g)[a]	Mass of levator ani-muscle (g)[a]	Ratio[b]
Control	0.20 ± 0.02	0.18 ± 0.02	–
Testosterone	0.76 ± 0.01	0.20 ± 0.01	0.05
1a	0.32 ± 0.01	0.44 ± 0.15	2.20
1b	0.39 ± 0.01	0.54 ± 0.01	1.90
2a	0.41 ± 0.01	0.56 ± 0.01	1.82
2b	0.39 ± 0.01	0.42 ± 0.13	1.28
3a	0.71 ± 0.01	0.73 ± 0.02	0.97
3b	0.66 ± 0.02	0.68 ± 0.02	1.09
4a	0.73 ± 0.01	0.75 ± 0.02	1.08
4b	0.44 ± 0.02	0.58 ± 0.01	1.68
5a	0.31 ± 0.01	0.43 ± 0.16	2.30
5b	0.75 ± 0.01	0.76 ± 0.02	1.06
6a	0.81 ± 0.02	0.19 ± 0.01	0.02
6b	0.83 ± 0.026	0.21 ± 0.02	0.06
7a	0.81 ± 0.01	0.23 ± 0.01	0.09
7b	0.82 ± 0.02	0.22 ± 0.02	0.06
8a	0.82 ± 0.01	0. 21 ± 0.02	0.06
8b	0.87 ± 0.01	0.25 ± 0.01	0.10
9a	0.83 ± 0.02	0.27 ± 0.01	0.14
9b	0.86 ± 0.02	0.28 ± 0.01	0.16
10a	0.91 ± 0.03	0.30 ± 0.03	0.17
10b	0.96 ± 0.02	0.31 ± 0.02	0.17
11a	0.97 ± 0.02	0.30 ± 0.02	0.16
11b	0.96 ± 0.02	0.24 ± 0.02	0.08

[a] Mean ± SEM (n = 8).
[b] Ratio of the mass gained by the levator ani-muscle to the mass gained by the prostate gland.

Table V. Effect of synthesized compounds on androgenic organs

Compound	Mass (g)[a]			
	Epididymis	Testis	Seminal vesicles	Vasdifference
Testosterone	0.36 ± 0.03[b]	0.70 ± 0.02[b]	0.63 ± 0.01[b]	0.19 ± 0.012[b]
1a	0.31 ± 0.04[c]	0.45 ± 0.04[c]	0.59 ± 0.01[bc]	0.72 ± 0.08[c]
1b	0.36 ± 0.03[b]	0.68 ± 0.02	0.58 ± 0.01[b]	0.19 ± 0.01[b]
2a	0.30 ± 0.03[c]	0.43 ± 0.04	0.56 ± 0.02[bc]	0.73 ± 0.021[b]
2b	0.28[b] ± 0.02[c]	0.41 ± 0.02	0.41 ± 0.02[bc]	0.13 ± 0.02[bc]
3a	0.29[b] ± 0.02[c]	0.39 ± 0.02	0.39 ± 0.02[bc]	0.14 ± 0.02[bc]
3b	0.37[a] ± 0.03[b]	0.74 ± 0.03	0.68 ± 0.02[b]	0.13 ± 0.02[bc]
4a	0.37[a] ± 0.03[b]	0.74 ± 0.03	0.61 ± 0.03[b]	0.12 ± 0.02[bc]
4b	0.15[b] ± 0.02[c]	0.34 ± 0.03	0.38 ± 0.01[c]	0.29 ± 0.04[c]
5a	0.37[a] ± 0.03[b]	0.74 ± 0.03	0.61 ± 0.02[b]	0.30 ± 0.05[c]
5b	0.22[b] ± 0.02[c]	0.31 ± 0.04	0.41 ± 0.03[b]	0.22 ± 0.06[b]
6a	0.34[a] ± 0.03[b]	0.39 ± 0.04	0.54 ± 0.03[b]	0.42 ± 0.02[b]
6b	0.35[a] ± 0.02[b]	0.42 ± 0.03	0.45 ± 0.02[b]	0.22 ± 0.02[b]
7a	0.36[a] ± 0.02[b]	0.51 ± 0.05	0.48 ± 0.02[b]	0.32 ± 0.02[b]
7b	0.32[a] ± 0.04[b]	0.52 ± 0.04	0.56 ± 0.02[b]	0.23 ± 0.02[b]
8a	0.32 ± 0.05[b,c]	0.42 ± 0.03	0.43 ± 0.03[b]	0.17 ± 0.02[b]
8b	0.32 ± 0.03[b,c]	0.39 ± 0.02	0.42 ± 0.02[b]	0.25 ± 0.03[b]
9a	0.32 ± 0.02[b,c]	0.56 ± 0.02	0.52 ± 0.02[b]	0.21 ± 0.02[b]
9b	0.32 ± 0.01[b,c]	0.47 ± 0.01	0.41 ± 0.02[b]	0.22 ± 0.02[b]
10a	0.22 ± 0.01[b,c]	0.46 ± 0.01	0.41 ± 0.02[b]	0.22 ± 0.02[b]
10b	0.22 ± 0.02[b,c]	0.42 ± 0.02	0.52 ± 0.02[b]	0.21 ± 0.02[b]
11a	0.24 ± 0.02[b,c]	0.43 ± 0.01	0.54 ± 0.02[b]	0.22 ± 0.02[b]
11b	0.52 ± 0.02[b,c]	0.48 ± 0.013	0.56 ± 0.02[b]	0.22 ± 0.02[b]

[a] Mean ± SE (n = 8).
[b] Significantly different from normal control value ($p \leq 0.05$).
[c] Significantly different from testosterone value ($p \leq 0.05$).

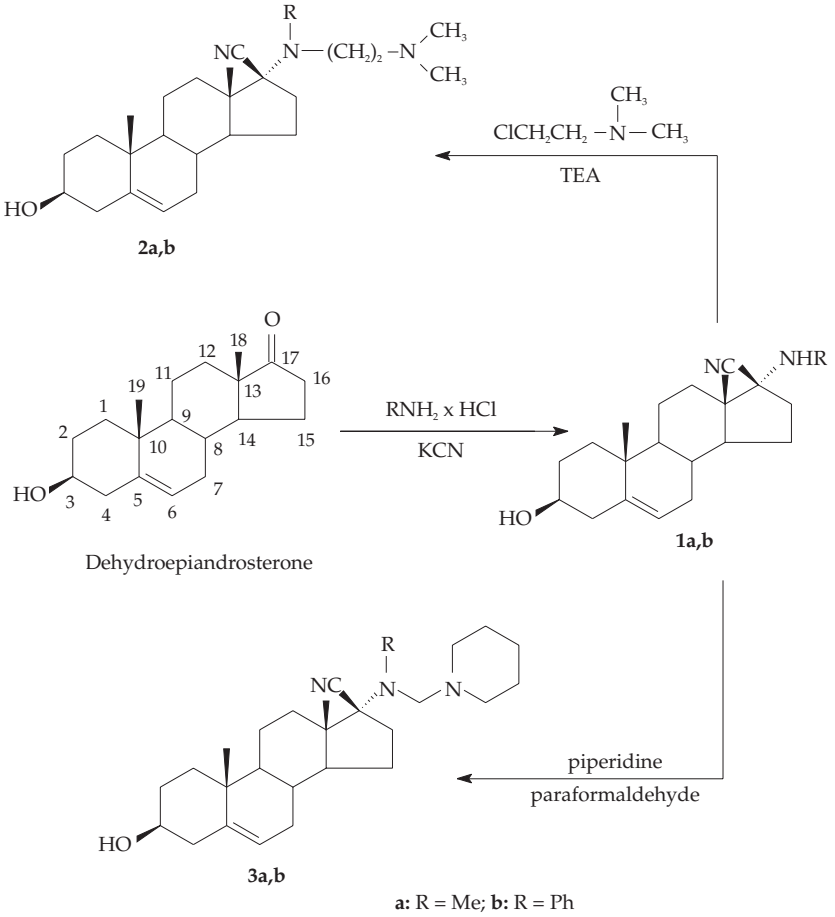
Groups of prepubertal albino rats (n = 8) 21 days old, were kept on a constant diet and tap water. Each animal was given daily a subcutaneous injection of the tested compound as well as testosterone as reference standard at a dose of 0.1 mg kg^{-1} for seven days. On day eight (22–26 hours after the last injection), the animals were killed, dissection of the levator ani muscle, the ventral prostate gland, testis, seminal vesicles, vas deference and epididymis were carried out and were weighed.

The ratio of the mass gain of the levator ani-muscle to the mass gain of the ventral prostate gland was calculated where the mass gain of the levator ani muscle indicates

the anabolic effect and the mass gain of the ventral prostate gland shows the androgenic effect of the tested compounds.

RESULTS AND DISCUSSION

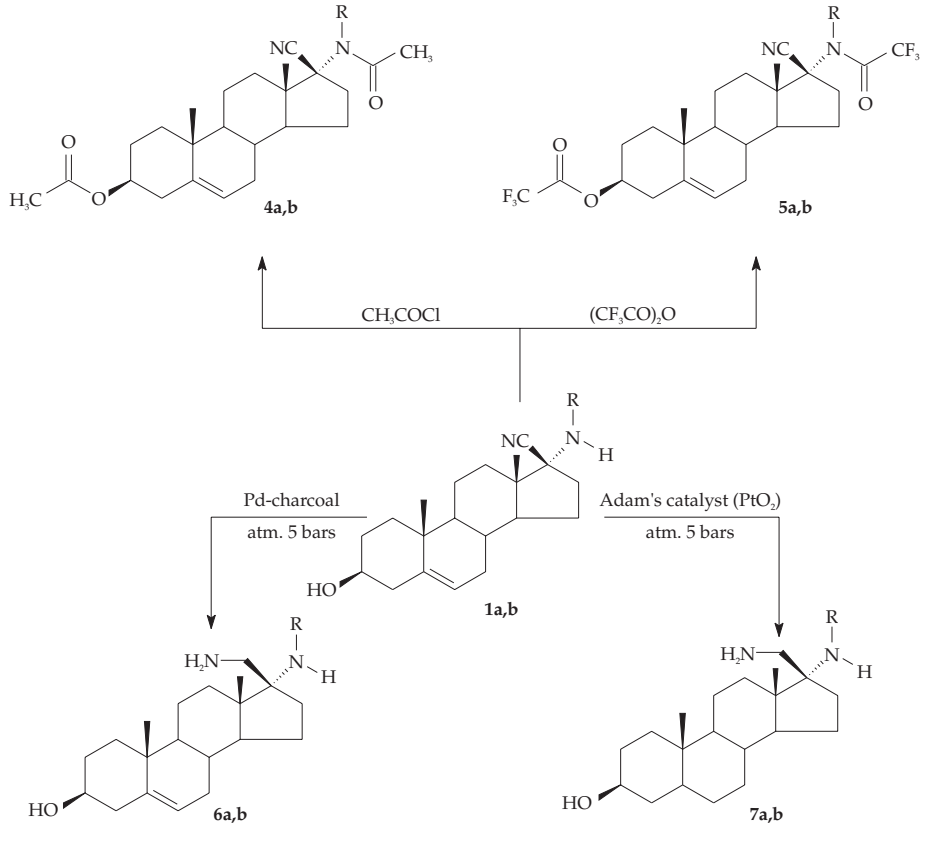
In the present work, we utilized Strechker synthesis to introduce the 17β-cyano--17α-substituted amino group into synthesized compounds, because the cyano group provides a wide variety of biological activities. Amino group serves to form water-soluble salts that increase the pharmacokinetics and pharmacodynamics of steroids such as Stanazolole® due to its increased absorption and distribution in plasma protein.



Scheme 1

Compounds **1a,b** were obtained by reacting dehydroepiandrosterone with primary amines, namely, methylamine or aniline in the presence of potassium cyanide. Reaction of compounds **1a,b** with dimethylamino-2-chloroethane in the presence of triethylamine as catalyst yielded *N,N*-dimethylethane derivatives **2a,b** while the reaction of **1a,b** with piperidine in the presence of paraformaldehyde gave the piperidyl derivatives **3a,b.** The IR spectra of **1-3** showed the absence of bands corresponding to ν(C=O) for dehydroepiandrosterone and the presence of a band at 2224–2227 cm^{-1} corresponding to ν(C≡N), and a broad band at 3448–3396 cm^{-1} corresponding to ν(NH) for dehydroepiandrosterone. The syntheses of compounds **1-3** are outlined in Scheme 1.

Acylation of the resulting compounds **1a,b** with acetylchloride or trifluoroacetic anhydride in boiling toluene gave the corresponding diprotected derivatives **4a,b** and **5a,b**, respectively. Also, catalytic hydrogenation of **1a,b** with palladium charcoal (Pd/

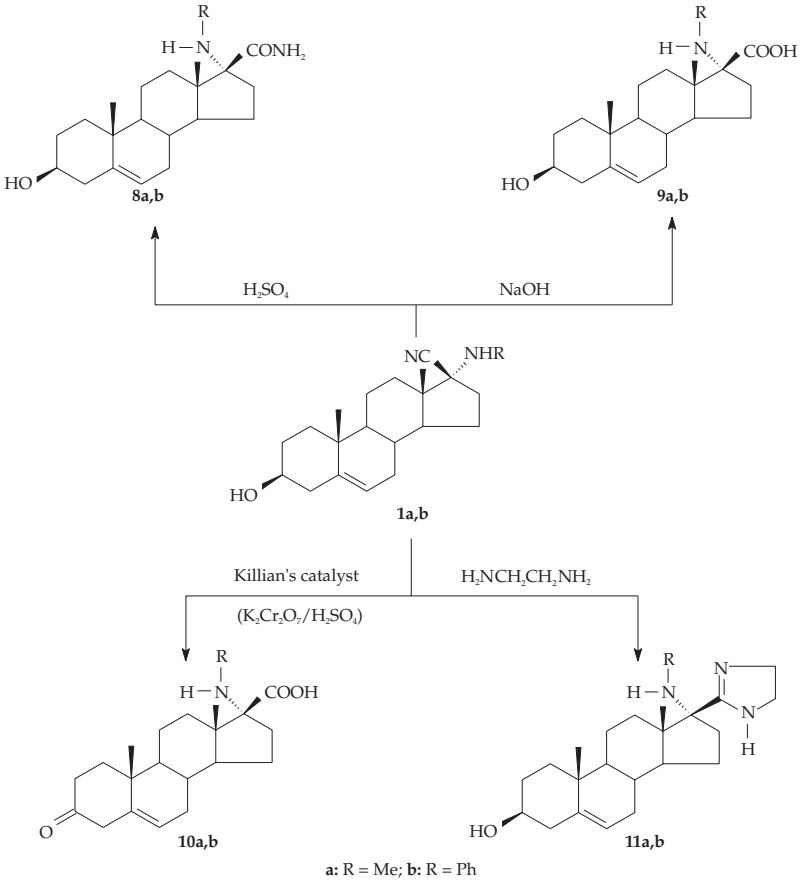


a: R = Me; **b:** R = Ph

Scheme 2

charcoal) afforded the corresponding primary amines **6a,b** without affecting the Δ^5-ene double bond, whereas with Adam's catalyst (PtO_2) it afforded the corresponding primary amines **7a,b** with hydrogenated Δ^5-ene double bond. The IR spectra of **4** and **5** showed the absence of bands ν(OH) at 3448–3378 cm^{-1} for the starting compound and the presence of bands corresponding to ν(C=O) for **4** and **5.** Also, the IR spectra of **6** and **7** showed the absence of bands ν(CN) at 2224 cm^{-1} for the starting compound and the presence of bands corresponding to $\nu(NH_2)$ for **6** and **7**. The syntheses of compounds **4**-**7** are outlined in Scheme 2.

Hydrolysis of compounds **1a,b** with sulphuric acid (H_2SO_4, 0.5 mol L^{-1}) or alcoholic sodium hydroxide (10%) gave the corresponding amide derivatives **8a,b** and the carboxylic acids **9a,b**, respectively. On the other hand, oxidation of **1a,b** with Killian reagent (chromic acid, as oxidizing agent) afforded the corresponding 3-oxo-analogues **10a,b** with hydrolyzed cyano group to carboxylic group. Condensation of compounds **1a,b** wi-



a: R = Me; **b:** R = Ph

Scheme 3

th 1,2-diaminoethane gave the corresponding imidazole derivatives **11a,b.** The IR spectra of **8-11** showed the absence of bands corresponding to ν(C≡N) for **1** and the presence of bands corresponding to ν(C=O) for compounds **8-10** and ν(NH) for **11.** The syntheses of compounds **8-11** are outlined in Scheme 3.

Acute toxicity

Initially, acute toxicity of the synthesized compounds was assayed by determining their LD_{50}. Interestingly, most compounds were less toxic than the reference drug, except compounds **1b, 4b, 6a, 7b** and **8b** (Table III). The LD_{50} (rats) was determined by injecting different increasing doses and calculating the dose that killed 50% of the animals.

Androgenic-anabolic activity

The newly synthesized compounds were then pharmacologically screened for their androgenic-anabolic potency on male albino rats.

From Tables IV and V, the ratio of the mass gained by the levator ani-muscle to the mass gained by the prostate gland was calculated, where the former indicates the anabolic activity and the latter shows the androgenic effect of the tested compounds. It was revealed that all the tested compounds have significant androgenic as well as anabolic effects. Regarding the androgenic activity indicated by the mass gained by the prostate gland, compounds **3a**, **6b-11b** showed high androgenic activity.

Compounds **1a, 1b, 2a, 2b, 3b, 4a, 4b, 5a** and **5b** showed potent anabolic activities where the ratio of mass gained by the levator ani-muscle (anabolic) to the mass gained by the ventral prostate were 2.20, 1.90, 1.82, 1.28, 1.09, 1.08, 1.68, 2.30 and 1.06 (Table IV).

It is evident from Table V that compounds **3a, 6b-11b** significantly increase the mass of male sex organs. Compound **5a** showed high anabolic activity, increasing the mass of both levator-ani muscle and prostate gland in a statistically significant manner. It increased the mass of the testicles but in a non-significant manner.

Structure activity relationship (SAR)

The presence of some groups (hydrogen bond donors) is beneficial for androgenic activities. The activity was found to decrease in the following order: **6a**, **6b, 8a, 7b, 11b** and **7a.** It was found that the anabolic activity was decreasing in the order: **5a, 1a, 1b, 4b, 2a, 3b, 4a** and **5b**, indicating that the presence of hydrogen bond acceptor is an important beneficial factor for anabolic activity.

CONCLUSIONS

Twenty-two steroidal derivatives were synthesized and tested for their androgenic--anabolic activities. The substituted steroidal structure containing 5-ene double bonds was found essential for androgenic-anabolic activity. A future work will involve the design of steroidal molecules of such features.

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S A Ž E T A K

Novi steroidni derivati sintetizirani iz 3β-hidroksiandrosten-17-ona

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U radu je opisana sinteza novih steroidnih derivata **1-11** koristeći 3β-hidroksiandrosten-17-on (dehidroepiandrosteron) kao početnu supstanciju. Androgeno-anaboličko djelovanje tih spojeva uspoređivano je s djelovanjem testosterona kao pozitivnom kontrolom. Navode se detaljni sintetski postupci, spektroskopska karakterizacija i podaci o toksičnosti (LD_{50}).

Ključne riječi: dehidroepiandrosteron, steroidni derivati, androgeno-anabolički steroidi

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