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Synthesis and some Reactions of 17α-Methyltestosterone Mannich Bases

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Abstract A series of Mannich bases **2a-c** was prepared *via* the reaction of 17α-methyltestosterone (**1**) with paraformaldehyde and the appropriate amine. Condensation of **2a** with **1** afforded **4**. Transamination reaction between **2b** and the appropriate primary aromatic amines gave the *sec.* Mannich bases **6a-c** and **7**. The novel androstanotriazolopyrimidine **11** and androstanopyridopyrimidine **15** were also prepared.

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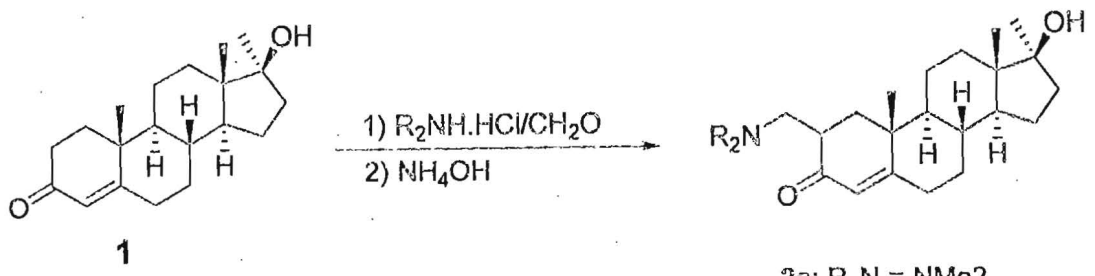
Introduction

Mannich bases are potentially versatile intermediates used for the synthesis of a variety of carbocyclic and heterocyclic compounds and natural alkaloids (Albonia *et al.*, 2004; Moiseev *et al.*, 1999; Tramontini *et al.*, 1990; Afsah *et al.*, 1990 and O'Neill *et al.*, 2003). In particular, the ketonic Mannich bases and their quaternary salts have been employed frequently as potential intermediates in the synthesis of compounds of pharmaceutical interest such as: pyrazoles (Afsah *et al.*, 2007), piperidines (Plati; Wenner 1949; Plati *et al.*, 1949 and Afsah *et al.*, 2008), diazepines (Roman *et al.*, 2002 and Insuasty *et al.*, 2000), quinolones (Andreani *et al.*, 1967), pyrimidines (Roth *et al.*, 1968) and triazepines (Hammouda *et al.*, 1993). In view of the increasing interest in the chemistry and biological activities of Mannich bases and as an extension of our studies (Afsah *et al.*, 1984; Afsah *et al.*, 1985 and Afsah *et al.*, 2011), we report here on the synthesis and some reactions of 17α-methyltestosterone Mannich bases which possess considerable synthetic and pharmaceutical interest.

Results and discussion

Mannich reaction of 17α-methyltestosterone (**1**) with either dimethylammonium, morpholinium or piperidinium chloride and paraformaldehyde gave after neutralization with ammonium hydroxide the corresponding Mannich bases 2-aminomethyl-17α-methyltestosterones (**2a-c**) in good yields (**c.f. Scheme 1**).



2a: R_2N = NMe2
2b: R_2N = 4-morpholinyl
2c: R_2N = 1-piperidinyl

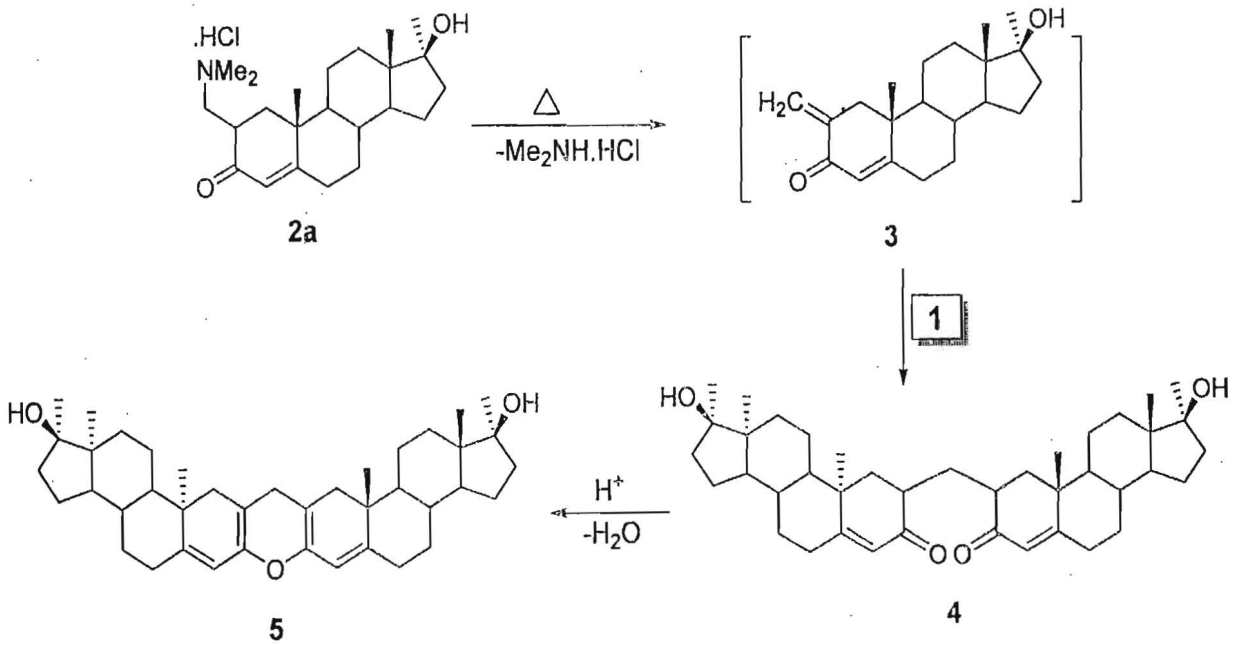
Scheme 1

The analytical and spectral data are constituent with the structures proposed for compounds **2a-c**. The IR spectra of the Mannich bases **2a-c** displayed a strong absorption band at ν = 1669 cm^{-1} for steroidal carbonyl group with a shoulder band at ν = 1619 cm^{-1} for unsaturated double bond. The ^1H NMR spectrum of **2a**, as an example, showed the steroidal three methyl groups (18-CH_3, 19-CH_3 and 17α-CH_3) and six hydrogen atoms of -$N(CH_3)_2$ as singlets at δ = 0.97, 0.99, 1.17 and 2.19 ppm, respectively. The mass spectrum of **2c** exhibited its molecular ion at *m/z* = 399. The ions at *m/z* = 380 and 340 are due to extrusion of H_2O and acetone molecules, these data are in line with the reported studies on the mass spectrum of **1** (Jackson *et al.* 1986).

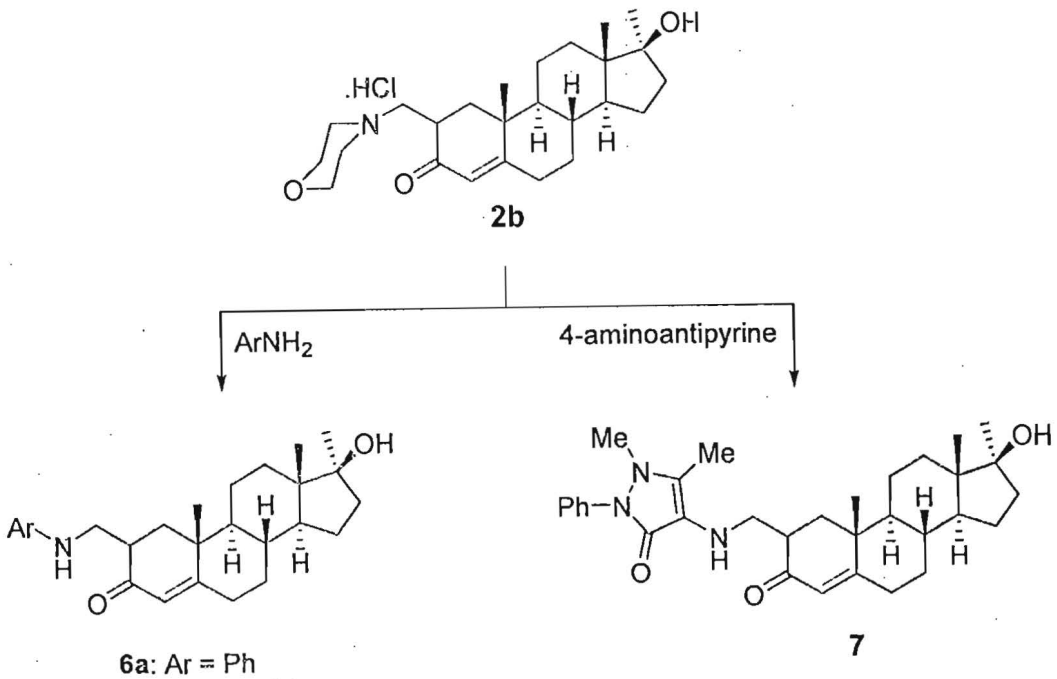
In the course of this study, the synthesis of methylene-2,2'-bis(17β-hydroxy-17α-methylandrost-4-en-3-one) (**4**) has been achieved by treating **2a** with **1**. It is believed that the Mannich base **2a** undergoes spontaneous deamination on prolonged heating to give the enone **3**, followed by Michael addition to **1** to give **4** as the end product, as depicted in Scheme 2.

In addition, compound **4** undergoes acid-catalyzed cyclization to afford bis(17β-hydroxy-17α-methylandrost-4-ene)[b,e]-4*H*-pyran (**5**). The structures of compounds **4** and **5** were supported by analytical and spectral data. Their mass spectra showed the molecular ions at *m/z* = 616 and 599 $[M+1]^+$, respectively. The appearance of a singlet in the ^1H NMR spectrum of **5** at δ = 3.35 ppm for pyran ring CH_2 group and the disappearance of the testosterone carbonyl band in its IR spectrum confirmed the newly condensed bisteroidal pyran skeleton **5**. In addition to its molecular ion at *m/z* = 616, the mass spectrum of **4** showed the ions at *m/z* = 300 (85%) and 315 (54%) as a result of cleavage at the methylene linkage. The ion at 550 (85%) is due to evolution of two H_2O molecules and two methyl radicals, and the ion at *m/z* = 500 (74%) is from extrusion of two acetone molecules.

In connection with the present study, a series of testosterone *secondary* Mannich bases **6a-c** and **7** was prepared *via* transamination between the testosterone Mannich base hydrochloride **2b** and aniline, *p*-toluidine, 2-aminoanthraquinone or 4-aminoantipyrine (**c.f. Scheme 3**). The structures of **6a-c** and **7** were confirmed by analytical and spectral data. The IR spectra of **6a-c** showed a broad band at the region ν = 3440-3250 cm^{-1} which corresponds to OH and NH groups, in addition to the enone group at ν = 1665 and 1617 cm^{-1}. The ^1H NMR spectrum of **6b**, as an example, showed besides the expected multiplets in the upfield region due to CH_2 and CH aliphatic protons, two singlets at δ = 1.98 (Ar-CH_3) and 6.44 ppm (Ar-NH) and two doublets at δ = 6.96 and 7.15 ppm aromatic protons. The mass spectra of **6a, b** showed their molecular ions M^+ at *m/z* = 407 and 421, respectively.



Scheme 2



6a: Ar = Ph
6b: Ar = *p*-tolyl
6c: Ar = anthraquinon-2-yl

Scheme 3

characteristic features of the ^{1}H NMR spectrum of **7** is two methyl singlets of the antipyrine unit at δ = 1.88 and 3.63 ppm and two multiplets of the aromatic protons at δ = 7.52 and 7.69 ppm. The NH and the olefinic testosterone singlets were at δ = 6.82 and 6.05 ppm, respectively. Its mass spectrum exhibited the molecular ion at *m/z* = 517 and the base peak at *m/z* = 112 due to the antipyrine moiety.

The scope of the Mannich reaction has been broadened by using primary heterocyclic amines such as 3-amino-1,2,4-triazole (**8**) and 6-amino-2-thiouracil (**12**). The reaction of 3-amino-1,2,4-triazole seemed to be a unique route for the synthesis of the interesting fused androstanotriazoloprimidine derivative **11**. The reaction pathway is described in Scheme 4. Therefore, Mannich reaction of **1** with formaldehyde and **8** gave the Mannich base **9**, which undergoes spontaneous cyclization in acidic medium to give **10**. The autoxidation of **10** yielded the novel androstanotriazolopyrimidine derivative **11**. Despite unsuccessful chromatography attempts to separate the products **10** and **11**, the spectral data inferred the suggested structures as outlined in Scheme 4.

The IR spectrum of the products **10** and **11** as a mixture showed the absence of the characteristic testosterone carbonyl band at ν = 1651 cm^{-1} and instead, two imino and olefinic C=C bands at ν = 1626 and 1604 cm^{-1} were appeared. Furthermore, the ^{1}H NMR spectrum confirmed the presence of the compounds **10** and **11** together in the ratio by approximately (1:1) based on:

(i) The signals of the expected methyl and aliphatic (CH_2, CH) protons of the testosterone moiety.

(ii) Two doublets at δ = 3.91 and 4.12 ppm with geminal coupling constant J = 12.5 Hz were attributable to methylene group of dihydropyrimidine moiety.

(iii) The olefinic testosterone singlet of **10** was somewhat upfielded at δ = 5.28 ppm instead of 5.70 ppm indicating the change of enone conjugation to diene conjugation system.

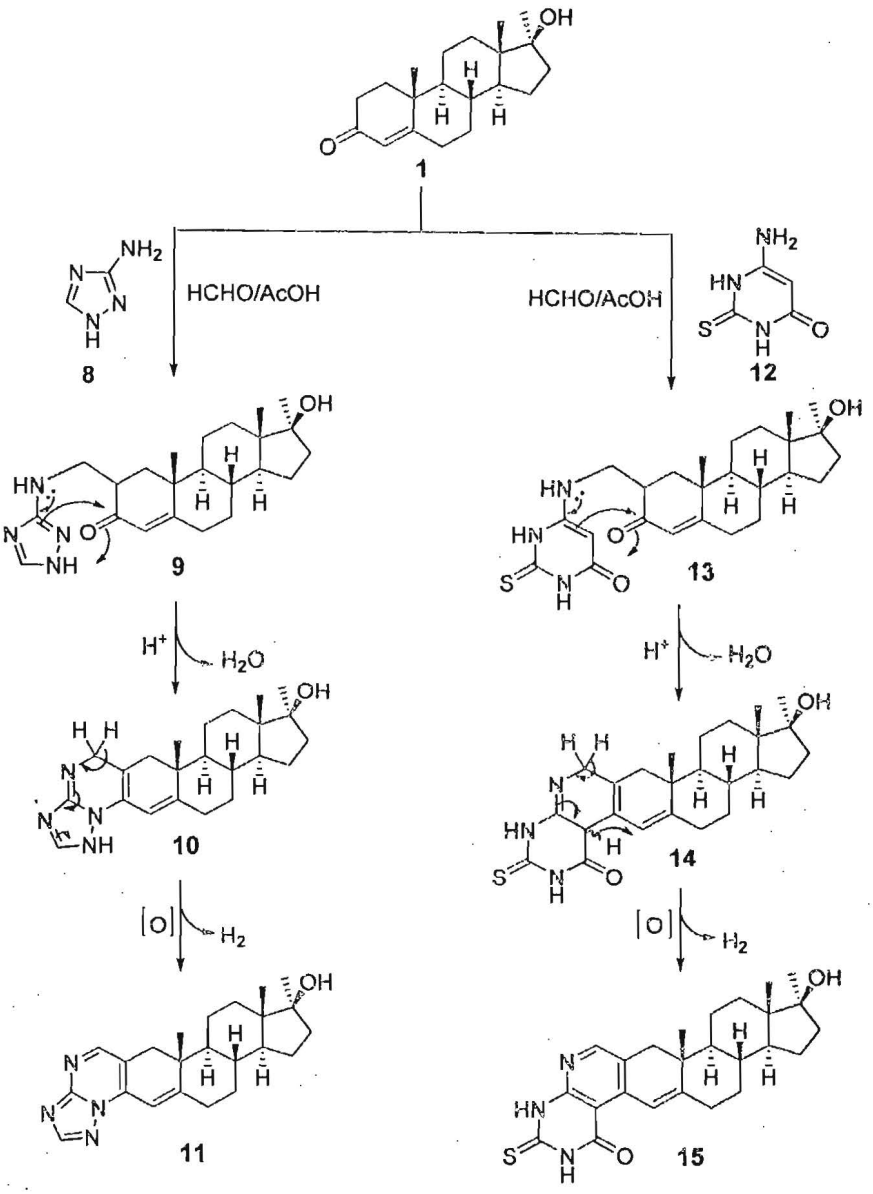
(iv) In addition to two neighboured singlets at δ = 7.04 & 7.05 ppm for C_3-Ha of triazole ring, two closed (N-H_b) singlets at δ = 7.45 and 7.46 ppm were observed as shown in tautomeric forms of compound **10** (**c.f. Fig. 1**).

(v) The presence of olefinic proton at δ = 6.48 ppm somewhat downfielded due to increasing dienoimine conjugation system of **11**.

(vi) The highly downfielded pyrimidine and triazole singlet protons of compound **11** existed at δ = 8.57 and 9.07 ppm.

The mass spectrum revealed clearly the autoxidation of **10** with evolution of hydrogen molecule to give the more stable androstanotriazolopyrimidine **11**. The fragmentation pattern showed the ion peak at *m/z* = 182 corresponding to methylbenzotriazolopyrimidine unit.

By the same manner, the novel condensed androstanopyridopyrimidine derivative was built *via* treatment of 6-amino-2-thiouracil (**12**) and formalin with compound **1** to give the *sec.* Mannich base **13**. Compound **13** was cyclized under the same reaction conditions to afford **14** which underwent autoxidation to give compound **15** as described in Scheme 4. The products **14** and **15** were elucidated as a mixture due to the unsuccessful chromatography attempts to separate them. The structures of **14** and **15** were confirmed on the basis of their spectral data. The ^{1}H NMR spectrum showed both of them in the ratio of about (1:1), the chemical shift of methylene dihydropyridine (compound **14**) was at δ = 4.13 ppm as two doublets, whereas the pyridine-H appeared as singlet at δ = 7.70 ppm. The mass spectrum gave two molecular ions M^+ at *m/z* = 439 and 437 which were in accordance with their molecular weights.



Scheme 4

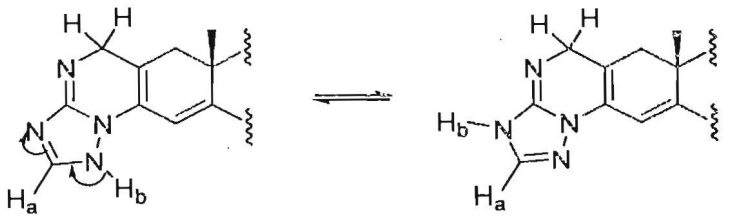


Figure 1: Tautomerism of compound **10**.

Experimental

All melting points are uncorrected and were recorded on an open glass capillaries using a Gallenkamp apparatus. Infrared spectra (IR) were recorded (KBr), (υ cm^{-1}) on a Mattson 5000 FTIR Spectrometer at Micro analytical Center, Faculty of Science, Mansoura University. The ^{1}H-NMR spectra were run on each of Bruker AC 300 (Faculty of Science,

Cairo University, Egypt), 400 (Faculty of Science, Kafr El-Sheikh University, Egypt), 600 MHz (King Abdel-Aziz University, Saudi Arabia Kingdom) or Joel ECA 500 MHz (National Research Center, Cairo, Egypt) instruments using TMS as an internal reference and $CDCl_3$ and DMSO-d_6 as solvents and chemical shift (δ) values are recorded in ppm. Mass spectra (MS) were recorded on (EI, 70 eV) MS equipment and/or a Varian MAT 311 instrument at Micro analytical Center, Faculty of Science, Cairo University, Egypt or Thermo Scientific ISQLC single quadrupole mass spectrometer at The Regional Center for Mycology and Biotechnology, El-Azhar University, Egypt. Elemental analyses (C, H and N) were carried out at the Microanalytical Center at Cairo University, Egypt. The results were found to be in good agreement with the calculated values. The course of the reaction and the purity of the synthesized compounds were monitored by TLC using silica gel pre-coated aluminum sheets (type 60 F254, Merck, Darmstadt, Germany) with visualization by irradiation with an ultraviolet lamp and the spots were detected by exposure to UV lamp at λ_{254} nm.

Synthesis of *tertiary* Mannich bases "Compounds 2a-c". General procedure

A mixture of 17α-methyltestosterone (1 g, 3.25 mmol), paraformaldehyde (0.1 g, 3.5 mmol) and the hydrochloride salt of dimethylamine, morpholine or piperidine (3.3 mmol) in absolute ethanol (10 mL) was refluxed for 1 hr with stirring. Thereafter, another 0.05 g paraformaldehyde was added and the refluxing was continued for 2-4 hrs (TLC control). The reaction mixture was poured in crushed ice (100 g) and neutralized by using ammonium hydroxide solution (30%). The organic product was extracted with ethyl acetate, dried over anhydrous magnesium sulfate, evaporated *in vacu* and the residue that formed was recrystallized from methanol/H_2O (2:1) to give **2a-c**.

2-Dimethylaminomethyl-17β-hydroxy-17α-methylandrost-4-en-3-one (2a): Pale yellow crystals, m.p. 114-116 ^{0}C, 69% yield.

Analysis: $C_{23}H_{37}NO_2$ (359.28) Calcd: C, 76.83%; H, 10.37%; N, 3.90%. Found: C, 76.61%; H, 10.58%; N, 3.76%.
IR (ν/cm-1): 3580-3350 (OH), 2950, 2863 (CH3, CH2), 1669 (C=O), 1619 (C=C).
^{1}H NMR (600 MHz, $CDCl_3$) (δ ppm): 0.97 (s, 3H, 18-CH3), 0.99 (s, 3H, 19-CH_3), 1.17 (s, 3H, 17α-CH_3), 1.17-2.65 (m, aliphatic CH_2, CH), 2.19 (s, 6H, $(CH_3)_2$N-), 5.77 (s, 1H, H-C_4).
MS (EI, 70 eV) (*m/z*, %): 360 (M^++1) (13.32), 359 (M^+) (13.32), 300 (M^+-acetone) (13.80), 178 (17.92), 172 (12.59), 162 (17.68), 148 (19.85), 126 (20.34), 69 (89.10), 57 (100).

2-(4′-Morpholinomethyl)-17β-hydroxy-17α-methylandrost-4-en-3-one (2b): Yellow crystals, m.p. 99-101 ^{0}C, 80% yield.
Analysis: $C_{25}H_{39}NO_3$ (401.29) Calcd: C, 74.77; H, 9.79; N, 3.49%. Found: C, 74.92; H, 9.98; N, 3.70%.
IR (ν/cm-1): 3600-3200 (br, OH), 2939, 2868 (CH3, CH2), 1661 (C=O), 1627 (C=C).
^{1}H NMR (500 MHz, $CDCl_3$) (δ ppm): 0.93 (s, 3H, 18-CH_3), 0.95 (s, 3H, 19-CH_3), 1.14 (s, 3H, 17α-CH_3), 1.14-4.12 (m, aliphatic testosterone and morpholine protons), 5.74 (s, 1H, H-C_4).
MS (EI, 70 eV) (*m/z*, %): 401 (M^+) (32.37), 382 (M^+-H_2O) (24.07), 351 (22.82), 315 (M^+-morpholine) (28.22), 274 (39.42), 124 (40.66), 108 (24.07), 86 (morpholine ion) (32.37), 80 (63.07), 64 (100).

2-(1′-Piperidinomethyl)-17β-hydroxy-17α-methylandrost-4-en-3-one (2c): Pale yellow crystals, m.p. 269-270 ^{0}C, 70% yield.
Analysis: $C_{26}H_{41}NO_2$ (399.31) Calcd: C, 78.15; H, 10.34; N, 3.51% Found: C, 78.54; H, 10.61; N, 3.80%.

IR (ν/cm^{-1}): 3700-3300 (br, OH), 2937, 2859 (CH_3, CH_2), 1669 (C=O), 1620 (C=C).
^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): 0.96 (s, 3H, 18-CH_3), 0.98 (s, 3H, 19-CH_3), 1.18 (s, 3H, 17α-CH_3), 1.18-2.12 (m, 23H, aliphatic CH_2, CH), 2.25-2.55 (m, 9H, H-C_2 & 2H-C_6 & 6H, -CH_2-N$(CH_2)_2$), 5.76 (s, 1H, H-C_4).
MS (EI, 70 eV) (*m/z*, %): 401 (M^++2) (38.03), 400 (M^++1) (49.30), 399 (M^+) (36.62), 380 (M^+-H_2O) (63.38), 366 (43.66), 340 (M^+-acetone) (62.68), 282 (64.79), 98 (*N*-

methylpiperidine ion) (100), 91 (tropylium ion) (100).

Synthesis of methylene-2,2′-bis(17β-hydroxy-17α-methylandrost-4-en-3-one) (4):

The compound **2a** was synthesized according to the above mentioned procedure. After the complete formation of **2a** (TLC control) and without its isolation, 17α-methyltestosterone (1 g, 3.25 mmol) was added. Then, the reaction mixture was refluxed for 3 hrs. On cooling and adding cold water (50 mL), the reaction mixture was neutralized by using NH_4OH (30%), the resulting precipitate was filtered off, dried and recrystallized from MeOH/H_2O mixture (3:1) to produce compound **4** as pale yellow crystals, m.p. 122-124 ^{0}C, 77% yield. **Analysis**: $C_{41}H_{60}O_4$ (616.92) Calcd: C, 79.82; H, 9.80%. Found: C, 80.11; H, 9.61%. **IR (ν/cm^{-1}):** 3550-3300 (br, OH), 2948, 2865 (CH_3, CH_2), 1667 (C=O), 1623 (C=C). **^{1}H NMR (300 MHz, $CDCl_3$) (δ ppm):** 0.96 (s, 6H, 18-CH_3, 18′-CH_3), 0.98 (s, 6H, 19-CH_3, 19′-CH_3), 1.18 (s, 6H, 17α-CH_3, 17α′-CH_3), 1.18-2.54 (m, aliphatic CH_2, CH), 3.51 (brs, 1H, 17β-OH), 4.11 (brs, 1H, 17β′-OH), 5.77 (s, 2H, H-C_4, H-C_4′). **MS (EI, 70 eV) (*m/z*, %):** 616 (M^+) (74.79), 550 [M^+-($2H_2O$+$2CH_3$)] (85.7), 500 (M^+-two acetone molecules) (74.79), 315 (M^+-methyltestosterone unit) (54.62), 300 (M^+-steroidal methyl moiety) (85.71), 176 (100), 93 (dimethylcyclopentadiene ion) (99.16).

Synthesis of bis(17β-hydroxy-17α-methylandrost-4-ene)[b,e]-4*H*-pyran (5):

Heating the above product **4** (0.3 g, 0.48 mmol) in a mixture of ethanol (10 mL) and conc. hydrochloric acid (0.5 mL) at 60-70 ^{0}C for 2-3 hrs (TLC control). After cooling, the reaction mixture was diluted using cold water and neutralized using NH_4OH. The resulting precipitate was filtered off, dried, washed with petroleum ether and purified *via* column chromatography (petroleum ether/ethyl acetate 7:3) to afford compound **5** as syrup, 57% yield. **Analysis:** $C_{41}H_{58}O_3$ (598.91) Calcd: C, 82.22; H, 9.76%. Found: C, 82.47; H, 9.91%. **^{1}H NMR (300 MHz, $CDCl_3$) (δ ppm):** 0.90 (s, 6H, 18-CH_3, 18′-CH_3), 1.09 (s, 6H, 19-CH_3, 19′-CH_3), 1.17 (s, 3H, 17α-CH_3), 1.18 (s, 3H, 17α′-CH_3), 1.18-2.51 (m, steroidal CH_2, CH), 3.35 (s, 2H, CH_2-pyran), 5.73 (s, 1H, H-C_4), 5.77 (s, 1H, H-C_4′). **MS (EI, 70 eV) (*m/z*, %):** 599 (M^++1) (0.35), 300 (2.80), 297 (10.92), 282 (5.93), 280 (9.39), 223 (trimethyldibenzopyran ion) (25.06), 208 (dimethyldibenzopyran ion) (17.99), 127 (47.17), 90 (49.16), 54 (-CH_2=CH-CH=CH_2-) (100).

Synthesis of compounds 6a-c and 7

A mixture of the Mannich base hydrochloride **2b** (0.44 g, 1 mmol) and each of the appropriate amine (aniline, *p*-toluidine, 2-aminoanthraquinone and/or 4-aminoantipyrine) (1 mmol) in 6 mL ethanol:H_2O (2:1) was refluxed for 3 hrs. After cooling, the reaction mixture was poured into crushed ice (50 g) and neutralized using diluted NH_4OH. The oily material that separated was extracted using ethyl acetate, dried over magnesium sulphate and purified chromatographically (petroleum ether/ethyl acetate) as eluent to give **6a-c** and **7**: **2-Phenylaminomethyl-17β-hydroxy-17α-methylandrost-4-en-3-one (6a):** Pale yellow crystals, m.p. 180-182 ^{0}C (eluent: petroleum ether/ethyl acetate 8:2), 71% yield. **Analysis:** $C_{27}H_{37}NO_2$ (407.59) Calcd: C, 79.56; H, 9.15; N, 3.32%. Found: C, 79.98; H, 9.61; N, 3.60%. **IR (ν/cm^{-1}):** 3600-3300 (br, OH), 3250 (NH), 2926, 2859 (CH_3, CH_2), 1665 (C=O), 1617 (C=C).
^{1}H NMR (500 MHz, $CDCl_3$) (δ ppm): 0.85 (s, 3H, 18-CH3), 0.94 (s, 3H, 19-CH_3), 1.15 (s, 3H, 17α-CH_3), 1.15-2.53 (m, testosterone CH_2, CH), 2.68 (d, 2H, -NH-$\underline{CH_2}$-, J = 12.55 Hz), 3.45 (m, 1H, H-C_2), 4.20 (brs, 1H, OH), 6.17 (s, 1H, H-C_4), 6.91-7.69 (m, 5H, Ar-H). **MS (EI, 70 eV) (*m/z*, %):** 407 (M^+) (65.32), 405 (M^+-2) (100), 336 (M^+-butan-2-one) (45.97), 314 (M^+-aniline) (57.26), 302 (M^+-$PhNHCH_2$, methyltestosterone ion) (65.32), 282 (70.16), 126 (91.94), 107 ($PhNHCH_3$ ion) (53.23).

2-(4'-Tolylaminomethyl)-17β-hydroxy-17α-methylandrost-4-en-3-one (6b): Greenish yellow oily product, (eluent: petroleum ether/ethyl acetate 8:2), 62% yield. **Analysis:** $C_{28}H_{39}NO_2$ (421.30) Calcd: C, 79.76; H, 9.32; N, 3.32%. Found: C, 79.91; H, 9.57; N, 3.56%.

IR (ν/cm^{-1}): 3650-3325 (br, OH), 3256 (NH), 2923, 2852 (CH_3, CH_2), 1679 (C=O), 1610 (C=C).

^{1}H NMR (300 MHz, $CDCl_3$) (δ ppm): 0.74 (s, 3H, 18-CH_3), 1.09 (s, 3H, 19-CH_3), 1.41 (s, 3H, 17α-CH_3), 1.98 (s, 3H, CH_3-Ar), 0.74-2.93 (m, aliphatic CH_2, CH), 5.40 (br, s, 1H, 17β-OH), 6.02 (s, 1H, H-C_4), 6.44 (s, 1H, NH), 6.96 (d, 2H, Ar-H, J = 8.1 Hz), 7.16 (d, 2H, Ar-H, J = 8.1 Hz). **MS (EI, 70 eV) (*m/z*, %):** 423 (M^++2) (71.82), 422 (M^++1) (71.82), 421 (M^+) (100), 405 (M^+-CH_4) (78.18), 404 (M^+-OH) (52.73), 349 [M^+-(CH_4+cyclopropanone)] (51.82), 240 (54.55), 180 (51.82), 106 (*p*-toluidine ion) (56.36).

2-(17β-Hydroxyl-17α-methylandrost-4-en-3-one-2-ylmethyl)aminoanthraquinone (6c): Pale red crystals, m.p. 277-279 ^{0}C (eluent: petroleum ether/ethyl acetate 3:2), 85% yield. **Analysis:** $C_{35}H_{39}NO_4$ (537.29) Calcd: C, 78.18; H, 7.31; N, 2.60%. Found: C, 78.44; H, 7.58; N, 2.28%.

IR (ν/cm^{-1}): 3444 (OH), 3351 (NH), 2945, 2867 (CH_3, CH_2), 1672 (C=O, steroid), 1649 (C=O, quinone).

^{1}H NMR (500 MHz, $CDCl_3$) (δ ppm): 0.74 (s, 3H, 18-CH_3), 1.09 (s, 3H, 19-CH_3), 1.42 (s, 3H, 17α-CH_3), 1.42-2.76 (m, testosterone CH_2, CH), 3.80 (brs, 1H, 17β-OH), 4.18 (t, 2H, NH-$\underline{CH_2}$-CH-), 5.82 (s, 1H, H-C_4), 7.54 (brs, 1H, NH), 7.18-8.20 (m, 7H, Ar-H). **MS (EI, 70 eV) (*m/z*, %):** 339 (M^++2) (2.81%), 314 (M^+-aminoanthraquinone) (3.18), 222 (aminoanthraquinone ion) (13.14), 126 (7.64), 105 (13.94), 91 (tropylium ion) (35.52), 55 (CH_3-CH=CH-CH_2-) (100).

4-(17β-Hydroxy-17α-methylandrost-4-en-3-one-2-ylmethyl)aminoantipyrine (7): Buff powder, m.p. 77-78 ^{0}C, (eluent: petroleum ether/ethyl acetate 3:2), 44% yield. **Analysis:** $C_{32}H_{43}N_3O_3$ (517.33) Calcd: C, 74.24; H, 8.37; N, 8.12%. Found: C, 74.58; H, 8.61; N, 7.90%.

IR (ν/cm^{-1}): 3433-3245 (br, OH, NH), 2927, 2857 (CH_3, CH_2), 1664 (C=O, steroid), 1647 (C=O, antipyrine).

^{1}H NMR (500 MHz, $CDCl_3$) (δ ppm): 0.88 (s, 3H, 18-CH_3), 0.90 (s, 3H, 19-CH_3), 1.24 (s, 3H, 17α-CH_3), 1.88 (s, 3H, CH_3-C=C-, antipyrine), 1.24-3.10 (m, aliphatic CH_2, CH), 3.63 (s, 3H, CH_3-N-, antipyrine), 5.34 (brs, 1H, 17β-OH), 6.05 (s, 1H, H-C_4), 6.82 (brs, 1H, NH), 7.52-7.69 (m, 5H, Ar-H). **MS (EI, 70 eV) (*m/z*, %):** 517 (M^+) (86.21), 502 (M^+-CH_3) (27.59), 486 (60.34), 469 (56.03), 337 (12.07), 314 (44.83), 186 (antipyrine ion) (54.31), 164 (16.38), 112 (dimethylpyrazolone ion) (100).

Synthesis of androstanotriazolopyrimidine and androstanopyridopyrimidine derivatives "Synthesis of 10, 11, 14 and 15". General procedure

A mixture of 17α-methyltestosterone **1** (1 g, 3.25 mmol), formalin (0.135 mL, 3.66 mmol) and either 3-amino-1,2,4-triazole or 6-amino-2-thiouracil (3.30 mmol) in the presence of conc. HCl (0.4 mL, 3.32 mmol) was dissolved in 10 mL glacial acetic acid and heated on water bath for 5 hrs (TLC control). On cooling, addition of crushed ice (100 g) and neutralization using NH_4OH (30%), the resulting precipitate was filtered off and washed well with cold water. Unsuccessful column chromatography attempts using pet.ether/ethyl acetate were carried out to separate the cyclized Mannich derivatives. The spectral data were carried as a mixture of them.

For 10 & 11: Colorless powder, 62% yield.

IR (ν/cm^{-1}): 3594-3281 (br, OH, NH), 2924, 2857 (CH_3, CH_2), 1651 (C=N), 1626 (C=N), 1604 (C=C).

^{1}H NMR (500 MHz, DMSO) (δ ppm): for the compound (10), 0.71 (s, 3H, 18-CH_3), 0.87 (s, 3H, 19-CH_3), 1.02 (s, 3H, 17α-CH_3), 1.04-3.05 (m, testosterone CH_2, CH), 3.91 (d, 1H, J = 12.5), 4.12 (d, 1H, J = 12.5), 5.28 (s, 1H, H-C_4), 7.04 (s, 1H, H-3 triazole, tautomer a), 7.05 (s, 1H, H-3 triazole, tautomer b), 7.45 (s, 1H, NH, triazole, tautomer a), 7.46 (s, 1H, NH, triazole, tautomer b). **For the compound (11),** 0.73 (s, 3H, 18-

CH_3), 0.86 (s, 3H, 19-CH_3), 1.04 (s, 3H, 17α-CH_3), 1.04-3.05 (m, testosterone CH_2, CH), 6.48 (s, 1H, H-C_4), 8.57 (s, 1H, pyrimidine ring), 9.07 (s, 1H, triazole ring). **MS (EI, 70 eV) (*m/z*, %):** 380 [M^+(**9**)] (46.22), 378 [M^+(**10**), M^+(**9**)-H_2] (74.79), 360 [M^+(**10**)-H_2O] (73.11), 306 [M^+(**10**)-butan-2-one] (66.39), 198 (dimethylbenzopyrimidotriazole unit) (45.38), 182 (methylbenzopyrimidotriazole unit) (94.96), 126 (58.82), 91 (troplium ion) (48.74).

For 14 & 15: Yellowish orange syrup, 68% yield.

IR (ν/cm^{-1}): 3550-3310 (br, OH), 3197 (NH), 2926, 2855 (CH_3, CH_2), 1727, 1662 (C=O), 1616 (C=N, C=C). **^{1}H NMR (300 MHz, DMSO) (δ ppm): for the compound 14,** 0.86 (s, 3H, 18-CH_3), 1.07 (s, 3H, 19-CH_3), 1.22 (s, 3H, 17α-CH_3), 1.28-2.95 (m, aliphatic CH_2, CH), 4.13 (two doublets, 2H, dihydropyridine), 7.06 (s, 1H, OH, NH), 7.48 (s, 1H, OH, NH). **For the compound 15,** 0.86 (s, 3H, 18-CH_3), 1.07 (s, 3H, 19-CH_3), 1.28 (s, 3H, 17α-CH_3), 1.28-2.95 (m, aliphatic CH_2, CH), 7.09 (s, 1H, OH, NH), 7.51 (s, 1H, OH, NH), 7.70 (s, 1H, pyridine-H).

MS (EI, 70 eV) (*m/z*, %): 439 [M^+(**14**)) (9.41], 437 [M^+(**15**), M^+(**14**)-H_2] (7.61), 386 [M^+(**15**)-(H_2O+2CH_4)] (6.72), 379 [M^+(**15**)-acetone] (6.05), 297 (8.85), 146 (14.78), 92 (10.30), 80 (methylcyclopentadiene ion) (100), 64 (44.46), 57 (28.00).

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تشييد وبعض تفاعلات قواعد مانش لمركب ١٧ألفا-ميثيل تيستوستيرون

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تم تشييد سلسله من قواعد مانش **2a–c** بتفاعل الميثيل تستوستيرون (١) مع البارافورمالدهيد والامين المناسب. تكاثف **2a** مع ١ أعطي ٤ . التبادل الاميني ل **2b** مع الامينات الارومانيه الاوليه المناسبه أدي الي تخليق سلسله من قواعد مانش االثانويه **7** & **6a–c**. أيضا تم تشييد مشتقات الأندروستانوترايازولوبيريميدين **11** والأندروستانوبيريدوبيريميدين **15** الجديده.