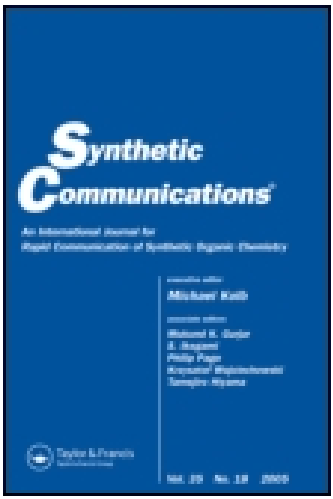

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SYNTHESIS OF STEROIDAL PYRIMIDINES

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Abstract

Selected aryl aldehydes were treated with 17-oxo-5-androsten-3β-yl acetate (I) to give the corresponding 16-arylidene 17-oxo-5-androsten-3β-yl acetates(IIa-e). Condensation of these chalcones with urea revealed the formation of the corresponding substituted pyrimidin-2'-ones (IIIa-e) respectively.

Discussion

Steroids are known to play an important role in the animal system, both from the biological and pharmacological analysis.[1,2] In recent years much attention of chemists and pharmocologists has focused on heterosteroids because of their modified or accentuated activities.[3,4] The extranucleo heterosteroids with pyrimidine fused in different positions of the steroidal ring systems possess significant antibiotic activities.[5-8]

In view of the pharmaceutical interest in steroids bearing heterocycles fused on ring D of the steroid nucleus[9-11], we wish to report a simple synthesis of heterosteroids in which C-16, 17 of the steroid are fused to a pyrimidine ring system. Thus, 17-oxo-5-androsten-3β-yl acetate (I) was treated

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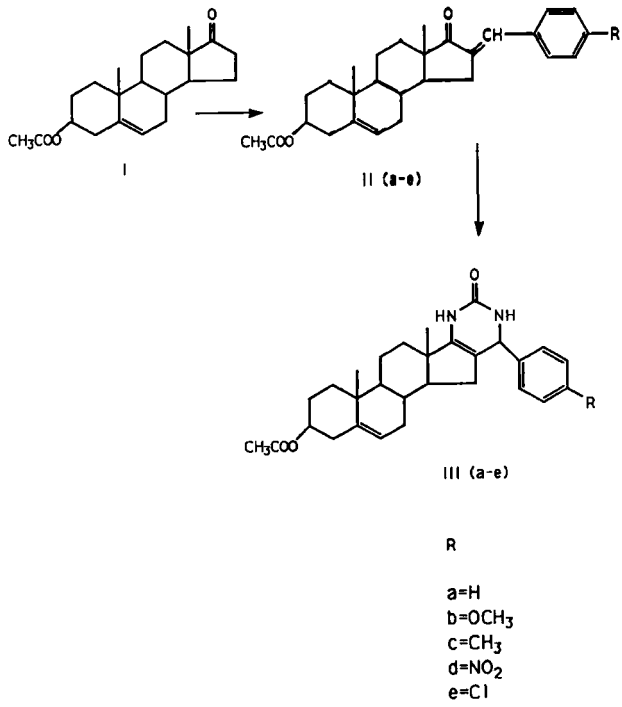

with various aromatic aldehydes (a-e) to give the corresponding C_{16} aryliden-17-oxo-5-androsten-3β-yl acetates[8] (II a-e, Table 1). These arylidene derivatives were characterized on the basis of their spectral data and elemental analysis (Table 1). The IR spectra of all the compounds showed strong absorption bands around 1735 cm^{-1}(CH_3COO), 1715 (5-membered α, β-unsaturated ketone), 1600 (C=C, aromatic), 1235 (C-O); The ^1H NMR spectra showed signals around δ 7.2-7.5 ppm (aromatic, H) 6.6 (s, 1H, =CHPh), 5.3 (m, 1H C_6-vinylic), 3.8 (m, 1H, $C_3\alpha$ H), 2.6 (m, 2H, C-15H) and 2.1 (s, 3H, CH_3COO^-). The UV absorbance maxima in the region 295-306nm for these chalcones suggests a trans-α, β-unsaturated ketone[8,12,13].

The above C-16-arylidene-17-oxo-5-androsten-3β-yl acetates (II a-e) on base catalyzed condensation with urea afforded the 6'-phenyl-5-androsteno[17,16-d]-1',3',6'-trihydropyrimidin-2'-one-3β-yl acetates[8], respectively (IIIa-e; Table 2). The IR spectra of the pyrimidines showed frequencies at 3300 cm^{-1} (N-H), 1715 (pyrimidine, C=O), 1600 (C=C, aromatic) and 1240 (C-O). The ^1H NMR spectra of the pyrimidines showed signals at δ 7.2-7.5 ppm (aromatic H), 7.1 and 8.2 (1H each, D_2O exchangeable, NH), 5.7 (s,

TABLE 1

Physical constants of 16-arylidene-17-oxo-5-androsten-3β-yl acetates[8] II (a-e):

Benzylidene derivatives II (a-e)	m.p. °C	C, H, N Analysis	Yield %
II.			
a. 16-Benzyliden -17- oxo-5-androsten-3β-ylacetate	190	Anal. Calcd for $C_{28}H_{34}O_3$: C,80.38; H,8.13. Found: C, 80.4; H, 8.12.	75
b. 16-[p-Methoxy- benzyliden]-17-oxo-5-androsteno-3β-yl acetate	210-12	Anal. Calcd for $C_{29}H_{36}O_4$: C, 77.67; H, 8.05. Found: C, 77.60; H, 8.0.	70
c. 16-[p-Methyl -benzyliden]-17-oxo-5-androsteno-3β-yl acetate	150-52	Anal. Calcd for $C_{29}H_{36}O_3$: C, 80.55; H, 8.33. Found: C, 80.50; H, 8.36.	76
d. 16-[p-Nitro- benzyliden]-17-oxo-5-androsteno-3β-yl acetate	168-70	Anal. Calcd for $C_{28}H_{33}NO_5$: C, 72.57; H, 7.12. Found: C, 72.58; H, 7.1.	70
e. 17-[p-Chloro -benzyliden]-17-oxo-5-androsteno-3β-yl acetate	194-96	Anal. Calcd for $C_{28}H_{33}O_3Cl$: C, 74.25; H, 7.30. Found: C, 74.21; H, 7.25	80

1H, pyrimidine CH), 5.3 (s, 1H, C-6 vinylic H), 2.8 (m, 2H, C-15H) and 2.0 (s, 3H, CH_3COO^-).

Experimental Section

General Information: Mass Spectra were performed on a Finnigan 4000 instrument at 70 eV and were recorded as m/e; proton NMR spectra were recorded in CDCl3 on a Bruker 250Ft-NMR spectrometer. IR spectra were recorded on a Perkin-Elmer 1600 series Ft-IR spectrometer. Analytical and preparative TLC were performed using Analtech brand silica gel plates.

Preparation of 16-arylidene-17-oxo-5-androsten-3β-yl acetates (II a-e): To a solution of 17-oxo-5-androsten-3β-yl acetate (I) (2.0g, 6.0 mmol) in ethanol (30 ml), aromatic aldehyde (10 mmol) and alcoholic potassium hydroxide solution (40%, 15ml) were added simultaneously while maintaining the temperature below 10°C. After 30 minutes, the reaction mixture was brought to room temperature and stirred for 24 hours. The reaction mixture was acidified with acetic acid and

TABLE 2

Physical constants of 6'-phenyl-5-androsteno [17,16-d] -1', 3', 6'- trihydro pyrimidin-2'-one-3β-yl acetates[8] (III a-e):

	Name of pyrimidine	m.p. °C	C,H,N Analysis	Yield %
III				
a.	6'-Phenyl-5-androsteno-17, 16-d]-1', 3', 6'-tri hydro pyrimidin-2'-one-3β-yl acetate	234-36	Anal. Calcd for C_{29} H 37 N_2 O_3: C, 75.48; H, 8.02, N 6.07. Found: C, 75.45; H, 8.0, N 6.0.	77
b.	6'-(p-Methoxy phenyl)-5-androsteno[17,16-d]-1',3',6'-trihydro pyrimidin-2'-one-3β-yl acetate	217	Anal. Calcd for C_{30} H 39 N_2 O_4: C, 73.31; H, 7.94, N 5.71. Found: C, 73.28; H, 7.90, N 5.70.	74
c.	6'-(p-Methyl phenyl)-5-androsteno-[17,16-d]-1'-3'6'-trihydro pyrimidin-2'-one-3β-yl acetate	226	Anal. Calcd for C_{30} H 39 N_2 O_3: C, 75.78; H, 8.21, N 5.89. Found: C, 75.76; H, 8.20 N 5.87.	75
d.	6'-(p-Nitro phenyl)-5-androsteno [17,16-d]-1',3',6'-trihydro pyrimidin-2'-one-3β-yl acetate	248	Anal. Calcd for C_{29} H 36 N_3 O_5: C, 68.77 H, 7.11, N 8.3. Found: C, 68.75 H, 7.05 N 8.28.	78
e.	6'-(p-Chloro phenyl)-5-androsteno [17,16-d]-1'.3',6'-trihydro pyrimidin-2'-one-3β-yl acetate	231-33	Anal. Calcd for C_{29} H 36 N_2 O_3 Cl: C, 70.30 H, 7.27, N 5.65. Found: C, 70.28 H, 7.24, N 5.63	77

poured onto ice cold water. The yellow solid obtained (1.7g) was homogeneous on TLC and crystallized from ethanol as colorless needles.

Preparation of 6'-aryl-5-androsteno [17,16-d]-1',3',6'-trihydropyrimidin-2'-one-3β-yl acetates (III a-e): To a solution of C_{16} arylidene derivative (II a-e) (2.0g, 5 mmol) in ethanol (40ml), urea (0.8g, 10 mmol) was added and the reaction mixture refluxed for 15 hours. An aqueous solution of sodium hydroxide (1N, 5ml) was added in small portions during the initial two hours. Ethanol was then removed under reduced pressure and the residue diluted with ice cold water

dried over anhydrous sodium sulfate and evaporated under reduced pressure to give the pyrimidine derivative as a yellow solid which was crystallized from methanol to give colorless needles. The elemental analysis of all compounds (Table 2, III a-e) were in agreement with proposed structures.

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