Novel Azaandrostane Derivatives for The Synthesis of 17β-(*N-tert*-Butyl carbamoyl)-4-aza-5α-androst-1-ene-3-one

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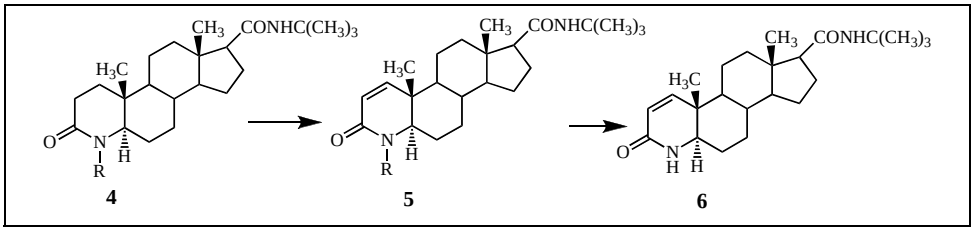
Received September 12, 2006



A new industrially viable process for the preparation of 17β-(*N-tert*-butyl carbamoyl)-4-aza-5α-androst-1-ene-3-one, also known by the generic name finasteride (**6**) from the new azaandrostane derivatives such as 17β-(*N-tert*-butyl carbamoyl)-4-benzoyl-4-aza-5α-androstane-3-one (**4**), 17β-(*N-tert*-butyl carbamoyl)-4-benzoyl-4-aza-5α-androst-1-ene-3-one (**5**) is reported. In this process, benzoyl group is demonstrated as a novel protecting group for lactamic NH group. The structures of newly prepared compounds were established on the basis of spectral data (IR, ^{1}H-NMR, and MS).

J. Heterocyclic Chem., **44**, 663 (2007).

INTRODUCTION

Finasteride is chemically known as 17β-(*N-tert*-butyl carbamoyl)-4-aza-5α-androst-1-ene-3-one (**6**), and functions as a α-reductase inhibitor [1] by converting the androgenic hormone, testosterone into intracellular androgenic metabolite dihydrotestosterone (DHT). Finasteride belongs to aza-steroid class of compounds and is used in the treatment of hyper androgenic conditions such as acne [2], hirsutism [3] and benign prostrate hypertrophy. Many synthetic approaches have been reported for finasteride preparation [4-12]. Chemical manipulation at the non-functionalised carbon site has been drawing much attention in the area of steroid chemistry [13]. One of the most important chemical reactions in the preparation of finasteride involves introduction of a carbon-carbon double bond at the non-fuctionalized C-1 position of azaandrosteriods. This dehydrogenation reaction could be achieved using the reagents such as benzeneseleninic anhydride [4], 2,2 pyridyldisulfide and sodium metaperiodate [5], *N*,*O*-bis-(trimethylsilyl)trifluoroacetamide (BSTFA) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) [6]. Dehydrogenation reaction using the above conventional reagents leads to unwanted toxic by-products such as selenium compounds and some of reported pharmacoepial impurities (Figure 1) 17β-(*N-tert*-butyl carbamoyl)-4-aza-5α-androstane-3-one (dihydrofinasteride) (**1**), methyl 3-oxo-4-aza-5α-androst-1-ene-17β-carboxylate (**2**) and 17β-(N-*tert*-butyl carbamoyl)-4-azaandrost-1,5-diene-3-one (**3**) and thus affords poor quality of finasteride drug substance. It was reported in the literature [12] that finasteride couldn't be easily purified using a conventional methods such as recrystallization where it is mixed with impurities such as **1-3**. Further, usages of highly toxic materials such as benzeneseleninic anhydride in the final stage of the preparation of drug substance should be avoided.

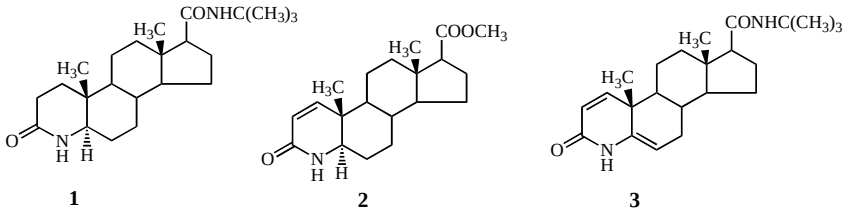


Figure-1: Structures of finasteride impurities

It is important to explore a new industrially viable synthetic route that could yield highly pure finasteride

without involving any lengthy purification steps and column chromatographic procedures [4]. The present work (Scheme 1) describes an industrially viable and improved process for the preparation of highly pure finasteride from new intermediates [11]. The major advantage of this synthetic route is that the dehydrogenation reaction is executed in the penultimate stage and further the resulting intermediate (**5**) can be easily purified by crystallization from methanol. Further, the deprotection of benzoyl group can be achieved using inexpensive reagents and with mild reaction conditions to afford pure finasteride.

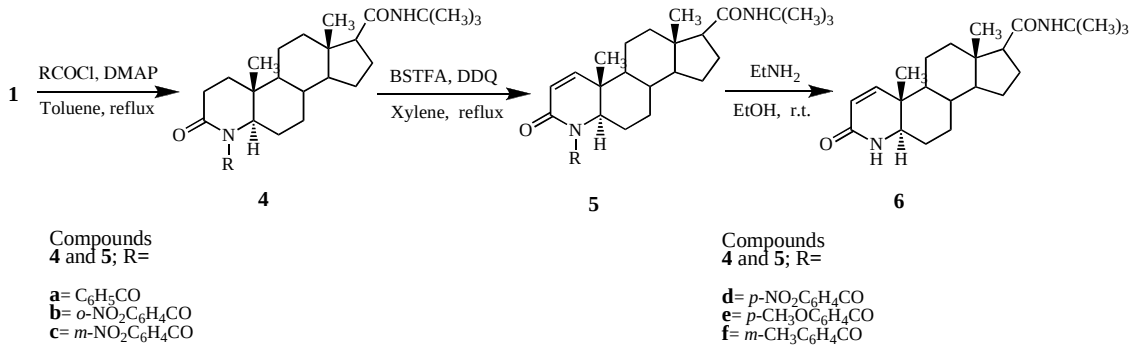
RESULTS AND DISCUSSION

17β-(*N-tert*-Butyl carbamoyl)-4-aza-5α-androstane-3-one (**1**) was treated with benzoyl chloride or substituted benzoyl chloride in the presence of 4-dimethylamino-pyridine to obtain *N*-benzoyldihydrofinasteride derivatives (**4a-f**). The structures of N-benzoyldihydrofinastide derivatives were characterized by IR, ^{1}H NMR and mass spectral data. The dehydrogenation at $\Delta^{1,2}$-position was achieved by silylating the amide functionality of the *N*-benzoyldihydrofinasteride using *N*,*O*-bis-(trimethylsilyl)-trifluoroacetamide (BSTFA).

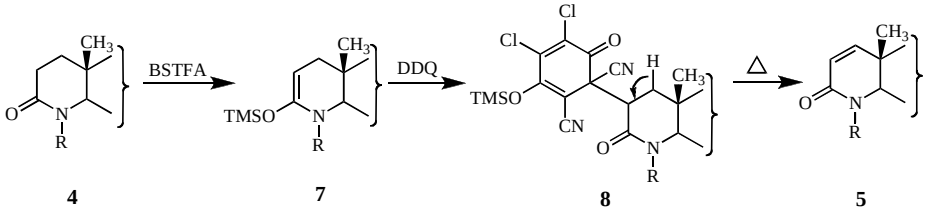
heating thermally decomposed [6] to favour the dehydrogenation at the $\Delta^{1,2}$ position and thus afford the *N*-benzoylfinasteride derivatives (**5a-f**) (Scheme 2). *N*-Benzoylfinasteride derivatives (**5a-f**) were crystallized from methanol to afford pure compounds. It is further observed that finasteride related impurities including the pharmacoepial impurities (**1-3**) are highly soluble in methanol thus get eliminated in the methanol filtrate.

One of the salient features of this work is that it provides a novel method for protection and deprotection of lactam NH group of azaandrostane derivatives. Few methods are available for protection of amide NH protection, however amide-protecting groups presented in the literature, do not represent protecting groups in true sense [14]. In this present work, finasteride was obtained after deprotecting the lactam N-benzoyl group of compounds (**5a-f**). We have attempted to use various acidic and basic conditions to deprotect the benzoyl group. Deprotection at acidic conditions was attempted with aqueous acetic acid and hydrochloric acid, but we failed to obtain desired deprotected product. Hydrolysis of benzoyl group was attempted with hydrazine hydrate [15] and found to yield finasteride with purity 97% contaminated with 3% of impurity (**1**). We assumed that

Scheme 1



Scheme 2



The silylation of amide facilitates enolization towards the Δ^2 position and thus favours the C-2 carbon of the silylated compound (**7**) to react with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to yield intermediate complex (**8**). This intermediate complex, on further

the formation of this impurity is due to the hydrazine-catalysed reduction of double bond. However, the deprotection of lactam N-benzoyl group of compounds was achieved advantageously by treating the N-benzoyl–finasteride derivatives (**5**) with 70% aqueous ethylamine

solution in ethanol. The crude finasteride product on further crystallization from the mixture of ethyl acetate and tetrahydrofuran yielded highly pure finasteride with purity > 99.9% as seen by HPLC method.

In conclusion, we have prepared new azaandrostane derivatives (**5a-f**), which are useful for the preparation of finasteride. Further, this synthetic route has the advantage to provide a new industrially viable process to prepare finasteride with more than 99.9% purity by the simple and convenient process. Also this work describes a method for the protection and deprotection of benzoyl group on the lactam NH group of azaandrostane derivatives.

EXPERIMENTAL

All melting points were determined with Polmon melting point apparatus. ^{1}H-NMR spectra were recorded on a Bruker 300 spectrometer. Chemical shifts are reported in ppm downfield from TMS as internal standard. Mass spectra are recorded in units of mass (*m*/*z*) and were recorded on Perkin Elmer PE SCIEX-API 2000 mass spectrometer. Elemental analyses were performed using a Heraeus CHN-O-Rapid instrument. Analytical HPLC [16] were run with Shimadzu VP series instrument at 210 nm.

17β-(*N-tert*-Butyl carbamoyl)-4-benzoyl-4-aza-5α-androstane-3-one (4a). To a mixture of 17β-(N-*tert*-butyl carbamoyl)-4-aza-5α-androstane-3-one (**1,** 100 g, 0.267 moles) obtained by the reported method [7], 4-dimethylamino-pyridine (42.40 g, 0.347 moles) and toluene (1000ml) was added benzoyl chloride (48.84 g, 0.347 moles). The reaction mixture was stirred at reflux for 5 hours, concentrated under reduced pressure. The residue was dissolved in methylene chloride (700ml) and washed with water (300 ml). The methylene chloride layer was concentrated under reduced pressure and added methanol (400ml). The precipitate thus obtained was collected by filtration, washed with methanol (50 ml) and dried to obtain 122 g (95%) of **4a** as a white powder with 99% purity as seen by HPLC method. Physical and spectral data of **4a** are given in Tables 1 and 2. Other members **4** are prepared by the same procedure using corresponding benzoyl chloride.

17β-(N-*tert*-butyl carbamoyl)-4-benzoyl-4-aza-5α-androst-1-ene-3-one (5a). To a solution of **4a** (100 g, 0.209 moles) in xylene (1000ml) was added 2,3-dichloro-5,6-dicyano-1,4-benzo-quinone (56.99 g, 0.251 moles) and stirred at 25-30 °C for 30 minutes. To this mixture was added *N*,*O*-bis-(trimethylsilyl)-trifluoroacetamide (215.06 g, 0.837 moles) over a period of 30 minutes. The mixture was stirred at 25-30 °C for 4 hours and at reflux for 12 hours. Then, the mass was concentrated under reduced pressure, and was added methanol (400 ml). The precipitated product was collected by filtration, washed with methanol and recrystallized from methanol (400 ml) to furnish 90 g (90%) of **5a** as a white powder with 99% purity as seen by HPLC method. Physical and spectral data of **5a** are given in Tables 1 and 2. Other members **5** are prepared by the same procedure.

Table 1

Physical and Analytical Data of Compounds **4a-f**, **5a-f** and **6**

Compd.	Yield %	Mp (°C)	IR (cm^{-1})			Mass	Formula	Elemental analysis % Calcd. / Found		
			N-H	C $(CH_3)_3$	C=O	$[M+H]^+$.	(M.W)	C	H	N
4a	95	190-192	3397	1393	1694, 1664	479.1	$C_{30}H_{42}N_2O_3$	75.28	8.84	5.85
							(478.67)	75.55	8.71	5.68
4b	91	244-246	3374	1392	1716, 1668	524.4	$C_{30}H_{41}N_3O_5$	68.81	7.89	8.02
							(523.66)	68.63	7.76	7.98
4c	88	213-215	3376	1390	1702, 1671	524.3	$C_{30}H_{41}N_3O_5$	68.81	7.89	8.02
							(523.66)	68.74	7.79	7.89
4d	87	278-280	3420	1393	1703, 1668	524.4	$C_{30}H_{41}N_3O_5$	68.81	7.89	8.02
							(523.66)	68.94	7.87	8.12
4e	88	206-208	3384	1392	1695, 1667	509.5	$C_{31}H_{44}N_2O_4$	73.19	8.72	5.51
							(508.69)	73.26	8.59	5.43
4f	90	205-207	3382	1391	1682, 1667	493.4	$C_{31}H_{44}N_2O_3$	75.57	9.00	5.69
							(492.69)	75.71	8.92	5.58
5a	90	209-211	3401	1394	1674, 1621	477.4	$C_{30}H_{40}N_2O_3$	75.59	8.46	5.88
							(476.65)	75.45	8.53	5.91
5b	84	230-232	3427	1397	1672, 1613	522.3	$C_{30}H_{39}N_3O_5$	69.07	7.54	8.06
							(521.69)	68.82	7.56	8.14
5c	84	157-159	3372	1393	1614, 1614	522.1	$C_{30}H_{39}N_3O_5$	69.07	7.54	8.06
							(521.69)	69.23	7.51	8.15
5d	81	269-271	3373	1397	1671, 1618	522.4	$C_{30}H_{39}N_3O_5$	69.07	7.54	8.06
							(521.69)	68.92	7.43	8.36
5e	83	249-251	3383	1396	1670, 1617	507.4	$C_{31}H_{42}N_2O_4$	73.49	8.36	5.53
							(506.68)	73.62	8.32	5.41
5f	86	246-248	3374	1394	1669, 1617	491.4	$C_{31}H_{42}N_2O_3$	75.88	8.63	5.71
							(490.68)	75.69	8.57	5.75
6	88	250-251	3348	1392	1688, 1668	373.4	$C_{23}H_{36}N_2O_2$	74.15	9.74	7.52
							(372.55)	74.40	9.65	7.41

Table 2
^{1}H-NMR Spectral Data of Compounds **4a-f**, **5a-f** and **6**

Compd.	^{1}H-NMR (δ, ppm, in deuteriochloroform)
4a	0.72 (s, 3H, CH_3), 0.93-1.11 (m, 3H), 1.22 (s, 3H, CH_3), 1.30-1.34 (m, 3H), 1.36 (s, 9H, ^{t}Bu), 1.41 (m, 3H), 1.67-1.75 (m, 3H), 1.78-1.83 (m, 2H), 1.96-2.06 (m, 3H), 2.15-2.18 (m, 1H), 2.48-2.68 (m, 2H), 3.68 (dd, 1H, J = 3.2, 11.8 Hz, C_5-H), 5.10 (s, 1H, N-H), 7.26-7.90 (m, 5H, Ar-H)
4b	0.71 (s, 3H, CH_3), 1.01 (m, 3H, CH_3), 1.26-1.32 (m, 3H), 1.35 (s, 9H, ^{t}Bu), 1.48-1.57 (m, 3H), 1.61-1.72 (m, 3H), 1.77-1.80 (m, 3H), 1.83-1.88 (m, 2H), 1.90-2.07 (m, 3H), 2.12-2.18 (m, 1H), 2.53-2.57 (m, 2H), 3.84 (dd, 1H, J = 2.4, 11.8 Hz, C_5-H), 5.10 (s, 1H, N-H), 7.26-8.13 (m, 4H, Ar-H)
4c	0.71 (s, 3H, CH_3), 0.93-1.1 (m, 3H), 1.24 (m, 3H, CH_3), 1.23-1.90 (m, 3H), 1.35 (s, 9H, ^{t}Bu), 1.39-1.56 (m, 3H), 1.65-1.75 (m, 4H), 1.85-1.91 (m, 1H), 1.96-2.06 (m, 3H), 2.14-2.17 (m, 1H), 2.50-2.56 (m, 1H), 2.63-2.70 (m, 1H), 3.69 (dd, 1H, J = 3.2, 11.8 Hz, C_5-H, N-H), 5.09 (s, 1H, N-H), 7.64 (t, 1H, J = 7.9, Ar-H), 8.11-8.61 (m, 3H, Ar-H)
4d	0.72 (s, 3H, CH_3), 0.93-0.98 (m, 1H), 1.02-1.14 (m, 2H), 1.21 (s, 3H, CH_3), 1.25-1.29 (m, 2H), 1.35 (s, 9H, ^{t}Bu), 1.42-1.51 (m, 3H), 1.57 (s, 3H), 1.66-1.75 (m, 3H), 1.90-2.03 (m, 3H), 2.14-2.17 (m, 1H), 2.43-2.49 (m, 1H), 2.61-2.67 (m, 1H), 3.68 (dd, 1H, J = 3.2, 11.8 Hz, C_5-H), 5.09 (s, 1H, N-H), 7.92 (d, 2H, J = 9.0 Hz, Ar-H), 8.27 (d, 2H, J = 9.0 Hz, Ar-H)
4e	0.71 (s, 3H, CH_3), 0.92-1.11 (m, 3H), 1.20 (s, 3H, CH_3), 1.23-1.30 (m, 3H), 1.36 (s, 9H, ^{t}Bu), 1.42-1.56 (m, 3H), 1.66-1.72 (m, 3H), 1.75-1.77 (m, 2H), 1.95-2.06 (m, 3H), 2.11-2.18 (m, 1H), 2.50-2.56 (m, 1H), 2.59-2.65 (m, 1H), 3.64 (dd, 1H, J = 3.2, 11.8 Hz, C_5-H), 3.87 (s, 3H, OCH_3), 5.10 (s, 1H, N-H), 6.95 (d, 2H, J = 9.1 Hz, Ar-H), 7.90 (d, 2H, J = 9.1 Hz, Ar-H)
4f	0.70 (s, 3H, CH_3), 0.91-1.11 (m, 3H), 1.21 (s, 3H, CH_3), 1.26-1.31 (m, 3H), 1.35 (s, 9H, ^{t}Bu), 1.41-1.55 (m, 3H), 1.66-1.76 (m, 4H), 1.79-1.80 (m, 1H), 1.95-2.05 (m, 3H), 2.13-2.17 (m, 1H), 2.39 (s, 3H, CH_3), 2.52-2.54 (m, 1H), 2.59-2.66 (m, 1H), 3.64 (dd, 1H, J = 3.2, 11.8 Hz, C_5-H), 5.08 (s, 1H, N-H), 7.26-7.38 (m, 2H, Ar-H), 7.65 (d, 1H, J = 7.4 Hz, Ar-H), 7.70 (s, 1H, Ar-H)
5a	0.73 (s, 3H, CH_3), 1.08-1.17 (m, 3H), 1.27 (s, 3H, CH_3), 1.25-1.31 (m, 2H), 1.37 (s, 9H, ^{t}Bu), 1.44-1.56 (m, 3H), 1.67-1.87 (m, 2H), 2.01-2.08 (m, 2H), 2.15-2.23 (m, 2H), 3.85 (dd, 1H, J = 3.2, 12.1 Hz, C_5-H), 5.12 (s, 1H, N-H), 5.88 (d, 1H, J = 10.1 Hz, C_2-H), 7.03 (d, 1H, J = 10.1 Hz, C_5-H), 7.28-7.93 (m, 5H, Ar-H)
5b	0.74 (s, 3H, CH_3), 0.97-1.17 (m, 3H), 1.21 (s, 3H, CH_3), 1.25-1.33 (m, 2H), 1.35 (s, 9H, ^{t}Bu), 1.46-1.56 (m, 2H), 1.67-1.79 (m, 3H), 1.80-1.93 (m, 1H), 2.01-2.07 (m, 2H), 2.12-2.18 (m, 1H), 2.46-2.54 (m, 2H), 3.79 (dd, 1H, J = 2.4, 11.8 Hz, C_5-H), 5.09 (s, 1H, N-H), 5.74 (d, 1H, J = 10.1 Hz, C_2-H), 7.01 (d, 1H, J = 10.1 Hz, C_5-H), 7.34 –8.28(m, 4H, Ar-H)
5c	0.73 (s, 3H, CH_3), 1.05-1.23 (m, 3H), 1.29 (s, 3H, CH_3), 1.25-1.31 (m, 2H), 1.36 (s, 9H, ^{t}Bu), 1.42-1.57 (m, 3H), 1.67-1.87 (m, 4H), 2.02-2.08 (m, 2H), 2.11-2.18 (m, 1H), 2.29-2.35 (m, 1H), 3.8 6 (dd, 1H, J = 2.4, 11.8 Hz, C_5-H), 5.09 (s, 1H, N-H), 5.86 (d, 1H, J = 10.1 Hz, C_2-H), 7.10 (d, 1H, J = 10.1 Hz, C_5-H), 7.64 (t, 1H, J = 7.9 Hz), 8.13-8.61 (m, 3H, Ar-H)
5d	0.73 (s, 3H, CH_3), 1.06-1.23 (m, 3H), 1.27 (s, 3H, CH_3), 1.25-1.31 (m, 2H), 1.36 (s, 9H, ^{t}Bu), 1.44-1.52 (m, 3H), 1.64-1.86 (m, 4H), 2.02-2.07 (m, 2H), 2.11-2.21 (m, 1H), 2.35-2.41 (m, 1H), 3.85 (dd, 1H, J = 2.4, 11.8 Hz, C_5-H), 5.09 (s, 1H, N-H), 5.85 (d, 1H, J = 10.1 Hz, C_2-H), 7.10 (d, 1H, J = 10.1 Hz, C_5-H), 7.95 (d, 2H, J = 8.8 Hz), 8.27 (d, 2H, J=8.8 Hz)
5e	0.71 (s, 3H, CH_3), 1.04-1.18 (m, 3H), 1.23 (s, 3H, CH_3), 1.22-1.32 (m, 2H), 1.35 (s, 9H, ^{t}Bu), 1.41-1.58 (m, 3H), 1.63-1.74 (m, 2H), 1.80-1.85 (m, 2H), 2.01-2.20 (m, 4H), 3.78 (dd, 1H, J = 2.4, 11.8 Hz, C_5-H), 3.86 (s, 3H, OCH_3), 5.09 (s, 1H, N-H), 5.89 (d, 1H, J = 10.1 Hz), 6.94 (d, 2H J = 9.1 Hz), 6.98 (d, 1H, J = 10.1 Hz, C_5-H), 7.90 (d, 2H, J = 9.1 Hz).
5f	0.71(s, 3H, CH_3), 1.06-1.15 (m, 2H), 1.26 (s, 3H, CH_3), 1.22-1.29 (m, 2H), 1.36 (s, 9H, ^{t}Bu), 1.39-1.53 (m, 3H), 1.65-1.77 (m, 3H), 1.80-1.86 (m, 1H), 2.01-2.08 (m, 2H), 2.10-2.17 (m, 2H), 2.39 (s, 3H, CH_3), 3.82 (dd, 1H, J = 2.4, 11.8 Hz, C_5-H), 5.10 (s, 1H, N-H), 5.87 (d, 1H, J = 10.1 Hz, C_2-H), 7.01 (d, 1H, J = 10.1 Hz, C_5-H), 7.30-7.38 (m, 2H, J = 9.1 Hz) 7.68-7.70 (m, 1H,Ar-H), 7.72 (s, 1H, Ar-H).
6	0.71 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.06-1.15 (m, 3H), 1.22-1.29 (m, 2H), 1.36 (s, 9H, ^{t}Bu), 1.40-1.48 (m, 2H), 1.57-1.65 (m, 3H), 1.67-1.77 (m, 3H), 1.95-2.06 (m, 2H), 2.15-2.22 (m, 1H), 3.32 (dd, 1H, J = 2.4, 11.7 Hz), 5.11 (s, 1H, N-H), 5.79 (d, 1H, J = 10.1 Hz, C_2-H), 6.06 (s, 1H, N-H), 6.78 (d, 1H, J = 10.1 Hz, C_5-H).

17β-(*N-tert*-Butyl carbamoyl)-4-aza-5α-androst-1-ene-3-one (6). To a suspension of **5a** (80 g, 0.168 moles) in ethanol (480 ml) was added a 70% aqueous ethylamine solution (54.02 g, 0.840 moles) and the resulting solution was stirred at 25-30 °C for 12 hours. Then, the reaction mass was concentrated under reduced pressure, and was added tetrahydrofuran (160 ml), ethyl acetate (160 ml) and water (480 ml). The resulting precipitate was stirred at 3-5 °C for 2 hours. The product was filtered, washed with water. This crude product was crystallized from a mixture of tetrahydrofuran (400 ml) and ethyl acetate (400 ml) to obtain 55.2 g (88%) of **6** as a white crystalline product with a purity of 99.9% as seen by HPLC method. (Having 0.05% of impurity **1**, 0.01% of impurity **3**). Physical and spectral data of **6** are given in Tables 1 and 2. Similarly the compounds **5b-f** can be treated with 70% aqueous ethylamine solution to get **6** by this procedure. Physical and spectral data of **6** are given in Tables 1 and 2.

Acknowledgement. Authors thank the management of Aurobindo pharma Ltd., Hyderabad for the permission to publish this work. Authors also thank the entire analytical research department for the valuable contribution to this work.

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[16] HPLC analyses were carried out only for compound 4a, 5a and 6 using Hypersil BDS C_{18} (250 mm X 4.6 mm), Intersil ODS-3V, 5μ (250 mm X 4.6 mm) and Novapak C18, 4μ (300 mm X 3.9 mm) column respectively.