Synthesis and Testosterone 5α-Reductase-Inhibitory Activity of 4-Aza-5α-androstane-17-carboxamide Compound with an Aromatic Moiety in the C-17 Carbamoyl Group

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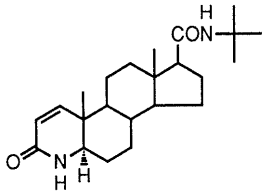
A series of 4-aza-5α-androstane compounds with one or two aromatic moieties in the carbamoyl group at the C-17 position were synthesized and their inhibitory activities for rat and human prostatic testosterone 5α-reductase were tested *in vitro*. Compounds with one aromatic moiety in the carbamoyl group showed high inhibitory activity for rat 5α-reductase, but little for human prostatic 5α-reductase. On the other hand, compounds with two aromatic moieties had potent inhibitory activities for both rat and human 5α-reductase. The structural requirements for potent inhibition for both enzymes are discussed in relation to the spatial arrangement of the C-17 carbamoyl group.

Key words testosterone 5α-reductase inhibitor; 4-aza-5α-androstane; steroid; prostatic hypertrophy; synthesis

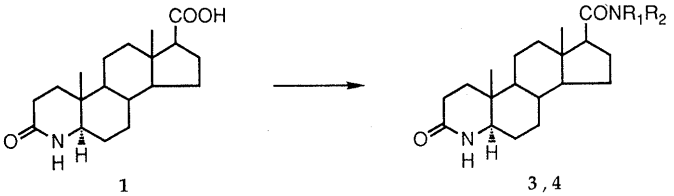
Testosterone 5α-reductase converts testosterone to 5α-dihydrotestosterone, which binds to androgen receptors, resulting in various hormonal activities. Benign prostatic hypertrophy is known to be caused by excessive accumulation of dihydrotestosterone.[2)] Inhibition of testosterone 5α-reductase can diminish the concentration of dihydrotestosterone in the prostate, which is expected to improve the pathology of this disease. Recently several steroid compounds were found to have 5α-reductase-inhibitory activities[3)] and among them, 4-azasteroid compounds were reported to have comparatively high inhibitory activities. One of the 4-azasteroid compounds, MK-906 (Finasteride, Chart 1), has been launched as a drug for benign prostatic hypertrophy in the United States.

Many natural steroids have biological activities. They have a wide variety of C-17 substituents such as oxo, hydroxy, acetyl, 1,5-dimethylhexyl, *etc.* The C-17 substituents are thought to play an important role in their biological activities.[4)] Typical 4-azasteroid compounds synthesized so far as testosterone 5α-reductase inhibitors, including MK-906, have alkyl groups in the carbamoyl



MK-906

Methods of amidation reactions



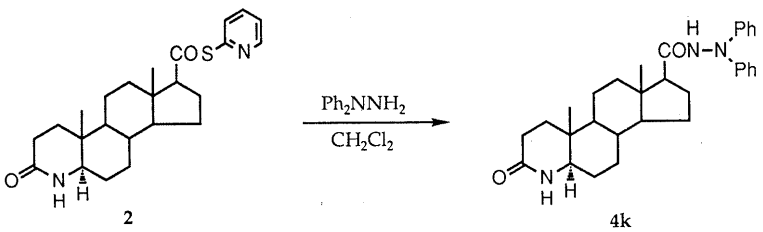
1 3, 4

(A) $SOCl_2$, Et_3N, CH_2Cl_2 and then R_1R_2NH

(B) Diethyl phosphorocyanidate, Et_3N, R_1R_2NH, CH_2Cl_2

(C) 2-Chloro-1-methylpyridinium iodide, Et_3N, R_1R_2NH, CH_3CN

(D)



2 4k

Chart 1

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moiety at the C-17 position.[3a,c] In view of the importance of the C-17 substituent of steroid compounds for biological activity, we considered that modifying the C-17 substituent of a 4-azasteroid compound might affect its binding affinity to testosterone 5α-reductase. In order to obtain a potent 5α-reductase inhibitor, we planned to introduce an aromatic group onto the C-17 carbamoyl moiety of a 4-aza-5α-androstane compound. We thought that the C-17 amide linkage would be useful for controlling the stereochemistry of the substituents. In this report, we describe the preparation of some 4-aza-5α-androstane compounds having aromatic groups in the C-17 side chain, and their testosterone 5α-reductase-inhibitory activities.[3d] Some compounds showed species differences in inhibitory activity (rat and human) and the structural requirements for potent inhibitory activities for both rat and human 5α-reductase are discussed.

Chemistry

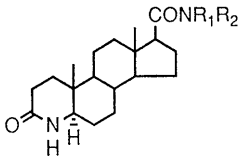
The saturated 4-aza-5α-androstane derivatives were synthesized from 3-oxo-4-aza-5α-androstane-17β-carboxylic acid **1**, which was prepared from commercially available pregnenolone according to the method reported by Rasmusson *et al.*[3a,b] Amidation reactions of **1** with amines were performed using the following four methods: method A, acid chloride method; method B, condensation using diethyl phosphorocyanidate; method C, condensation using 2-chloro-1-methylpyridinium iodide; and method D, using an activated ester, 2-pyridylthioester **2**[3b] (Chart 1). Compounds **3a**, **3c**, **3d**, **3e**, **3g**, **3h**, **3i**, **3j**, **3k**, **3l**, **3m**, **4a**, **4b**, and **4c** were synthesized according to method A: treatment of the carboxylic acid **1** with thionyl chloride followed by addition of the corresponding amines gave the products in 15—98% yields. Compounds **3f**, **4d**, **4e**, **4f**, **4g**, **4h**, **4i**, and **4l** were synthesized according to method B: reaction of the acid **1** with the corresponding amines in the presence of diethyl phosphorocyanidate and triethylamine afforded the amide products in 54—91% yields. Compounds **3b** and **4j** were synthesized according to method C: treatment of the acid **1** with the corresponding amines in the presence of 2-chloro-1-methylpyridinium iodide afforded the amide products **3b** and **4j** in 36 and 70% yields respectively. Compound **4k** was synthesized according to method D: reaction of the pyridylthioester **2**, prepared from the acid **1**, with 1,1-diphenylhydrazine in the presence of 4-dimethylaminopyridine afforded **4k** in 57% yield.

Results and Discussion

In vitro inhibitory activities for rat and human testosterone 5α-reductase were determined using the standard method.[3d] Table 1 shows the inhibitory activities of the compounds with one aromatic group on the C-17 side chain for rat and human 5α-reductase. In tests using rat 5α-reductase, the *N*-phenylcarbamoyl derivative **3a** showed stronger inhibitory activity than MK-906 (entry 1). The compounds possessing a heterocyclic group had moderate inhibitory activities, but were much weaker than **3a** (entries 2—6). Introduction of an electron-donating or withdrawing substituent at the *para* position of the phenyl group of the C-17 carbamoyl moiety of **3a** did not greatly affect the activitiy (entries 7, 9—12). Introduction of a methoxy moiety at the *ortho* position of the phenyl group slightly decreased the activity (entry 8). In contrast to the high inhibitory activity for rat 5α-reductase, these compounds showed very weak inhibitory activities for human 5α-reductase. Thus, it was found that the introduction of one phenyl group on the carbamoyl moiety at the C-17 position increased the inhibitory activity for rat 5α-reductase compared with MK-906, but markedly decreased the activity for human 5α-reductase.

Next, derivatives with two phenyl groups in the C-17 carbamoyl moiety were synthesized and their activities were tested. The results are summarized in Table 2.

Table 1. Inhibitory Activities of 4-Aza-5α-androstane Compounds Having One Aromatic Group in the C-17 Side Chain



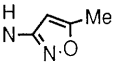
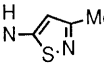
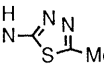
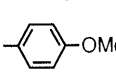
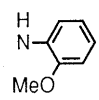
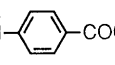
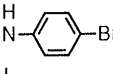
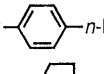
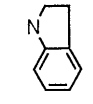
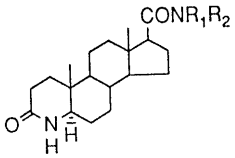
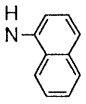
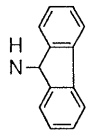
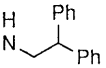
Entry	Compd. No.	NR_1R_2	Rat 5α-reductase % inhibition at 10^{-8} M	Human 5α-reductase relative inhibitory potency to MK-906 (MK-906 = 1)
1	**3a**		78	0.43
2	**3b**		48	0.29
3	**3c**		48	0.17
4	**3d**		56	0.20
5	**3e**		26	—
6	**3f**		59	—
7	**3g**		70	0.27
8	**3h**		50	0.17
9	**3i**		71	0.33
10	**3j**		80	0.16
11	**3k**		73	0.14
12	**3l**		76	0.25
13	**3m**		45	0.40
	MK-906		28	1

Table 2. Inhibitory Activities of 4-Aza-5α-androstane Compounds Having Two Aromatic Groups in the C-17 Side Chain



Entry	Compd. No.	NR_1R_2	Rat 5α-reductase % inhibition at 10^{-8} M	Human 5α-reductase relative inhibitory potency to MK-906 (MK-906 = 1)
1	**4a**		56	0.35
2	**4b**		41	4.5
3	**4c**		61	3.4
4	**4d**		74	4.7
5	**4e**		89	5.6
6	**4f**		89	3.7
7	**4g**		93	3.2
8	**4h**		94	3.2
9	**4i**		73	1.6
10	**4j**		66	3.9
11	**4k**		81	7.1
12	**4l**		80	0.27
	MK-906		28	1

The *N*-naphthylcarbamoyl compound **4a**, which has a condensed aryl group, had moderate inhibitory activity for rat 5α-reductase and this derivative again had quite weak inhibitory activity for the human enzyme (entry 1), like the monophenyl compound **3a**. The *N*,*N*-diphenylcarbamoyl derivative **4b** showed much weaker activity for rat 5α-reductase (entry 2) as compared with **3a** and **4a**. In contrast to the monophenyl compounds described above, **4b** showed potent inhibitory activity for human 5α-reductase (entry 2). Compounds **4c** and **4d**, with an extra methylene group between the nitrogen atom and the phenyl group in the C-17 carbamoyl moiety of **4b**, also showed high inhibitory activities for rat 5α-reductase (entries 3 and 4). These compounds also had high inhibitory activities for human 5α-reductase. The compounds with a diphenylmethyl or a 1,2-diphenylethyl group in the C-17 carbamoyl moiety similarly showed high inhibitory activities for both rat and human 5α-reductase. The *N*-diphenylmethylcarbamoyl derivative **4e** had an 89% inhibition rate for rat 5α-reductase and showed more than 5 times greater activity than MK-906 for the human enzyme (entry 5). The *N*,*N*-diphenylhydrazide compound **4k**, in which the methine carbon atom in the C-17 carbamoyl group of **4e** was replaced with a nitrogen atom, showed strong inhibitory activity comparable with that of **4e** for both enzymes (entry 11). In order to discover whether the chirality of the diphenylethyl group of **4f** influences its activity, two diastereomers **4g** and **4h** were synthesized and their activities were tested (entries 7 and 8). The (*S*)-1,2-diphenylethylcarbamoyl derivative **4g** and the (*R*)-derivative **4h** showed almost the same inhibitory activities and this indicates that the chirality of the substituent in the C-17 carbamoyl group is not important for inhibitory activity. Although substitution of the methine proton in the C-17 carbamoyl moiety of **4e** with a methyl group resulted in retention of high inhibitory activity for human 5α-reductase (entry 10), insertion of a methylene group between the nitrogen and the methine carbon of **4e** decreased the activity markedly (entry 12). In conclusion, 4-aza-5α-androstane compounds having one or two phenyl groups in the C-17 carbamoyl moiety showed very high inhibitory activities for rat 5α-reductase and two phenyl groups close to the C-17 amide group are required for high inhibitory activity for both rat and human 5α-reductase.

The molecular shape of the 4-aza-5α-androstane derivatives in the region of the C-17 substituents appears to be important for the species differences in the inhibitory activity. Compound **3a** with a phenylcarbamoyl group at the C-17 position showed potent inhibitory activity for rat 5α-reductase but weak activity against human 5α-reductase. On the other hand, compound **4e** with a diphenylmethylcarbamoyl group had potent inhibitory activity for both rat and human enzyme. From inspection of molecular models of **3a** and **4e**, it is supposed that the spatial arrangements of the phenyl groups of **3a** and **4e** are greatly different. In order to determine the actual spatial arrangements of the C-17 substituents of **3a** and **4e**, the compounds were subjected to X-ray crystallographic analysis. The molecular structures of **3a** and **4e** are illustrated in Fig. 1 as Ortep models. The phenyl ring of **3a** is almost in the plane formed by the carbonyl group and amide nitrogen at the C-17 position, namely, the space on both sides of the amide moiety is vacant. On the other hand, the two phenyl groups of **4e** have almost the same orientation relative to the amide plane: one phenyl group is located on the right perpendicular to the amide plane and the other is on the left. As a result, the space on each side of the amide plane is occupied by one phenyl moiety. This arrangement indicates that the existence of groups on both sides of the amide plane is required for high

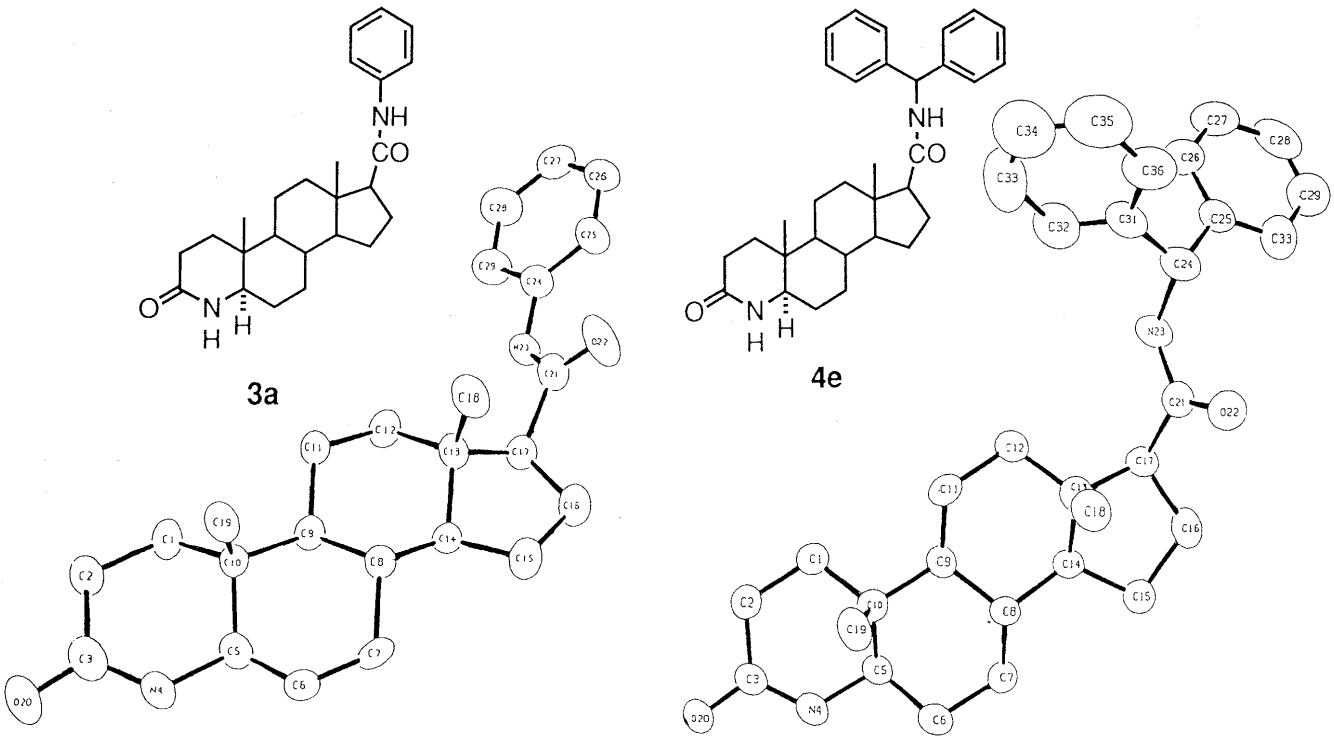


Fig. 1. Structures of **3a** and **4e**

Table 3. Fractional Atomic Coordinates ($\times 10^4$) and Thermal Parameters (Å^2) of **3a**, with Estimated Standard Deviations in Parentheses

Atom	x	y	z	B_{eq}
C1	10091 (5)	4308 (7)	8288 (7)	5.7 (2)
C2	9888 (5)	3690 (7)	9462 (7)	5.7 (3)
C3	9087 (5)	3487 (6)	9663 (8)	6.3 (3)
N4	8595 (4)	3706 (6)	8814 (6)	5.7 (2)
C5	8798 (5)	4243 (6)	7661 (7)	5.4 (2)
C6	8204 (4)	4005 (8)	6729 (7)	6.3 (3)
C7	8365 (4)	4666 (8)	5642 (8)	6.4 (3)
C8	9135 (4)	4513 (7)	5148 (7)	4.7 (2)
C9	9710 (4)	4700 (6)	6142 (7)	4.4 (2)
C10	9555 (4)	3978 (6)	7263 (6)	4.3 (2)
C11	10491 (4)	4660 (7)	5677 (7)	5.1 (2)
C12	10610 (4)	5419 (7)	4643 (7)	5.3 (2)
C13	10073 (4)	5247 (6)	3645 (7)	4.8 (2)
C14	9293 (4)	5341 (7)	4166 (7)	4.8 (2)
C15	8810 (5)	5352 (7)	3076 (8)	6.2 (3)
C16	9254 (5)	5964 (7)	2130 (8)	6.4 (3)
C17	10011 (5)	6154 (6)	2713 (7)	5.0 (2)
C18	10236 (5)	4163 (6)	2993 (7)	6.2 (3)
C19	9654 (5)	2780 (6)	6956 (7)	5.5 (2)
O20	8862 (4)	3118 (5)	10640 (5)	8.2 (2)
C21	10677 (5)	6234 (7)	1828 (7)	5.7 (3)
O22	10672 (4)	5766 (5)	889 (5)	8.5 (2)
N23	11198 (3)	6863 (5)	2227 (5)	5.0 (2)
C24	11906 (5)	7074 (6)	1685 (7)	5.6 (2)
C25	12063 (5)	6832 (8)	517 (8)	6.8 (3)
C26	12731 (5)	7123 (8)	40 (8)	7.6 (3)
C27	13249 (5)	7602 (8)	742 (9)	7.9 (3)
C28	13092 (6)	7837 (8)	1931 (10)	8.1 (3)
C29	12404 (5)	7558 (7)	2401 (9)	6.6 (3)
MCLA	1833 (2)	2835 (3)	699 (5)	14.2 (2)
MCLB	2707 (3)	4234 (4)	2088 (5)	15.4 (2)
MC	2291 (12)	3974 (12)	692 (15)	15.0 (8)

inhibitory activity against both rat and human 5α-reductase. The structural features of those compounds, showing potent inhibitory activity against human 5α-

Table 4. Fractional Atomic Coordinates ($\times 10^4$) and Thermal Parameters (Å^2) of **4e**, with Estimated Standard Deviations in Parentheses

Atom	x	y	z	B_{eq}
C1	4961 (3)	3610 (3)	2478 (8)	6.2 (2)
C2	4990 (3)	4291 (4)	1928 (8)	7.6 (3)
C3	4485 (3)	4558 (3)	1427 (6)	5.6 (2)
N4	4016 (2)	4216 (3)	1530 (5)	6.1 (2)
C5	3977 (3)	3553 (3)	2036 (6)	5.4 (2)
C6	3394 (3)	3392 (3)	2366 (7)	6.9 (3)
C7	3359 (3)	2676 (3)	2786 (7)	6.7 (2)
C8	3766 (2)	2526 (3)	3734 (6)	4.9 (2)
C9	4358 (3)	2739 (3)	3420 (6)	4.9 (2)
C10	4392 (3)	3460 (3)	2999 (6)	5.0 (2)
C11	4775 (3)	2553 (3)	4367 (7)	5.9 (2)
C12	4758 (3)	1831 (3)	4701 (6)	5.4 (2)
C13	4171 (3)	1608 (3)	4977 (6)	5.4 (2)
C14	3776 (2)	1790 (3)	3997 (6)	5.0 (2)
C15	3251 (3)	1413 (4)	4265 (7)	7.1 (3)
C16	3467 (3)	753 (4)	4762 (7)	7.1 (3)
C17	4086 (3)	843 (3)	4989 (6)	5.4 (2)
C18	3988 (3)	1894 (4)	6138 (7)	6.9 (2)
C19	4298 (3)	3948 (3)	4007 (7)	7.3 (3)
O20	4487 (2)	5112 (2)	955 (4)	5.8 (1)
C21	4296 (3)	512 (3)	6063 (6)	5.4 (2)
O22	4001 (2)	414 (3)	6901 (4)	7.3 (2)
N23	4829 (2)	344 (3)	6068 (5)	5.9 (2)
C24	5110 (3)	44 (4)	7037 (6)	6.6 (2)
C25	5585 (3)	433 (3)	7501 (7)	6.9 (2)
C26	5870 (4)	868 (5)	6865 (9)	10.8 (4)
C27	6329 (5)	1204 (6)	7323 (11)	15.2 (6)
C28	6481 (5)	1115 (5)	8394 (10)	14.0 (5)
C29	6193 (5)	662 (6)	9056 (8)	13.4 (5)
C30	5741 (4)	334 (5)	8623 (8)	9.9 (3)
C31	5277 (3)	−676 (4)	6721 (7)	6.8 (3)
C32	5823 (3)	−814 (4)	6445 (8)	8.3 (3)
C33	5972 (4)	−1459 (4)	6145 (9)	9.8 (3)
C34	5566 (5)	−1937 (4)	6127 (10)	12.0 (4)
C35	5048 (4)	−1804 (5)	6321 (11)	11.9 (4)
C36	4881 (4)	−1147 (5)	6642 (10)	10.5 (4)
OW	2911 (2)	196 (3)	7600 (4)	8.2 (2)

reductase (Table 2), are similar to those of **4e**.[5]

In conclusion, we synthesized 4-aza-5α-androstane derivatives with one or two aromatic groups in the C-17 carbamoyl moiety. The compounds with one aromatic group in the C-17 carbamoyl moiety had potent inhibitory activities only for rat 5α-reductase. In contrast, the derivatives with two phenyl groups showed strong inhibitory activities for both rat and human enzymes. It is suggested that the existence of groups on both sides of the amide plane of the C-17 carbamoyl group is important for potent inhibitory activity for both rat and human 5α-reductase.

Experimental

Melting points are uncorrected. ^{1}H-NMR spectra were measured with a JEOL JNM-GX270 or JEOL JNM-EX270 spectrometer (270 MHz) using tetramethylsilane as an internal standard. Chemical shifts are given in δ values (ppm). IR spectra were measured with a Nic. 5SXC, JASCO A-302, JASCO FT/IR8300, JASCO FT/IR8900, or JASCO A-102 spectrometer. Mass spectra were measured with a JEOL JMS-D300, JMS-AX505H, or JMS-AX505W spectrometer. Unit cell parameters and intensity data for X-ray crystallography were measured on an automatic four-circle diffractometer with graphite-monochromated CuK_α radiation at 25 °C. Thin-layer chromatography (TLC) was run on silica gel-coated plates (E. Merck, Silica gel 60F_{254} precoated) with a thickness of 0.25 mm. Silica gel 60 (E. Merck, 70—230 mesh) was used for column chromatography.

Amidation Reaction of the Carboxylic Acid 1. Method A. *N*-[3-(5-Methylisoxazolyl)]-3-oxo-4-aza-5α-androstane-17β-carboxamide (3c) 2,6-Lutidine (100 μl, 0.86 mmol) and thionyl chloride (25 μl, 0.34 mmol) were added to a suspension of 3-oxo-4-aza-5α-androstane-17β-carboxylic acid **1** (100 mg, 0.31 mmol) in dry CH_2Cl_2 (3.0 ml) and the whole was stirred at room temperature for 1 h. 3-Amino-5-methylisoxazole (50 mg, 0.51 mmol) was then added to the reaction mixture and the whole was further stirred for 30 min, then diluted with water and extracted with CH_2Cl_2. The combined organic layer was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine and dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was chromatographed on a silica gel column. Elution with 50—60% acetone in CH_2Cl_2 gave a residue, which was treated with Et_2O to afford **3c** (83 mg, 66%) as a white powder. mp 170—172 °C. Crystallization from CH_2Cl_2 afforded an analytical sample. ^{1}H-NMR ($CDCl_3$) δ: 0.73 (3H, s), 0.75—2.47 (20H, m), 0.91 (3H, s), 2.40 (3H, s), 3.07 (1H, dd, J=5, 11 Hz), 5.88 (1H, s), 6.75 (1H, s), 8.16 (1H, s). IR (KBr): 3228, 2938, 2871, 1702, 1659, 1621 cm^{-1}. HR-MS *m/z*: Calcd for $C_{23}H_{33}N_3O_3$ (M^+): 399.2522. Found: 399.2529. *Anal.* Calcd for $C_{23}H_{33}N_3O_3 \cdot 1/10H_2O$: C, 68.83; H, 8.34; N, 10.47. Found: C, 68.52; H, 8.33; N, 10.14.

Method B. *N*-Diphenylmethyl-3-oxo-4-aza-5α-androstane-17β-carboxamide (4e) Triethylamine (100 μl, 0.72 mmol), benzhydrylamine (100 mg, 0.61 mmol), and diethyl phosphorocyanidate (75 μl, 0.50 mmol) were added to a suspension of **1** (100 mg, 0.31 mmol) in dry CH_2Cl_2 (3.0 ml) and the whole was stirred at room temperature for 24 h, then diluted with water and extracted with CH_2Cl_2. The combined organic layer was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine and dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was chromatographed on a silica gel column. Elution with 30—40% acetone in CH_2Cl_2 gave a residue, which was treated with Et_2O to afford **4e** (137 mg, 90%) as a white powder. mp 149—151 °C. Crystallization from EtOH afforded an analytical sample. ^{1}H-NMR ($CDCl_3$) δ: 0.67 (3H, s), 0.70—2.00 (15H, m), 0.90 (3H, s), 2.15—2.30 (3H, m), 2.37—2.47 (2H, m), 3.03 (1H, dd, J=5, 10 Hz), 5.46 (1H, br), 5.88 (1H, d, J=9 Hz), 6.28 (1H, d, J=9 Hz), 7.20—7.38 (10H, m). IR (KBr): 3288, 2935, 2868, 1664 cm^{-1}. HR-MS *m/z*: Calcd for $C_{32}H_{40}N_2O_2$ (M^+): 484.3089. Found: 484.3091. *Anal.* Calcd for $C_{32}H_{40}N_2O_2 \cdot 1/2H_2O$: C, 77.85; H, 8.50; N, 5.67. Found: C, 77.61; H, 8.42; N, 5.67.

Method C. *N*-(1,1-Diphenylethyl)-3-oxo-4-aza-5α-androstane-17β-carboxamide (4j) Triethylamine (150 μl, 1.08 mmol), 1,1-diphenylethylamine[6] (150 mg, 0.76 mmol), and 2-chloro-1-methylpyridinium iodide (200 mg, 0.78 mmol) were added to a suspension of **1** (150 mg, 0.47 mmol) in dry acetonitrile (5.0 ml) and the whole was refluxed for 3 h, then diluted with water and extracted with CH_2Cl_2. The combined organic layer was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine and dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was chromatographed on a silica gel column. Elution with 40—45% acetone in CH_2Cl_2 gave a residue, which was treated with Et_2O to give **4j** (165 mg, 70%) as a pale yellow powder. mp 168—170 °C. Crystallization from a mixture of CH_2Cl_2 and EtOAc afforded an analytical sample. ^{1}H-NMR ($CDCl_3$) δ: 0.70 (3H, s), 0.70—2.25 (17H, m), 0.90 (3H, s), 2.20 (3H, s), 2.35—2.50 (3H, m), 3.05 (1H, dd, J=5, 10 Hz), 5.44 (1H, br), 5.98 (1H, br), 7.20—7.40 (10H, m). IR (KBr): 3300, 2937, 2869, 1665 cm^{-1}. HR-MS *m/z*: Calcd for $C_{33}H_{42}N_2O_2$ (M^+): 498.3246. Found: 498.3249. *Anal.* Calcd for $C_{33}H_{42}N_2O_2 \cdot H_2O$: C, 76.71; H, 8.58; N, 5.42. Found: C, 76.72; H, 8.77; N, 5.12.

Method D. *N,N*-Diphenyl-3-oxo-4-aza-5α-androstane-17β-carbohydrazide (4k) 1,1-Diphenylhydrazine (400 mg, 2.17 mmol) and 4-dimethylaminopyridine (5.0 mg) were added to a solution of *S*-2-pyridyl-3-oxo-4-aza-5α-androstane-17β-thiocarboxylate **2**[3b] (200 mg, 0.49 mmol) in dry CH_2Cl_2 (5.0 ml) and the mixture was stirred at room temperature for 24 h. It was concentrated to dryness and the residue was chromatographed on a silica gel column. Elution with 50% acetone in CH_2Cl_2 gave a residue, which was treated with Et_2O to give **4k** (135 mg, 57%) as a pale yellow powder. mp 185—187 °C. Crystallization from a mixture of CH_2Cl_2 and EtOAc afforded an analytical sample. ^{1}H-NMR ($CDCl_3$) δ: 0.70 (3H, s), 0.75—1.92 (15H, m), 0.90 (3H, s), 2.05 (1H, m), 2.17—2.44 (4H, m), 3.05 (1H, dd, J=5, 11 Hz), 5.45 (1H, br), 6.98—7.05 (2H, m), 7.12 (4H, d, J=8 Hz), 7.22—7.32 (4H, m), 7.50 (1H, br). IR (KBr): 3198, 2934, 2871, 1699, 1654, 1589 cm^{-1}. HR-MS *m/z*: Calcd for $C_{31}H_{39}N_3O_2$ (M^+): 485.3043. Found: 485.3042. *Anal.* Calcd for $C_{31}H_{39}N_3O_2 \cdot 1/5H_2O$: C, 76.10; H, 8.12; N, 8.59. Found: C, 76.09; H, 8.20; N, 8.48.

***N*-Phenyl-3-oxo-4-aza-5α-androstane-17β-carboxamide (3a)** Application of method A to **1** and aniline gave **3a** as a white powder in 30% yield. mp 223—225 °C. Crystallization from EtOH afforded an analytical sample. ^{1}H-NMR ($CDCl_3$) δ: 0.75—2.50 (20H, m), 0.78 (3H, s), 0.92 (3H, s), 3.01 (1H, dd, J=5, 11 Hz), 5.52 (1H, br), 6.98 (1H, br), 7.10 (1H, t, J=8 Hz), 7.33 (2H, t, J=8 Hz), 7.51 (2H, d, J=8 Hz). IR (KBr): 3300, 3275, 2939, 2872, 1666, 1649, 1599 cm^{-1}. HR-MS *m/z*: Calcd for $C_{25}H_{34}N_2O_2$ (M^+): 394.2620. Found: 394.2621. *Anal.* Calcd for $C_{25}H_{34}N_2O_2 \cdot 1/2H_2O$: C, 74.59; H, 8.67; N, 6.93. Found: C, 74.94; H, 8.71; N, 6.62.

***N*-(2-Pyridyl)-3-oxo-4-aza-5α-androstane-17β-carboxamide (3b)** Application of method C to **1** and 2-aminopyridine gave **3b** as a pale yellow powder in 36% yield. mp 167—169 °C. Crystallization from CH_2Cl_2 afforded an analytical sample. ^{1}H-NMR ($CDCl_3$) δ: 0.75—2.45 (20H, m), 0.76 (3H, s), 0.90 (3H, s), 3.08 (1H, dd, J=5, 12Hz), 5.53 (1H, br), 7.02 (1H, m), 7.70 (1H, m), 7.78 (1H, br), 8.20—8.28 (2H, m). IR (KBr): 3210, 2937, 2870, 1693, 1664, 1594, 1577 cm^{-1}. HR-MS *m/z*: Calcd for $C_{24}H_{33}N_3O_2$ (M^+): 395.2573, Found: 395.2579. *Anal.* Calcd for $C_{24}H_{33}N_3O_2 \cdot 1/2H_2O$: C, 71.25; H, 8.47; N, 10.39. Found: C, 71.22; H, 8.14; N, 9.98.

***N*-[5-(3-Methylisothiazolyl)]-3-oxo-4-aza-5α-androstane-17β-carboxamide (3d)** Application of method A to **1** and 5-amino-3-methylisothiazole gave **3d** as a white powder in 15% yield. mp 230—232 °C. Crystallization from a mixture of $CHCl_3$ and EtOH afforded an analytical sample. ^{1}H-NMR ($CDCl_3$) δ: 0.75—2.57 (20H, m), 0.78 (3H, s), 0.97 (3H, s), 2.46 (3H, s), 3.12 (1H, dd, J=5, 11 Hz), 5.55 (1H, br), 6.66 (1H, s), 8.65 (1H, br). IR (KBr): 3249, 2938, 2872, 1657, 1553 cm^{-1}. HR-MS *m/z*: Calcd for $C_{23}H_{33}N_3O_2S$ (M^+): 415.2293. Found: 415.2289. *Anal.* Calcd for $C_{23}H_{33}N_3O_2S$: C, 66.47; H, 8.00; N, 10.11. Found: C, 66.42; H, 8.12; N, 9.78.

***N*-[2-(5-Methyl-1,3,4-thiadiazolyl)]-3-oxo-4-aza-5α-androstane-17β-carboxamide (3e)** Application of method A to **1** and 2-amino-5-methyl-1,3,4-thiadiazole gave **3a** as a pale yellow powder in 16% yield. mp 205—209 °C. Crystallization from a mixture of CH_2Cl_2 and EtOAc afforded an analytical sample. ^{1}H-NMR ($CDCl_3$) δ: 0.73 (3H, s), 0.75—1.65 (11H, m), 0.90 (3H, s), 1.73—1.98 (5H, m), 2.23—2.45 (3H, m), 2.65 (1H, m), 2.69 (3H, s), 3.08 (1H, dd, J=4, 12 Hz), 5.85 (1H, s), 10.91 (1H, br). IR (KBr): 3187, 2937, 2871, 1663 cm^{-1}. HR-MS *m/z*: Calcd for $C_{22}H_{32}N_4O_2S$ (M^+): 416.2246. Found: 416.2260. *Anal.* Calcd for $C_{22}H_{32}N_4O_2S \cdot H_2O$: C, 60.80; H, 7.89; N, 12.89; S, 7.38. Found: C, 60.80; H, 7.62; N, 12.70; S, 7.32.

***N*-(2-Thiazolyl)-3-oxo-4-aza-5α-androstane-17β-carboxamide (3f)** Application of method B to **1** and 2-aminothiazole gave **3f** as a white powder in 62% yield. mp 273—275 °C. Crystallization from CH_2Cl_2

afforded an analytical sample. ^{1}H-NMR ($CDCl_3+CD_3OD$) δ: 0.75 (3H, s), 0.85—1.68 (11H, m), 0.90 (3H, s), 1.75—1.98 (5H, m), 2.25—2.55 (4H, m), 3.09 (1H, dd, $J=4$, 12 Hz), 7.00 (1H, d, $J=4$ Hz), 7.41 (1H, d, $J=4$ Hz). IR (KBr): 3189, 3062, 2937, 2870, 1650 cm^{-1}. HR-MS *m/z*: Calcd for $C_{22}H_{31}N_3O_2S$ (M^+): 401.2137. Found: 401.2132. *Anal.* Calcd for $C_{22}H_{31}N_3O_2S\cdot 1/2H_2O$: C, 64.36; H, 7.85; N, 10.23; S, 7.81. Found: C, 64.07; H, 7.71; N, 10.07; S, 7.72.

***N*-(4-Methoxyphenyl)-3-oxo-4-aza-5α-androstane-17β-carboxamide (3g)** Application of method A to **1** and 4-methoxyaniline gave **3g** as a white powder in 41% yield. mp 173—175 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.75—2.50 (20H, m), 0.78 (3H, s), 0.92 (3H, s), 3.08 (1H, dd, $J=5$, 11 Hz), 3.79 (3H, s), 5.42 (1H, br), 6.87 (2H, d, $J=10$ Hz), 6.89 (1H, br), 7.41 (2H, d, $J=10$ Hz). IR (KBr): 3310, 2936, 2870, 1667 cm^{-1}. HR-MS *m/z*: Calcd for $C_{26}H_{36}N_2O_3$ (M^+): 424.2726. Found: 424.2724. *Anal.* Calcd for $C_{26}H_{36}N_2O_3\cdot 1/5H_2O$: C, 72.93; H, 8.57; N, 6.54. Found: C, 72.55; H, 8.56; N, 6.14.

***N*-(2-Methoxyphenyl)-3-oxo-4-aza-5α-androstane-17β-carboxamide (3h)** Application of method A to **1** and 2-methoxyaniline gave **3h** as a white powder in 40% yield. mp 168—170 °C. Crystallization from CH_2Cl_2 afforded an analytical sample. ^{1}H-NMR ($CDCl_3$) δ: 0.75 (3H, s), 0.78—2.47 (20H, m), 0.91 (3H, s), 3.08 (1H, dd, $J=5$, 11 Hz), 3.88 (3H, s), 5.40 (1H, br), 6.87 (1H, dd, $J=1$, 10 Hz), 6.93—7.07 (2H, m), 7.66 (1H, br), 8.39 (1H, dd, $J=1$, 7 Hz). IR (KBr): 3200, 2937, 2870, 1669, 1601 cm^{-1}. HR-MS *m/z*: Calcd for $C_{26}H_{36}N_2O_3$ (M^+): 424.2726. Found: 424.2724. *Anal.* Calcd for $C_{26}H_{36}N_2O_3$: C, 73.55; H, 8.55; N, 6.60. Found: C, 73.26; H, 8.50; N, 6.21.

***N*-(4-Acetylphenyl)-3-oxo-4-aza-5α-androstane-17β-carboxamide (3i)** Application of method A to **1** and 4-acetylaniline gave **3i** as a pale yellow powder in 20% yield. mp 179—181 °C. Crystallization from CH_2Cl_2 afforded an analytical sample. ^{1}H-NMR ($CDCl_3$) δ: 0.75—2.48 (20H, m), 0.77 (3H, s), 0.92 (3H, s), 2.57 (3H, s), 3.07 (1H, dd, $J=6$, 12 Hz), 5.48 (1H, br), 7.17 (1H, br), 7.62 (2H, d, $J=9$ Hz), 7.94 (2H, d, $J=9$ Hz). IR (KBr): 3320, 2937, 2871, 1668, 1592 cm^{-1}. HR-MS *m/z*: Calcd for $C_{27}H_{36}N_2O_3$ (M^+): 436.2726. Found: 436.2737. *Anal.* Calcd for $C_{27}H_{36}N_2O_3\cdot 1/2H_2O$: C, 72.78; H, 8.37; N, 6.29. Found: C, 72.64; H, 7.99; N, 6.30.

***N*-(4-Bromophenyl)-3-oxo-4-aza-5α-androstane-17β-carboxamide (3j)** Application of method A to **1** and 4-bromoaniline gave **3j** as a white powder in 34% yield. mp 277—280 °C. Crystallization from CH_2Cl_2 afforded an analytical sample. ^{1}H-NMR ($CDCl_3$) δ: 0.75—2.47 (20H, m), 0.76 (3H, s), 0.91 (3H, s), 3.08 (1H, dd, $J=5$, 11 Hz), 5.72 (1H, br), 6.98 (1H, br), 7.39—7.42 (4H, br). IR (KBr): 3310, 2937, 2870, 1664, 1589 cm^{-1}. HR-MS *m/z*: Calcd for $C_{25}H_{33}{}^{79}BrN_2O_2$ (M^+): 472.1725. Found: 472.1726. *Anal.* Calcd for $C_{25}H_{33}BrN_2O_2\cdot 1/2H_2O$: C, 62.24; H, 7.10; N, 5.81. Found: C, 62.51; H, 7.11; N, 5.70.

***N*-(4-Trifluoromethylphenyl)-3-oxo-4-aza-5α-androstane-17β-carboxamide (3k)** Application of method A to **1** and 4-trifluoromethylaniline gave **3k** as a pale yellow powder in 55% yield. mp 284—287 °C. Crystallization from CH_2Cl_2 afforded an analytical sample. ^{1}H-NMR ($CDCl_3$) δ: 0.75—2.47 (20H, m), 0.77 (3H, s), 0.92 (3H, s), 3.07 (1H, dd, $J=5$, 11 Hz), 5.47 (1H, br), 7.07 (1H, br), 7.57 (2H, d, $J=9$ Hz), 7.65 (2H, d, $J=9$ Hz). IR (KBr): 3270, 2970, 2940, 1695, 1658, 1604 cm^{-1}. HR-MS *m/z*: Calcd for $C_{26}H_{33}F_3N_2O_2$ (M^+): 462.2494. Found: 462.2496. *Anal.* Calcd for $C_{26}H_{33}F_3N_2O_2\cdot 1/5H_2O$: C, 66.99; H, 7.22; N, 6.01. Found: C, 66.84; H, 7.31; N, 5.81.

***N*-(4-*n*-Butylphenyl)-3-oxo-4-aza-5α-androstane-17β-carboxamide (3l)** Application of method A to **1** and 4-*n*-butylaniline gave **3l** as a white powder in 28% yield. mp 226—228 °C. Crystallization from CH_2Cl_2 afforded an analytical sample. ^{1}H-NMR ($CDCl_3$) δ: 0.75—2.48 (27H, m), 0.77 (3H, s), 0.91 (3H, s), 2.57 (2H, t, $J=8$ Hz), 3.08 (1H, dd, $J=5$, 11 Hz), 5.59 (1H, br), 6.91 (1H, br), 7.12 (2H, d, $J=9$ Hz), 7.40 (2H, d, $J=9$ Hz). IR (KBr): 3310, 2933, 2870, 1668, 1595 cm^{-1}. HR-MS *m/z*: Calcd for $C_{29}H_{42}N_2O_2$ (M^+): 450.3246. Found: 450.3239. *Anal.* Calcd for $C_{29}H_{42}N_2O_2\cdot 1/2H_2O$: C, 75.78; H, 9.43; N, 6.09. Found: C, 76.08; H, 9.12; N, 5.86.

17β-[1-(2,3-Dihydroindolyl)carbonyl]-3-oxo-4-aza-5α-androstane (3m) Application of method A to **1** and 2,3-dihydroindole gave **3m** as a white powder in 38% yield. mp 195—197 °C. Crystallization from CH_2Cl_2 afforded an analytical sample. ^{1}H-NMR ($CDCl_3$) δ: 0.75—2.75 (20H, m), 0.86 (3H, s), 0.92 (3H, s), 3.04 (1H, dd, $J=5$, 11 Hz), 3.15 (2H, t, $J=9$ Hz), 4.08 (1H, dd, $J=9$, 18 Hz), 4.20 (1H, dd, $J=9$, 18 Hz), 5.45 (1H, br), 7.00 (1H, t, $J=7$ Hz), 7.16—7.22 (2H, m), 8.28 (1H, d, $J=7$ Hz). IR (KBr): 3205, 2937, 2870, 1669, 1598 cm^{-1}. HR-MS *m/z*: Calcd for $C_{27}H_{36}N_2O_2$ (M^+): 420.2777. Found: 420.2773. *Anal.* Calcd for $C_{27}H_{36}N_2O_2\cdot 1/10H_2O$: C, 76.78; H, 8.64; N, 6.63. Found: C, 76.42; H, 8.60; N, 6.61.

***N*-(1-Naphthyl)-3-oxo-4-aza-5α-androstane-17β-carboxamide (4a)** Application of method A to **1** and 1-aminonaphthalene gave **4a** as a pale pink powder in 44% yield. mp 201—203 °C. Crystallization from CH_2Cl_2 afforded an analytical sample. ^{1}H-NMR ($CDCl_3$) δ: 0.75—2.60 (20H, m), 0.85 (3H, s), 0.89 and 0.92 (together 3H, each s), 3.10 (1H, m), 5.45 (1H, br), 7.40 (1H, br), 7.47—7.57 (3H, m), 7.68 (1H, d, $J=7$ Hz), 7.78—7.90 (2H, m), 8.05 (1H, d, $J=7$ Hz). IR (KBr): 3292, 2936, 2869, 1668, 1597 cm^{-1}. HR-MS *m/z*: Calcd for $C_{29}H_{36}N_2O_2$ (M^+): 444.2777. Found: 444.2792. *Anal.* Calcd for $C_{29}H_{36}N_2O_2\cdot 1/2H_2O$: C, 76.79; H, 8.22; N, 6.17. Found: C, 76.85; H, 7.86; N, 6.18.

***N,N*-Diphenyl-3-oxo-4-aza-5α-androstane-17β-carboxamide (4b)** Application of method A to **1** and diphenylamine gave **4b** as a pale gray powder in 98% yield. mp 153—155 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.60—2.30 (17H, m), 0.89 (3H, s), 0.92 (3H, s), 2.38 (2H, m), 2.72 (1H, t, $J=9$ Hz), 2.97 (1H, dd, $J=5$, 11 Hz), 5.41 (1H, br), 7.00—7.38 (10H, m). IR (KBr): 3200, 2936, 1669, 1589 cm^{-1}. HR-MS *m/z*: Calcd for $C_{31}H_{38}N_2O_2$ (M^+): 470.2934. Found: 470.2917. *Anal.* Calcd for $C_{31}H_{38}N_2O_2\cdot 1/2H_2O$: C, 77.63; H, 8.20; N, 5.84. Found: C, 77.91; H, 8.03; N, 5.85.

***N*-Benzyl-*N*-phenyl-3-oxo-4-aza-5α-androstane-17β-carboxamide (4c)** Application of method A to **1** and *N*-benzylphenylamine gave **4c** as a white powder in 88% yield. mp 225—227 °C. Crystallization from CH_2Cl_2 afforded an analytical sample. ^{1}H-NMR ($CDCl_3$) δ: 0.55—0.97 (4H, m), 0.88 (3H, s), 0.89 (3H, s), 1.20—1.86 (13H, m), 2.16 (1H, m), 2.34—2.43 (2H, m), 2.95 (1H, dd, $J=6$, 10 Hz), 4.76 (1H, d, $J=14$ Hz), 4.98 (1H, d, $J=14$ Hz), 5.40 (1H, br), 6.90—6.94 (2H, m), 7.17—7.33 (8H, m). IR (KBr): 3295, 3195, 2941, 2870, 1655, 1594 cm^{-1}. HR-MS *m/z*: Calcd for $C_{32}H_{40}N_2O_2$ (M^+): 484.3090. Found: 484.3093. *Anal.* Calcd for $C_{32}H_{40}N_2O_2$: C, 79.30; H, 8.32; N, 5.78. Found: C, 79.29; H, 8.25; N, 5.74.

***N,N*-Dibenzyl-3-oxo-4-aza-5α-androstane-17β-carboxamide (4d)** Application of method B to **1** and dibenzylamine gave **4d** as a white powder in 79% yield. mp 207—209 °C. Crystallization from EtOAc afforded an analytical sample. ^{1}H-NMR ($CDCl_3$) δ: 0.70—1.90 (17H, m), 0.89 (3H, s), 0.91 (3H, s), 2.30—2.50 (2H, m), 2.73 (1H, t, $J=8$ Hz), 3.03 (1H, dd, $J=5$, 10 Hz), 3.73 (1H, d, $J=15$ Hz), 4.16 (1H, d, $J=16$ Hz), 4.91 (1H, d, $J=16$ Hz), 5.40 (1H, br), 5.45 (1H, d, $J=15$ Hz), 7.20—7.32 (10H, m). IR (KBr): 3196, 2933, 1669, 1633 cm^{-1}. HR-MS *m/z*: Calcd for $C_{33}H_{42}N_2O_2$ (M^+): 498.3246. Found: 498.3251. *Anal.* Calcd for $C_{33}H_{42}N_2O_2$: C, 79.48; H, 8.49; N, 5.62. Found: C, 79.21; H, 8.34; N, 5.58.

***N*-[(1-*R*,*S*)-1,2-Diphenylethyl]-3-oxo-4-aza-5α-androstane-17β-carboxamide (4f)** Application of method B to **1** and 1,2-diphenylethylamine gave **4f** as a white powder in 91% yield. mp 125—127 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.48 and 0.50 (total 3H, each s), 0.70—2.20 (18H, m), 0.88 and 0.89 (total 3H, each s), 2.35—2.47 (2H, m), 2.97—3.30 (3H, m), 5.20—5.60 (3H, m), 7.02—7.37 (10H, m). IR (KBr): 3300, 2935, 1664 cm^{-1}. HR-MS *m/z*: Calcd for $C_{33}H_{42}N_2O_2$ (M^+): 498.3246. Found: 498.3229. *Anal.* Calcd for $C_{33}H_{42}N_2O_2$: C, 79.48; H, 8.49; N, 5.62. Found: C, 79.09; H, 8.20; N, 5.56.

***N*-[(1*S*)-1,2-Diphenylethyl]-3-oxo-4-aza-5α-androstane-17β-carboxamide (4g)** Application of method B to **1** and (1*S*)-1,2-diphenylethylamine[7] gave **4g** as a white powder in 83% yield. mp 235—237 °C. Crystallization from a mixture of CH_2Cl_2 and EtOAc afforded an analytical sample. ^{1}H-NMR ($CDCl_3$) δ: 0.50 (3H, s), 0.70—2.15 (18H, m), 0.87 (3H, s), 2.37—2.47 (2H, m), 3.00—3.20 (3H, m), 5.26 (1H, q, $J=5$ Hz), 5.47 (1H, br), 5.58 (1H, d, $J=5$ Hz), 7.00—7.40 (10H, m). IR (KBr): 3295, 2938, 2872, 1663 cm^{-1}. HR-MS *m/z*: Calcd for $C_{33}H_{42}N_2O_2$ (M^+): 498.3246. Found: 498.3232. *Anal.* Calcd for $C_{33}H_{42}N_2O_2$: C, 79.48; H, 8.49; N, 5.62. Found: C, 79.21; H, 8.59; N, 5.60.

***N*-[(1*R*)-1,2-Diphenylethyl]-3-oxo-4-aza-5α-androstane-17β-carboxamide (4h)** Application of method B to **1** and (1*R*)-1,2-diphenylethylamine[7] gave **4h** as a white powder in 83% yield. mp 264—266 °C. Crystallization from a mixture of CH_2Cl_2 and EtOAc afforded an analytical sample. ^{1}H-NMR ($CDCl_3$) δ: 0.46 (3H, s), 0.65—2.22 (18H, m), 0.88 (3H, s), 2.45—2.55 (2H, m), 2.77—3.20 (3H, m), 5.33 (1H, q, $J=5$ Hz), 5.48 (1H, d, $J=5$ Hz), 6.80 (1H, br), 7.10—7.40 (10H, m). IR (KBr): 3218, 2935, 1663 cm^{-1}. HR-MS *m/z*: Calcd for $C_{33}H_{42}N_2O_2$ (M^+): 498.3246. Found: 498.3248. *Anal.* Calcd for $C_{33}H_{42}N_2O_2$: C, 79.48; H, 8.49; N, 5.62. Found: C, 79.44; H, 8.68; N, 5.63.

***N*-(9-Fluorenyl)-3-oxo-4-aza-5α-androstane-17β-carboxamide (4i)** Application of method B to **1** and fluorene gave **4i** as a white powder in 84% yield. mp 244—246 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.72—1.95 (15H,

m), 0.86 (3H, s), 0.90 (3H, s), 2.16—2.42 (5H, m), 3.03 (1H, dd, $J=6$, 11 Hz), 5.47 (1H, br), 5.56 (1H, d, $J=9$ Hz), 6.32 (1H, d, $J=9$ Hz), 7.28—7.35 (2H, m), 7.40 (2H, t, $J=7$ Hz), 7.56 (2H, t, $J=7$ Hz), 7.71 (2H, d, $J=7$ Hz). IR (KBr): 3350, 2937, 2865, 1659 cm^{-1}. HR-MS *m/z*: Calcd for $C_{32}H_{38}N_2O_2$ (M^+): 482.2934. Found: 482.2944. *Anal.* Calcd for $C_{32}H_{38}N_2O_2 \cdot 1/2H_2O$: C, 78.17; H, 8.00; N, 5.70. Found: C, 78.33; H, 8.08; N, 5.72.

***N*-(2,2-Diphenylethyl)-3-oxo-4-aza-5α-androstane-17β-carboxamide (4l)** Application of method B to **1** and 2,2-diphenylethylamine gave **4l** as a white powder in 81% yield. mp 228—230 °C. Crystallization from a mixture of CH_2Cl_2 and EtOAc afforded an analytical sample. ^{1}H-NMR ($CDCl_3$) δ: 0.54 (3H, s), 0.63—2.20 (18H, m), 0.88 (3H, s), 2.36—2.54 (2H, m), 3.00 (1H, dd, $J=5$, 11 Hz), 3.74 (1H, ddd, $J=5$, 10, 15 Hz), 4.07 (1H, ddd, $J=5$, 10, 15 Hz), 4.21 (1H, t, $J=10$ Hz), 5.20 (1H, br t, $J=5$ Hz), 5.42 (1H, br), 7.18—7.37 (10H, m). IR (KBr): 3282, 3189, 2934, 1662 cm^{-1}. HR-MS *m/z*: Calcd for $C_{33}H_{42}N_2O_2$ (M^+): 498.3246. Found: 498.3247. *Anal.* Calcd for $C_{33}H_{42}N_2O_2$: C, 79.48; H, 8.49; N, 5.62. Found: C, 79.21; H, 8.65; N, 5.52.

X-Ray Crystallographic Analysis A crystal of **3a** for X-ray crystallographic analysis was obtained from a saturated solution of **3a** in methylene chloride. The crystal data are as follows: $C_{25}H_{34}N_2O_2 \cdot CH_2Cl_2$, F.W. = 479.5, crystal system: triclinic, space group: $P2_12_12_1$, lattice parameters: $a=18.216(6)$ Å, $b=12.374(11)$ Å, $c=11.236(8)$ Å, $V=2532.4(31)$ Å^3, $Z=4$, $D_c=1.26$ g·cm^{-3}, $R=0.069$. A crystal of **4e** for X-ray crystallographic analysis was obtained from a saturated solution of **4e** in ethanol. The crystal data are as follows: $C_{32}H_{40}N_2O_2 \cdot H_2O$, F.W. = 502.7, crystal system: triclinic, space group: $P2_12_12_1$, lattice parameters: $a=24.080$ Å, $b=20.291(6)$ Å, $c=11.639(1)$ Å, $V=5687(2)$ Å^3, $Z=8$, $D_c=1.17$ g·cm^{-3}, $R=0.049$.

Preparation of 5α-Reductase from Human and Rat Prostates Human and rat prostates were each minced into small pieces. The minced tissue was homogenized in approximately 3 tissue volumes of buffer A (20 mM potassium phosphate, pH 6.5, containing 0.32 M sucrose, 1 mM dithiothreitol, 50 μM NADPH, and 0.001% phenylmethylsulfonyl fluoride (PMSF)), first with a Polytron (Kinematica GmbH) and then with a Teflon-glass homogenizer. The homogenate was centrifuged at 140000 × *g* for 60 min and then the pellets were washed with approximately 3 tissue volumes of buffer A. The washed pellets were used as the 5α-reductase.

5α-Reductase Assay The reaction solution contained 1 μM [^{14}C] testosterone, 1 mM dithiothreitol, 40 mM buffer (potassium phosphate, pH 6.5, for the rat enzyme; Tris–citrate, pH 5.5, for the human enzyme), prostatic particulates (0.2—1 mg protein) and 0.5 mM NADPH in a final volume of 0.5 ml. A test sample was added in 5 μl of dimethyl sulfoxide (DMSO) and the control tube received the same volume of DMSO. The reaction was carried out for 10—30 min and then stopped with 2 ml of ethyl acetate containing testosterone, 5α-dihydrotestosterone, and androstenedione (10 μg each). After centrifugation at 1000 × *g* for 5 min, the ethyl acetate phase (upper) was transferred to a tube and then evaporated to dryness under nitrogen. The steroid was taken up in 30 μl of ethyl acetate and the solution was applied to a Whatman LK5DF or LK6DF silica plate, which was developed in ethyl acetate–cyclohexane (1 : 1) at room temperature. The plate was air-dried and the chromatography was repeated. The radioactivity profile was determined with a bio-image analyzer (Fuji Film Co., Ltd.).

References and Notes

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