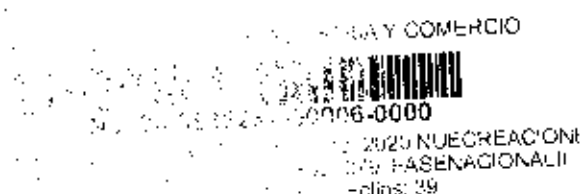


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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____



Re: P1.-MERCK & CO., INC.-Solicitud de Patente de Invención en Fase Nacional PCT para "DERIVADOS DE 4-AZASTEROIDES FLUORADOS COMO MODULADORES DEL RECEPTOR DE ANDROGENOS.-Clase A61K 31/473.-Expediente número 04-088.823.-

1. Me refiero al auto dictado por ese Despacho notificado mediante fijación en lista de 25 de Enero de 2008.

2. De acuerdo con el Concepto Técnico No. 78 se requiere del solicitante la presentación de los artículos:

- ✓ **BROOKS J.R. ET AL.: "Reductase inhibitory and anti-androgenic activities of some 4-azasteroids in the rat" STEROIDS vol. 47, 1986, pages 1-19.**
- ✓ **RASMUSSEN G.H. ET AL.: "Azasteroids: structure-activity relationship for inhibition of 5-alpha-reductase and of androgen receptor binding" J. MED. CHEM. vol. 29, 1986, pages 2298-2315.**

3. Para responder a los requerimientos del señor Examinador de conformidad con el Artículo 46 de la Decisión 486, anexo me permito presentar a ese Despacho copia de los siguientes documentos solicitados:

LA

- BROOKS J.R. ET AL.: "5 α -reductase inhibitory and anti-androgenic activities of some 4-azasteroids in the rat" STEROIDS vol. 47, 1986, pages 1-19.
- RASMUSSEN G.H. ET AL.: "Azasteroids: structure-activity relationship for inhibition of 5-alpha-reductase and of androgen receptor binding" J. MED. CHEM. vol. 29, 1986, pages 2298-2315.

4. En vista de lo anterior, ruego a usted tomar atenta nota y proceder de conformidad.

Señor Superintendente,



ALICIA LLOREDA RICAURTE

T.P. 53.215

191
188

5 α -REDUCTASE INHIBITORY AND ANTI-ANDROGENIC ACTIVITIES
OF SOME 4-AZASTEROIDS IN THE RAT

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ABSTRACT

Inhibition of 5 α -reductase and anti-androgenicity were studied in rats treated with various 4-azasteroids. The known inhibitor, N,N-diethyl-4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carboxamide (4-MA) served as a reference compound, and analogs of this basic molecule were assayed. Enhancement of enzyme inhibitory potency was usually seen with Δ^1 analogs, whereas reduction in activity was noted with substituents such as Δ^5 , a spirotetrahydrofuran ring at C-17 or 4-deaza groups.

Many of the 4-azasteroids had a much greater oral anti-androgenic effect against testosterone propionate (TP) than dihydrotestosterone propionate (DHTP). This difference in activity versus the two androgens is believed to reflect the necessity for TP to undergo reduction to DHT before becoming capable of stimulating prostatic growth. Inhibition of 5 α -reductase by active compounds prevented the conversion, thereby producing an anti-androgenic effect. In this regard, certain Δ^1 analogs of 4-MA, particularly those bearing a 17 β -(N-tert butylcarbamoyl) group, proved very effective against TP but were relatively inactive versus DHTP.

INTRODUCTION

The enzyme Δ^4 -3-ketosteroid 5 α -reductase has been found in the male sex accessory glands of several species (1). Among other actions, it catalyzes the conversion of testosterone (T) to 5 α -dihydrotestosterone (DHT) in the rat (2,3), dog (4), and human (5). Dihydrotestosterone has been proposed as being the active metabolite primarily responsible for prostate growth (2), a view which is supported by reports of increased levels of DHT in the hyperplastic prostates of men (6) and dogs (7). Also, a hereditary lack of 5 α -reductase is associated with very small prostate size in adult men (8). Increased local concentrations of DHT have been noted in acne vulgaris (9,10), and higher *in vitro* conversion rates of labeled T to 5 α -reduced metabolites were obtained with skin from hirsute, as compared to normal, women (11,12).

182

2 Brooks *et al*

Inhibition of 5 α -reductase should lead to a reversal or amelioration of the disease states cited above. A search for a chemical inhibitor of 5 α -reductase lacking the potential side effects of such known inhibitors as progesterone (13) or deoxycorticosterone acetate (14) led to the discovery of 4-MA, 17 β -N,N-diethyl-4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carboxamide (15). The chemistry and kinetics of 4-MA and certain related compounds have been described in a series of papers from these laboratories (16-20). The present report details results obtained with various 4-azasteroids in *in vivo* assays for 5 α -reductase inhibitory and anti-androgenic activities. Certain structure-activity relationships are noted and discussed.

EXPERIMENTAL

Determination of 5 α -reductase inhibition

The procedures used to determine the *in vivo* inhibition of 5 α -reductase in rat prostate were described previously (15). In brief, intact male rats weighing approximately 200-220 g were placed in groups of 3-4 animals each. In the earlier assays, the rats were treated by subcutaneous injection at 0 and 20 h and sacrificed at 24 h. However, in the majority of the tests, they were treated only once, 4 h prior to their sacrifice by decapitation. The ventral prostate was removed and homogenized in buffer. In the earlier tests, the prostates were pooled by group before being homogenized, but in later assays they were homogenized individually. Ethyl acetate was used to extract steroids from the homogenates, and the extracts were fractionated on a Sephadex LH20 column to separate T and DHT. The respective fractions were subjected to radioimmunoassay (21) to determine their concentrations of T and DHT. Here again, a more detailed account of the RIA procedures used in our laboratory has been reported (15).

Anti-androgen assay (castrate rats)

Immature male Crl:CD (SD) BR rats weighing about 50 g were obtained from Charles River Labs (Wilmington, MA). They were castrated, and on the following day the 7-day experimental period was begun. Stimulated controls received a daily sc injection of 0.1-0.25 mL cottonseed oil (5% ethanol) vehicle containing either 10 μ g testosterone propionate (TP) or 20 μ g dihydrotestosterone propionate (DHTP). They were also given 0.25-0.5 mL of vehicle daily via an oral feeding needle. Treatment rats received either TP or DHTP by sc injection and, in addition, were given a daily oral dose of one of the test 4-azasteroids. The animals were sacrificed on the eighth day, and the ventral prostate was removed and weighed to the nearest milligram.

Anti-androgen assay (intact rats)

Intact male rats (Charles River) weighing about 200 g were used. They were dosed daily for 14 days using an oral feeding needle. Vehicle controls received 1 mL cottonseed oil (5% ETOH) daily per 250 g body weight, while

186

ANTI-ANDROGENIC ACTIVITY OF 4-AZASTEROIDS

3

treated rats received a 4-azasteroid at the dosage level of 50 mg/kg/day. On the day after the last dose, the rats were sacrificed, and the ventral prostate and seminal vesicles were removed and weighed to the nearest milligram.

Table 1. Names of the compounds assayed for 5 α -reductase inhibitory and/or anti-androgenic activity.

Compound	Name
1	N,N-diethyl-4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carboxamide
2	N,N-diethyl-3-oxo-4-aza-5 α -androstane-17 β -carboxamide
3	N,N-diethyl-4-methyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide
4	N,N-diethyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide
5	N,N-diethyl-4-methyl-1 α ,2 α -methylene-3-oxo-4-aza-5 α -androstane-17 β -carboxamide
6	N,N-diethyl-2 β -fluoro-4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carboxamide
7	N,N-diethyl-4-methyl-3-oxo-4-aza-D-homo-5 α -androstane-17 β -carboxamide
8	N,N-diethyl-4-methyl-3-oxo-4-aza-5 α -pregn-17(20)-(E)-en-21-amide
9	N,N-diethyl-4-methyl-3-oxo-4-aza-5 α -pregn-20(E)-ene-21-carboxamide
10	N,N-bis(1-methylethyl)-4-methyl-3-oxo-4-azaandrost-5-ene-17 β -carboxamide
11	N,N-bis(1-methylethyl)-4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carboxamide
12	N,N-bis(1-methylethyl)-3-oxo-4-aza-5 α -androstane-17 β -carboxamide
13	N,N-bis(1-methylethyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide
14	N,N-diethyl-4-methyl-3-oxo-4-aza-5 α -pregnane-20(S)-carboxamide
15	N,N-diethyl-4-methyl-3-oxo-4-aza-5 α -cholan-24-amide
16	N-octyl-4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carboxamide
17	22(RS)-methyl-4-aza-21-nor-5 α -cholan-3,20-dione
18	22(RS)-methyl-4-aza-21-nor-5 α -chol-1-ene-3,20-dione
19	4,22(RS)-dimethyl-4-aza-21-nor-5 α -cholan-3,20-dione
20	4,22(RS)-dimethyl-4-aza-21-nor-5 α -chol-1-ene-3,20-dione
21	17 β -(2-hydroxy-1(S)-methylethyl)-4-methyl-4-aza-5 α -androstan-3-one
22	17 β -hydroxy-4-methyl-4-aza-5 α -androst-1-en-3-one
23	17 β -hydroxy-4-methyl-4-azaandrost-1,5-dien-3-one
24	17 β -hydroxy-4-aza-5 α -androst-1-en-3-one
25	sodium 4-methyl-3-oxo-4-aza-5 α -pregnane-20(S)-carboxylate
26	sodium 3-oxo-4-aza-5 α -pregnane-20(S)-carboxylate
27	sodium 4-methyl-3-oxo-4-aza-5 α -pregn-1-ene-20(S)-carboxylate
28	sodium 3-oxo-4-aza-5 α -pregn-1-ene-20(S)-carboxylate
29	3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide
30	4-methyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide
31	N-ethyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide
32	N-ethyl-4-methyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide
33	N-(1,1-dimethylethyl)-4-methyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide
34	N-(1,1-dimethylethyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide
35	17 β -(1H-pyrrol-2-ylcarbonyl)-4-aza-5 α -androstan-3-one
36	4-methyl-17 β -(1H-pyrrol-2-ylcarbonyl)-4-aza-5 α -androst-1-en-3-one
37	17 β -(1H-pyrrol-2-ylcarbonyl)-4-aza-5 α -androst-1-en-3-one

183

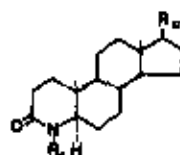
4 Brooks et al

38	2',3'-tetrahydrofuran-2'-spiro-17-(4-methyl-4-aza-5 α -androstan-3-one)
39	methyl 3-oxo-4-aza-5 α -androstan-17 β -carboxylate
40	potassium 3-oxo-4-aza-5 α -androstan-17 β -carboxylate
41	N,N-diethyl-4-methyl-3-oxo-4-azaandrostan-5-ene-17 β -carboxamide
42	17 β -hydroxy-4-methyl-4-aza-5 α -androstan-3-one
43	4-methyl-4-aza-5 α -pregnane-3,20-dione
44	4-aza-5 α -pregnane-3,20-dione
45	17 β -hydroxy-4-methyl-4-aza-1 β -nor-5 α -androstan-3-one
46	17 β -hydroxy-4-methyl-4-azaandrostan-5-en-3-one
47	4-methyl-4-azapregn-5-ene-3,20-dione
48	2',3'-tetrahydrofuran-2'-spiro-17-(4-methyl-4-aza-5-androsten-3-one)
49	2',3'-tetrahydrofuran-2'-spiro-17-(4-aza-5 α -androstan-3-one)
50	sodium 4-methyl-3-oxo-4-aza-5 α -pregn-17(20E)-ene-21-oate
51	N,N-diethyl-4-methyl-3-oxo-4-aza-5 α -pregnan-21-amide
52	2',3'-tetrahydrofuran-2'-spiro-17-(4,7 β -dimethyl-4-aza-5 α -androstan-3-one)
53	4-methyl-3-oxo-4-azapregn-5-ene-20(8)-carboxylic acid
54	sodium 4-methyl-3-oxo-4-aza-5 α -cholan-24-oate
55	sodium 4-methyl-3-oxo-4-aza-5 α -androstan-17 β -carboxylate
56	17 β -(diethylamino carbonyl)-3-methoxy-4-methyl-4-azonia-5 α -androstan-3-ene-methylsulfate hemihydrate
57	N,N-diethyl-4-ethyl-3-oxo-4-aza-5 α -androstan-17 β -carboxamide
58	N,N-diethyl-4-acetyl-3-oxo-4-aza-5 α -androstan-17 β -carboxamide
59	4-oxo-4a-aza-A-homo-5 α -androstan-17 β -yl-acetate
60	methyl 4-cyano-3-oxo-4-androsten-17 β -carboxylate
61	N,N-diethyl-4-cyano-3-oxo-4-androsten-17 β -carboxamide

RESULTS AND DISCUSSION

The chemical structures of the sixty-one compounds used in these studies are shown in Tables 2 and 3. The primary variations between these azasteroids include whether the C₁-C₂ position is saturated, whether there is a methyl or a proton attached to the nitrogen atom in the A-ring, and the nature of the C₁₇ side chain. There are also several Δ^5 compounds, two 4-deaza steroids, and a few which possess other groups. Fifty-seven of the compounds were tested to determine the effect of their acute administration on prostatic T and DHT concentrations in intact, young adult male rats. Results obtained in those tests are also shown in Tables 2 and 3.

Table 2. The structural characteristics of various 4-azasteroids together with their subcutaneous 5 α -reductase inhibitory potencies; 5 α -reductase inhibition is indicated by treatment-induced changes in the concentrations of testosterone (T) and dihydrotestosterone (DHT) in the ventral prostates of intact, young adult male rats.



(a) Results of assays in which the prostates were pooled by group for androgen determination. Groups of 3-8 rats were treated at 0 and 20 h and sacrificed at 24 h.

Compound	Substituents			Total dose (mg)	Prostatic androgen concentrations as % of control	
	R ₄	R ₁₇	Other		T	DHT
1	-CH ₃	β -CON(C ₂ H ₅) ₂		20	600*	25*
2	-H	β -CON(C ₂ H ₅) ₂		20	560	31
39	-H	β -CO ₂ CH ₃		20	281	94
40	-H	β -CO ₂ K		20	145	113
41	-CH ₃	β -CON(C ₂ H ₅) ₂	Δ^5	20	548	82
59	-H	β -OCOCH ₃	A-homo	20	225	119
60	-C $\equiv$ N	β -CO ₂ CH ₃	4-desaza- Δ^4	20	270	120
61	-C $\equiv$ N	β -CON(C ₂ H ₅) ₂	4-desaza- Δ^4	20	173	72

(b) Results from tests in which androgen determinations were made using prostates pooled by group from groups of 3 rats treated 4 h prior to sacrifice.

1	-CH ₃	β -CON(C ₂ H ₅) ₂		1	332**	47**
42	-CH ₃	β -OH		1	105	51
43	-CH ₃	β -COCH ₃		1	502	60
44	-H	β -COCH ₃		10	225	46
45	-CH ₃	β -OH	19-nor	10	240	53
46	-CH ₃	β -OH	Δ^5	10	992	150
47	-CH ₃	β -COCH ₃	Δ^5	10	138	97
48	-CH ₃	α -CH ₂ CH ₂ CH ₂ O- β	Δ^5	10	122	62
49	-H	α -CH ₂ CH ₂ CH ₂ O- β		10	191	77

* Average of 6 assays.

** Average of 4 assays.

The androgen concentration data shown in Table 2(a) and 2(b) were compiled using prostates which had been pooled by experimental group before being homogenized and extracted. Statistical analysis of these results was not possible since pooling of the prostates meant that there was only one replicate for each group. Therefore, the androgen concentrations are shown merely as a percentage of the vehicle-treated control values.

The results presented in Table 2(a) were obtained with rats which had been treated at 0 and 20 h and sacrificed at 24 h. Two of the eight compounds tested in this manner reduced DHT concentration very effectively and increased that of T. These were compounds 1 (4-MA) and 2. They differed only in that 1 possessed a 4-NCH₃ group, whereas 2 had a 4-NH. Compound 41, which was identical to 1 except for being unsaturated at C₅, showed little ability to reduce the DHT concentration. This suggested that the Δ^5 modification reduced 5 α -reductase inhibiting potency.

4-Cyano Δ^4 -steroids 80 and 81 were inactive although the D-ring of 81 was the same as in the active compounds 1 and 2. That indicated a particular A-ring configuration was necessary for activity. However, 39 and 40 have A-rings identical to that of 2, and they were not active, so it appeared that both the A and D rings have to have essential determinants for inhibitory potency. Compound 59, with an A-homo ring, also failed to reduce the DHT concentration. These initial results indicated that maximal activity was seen with compounds having a 4-aza-5 α -androstan-3-one configuration of the A-ring and a 17 β -N,N-diethylcarbamoyl group on the D-ring.

The second group of 4-azasteroids tested yielded the results shown in

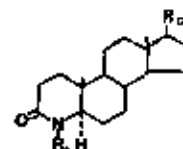
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Table 2(b). Each compound was given as a single injection 4 h before sacrifice. Androgen determinations were again done on prostates pooled by group before being processed. Compound 1 was highly active even at a much lower dose than that previously used. Compounds 42, a DHT analog, and 43, which is chemically related to progesterone, showed good activity. A reduction in activity, again, was noted with the presence of the Δ^5 group. This was well illustrated by comparison of the high activity of 42 and 43 with the low potency of their Δ^5 counterparts 46 and 47, respectively. Compounds 48 and 49, bearing 20-spiro substituents, were essentially inactive.

The compounds listed in Table 3 were assayed using animals which were treated 4 h prior to sacrifice. Prostatic concentrations of T and DHT were determined for each individual rat, and this allowed differences between control and treatment groups to be analyzed for statistical significance by means of Student's t-test.

The values shown for 1 indicate it is a relatively good inhibitor of 5 α -reductase. Good inhibition was also obtained with 8, 9, 15, 16, 19, 50, and 53, all of which had an A-ring identical to that of 1. They did exhibit a number of variations of the D-ring side chain, and this further emphasized the fact that modifications in this region do not necessarily lead to a loss in activity. Similarly, some alterations of the A-ring are also possible. For instance, several Δ^1 compounds (3, 4, 13, 18, 20, 22, 23, 27, 28, 29, 31, 32, 33, 34, 36, and 37) showed very good inhibitory potency as did 6, 7, 56, and 57 which had various other modifications. The difference in activity between 57 and 58 is interesting since they are similar except that 57 is a 4-ethyl, while 58 is a 4-acetyl compound.

Table 3. Structural characteristics and acute subcutaneous 5 α -reductase inhibitory potencies of 4-azasteroids. Inhibitory activity is indicated by treatment-induced changes in the concentrations of testosterone (T) and dihydrotestosterone (DHT) in the ventral prostate of intact, young adult male rats.



Compound	Substituents			Dose mg	N	Androgen concentration ng/100 mg tissue $\pm$ SEM			
	R ₄	R ₁₇	Other			T	P	DHT	P
Control				-	6	0.23 $\pm$ 0.03		1.37 $\pm$ 0.16	
<u>1</u>	-CH ₃	β -CON(C ₂ H ₅) ₂		1	6	0.80 $\pm$ 0.08	***	1.06 $\pm$ 0.07	
Control				-	3	0.26 $\pm$ 0.03		1.51 $\pm$ 0.09	
<u>3</u>	-CH ₃	β -CON(C ₂ H ₅) ₂	Δ^1	3	3	0.73 $\pm$ 0.17	*	0.96 $\pm$ 0.16	*
<u>55</u>	-CH ₃	β -CO ₂ Na		3	3	0.49 $\pm$ 0.08		0.79 $\pm$ 0.13	*
	-CH ₃	β -CON(C ₂ H ₅) ₂		3	3	0.29 $\pm$ 0.04		1.10 $\pm$ 0.16	
Control				-	4	0.11 $\pm$ 0.01		1.50 $\pm$ 0.11	
<u>4</u>	-H	β -CON(C ₂ H ₅) ₂	Δ^1	1	3	1.00 $\pm$ 0.18	**	0.43 $\pm$ 0.03	***
<u>29</u>	-H	β -CONH ₂	Δ^1	0.5	3	0.37 $\pm$ 0.10	*	1.14 $\pm$ 0.07	
<u>31</u>	-H	β -CONHC ₂ H ₅	Δ^1	0.5	3	0.74 $\pm$ 0.13	**	0.64 $\pm$ 0.09	***
Control				-	4	0.24 $\pm$ 0.06		2.36 $\pm$ 0.33	
<u>6</u>	-CH ₃	β -CON(C ₂ H ₅) ₂	2 β -flugro	3	4	0.58 $\pm$ 0.06	**	1.04 $\pm$ 0.20	*
<u>23</u>	-CH ₃	β -OH	Δ^1 Δ^5	3	4	1.32 $\pm$ 0.13	***	0.68 $\pm$ 0.11	**
Control				-	3	0.22 $\pm$ 0.01		1.99 $\pm$ 0.42	
<u>7</u>	-CH ₃	β -CON(C ₂ H ₅) ₂	D-homo	6	3	1.02 $\pm$ 0.06	***	0.63 $\pm$ 0.17	*
<u>57</u>	-C ₂ H ₅	β -CON(C ₂ H ₅) ₂		10	4	1.10 $\pm$ 0.23	*	0.36 $\pm$ 0.03	**

(continued)

Table 3 (Continued)

Control 8 50	-CH ₃ -CH ₃	=CHCON(C ₂ H ₅) ₂ =CHCO ₂ Na ₂ S ₂	-	3 3 3	0.34 ± 0.04 0.85 ± 0.12 0.62 ± 0.15	**	2.59 ± 1.37 1.18 ± 0.09 1.09 ± 0.14
Control 9	-CH ₃	β-CH=CHCON(C ₂ H ₅) ₂	-	3 5	0.54 ± 0.07 0.79 ± 0.03	*	4.05 ± 0.99 0.31 ± 0.06
Control 13	-H	β-CQN(I-C ₃ H ₇) ₂	Δ ¹	3 4	0.41 ± 0.05 0.41 ± 0.06		1.05 ± 0.13 0.29 ± 0.13
Control 14 25	-CH ₃ -CH ₃	β-CH(CH ₃)CON(C ₂ H ₅) ₂ β-CH(CH ₃)CO ₂ Na ₂ S ₂	-	3 1 1	0.26 ± 0.06 0.44 ± 0.05 0.63 ± 0.15		1.26 ± 0.18 1.01 ± 0.18 0.90 ± 0.10
Control 15 54	-CH ₃ -CH ₃	β-CH(CH ₃)CH ₂ CH ₂ CON(C ₂ H ₅) ₂ β-CH(CH ₃)CH ₂ CH ₂ CO ₂ Na ₂ S ₂	-	3 3 3	0.28 ± 0.05 0.88 ± 0.02 0.55 ± 0.02	**	2.52 ± 0.31 1.53 ± 0.23 1.79 ± 0.24
Control 16	-CH ₃	β-CONH(CH ₂) ₇ CH ₃	-	3 3	0.37 ± 0.12 0.77 ± 0.10		2.36 ± 0.18 1.41 ± 0.03
Control 17 58	-H -COCH ₃	β-COCH(CH ₃)C ₂ H ₅ β-CON(C ₂ H ₅) ₂	-	3 5 5	0.08 ± 0.01 0.88 ± 0.07 0.07 ± 0.03	**	2.31 ± 0.21 1.03 ± 0.25 3.33 ± 1.10
Control 18	-H	β-COCH(CH ₃)C ₂ H ₅	Δ ¹	5 0.33	0.14 ± 0.02 0.36 ± 0.11		1.87 ± 0.12 1.04 ± 0.08
Control 19	-CH ₃	β-COCH(CH ₃)C ₂ H ₅	-	4 10	0.21 ± 0.02 0.71 ± 0.03	***	2.01 ± 0.26 0.28 ± 0.07

(continued)

Table 3 (Continued)

Control									
<u>20</u>	-CH ₃	β -COCH(CH ₃)C ₂ H ₅	Δ^1	-	4	0.10 $\pm$ 0.03		1.77 $\pm$ 0.22	
<u>35</u>	-H	β -CO (2 pyrrol)	Δ^1	5	3	0.50 $\pm$ 0.08	**	0.96 $\pm$ 0.19	*
<u>36</u>	-CH ₃	β -CO (2 pyrrol)	Δ^1	3	3	0.46 $\pm$ 0.16	*	0.47 $\pm$ 0.10	**
<u>37</u>	-H	β -CO (2 pyrrol)	Δ^1	5	3	0.20 $\pm$ 0.03		1.14 $\pm$ 0.18	
				5	3	0.54 $\pm$ 0.10	*	0.54 $\pm$ 0.06	**
Control									
<u>21</u>	-CH ₃	β -CH(CH ₃)CH ₂ OH		-	3	0.27 $\pm$ 0.03		2.08 $\pm$ 0.14	
<u>51</u>	-CH ₃	β -CH ₂ CON(C ₂ H ₅) ₂		1	3	0.82 $\pm$ 0.03	***	1.98 $\pm$ 0.28	
				1	3	0.88 $\pm$ 0.17	*	1.77 $\pm$ 0.17	
Control									
<u>22</u>	-CH ₃	β -OH	Δ^1	-	4	0.24 $\pm$ 0.07		0.75 $\pm$ 0.15	
				9	4	0.24 $\pm$ 0.03		0.19 $\pm$ 0.02	*
Control									
<u>24</u>	-H	β -OH	Δ^1	-	4	0.17 $\pm$ 0.07		2.22 $\pm$ 0.25	
				3	4	0.76 $\pm$ 0.11	**	1.59 $\pm$ 0.31	
Control									
<u>26</u>	-H	β -CH(CH ₃)CO ₂ Na	Δ^5	-	4	0.11 $\pm$ 0.01		0.86 $\pm$ 0.26	
<u>27</u>	-CH ₃	β -CH(CH ₃)CO ₂ Na	Δ^1	5	3	1.00 $\pm$ 0.13	***	0.15 $\pm$ 0.05	
<u>28</u>	-H	β -CH(CH ₃)CO ₂ Na	Δ^1	5	3	0.40 $\pm$ 0.03	***	0.19 $\pm$ 0.03	
				5	3	0.40 $\pm$ 0.11	*	0.13 $\pm$ 0.01	
Control									
<u>30</u>	-CH ₃	β -CONH ₂	Δ^1	-	4	0.17 $\pm$ 0.06		1.97 $\pm$ 0.37	
<u>32</u>	-CH ₃	β -CONHC ₂ H ₅	Δ^1	5	3	0.17 $\pm$ 0.05		2.14 $\pm$ 0.52	
				5	3	0.31 $\pm$ 0.11		0.34 $\pm$ 0.02	**
Control									
<u>33</u>	-CH ₃	β -CONHC(CH ₃) ₃	Δ^1	-	4	0.13 $\pm$ 0.03		2.20 $\pm$ 0.22	
				0.03	3	0.54 $\pm$ 0.12	*	2.13 $\pm$ 0.30	
				0.10	3	0.61 $\pm$ 0.05	***	1.15 $\pm$ 0.24	*
				0.30	3	0.69 $\pm$ 0.08	***	0.70 $\pm$ 0.15	**
<u>34</u>	-H	β -CONHC(CH ₃) ₃	Δ^1	0.03	3	0.68 $\pm$ 0.13	**	0.61 $\pm$ 0.02	**
				0.10	3	1.23 $\pm$ 0.11	***	0.47 $\pm$ 0.07	**

(continued)

Table 3 (Continued)

Control						
<u>38</u>	-CH ₃	α-CH ₂ CH ₂ CH ₂ CH ₂ O-β	-	3	0.42 ± 0.06	1.72 ± 0.29
<u>52</u>	-CH ₃	α-CH ₂ CH ₂ CH ₂ CH ₂ O-β	10	3	0.47 ± 0.03	1.42 ± 0.31
			7β-CH ₃	3	1.22 ± 0.25 *	1.51 ± 0.17
Control						
<u>59</u>	-CH ₃	β-CHCH ₃ CO ₂ Na	-	3	0.27 ± 0.02	2.02 ± 0.28 *
			Δ ⁵	2	0.74 ± 0.12 **	0.78 ± 0.15 *
Control ^b						
<u>56</u>	-CH ₃	β-CON(C ₂ H ₅) ₂	-	3	0.42 ± 0.06	1.28 ± 0.16 *
			Δ ³ , 3-OCH ₃	3	0.64 ± 0.07	0.64 ± 0.08 *

* P < 0.05.

** P < 0.01.

***p < 0.001.

^a Control rats received 1 mL of cottonseed oil (10% ETOH) by subcutaneous injection 4 h before sacrifice.^b Compound 56 is a methosulfate salt.

189

191

150

Anti-androgen assays utilizing castrate, androgen-treated immature male rats were conducted with thirty-eight compounds. The t-test for statistical significance was used to compare data from TP- or DHTP-stimulated controls against those from treatment groups. The results are shown in Table 4.

Table 4. Effect of oral administration of 4-azasteroids on testosterone propionate (TP) or dihydrotestosterone propionate (DHTP) induced growth of the ventral prostate (VP) of immature castrate male rats.

Compound	Daily dose (mg)	VP weights (mg $\pm$ SEM)			
		N	TP	N	DHTP
TP	0.01	7	39 $\pm$ 4	-	-
DHTP	0.02	-	-	7	31 $\pm$ 1
<u>1</u>	0.2	7	32 $\pm$ 3	7	32 $\pm$ 2
	0.6	7	29 $\pm$ 2*	7	37 $\pm$ 2*
	1.8	7	27 $\pm$ 2*	7	33 $\pm$ 3
	5.4	7	19 $\pm$ 2**	7	26 $\pm$ 2
<u>2</u>	0.2	7	32 $\pm$ 3	7	38 $\pm$ 3
	0.6	7	29 $\pm$ 2*	7	36 $\pm$ 2*
	1.8	7	30 $\pm$ 1*	7	38 $\pm$ 2*
	5.4	7	23 $\pm$ 2**	7	34 $\pm$ 2
TP	0.01	10	40 $\pm$ 3	-	-
DHTP	0.02	-	-	9	43 $\pm$ 2
<u>3</u>	0.1	6	35 $\pm$ 4	6	45 $\pm$ 2
	0.5	6	30 $\pm$ 3*	6	42 $\pm$ 3
	2.5	6	17 $\pm$ 2***	6	40 $\pm$ 3
<u>4</u>	0.1	6	31 $\pm$ 3	6	47 $\pm$ 1
	0.5	6	30 $\pm$ 3*	6	50 $\pm$ 3*
	2.5	6	22 $\pm$ 3**	6	45 $\pm$ 4
<u>29</u>	0.1	6	28 $\pm$ 3**	6	53 $\pm$ 2**
	0.5	5	25 $\pm$ 3*	6	43 $\pm$ 3
	2.5	6	18 $\pm$ 2***	6	39 $\pm$ 2
<u>30</u>	0.1	6	42 $\pm$ 3	6	45 $\pm$ 3
	0.5	6	30 $\pm$ 3*	6	43 $\pm$ 3
	2.5	6	24 $\pm$ 4**	5	34 $\pm$ 2**
<u>31</u>	0.1	6	24 $\pm$ 1**	6	47 $\pm$ 3
	0.5	6	27 $\pm$ 2**	6	42 $\pm$ 4
	2.5	6	21 $\pm$ 3***	6	45 $\pm$ 3
<u>32</u>	0.1	6	26 $\pm$ 4*	6	47 $\pm$ 2
	0.5	6	28 $\pm$ 3*	6	44 $\pm$ 2
	2.5	6	22 $\pm$ 1***	6	40 $\pm$ 5

(continued)

193

ANTI-ANDROGENIC ACTIVITY OF 4-AZASTEROIDS

13

Table 4 (Continued)

TP	0.01	8	34 ± 4	-	-
DHTP	0.02	-	-	8	38 ± 3
<u>5</u>	0.5	6	38 ± 7	8	40 ± 2
	1.5	6	28 ± 2	8	34 ± 3
	4.5	6	33 ± 3	6	31 ± 2
<u>9</u>	0.5	6	28 ± 3	8	39 ± 3
	1.5	6	20 ± 3*	8	32 ± 4
	4.5	6	19 ± 2**	6	21 ± 3**
TP	0.01	8	55 ± 4	-	-
DHTP	0.02	-	-	6	51 ± 5
<u>6</u>	0.5	6	42 ± 5	8	47 ± 4
	1.5	6	48 ± 6	6	33 ± 4*
	4.5	6	33 ± 5**	6	39 ± 4
<u>17</u>	0.5	6	45 ± 3	6	40 ± 3
	1.5	6	39 ± 2**	8	42 ± 4
	4.5	6	35 ± 2**	6	38 ± 5
TP	0.01	8	26 ± 3	-	-
DHTP	0.02	-	-	6	24 ± 2
<u>7</u>	0.5	8	24 ± 2	8	23 ± 3
	1.5	6	18 ± 3	8	28 ± 3
	4.5	6	15 ± 2*	8	22 ± 4
<u>19</u>	0.5	8	18 ± 3	6	24 ± 3
	1.5	6	19 ± 3	6	28 ± 3
	4.5	6	14 ± 1**	6	18 ± 1*
TP	0.01	8	41 ± 3	-	-
DHTP	0.02	-	-	8	40 ± 2
<u>8</u>	0.2	8	38 ± 2	8	38 ± 3
	0.6	8	33 ± 3	8	29 ± 2**
	1.8	8	33 ± 2**	8	38 ± 3
	5.4	8	22 ± 3***	8	31 ± 3

(continued)

192

Table 4 (Continued)

TP	0.01	6	43 ± 2	-	-
DHTP	0.02	-	-	6	48 ± 2
<u>10</u>	0.5	6	42 ± 3	6	43 ± 6
	1.5	6	34 ± 3*	6	45 ± 5
	4.5	6	24 ± 4**	6	36 ± 4*
<u>35</u>	0.5	6	46 ± 2	6	44 ± 4
	1.5	6	37 ± 3	6	41 ± 5
	4.5	6	37 ± 1*	6	46 ± 4
TP	0.01	7	39 ± 2	-	-
DHTP	0.02	-	-	7	41 ± 3
<u>11</u>	0.2	7	40 ± 2	7	37 ± 2
	0.6	7	36 ± 2	7	37 ± 2
	1.8	7	20 ± 2***	7	39 ± 3
	5.4	7	17 ± 2***	7	20 ± 2***
TP	0.01	8	38 ± 2	-	-
DHTP	0.02	-	-	8	38 ± 3
<u>12</u>	0.2	8	37 ± 4	8	36 ± 2
	0.6	8	33 ± 2	7	33 ± 3
	1.8	8	25 ± 3**	8	30 ± 2*
	5.4	8	21 ± 2***	8	37 ± 4
TP	0.01	6	41 ± 2	-	-
DHTP	0.02	-	-	6	30 ± 2
<u>13</u>	0.5	6	23 ± 4**	6	37 ± 4
	1.5	5	15 ± 1***	5	31 ± 3
	4.5	5	14 ± 3***	5	29 ± 3
TP	0.01	6	38 ± 2	-	-
DHTP	0.02	-	-	6	45 ± 3
<u>14</u>	0.1	6	43 ± 3	5	43 ± 5
	0.5	6	37 ± 3	6	44 ± 3
	2.5	6	28 ± 3**	6	45 ± 3
<u>15</u>	0.1	6	41 ± 2	6	50 ± 3
	0.5	6	41 ± 2	6	49 ± 3
	2.5	6	31 ± 2*	6	43 ± 4

(continued)

ANTI-ANDROGENIC ACTIVITY OF 4-AZASTEROIDS

15

Table 4 (Continued)

TP	0.01	6	44 ± 2	-	-
DHTP	0.02	-	-	6	49 ± 2
<u>16</u>	0.1	6	54 ± 2**	6	60 ± 1
	0.5	6	45 ± 4	6	46 ± 2
	2.5	6	40 ± 7	6	37 ± 5
TP	0.01	6	42 ± 3	-	-
DHTP	0.02	-	-	6	48 ± 3
<u>18</u>	0.5	6	26 ± 3**	6	41 ± 3
	1.5	6	23 ± 4**	6	38 ± 6
	4.5	6	23 ± 4**	6	47 ± 3
<u>22</u>	0.5	6	44 ± 4	6	51 ± 3
	1.5	6	47 ± 3	6	49 ± 2
	4.5	6	50 ± 5	6	54 ± 3
TP	0.01	6	44 ± 2	-	-
DHTP	0.02	-	-	6	40 ± 3
<u>20</u>	0.1	6	32 ± 2**	6	41 ± 3
	0.5	6	29 ± 3***	6	38 ± 2
	2.5	6	28 ± 2***	6	41 ± 4
<u>26</u>	0.1	6	35 ± 4	6	38 ± 2
	0.5	5	32 ± 2**	6	40 ± 2
	2.5	6	20 ± 2***	6	38 ± 4
<u>27</u>	0.1	6	33 ± 3***	6	42 ± 1
	0.5	5	27 ± 2***	6	43 ± 3
	2.5	6	24 ± 2***	6	44 ± 4
<u>28</u>	0.1	6	28 ± 3***	6	36 ± 3
	0.5	5	24 ± 2***	6	52 ± 2
	2.5	6	24 ± 2***	6	46 ± 4
<u>36</u>	0.1	6	34 ± 3*	6	46 ± 2
	0.5	6	35 ± 2*	6	48 ± 5
	2.5	6	26 ± 4**	6	39 ± 2
<u>37</u>	0.1	6	31 ± 3**	6	39 ± 4
	0.5	6	26 ± 2***	6	46 ± 5
	2.5	6	24 ± 3***	6	43 ± 2

(continued)

103

Table 4 (Continued)

TP	0.01	10	48 ± 3	-	-
DHTP	0.02	-	-	10	48 ± 2
<u>21</u>	0.1	7	46 ± 3	7	47 ± 2
	0.5	7	34 ± 2**	7	42 ± 3
	2.5	7	25 ± 3***	7	51 ± 3
<u>25</u>	0.1	7	38 ± 3*	7	43 ± 4
	0.5	7	35 ± 2**	7	52 ± 3
	2.5	7	26 ± 3***	7	42 ± 4
TP	0.01	6	48 ± 4	-	-
DHTP	0.02	-	-	6	49 ± 2
<u>23</u>	0.5	6	42 ± 3	6	46 ± 3
	1.5	6	41 ± 5	6	36 ± 2**
	4.5	6	33 ± 1**	6	37 ± 3**
<u>24</u>	0.5	6	35 ± 5	6	45 ± 2
	1.5	6	25 ± 3*	6	41 ± 3
	4.5	6	20 ± 3***	6	39 ± 3
TP	0.01	6	41 ± 2	-	-
DHTP	0.02	-	-	6	43 ± 3
<u>33</u>	0.1	6	34 ± 3	6	50 ± 4
	0.5	6	23 ± 3**	6	45 ± 4
	2.5	6	19 ± 2***	6	40 ± 4
<u>34</u>	0.1	6	23 ± 2***	6	43 ± 2
	0.5	6	26 ± 1***	6	40 ± 3
	2.5	6	20 ± 3***	6	46 ± 2
TP	0.01	6	49 ± 4	-	-
DHTP	0.02	-	-	6	41 ± 2
<u>38</u>	0.2	6	44 ± 2	6	49 ± 2*
	0.6	6	41 ± 2*	6	38 ± 3
	1.8	6	38 ± 4*	6	38 ± 2
	5.4	6	30 ± 1***	6	38 ± 2

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Those tests provided more quantitative results than did the acute studies. In TP-treated rats, test compound administration usually caused a severe, dose-related reduction in ventral prostate weight. In contrast, few of these steroids

197

had a major effect on the prostate weight of animals treated with DHTP. Here again, these results are believed to be due chiefly to inhibition of 5 α -reductase. The data obtained are consistent with DHT being the active androgen at the cellular level in the prostate. The 4-azasteroids, being for the most part potent 5 α -reductase inhibitors, attenuated the conversion of TP to DHT and thus limited the amount of DHT available to the prostate. Compounds which reduced prostate growth in both TP- and DHTP-treated rats probably did so by interfering with androgen receptor binding or androgen transport as well as by inhibiting 5 α -reductase. That statement is based on the assumption that the androgenic action of DHT should not be influenced by the presence of a pure 5 α -reductase inhibitor and the knowledge that certain of these 4-azasteroids compete with DHT for binding sites on the prostatic androgen receptor (22). Compounds that significantly reduced prostate growth in TP- and also DHTP-treated animals included 6, 8, 9, 10, 11, 19, 23, and 30. Those which caused a significant inhibition of TP-induced prostate growth yet which showed little tendency to impede prostate growth in DHTP-treated rats included: 1, 2, 3, 4, 7, 12, 13, 14, 15, 17, 18, 20, 21, 24, 25, 26, 27, 28, 29, 31, 32, 33, 34, 35, 36, 37, and 38. Compounds 5, 16, and 22 did not exhibit anti-androgenic activity versus either TP or DHTP.

Six of these azasteroids, 4, 18, 31, 32, 33, and 34, showed good activity in the acute assay and were also highly active against TP, but not DHTP, in the castrate rat anti-androgen assay. It is of interest that each of the six is a Δ^1 compound. Although this suggests that unsaturation at the C₁-C₂ position is associated with good specificity insofar as 5 α -reductase inhibiting properties are concerned, the evidence is not wholly conclusive. For example, 30, a Δ^1 steroid, exhibited good anti-androgenicity against TP and DHTP yet showed little or no ability to reduce prostatic DHT in the acute 5 α -reductase inhibition assay.

195

The results of the single chronic test carried out with intact young adult male rats are shown in Table 5.

Table 5. Effect of 14 days oral treatment with 4-azasteroids on sex accessory gland weights of intact, young adult (200 g) male rats.

Compound ^a	No. rats	Organ weights (mg $\pm$ SEM)	
		Ventral prostate	Seminal vesicles
Controls ^b	7	343 $\pm$ 21	448 $\pm$ 24
<u>1</u>	7	240 $\pm$ 9**	337 $\pm$ 19**
<u>2</u>	7	252 $\pm$ 21**	342 $\pm$ 27*
<u>3</u>	7	183 $\pm$ 9***	249 $\pm$ 22***
<u>8</u>	5	203 $\pm$ 29**	322 $\pm$ 16**
<u>11</u>	7	253 $\pm$ 12**	324 $\pm$ 26**
<u>12</u>	7	200 $\pm$ 15***	265 $\pm$ 7***
<u>16</u>	7	276 $\pm$ 23	410 $\pm$ 27
<u>25</u>	7	172 $\pm$ 11***	243 $\pm$ 19***

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

^a The dosage level for all compounds was 50 mg/kg/day.

^b Controls received 1 mL cottonseed oil:ETOH (95:5) vehicle per 250 g body weight per day.

Each of the eight compounds, with the exception of 16, caused a significant decrease in the weight of the ventral prostate and seminal vesicles relative to vehicle-treated controls. Body weights were not affected. The decreases in sex accessory gland weights are thought to have resulted from inhibition of 5 α -reductase, since several of the eight compounds were tested in the parabiotic rat model and they failed to suppress gonadotropin release (unpublished). Seven of the eight steroids had been shown to reduce ventral prostate weight increases in TP-treated castrate rats. Here again, only 16 failed to exert an anti-androgenic effect against TP. It would appear that the results obtained with these eight compounds in the two types of anti-androgen assay are closely parallel.

198

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Azasteroids: Structure-Activity Relationships for Inhibition of 5 α -Reductase and of Androgen Receptor Binding

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A series of steroids, primarily 4-azasteroids, were prepared and tested *in vitro* as inhibitors of human and rat prostatic 5 α -reductase and of binding of dihydrotestosterone to the rat androgen receptor. The primary structural modifications were changes of the A ring and of moieties attached at the C-17 position of the steroid nucleus. New A-ring modifications included the 4-cyano-3-oxo- Δ^4 system in the carbocyclic series and 1 α -CN, 1 α -CH₃, 1 α ,2 α -CH₃, 2 β -F, 2-aza, 2-oxa, and A-homo changes in the 3-oxo-4-aza series. In addition, 4-azasteroids with a D-homo ring or methyl substitution at C-7 (α and β) or C-18 (α and β) were prepared. The majority of the C-17 substituents were prepared from reactive intermediates derived from the 17 β -COOH. Enhanced 5 α -reductase inhibition in both the human and rat enzyme assays is seen with 4-CN substitution on 3-oxo- Δ^4 steroids and with a C-17 side chain incorporating a lipophilically substituted semipolar group on the 4-aza-3-oxo-5 α -androsterane nucleus. Fewer highly active compounds were found in the human enzyme assay than in the rat assay. Structural requirements for inhibition of the rat androgen receptor are much different from those for inhibition of the enzyme. The 17 β -OH moiety enhances potency more than any other feature while introduction of double bonds at C-1 or C-5 in the azasteroid gives a small improvement. Azasteroids unsubstituted at the 4-position show greatly diminished receptor activity.

The enzyme 5 α -reductase and the intracellular androgen receptor serve as important regulators of hormone action in androgen-sensitive cells. Although the receptor appears to be an obligate intermediate in all androgen hormonal expression, the enzyme, which converts testosterone (T) to the more potent androgen 5 α -dihydrotestosterone (DHT), is absent in certain androgen-sensitive tissues such as adult testis and muscle.^{1,2,14} Human males born with deficient androgen receptor action exhibit a female phenotype, complete with breast development, in spite of high levels of circulating T.³ Not unexpectedly then, treatment of normal males with agents that interfere with receptor action results in a feminizing effect, including gynecomastia and loss of libido.⁴⁻⁶ Males with a deficiency of 5 α -reductase are born with poorly developed external genitalia and are often raised as girls.⁷ At puberty the phallus enlarges, a male habitus develops, and male psychosexual orientation takes place, all in the relative absence of DHT. As adults, these men show little beard growth and no temporal recession of the hairline and have prostate glands that remain small throughout life. It would appear that, except for a short, critical period when fetal development of external genitalia is occurring, treatment with a 5 α -reductase inhibitor should have no deleterious effects. Indeed, an agent that could lower levels of DHT without interfering with T levels may be useful and safe in the treatment of acne, alopecia, and benign prostatic hypertrophy.

Several reports have described the inhibition of 5 α -reductase by a series of 4-azasteroids.⁸⁻¹¹ The *in vitro* activity of these compounds has been demonstrated in different tissues,^{10,12-15,17} in different species,¹⁰ and in different disease states.^{10,16}

In addition, some structural features that prevent or reduce the androgen receptor binding of this class of steroids have been explored.¹¹ From such data, selection of high-potency, selective 5 α -reductase inhibitors for *in vivo* studies could be made and the relative utility of T and DHT in animal models could be explored.

Described below is the preparation of a number of these inhibitors, as well as an extensive structure-activity study resulting from the preliminary screens to which these and related compounds were submitted.

Chemistry.¹⁸ The 4-azasteroids described in this paper were all prepared from 3-keto- Δ^4 precursors 2 by the steps of oxidative cleavage to give seco acids 3, ring closure with the appropriate amine at high temperature to give the ene lactams 4-8, and then hydrogenation over a platinum catalyst to selectively afford the 5 α -4-azasteroids 9-11 (Scheme I; see the Experimental Section, preparation of 9g, and ref 8 for applicable R and R₁). In the case of the hydrazide 7x, catalytic hydrogenation led to extensive hydrogenolysis of the nitrogen nitrogen bond. The Δ^5 double bond of this compound could be reduced with sodium cyanoborohydride in formic acid but only with concomitant formylation of the amino group to give 12x. Similar borohydride reduction of compounds of types 4

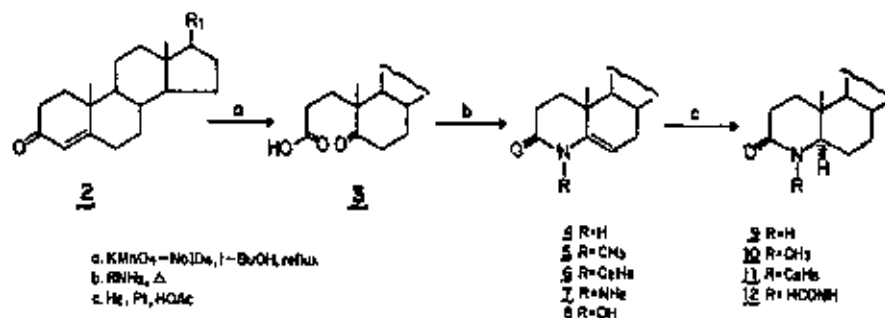
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- (18) For the method of compound numbering, see footnote c, Table I.

¹ Department of Synthetic Chemical Research.

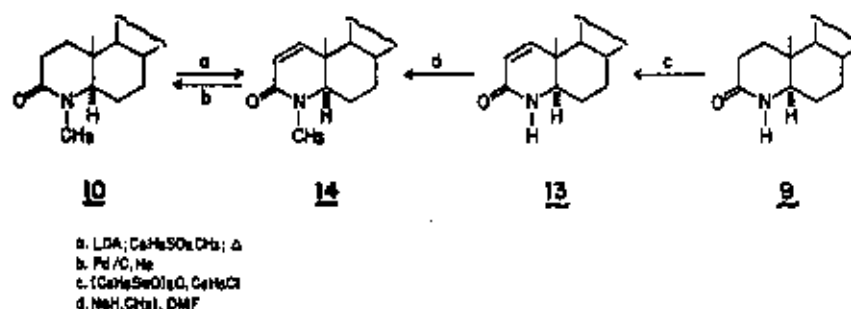
² Department of Biochemical Endocrinology.

201

Scheme I



Scheme II

Table I. In Vitro Activities of Substituted Androstan-3-ones^a

no.	substituents		ref ^b	in vitro bioactivity		
	R	other		human 5 α -R: IC ₅₀ /IC ₁₀ 10x	rat 5 α -R: IC ₅₀ 10 ⁻⁸ M	rat receptor IC ₅₀ 10 ⁻⁸ M
1a ^c	β -OH		39		>>100	0.22
2a	β -OH	Δ^4	39		180	0.82
1b	$=\text{O}$		39			2.00
2b	$=\text{O}$	Δ^4	39			6.40
87	β -OH	Δ^1	39			0.15
2g	β -COOH	Δ^4	39	61	66	890
2h	β -COOCH ₃	Δ^4	39	44	48	14
2x	β -CON(C ₂ H ₅) ₂	Δ^4	8	44	76	34
17x	β -CON(C ₂ H ₅) ₂	Δ^4 , 4-CN		0.83	2.9	130
1ax	α -CH ₂ CH ₂ CH ₂ O- β		11		>>100	2.3
2ax	α -CH ₂ CH ₂ CH ₂ O- β	Δ^4	35		110	8.9
94	α -CH ₂ CH ₂ CH ₂ O- β	Δ^4 , 19-nor	35		160	3.0
17ax	α -CH ₂ CH ₂ CH ₂ O- β	Δ^4 , 4-CN		13		
88	α -OCOCH ₃ , β -COCH ₃	Δ^4 , 6-CH ₃	40	>160	16	1.2
89	β -COCH ₃	Δ^4 , 11 α -OH	38	>>80		83

^a Unless otherwise indicated, 17 β -substituted 5 α -androstan-3-one structures are assumed. ^b The numbers in this column refer to footnotes in the paper and provide the source of previously described substances. ^c The lower-case alphabetic characters in the compound numbers refer to the type of side chain at C-17 (see Table VI) while the numeric character refers to the variously substituted ring systems to which they are attached (see schemes).

and 5 resulted in double-bond saturation but gave an undesirable mixture of 5 α - and 5 β -isomers.

Because of the enhanced in vivo activity¹⁸ of several of the Δ^1 -azasteroids, a number of these compounds were prepared (see Table IV). The preferred method for preparation of Δ^1 -azasteroids was the seleninic anhydride dehydrogenation²⁰ of the unsubstituted lactams 9 in re-

fluxing chlorobenzene (Scheme II). This reaction proceeds well (>50% yield) when the side chain at C-17 is an amide, ester, ketone, *tert*-butyldimethylsiloxane, or spirotetrahydrofuran to give the corresponding unsaturated lactams 13. This reagent was unsatisfactory to prepare Δ^1 derivatives of 4-alkyl, Δ^6 , or 17-carboxy 4-azasteroids. Methylation of compounds 13 with methyl iodide and sodium hydride in DMF provided a high-yield approach to the azasteroids 14, including those containing a secondary amide at the C-17 side chain. Alternately, the 1,2-double bond could be incorporated in the 4-methyl compounds 10 by pyrolysis of 2-phenylsulfinyl intermediates generated

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Table II. In Vitro Activities of 17-Substituted-4-azaandrostan-3-ones

202

199

no.	substituents		ref	in vitro bioactivity		
	R ₁	R ₂		human 5α-R: IC ₅₀ /IC ₅₀ 10x	rat 5α-R: IC ₅₀ 10 ⁻⁸ M	rat receptor: IC ₅₀ 10 ⁻⁸ M
9a	H	β-OH	41		25	93
10a	CH ₃	β-OH	8	>50	15	1.9
9d	H	β-COCH ₃	8		5	8800
10d	CH ₃	β-COCH ₃	8	27	2.3	21
9c	H	β-CHOHCH ₃		>500	4.5	930
10c	CH ₃	β-CHOHCH ₃	42	17	1.9	7.4
10e	CH ₃	α-OH, β-CHOHCH ₃	8	>500	0.76	190
10f	CH ₃	β-CH(CH ₃)CH ₂ OH	8	15	0.38	86
9g	H	β-CO ₂ K			2.6	>10000
10g	CH ₃	β-CO ₂ Na	8	92	3.7	910
9h	H	β-CO ₂ CH ₃		42		
10h	CH ₃	β-CO ₂ CH ₃	8	17	0.76	12
9i	H	β-CONH ₂		150		>10000
10i	CH ₃	β-CONH ₂	8		1.7	44
10j	CH ₃	β-CONHCH ₃		28	3.8	110
10k	CH ₃	β-CONHC ₂ H ₅	8	8.4	1.2	110
10l	CH ₃	β-CONHCH(CH ₃) ₂		4.0		
9m	H	β-CONHC(CH ₃) ₃		1.7	0.63	>10000
10m	CH ₃	β-CONHC(CH ₃) ₃		1.1	0.066	68
10n	CH ₃	β-CONH(CH ₂) ₂ CH ₃		2.4		25
9o	H	β-CONH(CH ₂) ₄ CH ₃		2.4	0.013	520
10o	CH ₃	β-CONH(CH ₂) ₄ CH ₃	8	4.0	0.021	13
9p	H	β-CONHC(CH ₃) ₂ CH ₂ C(CH ₃) ₃		0.56		
10p	CH ₃	β-CONHC(CH ₃) ₂ CH ₂ C(CH ₃) ₃		0.52		
10q	CH ₃	β-CONHC(CH ₃) ₂ H ₃₅ (oleyl)		25	2	1700
10r	CH ₃	β-CONHCH ₂ CH ₂ OH		>82.5	9.3	170
10s	CH ₃	β-CONHC(CH ₃) ₂ CH ₂ OH		2		94
10v	CH ₃	β-CONHCH ₂ CON(C ₂ H ₅) ₂		11		
10w	CH ₃	β-CONHCH ₂ CH(OCH ₃) ₂		20	0.46	79
9x	H	β-CON(C ₂ H ₅) ₂	8	1.2	4.1	>10000
10x	CH ₃	β-CON(C ₂ H ₅) ₂	8	1	1.1	280
9y	H	β-CON(i-C ₄ H ₉) ₂		1.5	1.1	>10000
10y	CH ₃	β-CON(i-C ₄ H ₉) ₂	8	0.82	0.85	1400
10z	CH ₃	β-CON(n-C ₄ H ₉) ₂		>125	3.3	4600
10aa	CH ₃	β-CON(C ₂ H ₅)CH ₂ CH ₂ OH		8		
10ab	CH ₃	β-CON(C ₂ H ₅) ₂ O		5.6	2.7	1000
10ac	CH ₃	β-CH ₂ CO ₂ C ₂ H ₅	8	29	0.68	6.6
10ad	CH ₃	β-CH ₂ CON(C ₂ H ₅) ₂	8	2	0.79	56
10af	CH ₃	=CHCON(C ₂ H ₅) ₂	8	1.5	0.25	93
9ah	H	β-CH(CH ₃)CO ₂ Na		9.2		>10000
10ah	CH ₃	β-CH(CH ₃)CO ₂ Na	8	8	0.17	4600
10ai	CH ₃	β-CH(CH ₃)CO ₂ CH ₃		143	2.2	98
10aj	CH ₃	β-CH(CH ₃)CON(C ₂ H ₅) ₂	8	390	1.3	4800
10ak	CH ₃	β-CH(CH ₃)(CH ₂) ₂ CO ₂ Na	8	81	0.36	2100
10al	CH ₃	β-CH(CH ₃)(CH ₂) ₂ CON(C ₂ H ₅) ₂	8	27	0.94	48
10an	CH ₃	β-CH(CH ₃)CN		>62	0.76	28
10ao	CH ₃	β-CN		88		
10ap	CH ₃	β-(2-oxazoliny)		11		
10aq	CH ₃	β-(4,4-dimethyl-2-oxazoliny)		123		
9ar	H	α-CH ₂ CH ₂ CH ₂ O-β	8	735	0.3	250
10ar	CH ₃	α-CH ₂ CH ₂ CH ₂ O-β	8	144	3.7	14
11ar	C ₂ H ₅	α-CH ₂ CH ₂ CH ₂ O-β	8		117	1300
10as	CH ₃	α-CH ₂ CH ₂ CO ₂ β		>6	4	8.9
9at	H	β-COCH ₂ CH(CH ₃) ₂		4.2		>10000
10at	CH ₃	β-COCH ₂ CH(CH ₃) ₂		2.7		
9au	H	β-COCH(CH ₃)C ₂ H ₅		4.0	0.12	>10000
10au	CH ₃	β-COCH(CH ₃)C ₂ H ₅		>1, <6	0.19	42
9av	H	β-CO(2-pyrrolyl)		3.6		1500
10av	CH ₃	β-CO(2-pyrrolyl)		2.0		8.9
9aw	H	β-CO ₂ C(CH ₃) ₃		8.6		
10aw	CH ₃	β-CO ₂ C(CH ₃) ₃		>6, <30		
10ax	CH ₃	β-COBC(CH ₃) ₃		47		
10ay	CH ₃	β-COCHN ₂	43	<6		58
10az	CH ₃	β-NHCOCH ₃	8	>230	27	140
10ba	CH ₃	α-NHCOCH ₃	8	>500	5.8	4000

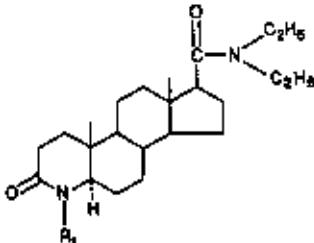
in two steps as described previously⁸ or by reaction of the enolate of 10 with methyl benzenesulfinate. The double

bond of 14at was selectively hydrogenated in the presence of a Pd/C catalyst.

Table III. In Vitro Activities of Analogues of 4-MA (10x)

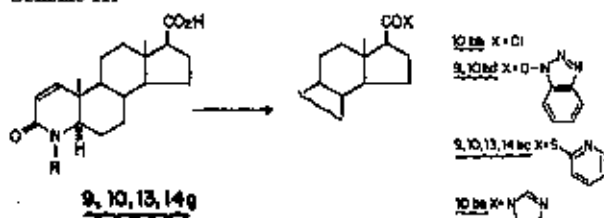
203

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no.	substituents		ref	in vitro bioactivity		
	R ₁	other		human 5α-R: IC ₅₀ /IC ₅₀ 10x	rat 5α-R: IC ₅₀ 10 ⁻⁸ M	rat receptor: IC ₅₀ 10 ⁻⁸ M
10x	CH ₃		8	1	1.1	280
9x	H		8	1.2	4.1	>10000
11x	C ₂ H ₅		8	>125		3200
82	CH ₃ CO			>150		
12x	HCONH			>8	40	>1000
79	H	5β-H		>125	>100	>1000
23	CH ₃	1α-CN		>150	>100	>1000
24	CH ₃	1α-CH ₃		7	8.8	1800
98	CH ₃	2β-CH ₃	8	3.6	2.0	810
25	CH ₃	1α,2α-CH ₃		1.3	2.0	270
91	CH ₃	1α,2α-O	8	63		71
29	CH ₃	2β-F		6.0		180
92	CH ₃	2α-OH	8		48	320
31	CH ₃	2α-OCH ₃		>30		>1000
30	CH ₃	2β-OCH ₃		15		>1000
88	CH ₃	2-(OCH ₃) ₂		28		
85	CH ₃	2=O	8		34	5000
93	CH ₃	3=NOH	8		10	54
37	H	A-homo		5.5		>1000
38	CH ₃	A-homo		>30		80
48	H	D-homo		5.4		
49	CH ₃	D-homo		1.6		710
54	CH ₃	2-aza		44	50	180
55	CH ₃	2-oxa		25	50	370

Scheme III



Many of the azasteroids with a carbonyl group attached to C-17 were prepared from the corresponding 17-carboxy precursor via an activated intermediate (Scheme III). Amides of the saturated 4-methyl acid 10g were conveniently prepared from the acid chloride 10bb. The 4-unsubstituted acid 9g reacted at the 4-position under conditions of acid chloride formation (oxalyl chloride, toluene, THF). However, the hydroxybenzotriazole ester of 9g or 10g could be prepared and isolated or used *in situ*²¹ to prepare the corresponding 17-amide derivatives without involvement of the 4-position. The 2-pyridylthio esters²² provided the most versatility as intermediates, as they could be prepared from a variety of A-ring-modified 17-carboxy azasteroids. Reaction of these pyridylthio esters with amines gave amides, with Grignard reagents at low temperature gave ketones,²³ with *tert*-butyl alcohol in the

presence of silver ion gave the corresponding ester, and with Raney nickel gave the 17-carbinol (Scheme XII). The thiol ester 10ax was prepared by treatment of a DMF solution of the acid 10g sequentially with carbonyldiimidazole and *tert*-butyl mercaptan in the presence of magnesium ethoxide.²⁴

The mixture of epoxides obtained by reaction of the α,β -unsaturated ketones 2x or 2ar with alkaline hydrogen peroxide was converted to base-soluble dicyano compounds 16x or 16ar, respectively, on treatment with sodium cyanide in alcohol. Gentle pyrolysis of each of these compounds afforded the corresponding 4-cyano- Δ^4 -steroids, 17x or 17ar (Scheme IV).

Dehydration of the primary amides 10am (Scheme V) and 10i with phosphorus oxychloride in pyridine afforded the nitriles 10an and 10ao, respectively. The hydroxy amides 10r and 10s underwent cyclodehydration on treatment with toluenesulfonyl chloride in pyridine to give the corresponding oxazines, 10ap and 10aq.

The spiro lactone 10as was conveniently prepared by reaction of the corresponding spiroether 10ar with di-sodium chromate in acetic anhydride-acetic acid (Scheme VI).

Early attempts to react the Δ^1 -azasteroid 14x with dimethylloxosulfonium methylide (DMSM) resulted in no reaction. To enhance the reactivity of the 1-position of the Δ^1 -azasteroid system to Michael-type additions, the 2,2-bis(phenylthio) derivative 18 was oxidized to the

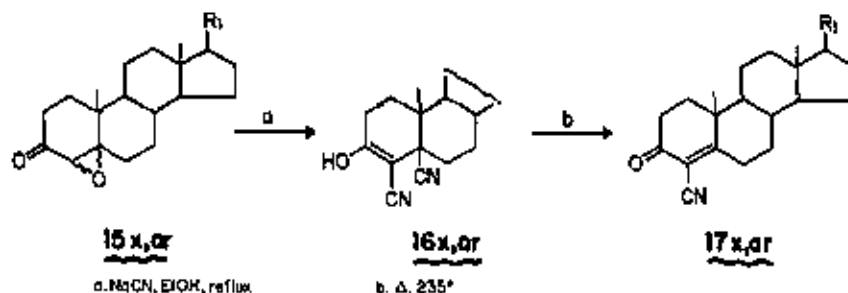
(21) Formstecher, P.; Lustenberger, P.; Dautrevaux, M. *Steroids* 1980, 35, 265.

(22) Araki, M.; Sakata, S.; Takai, H.; Mukayama, T. *Bull. Chem. Soc. Jpn.* 1974, 47, 1777.

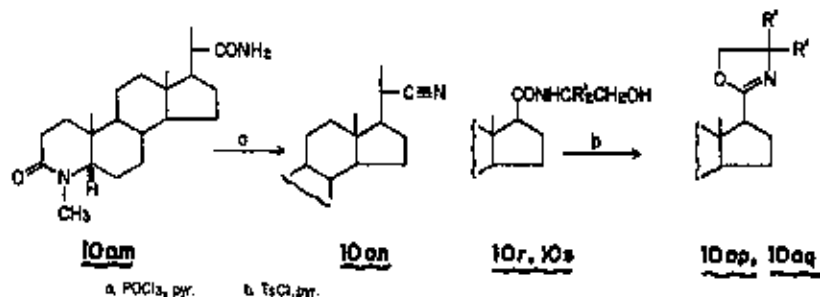
(23) Nicolaou, K. C.; Claremon, D. A.; Papahadjis, D. P. *Tetrahedron Lett.* 1981, 22, 4647.

(24) Ohta, S.; Okamoto, M. *Tetrahedron Lett.* 1981, 22, 3245.

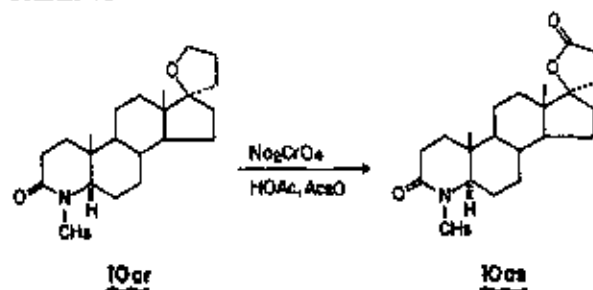
Scheme IV



Scheme V



Scheme VI

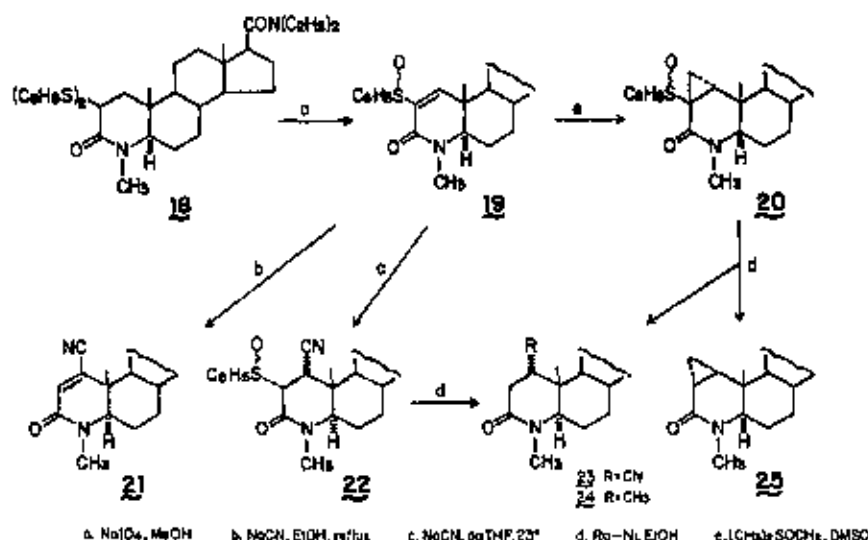


phenylsulfinyl compound 19 (Scheme VII). This material reacted smoothly in refluxing ethanolic sodium cyanide to give the 1-cyano- Δ^1 -azasteroid 21. At room temperature, a saturated cyano compound (22) was obtained from this reaction. Raney nickel desulfurization of 22 gave the 1-cyano compound 23. The sulfinyl compound 19 (a mixture

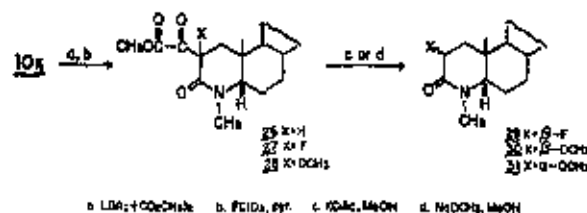
of isomers at sulfur) reacted with DMSM to give a mixture of 1 α ,2 α -methylene products (20). Desulfurization of 20 gave a single 1 α ,2 α -methylene azasteroid (25) and the 1 α -methyl compound 24.

To introduce a fluorine at the 2-position, the enolate generated from LDA and 10x reacted with methyl oxalate to give 26 (Scheme VIII). Reaction of 26 with perchloryl fluoride in pyridine afforded the corresponding 2-fluoro steroid 27. Removal of the oxalyl side chain of 27 with potassium acetate in methanol was slow and incomplete. In addition to the desired fluoro compound 29, there were obtained starting material and the major product, the methoxy compound 28. This latter compound on treatment with sodium methoxide in methanol gave a mixture of 2 α - and 2 β -methoxy analogues, 31 and 30, which were separated and identified by the NMR shifts of the angular 19-CH₃ (0.83 ppm for 31, 0.88 ppm for 30). The β -orientation was assigned to the 2-fluorine of 29 on the basis of the NMR shift of the 19-CH₃, which appeared as

Scheme VII



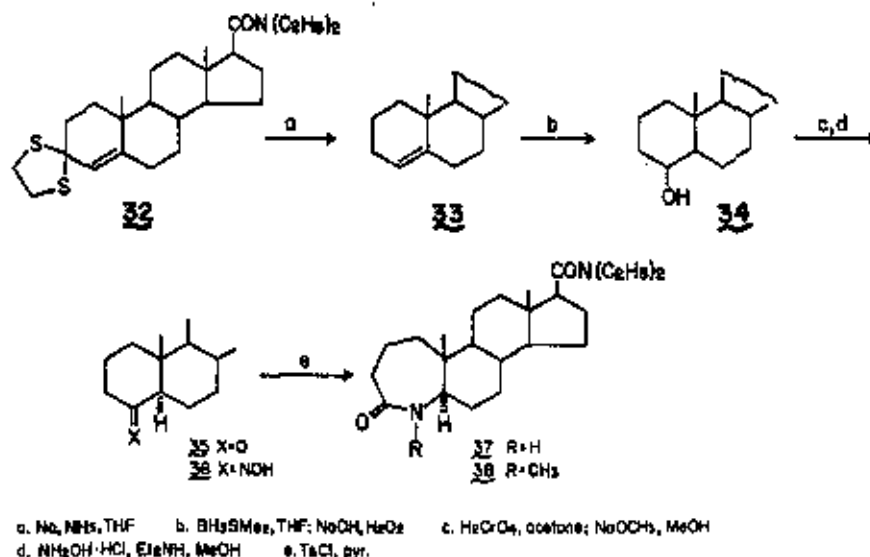
Scheme VIII



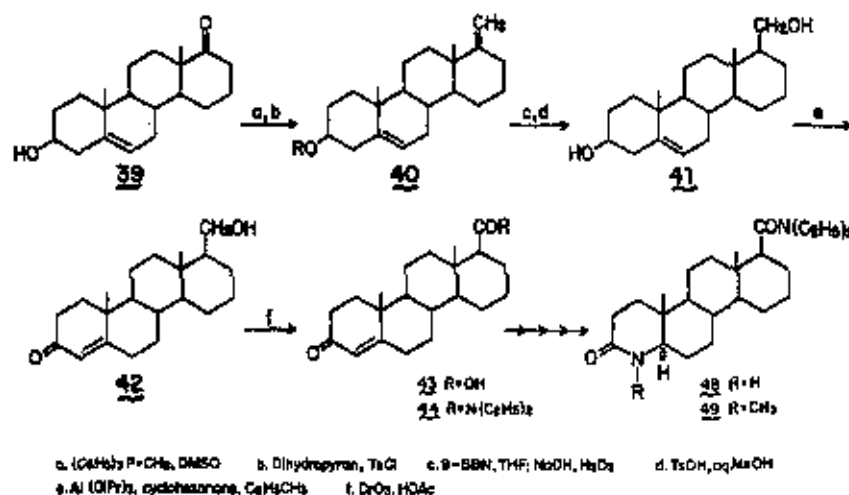
a doublet ($J = 1 \text{ Hz}$) at 0.94 ppm.

The A-homo azasteroids **37** and **38** were prepared by the route shown in Scheme IX. Because of the carbamoyl side chain, the hydroboration step was carried out with the chemically more selective reagent borane-methyl sulfide complex. Although the amide was unreactive with this reagent, the α - to β -selectivity in the hydration of the Δ^4 -bond was low, and it was necessary to equilibrate the ketone mixture obtained in the oxidation of **34** to optimize

Scheme IX



Scheme X



Scheme XI

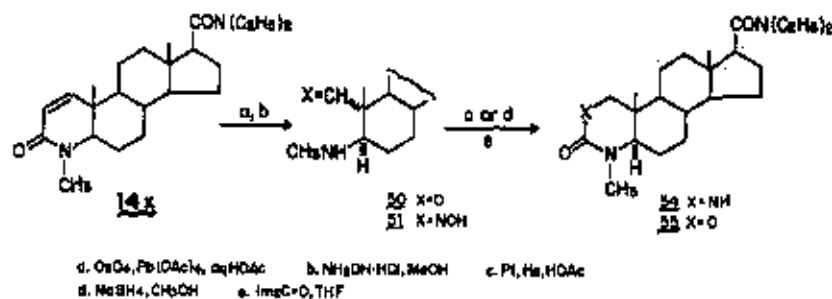
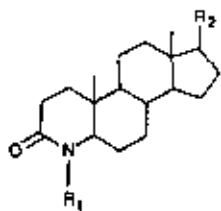


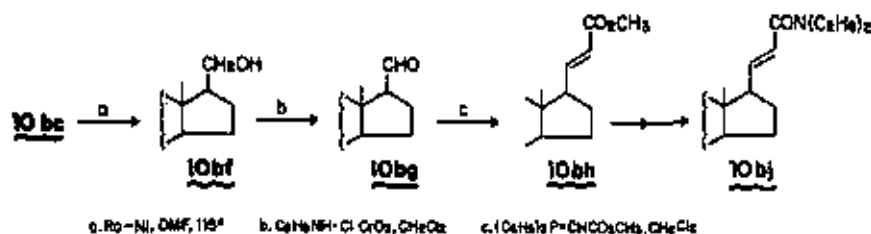
Table IV. In Vitro Activities of Unsaturated 4-Azasteroids



no.	substituents		unsaturation	in vitro bioactivity		
	R ₁	R ₂		human 5α-R: IC ₅₀ /IC ₅₀ 16x	rat 5α-R: IC ₅₀ 10 ⁻⁶ M	rat receptor: IC ₅₀ 10 ⁻⁶ M
13a	H	β-OH	Δ ¹	100		17
14a	CH ₃	β-OH	Δ ¹	>30		0.24
13b	H	β-CO ₂ CH ₃	Δ ¹	36		320
14b	CH ₃	β-CO ₂ CH ₃	Δ ¹	>150		1.3
13l	H	β-CONH ₂	Δ ¹	88		>1000
14l	CH ₃	β-CONH ₂	Δ ¹	>150		15
13k	H	β-CONHC ₂ H ₅	Δ ¹	15		>1000
14k	CH ₃	β-CONHC ₂ H ₅	Δ ¹	150		8.3
14o	CH ₃	β-CONH(CH ₂) ₂ CH ₃	Δ ¹	>6		34
13m	H	β-CONHC(CH ₃) ₃	Δ ¹	0.55	0.68	>10000
14m	CH ₃	β-CONHC(CH ₃) ₃	Δ ¹	6.0	1.3	16
13p	H	β-CONHC(CH ₂) ₂ CH ₂ C(CH ₃) ₃	Δ ¹	1.2		>10000
14p	CH ₃	β-CONHC(CH ₂) ₂ CH ₂ C(CH ₃) ₃	Δ ¹	3.0		
13x ^a	H	β-CON(C ₂ H ₅) ₂	Δ ¹	6.1	14	>10000
14x ^a	CH ₃	β-CON(C ₂ H ₅) ₂	Δ ¹	22	28	46
13y	H	β-CON(<i>i</i> -C ₄ H ₉) ₂	Δ ¹	1.6	7.9	1800
14y	CH ₃	β-CON(<i>i</i> -C ₄ H ₉) ₂	Δ ¹	10	43	1000
13bc	H	β-COS(2-pyridinyl)	Δ ¹	1.0		>1000
14bc	CH ₃	β-COS(2-pyridinyl)	Δ ¹	>150		10
13ai	H	β-CH(CH ₃)CO ₂ CH ₃	Δ ¹	30		>10000
14ai	CH ₃	β-CH(CH ₃)CO ₂ CH ₃	Δ ¹	150		27
13ab	H	β-CH(CH ₃)CO ₂ Na	Δ ¹	4.5		>10000
14ab	CH ₃	β-CH(CH ₃)CO ₂ Na	Δ ¹	>25		>10000
13at	H	β-COCH ₂ CH(CH ₃) ₂	Δ ¹	1.8		>10000
14at	CH ₃	β-COCH ₂ CH(CH ₃) ₂	Δ ¹	30		
13au	H	β-COCH(CH ₃)C ₂ H ₅	Δ ¹	7.6	5.0	>10000
14au	CH ₃	β-COCH(CH ₃)C ₂ H ₅	Δ ¹	50	12	6.4
13av	H	β-CO(2-pyrrolyl)	Δ ¹	10		800
14av	CH ₃	β-CO(2-pyrrolyl)	Δ ¹	33		1.5
13ar	H	α-CH ₂ CH ₂ CH ₂ O-β	Δ ¹	1000	43	160
14ar	CH ₃	α-CH ₂ CH ₂ CH ₂ O-β	Δ ¹	1260	43	11
5a ^a	CH ₃	β-OH	Δ ³			0.74
5j	CH ₃	β-CONHCCH ₃	Δ ³	37	14	40
5x ^a	CH ₃	β-CON(C ₂ H ₅) ₂	Δ ³	4.5		
4y	H	β-CON(<i>i</i> -C ₄ H ₉) ₂	Δ ⁶	4.0	8.6	1400
5y ^a	CH ₃	β-CON(<i>i</i> -C ₄ H ₉) ₂	Δ ⁶	1.6		1000
8l	CH ₃	β-CON(<i>i</i> -C ₃ H ₇) ₂	Δ ^{1,5}	27		840
5ab ^a	CH ₃	β-CH(CH ₃)CO ₂ Na	Δ ⁶	5.2	1.3	2500
5ae	CH ₂	—CHCO ₂ C ₂ H ₅ (E)	Δ ^{5,17(20)}	100		
10b ^j	CH ₃	β-CH=CHCON(C ₂ H ₅) ₂ (E)	Δ ²⁰	2.0		

^aThese compounds are described in ref 8.

Scheme XII



the yield of the desired 5α-4-keto steroid 35. Oxime formation, to give the anti isomer, Beckmann rearrangement with toluenesulfonyl chloride in pyridine, and alkylation with methyl iodide all proceeded cleanly to give the 5α-steroids indicated.

The 17α-ketone of *D*-homodehydroisandrosterone²⁵ was

converted to a diethylcarbamoyl group as shown in Scheme X. The protected Wittig reaction product 40 was selectively hydroborated on the α-face of the exocyclic olefin with 9-borobicyclononane to give the diol 41 after oxidation and protecting-group removal. Oppenauer oxidation of 41 was only partially selective for the A-ring hydroxyl group to give 42 (61%), as further oxidation to give the corresponding 17α-carboxaldehyde accounted for 30% of the reaction product. Chromic acid oxidation of 42 gave the

Scheme XIII

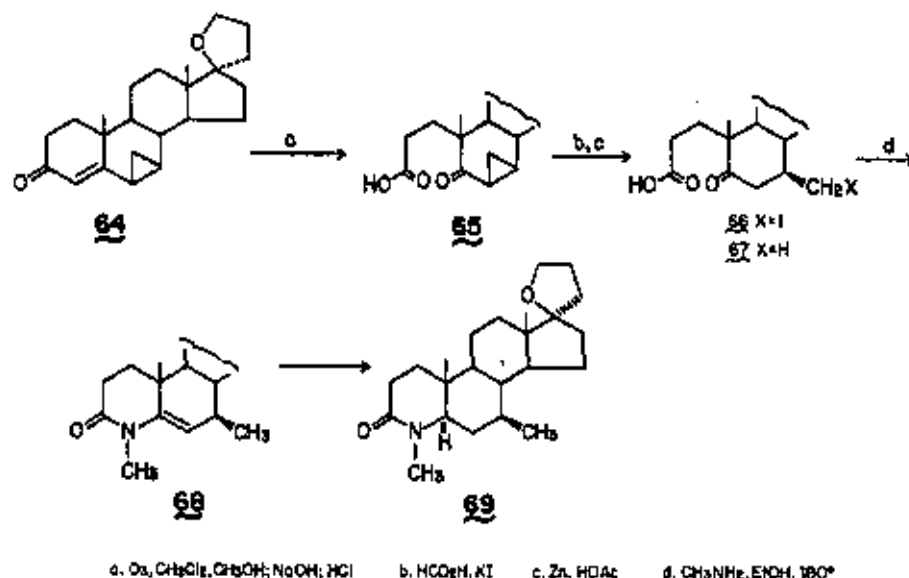


Table V. In Vitro Activities of Other 4-Azasteroid Derivatives

no.	substituents			in vitro bioactivity		
	R_1	R_2	other	human $5\alpha\text{-R}$: $\text{IC}_{50}/\text{IC}_{50} 10x$	rat $5\alpha\text{-R}$: $\text{IC}_{50}, 10^{-6} \text{ M}$	rat receptor: $\text{IC}_{50}, 10^{-9} \text{ M}$
82	CH_3	$\beta\text{-COCH}_3$	$16\alpha\text{-CH}_3$	22	0.84	29
83	CH_3	$\beta\text{-COCH}_3$	$16\beta\text{-CH}_3$		1.6	860
60	CH_3	$\beta\text{-CHOHCH}_3$	$16\alpha\text{-CH}_3$	250	0.28	17
80	CH_3	$\beta\text{-CON}(\text{i-C}_3\text{H}_7)_2$	$5\beta\text{-H}$	>30	100	>1000
89	CH_3	$\alpha\text{-CH}_2\text{CH}_2\text{CH}_2\text{O}-\beta$	$7\beta\text{-CH}_3$		0.46	50
88	CH_3	$\alpha\text{-CH}_2\text{CH}_2\text{CH}_2\text{O}-\beta$	$\Delta^5, 7\beta\text{-CH}_3$	100		
72	CH_3	$\alpha\text{-CH}_2\text{CH}_2\text{CH}_2\text{O}-\beta$	$\Delta^5, 7\alpha\text{-CH}_3$	>150		
76	CH_3	$\alpha\text{-CH}_2\text{CH}_2\text{CH}_2\text{O}-\beta$	19-nor	>150		200
74	CH_3	$\alpha\text{-CH}_2\text{CH}_2\text{CH}_2\text{O}-\beta$	$\Delta^5, 19\text{-nor}$	>80		24
76	CH_3	$\alpha\text{-CH}_2\text{CH}_2\text{CH}_2\text{O}-\beta$	$\Delta^{5,10}, 19\text{-nor}$	>80		16
7x	NH	$\beta\text{-CON}(\text{C}_2\text{H}_5)_2$	Δ^5		3.6	540
8x	OH	$\beta\text{-CON}(\text{C}_2\text{H}_5)_2$	Δ^5		22	19
84	H	$\beta\text{-CONH}_2$	$1\alpha\text{-OCH}_3$	>150		>10000
21	CH_3	$\beta\text{-CON}(\text{C}_2\text{H}_5)_2$	$\Delta^5, 1\text{-CN}$	>150	>100	>1000

carboxy steroid 43, which, in turn, was converted to the *N,N*-diethyl amide 44 via the acid chloride procedure. The corresponding azasteroids 48 and 49 were prepared from 44 as described above (Scheme I).

A nitrogen or oxygen atom could be substituted for C-2 in the azasteroids as shown in Scheme XI. Oxidative cleavage of the Δ^1 -azasteroid 14x with $\text{Pb}(\text{OAc})_4\text{-OsO}_4$ in acetic acid afforded the seco amino aldehyde 50. The oxime of this material was hydrogenated to give an intermediate diamine, which reacted with carbonyldiimidazole to give the diaza analogue 54. Similarly, borohydride reduction of 50 gave an amino alcohol, which was ring closed to the 2-oxa-4-azasteroid 55.²⁶

Reaction of the pyridylthio ester 10bc with Raney nickel gave the 17β -carbinol 10bf (Scheme XII). Oxidation of

10bf to the aldehyde with pyridinium chlorochromate and subsequent condensation with the stable ylide, methyl (triphenylphosphoranylidene)acetate, led to the trans unsaturated ester 10bh. The amide 10bf was obtained after saponification and amidation by using the hydroxy-benzotriazole activation procedure.

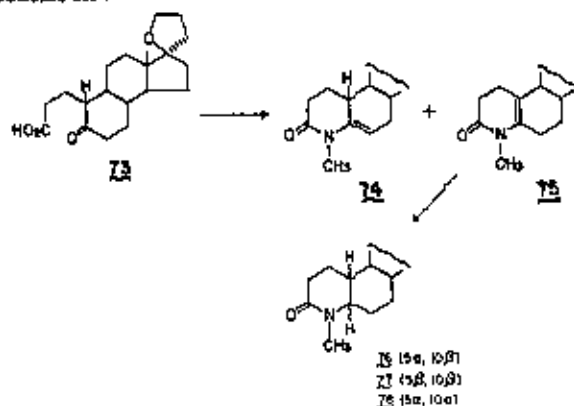
To provide a precursor for a 7β -methyl-substituted azasteroid, the $6\beta,7\beta$ -methylene steroid 64²⁷ was ozonized to give the seco acid 65 (Scheme XIII). The cyclopropane ring of 65 was cleaved by hydroiodic acid, and the intermediate iodomethyl compound was reduced with zinc to give a methyl compound 67 of the desired stereochemistry. Ring closure and reduction of 67 (Scheme I) afforded the corresponding azasteroid 69.

The ring closure of the 19-nor seco acid 78 led to a mixture of Δ^5 and $\Delta^{5,10}$ steroids, 74 and 75 (Scheme XIV).

(26) An alternate route to these oxa-4-azasteroids has recently been reported: Weintraub, P. M.; Blohm, T. R.; Laughlin, M. J. *Med. Chem.* 1985, 28, 881.

(27) Arth, G. E.; Reynolds, G. F.; Rasmussen, G. H.; Chen, A.; Patchett, A. A. *Tetrahedron Lett.* 1974, 291.

Scheme XIV



Hydrogenation of 74 led to the trans ring isomer 76 as the major product, but two other isomers, presumably 77 and 78, were also isolated from this step.

Structure-Activity Relationships. Tables I-V list compounds and their *in vitro* activity as inhibitors of human 5α-reductase, rat 5α-reductase, and rat androgen receptor binding. Table I contains steroids with a fully carbocyclic ring system, Table II contains 17-substituted 4-azaandrostan-3-ones, Table III describes analogues of 4-MA (10x), Table IV features unsaturated azaandrostan-3-ones, and Table V includes various other analogues of the basic azasteroid structure. The IC_{50} value of each steroid was measured and is reported as such in the rat enzyme and rat receptor assays (last two columns, Tables I-V) while for the human 5α-reductase, which showed some assay-to-assay variability, the inhibition is expressed as a ratio of the inhibitor IC_{50} value to the IC_{50} value of compound 10x,^{28,29} used as a standard in each assay. The three assays were not run concurrently, and as a result, many compounds were not tested in each due to time restraints or compound availability. In general, a double "greater than" sign (>>) indicates no activity at the indicated concentration while a single sign (>) indicates partial inhibition at the highest level tested.

The results of this study confirm and extend our earlier observations.^{8,10,11} Some of these data are included here for completeness. The purpose of the study was to define the limits of molecular change for this class of compounds for activity in each of these assays, to optimize activity as 5α-reductase inhibitors, and to provide a base from which a correlation with *in vivo* results could be determined.

Rat Androgen Receptor. Dihydrotestosterone (1a) contains the optimal features for interaction with its receptor, notably, 17β-OH, 3-oxo, and the all-trans 5α-reduced steroid skeleton. In the carbocyclic systems (Table I), incorporation of a Δ⁴ double bond results in a compound (87) of equal or slightly increased binding activity whereas a Δ⁴ double bond (2a,b,ar) decreases activity relative to the 5α-saturated parent. Loss of the angular methyl group (94) increases, while a 4-CN (17x) greatly diminishes, the receptor antagonism of Δ⁴ steroids. The order of activity for 17-substituents falls off for the carbocyclic steroids in the order 17β-OH, 17=O, 17-spiro THF, 17β-CO₂CH₃, 17β-CON(C₂H₅)₂, and 17β-COOH. The progesterone analogues, 88 and 89, reported as 5α-reductase inhibitors

Table VI. 17-Substituted Azasteroids (Schemes I-IV)

a	β-OH	af	-CHCON(C ₂ H ₅) ₂ (E)
b	=O	ah	β-CH(CH ₃)CO ₂ H (Na)
c	β-CHOHCH ₃	aj	β-CH(CH ₃)CO ₂ CH ₃
d	β-COCH ₃	ak	β-CH(CH ₃)CON(C ₂ H ₅) ₂
e	α-OH,β-CHOHCH ₃	al	β-CH(CH ₃)(CH ₂) ₄ CO ₂ H (Na)
f	β-CH(CH ₃)CH ₂ OH	am	β-CH(CH ₃)(CH ₂) ₄ CON(C ₂ H ₅) ₂
g	β-CO ₂ H(K)	an	β-CH(CH ₃)CONH ₂
h	β-CO ₂ CH ₃	ao	β-CH(CH ₃)CN
i	β-CONH ₂	ap	β-(2-oxazolonyl)
j	β-CONHCH ₃	aq	β-(4,4-dimethyl-2-oxazolonyl)
k	β-CONHC ₂ H ₅	ar	α-CH ₂ CH ₂ CH ₂ O-β
l	β-CONHCH(CH ₃) ₂	as	α-CH ₂ CH ₂ CO ₂ β
m	β-CONHC(CH ₃) ₃	at	β-COCH ₂ CH(CH ₃) ₂
n	β-CONH(CH ₂) ₄ CH ₃	au	β-COCH(CH ₃)C ₂ H ₅
o	β-CONH(CH ₂) ₄ CH ₃	av	β-CO(2-pyrrolyl)
p	β-CONHC(CH ₃) ₂ CH ₂ C(CH ₃) ₃		
q	β-CONHC ₁₀ H ₁₉ (oleyl)	aw	β-CO ₂ C(CH ₃) ₃
r	β-CONHCH ₂ CH ₂ OH	ax	β-COSCH(CH ₃) ₃
s	β-CONHC(CH ₃) ₂ CH ₂ OH	ay	β-COCHN ₂
t	β-CONHCH ₂ CO ₂ CH ₃	az	β-NHCOCH ₃
u	β-CONHCH ₂ CO ₂ H	ba	α-NHCOCH ₃
v	β-CONHCH ₂ CON(C ₂ H ₅) ₂	bb	β-COCl
w	β-CONHCH ₂ CH(OCH ₃) ₂	bc	β-COS(2-pyridinyl)
x	β-CON(C ₂ H ₅) ₂	bd	β-CO ₂ (1-benzotriazolyl)
y	β-CON(i-C ₃ H ₇) ₂	be	β-CO(1-imidazolyl)
z	β-CON(n-C ₄ H ₉) ₂	bf	β-CH ₂ OH
aa	β-CON(C ₂ H ₅)-CH ₂ CH ₂ OH	bg	β-CHO
ab	β-CON(C ₂ H ₅) ₂ O	bh	β-CH=CHCO ₂ CH ₃
ac	β-CH ₂ CO ₂ C ₂ H ₅	bi	β-CH=CHCO ₂ H
ad	β-CH ₂ CON(C ₂ H ₅) ₂	bj	β-CH=CHCON(C ₂ H ₅) ₂
ae	-CHCO ₂ C ₂ H ₅	bk	β-OSi(CH ₃) ₂ C(CH ₃) ₃

with antiprosthetic³⁰ and antisebtophobic³¹ activities, had, respectively, strong and moderate activity in the receptor assay.

The receptor activity of the 4-azasteroids (Tables II-V) varied dramatically depending on the nature of substitution on the A-ring 4-nitrogen. When only a hydrogen was attached to this position (R₁ = H), receptor activity was greatly diminished relative to the parent carbocyclic steroid or to the corresponding methyl derivative (R₁ = CH₃). Except for the 4-hydroxy-Δ⁵ compound 8x, other substitutions at the 4-position led to decreased activity (11x, 11ar, 12x, and 7x). Other A-ring modifications of the standard inhibitor 10x afforded enhancement by addition of Δ¹ (14x), 3-oximino (93), A-homo (38), and 1α,2α-epoxy (81) moieties, while permissive effects were seen with the 2-aza (54), 2β-fluoro (29), 1α,2α-methylene (25), 2α-OH (92), and 2-oxa (55) analogues (Table III). There was a loss of receptor antagonism by analogues containing 2β-methyl (90), 1α-methyl (24), 2-oxo (85), 2α- or 2β-methoxy (31, 80), 1-cyano-Δ¹ (21), and 1α-cyano (23) functionalities.

Unsaturation of the azasteroids at C_{5β} increased receptor activity (5j, 5y, 5ah, 74, 81). Other activity-decreasing modifications of the ring system include the 7β-methyl (69), 16β-methyl (68), D-homo (49), and 19-nor (76) analogues. A permissive effect was shown by a 16α-methyl (60, 62). An A:B cis ring fusion (80) destroys receptor activity.

A range of 17-substituted azasteroids was investigated (Table II) and found to conform to that seen with the fully

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209
70x

carbocyclic system. Thus, in decreasing order of receptor activity are active compounds with the following side chains: 17 β -OH (10a), 17 β -CH₂CO₂C₂H₅ (10ac), 17 β -CHOHCH₃ (10c), the spiro lactone (10as), the ketopyrrole (10av), 17 β -CO₂CH₃ (10h), 17 β -CONH(CH₂)₂CH₃ (10o), 17-spiro THF (10ar), 17 β -COCH₃ (10d), 17 β -CONH(CH₂)₂CH₃ (10n), 17 β -CH(CH₃)CN (10an), and 17 β -CONH₂ (10i).

Carboxyl-containing side chain analogues were very weak antagonists (10g, 10ah, 10ak), as were analogues with hydrogen-bonding groups in the 17 α -position (10e, 10ba). The activity of compounds substituted with alkyl groups on the α -face of the D-ring (10ar, 10as, 62, 60) might indicate that the androgen receptor has a lipophilic preference at this site of the steroid. In general, linear chains of C-17 ketones (10d vs. 10au), esters (10h, 10ac, vs. 10ai), and amides (10n, 10o vs. 10m, 10y) were more active than related branched derivatives. The exceptions are the planar pyrrolyl lactone 10av and the cholan acid derivative 10al. Very long chain aliphatic amides were inactive (10q, 10z).

Thus, it is possible to prepare an azasteroid (i.e., 14a) that competes for the androgen receptor as avidly as dihydrotestosterone. However, by leaving the ring nitrogen unsubstituted and inserting a side chain of low affinity, a compound devoid of receptor activity can be obtained.

Rat Prostatic 5 α -Reductase. It is clear from an inspection of Table I that the structural requirements for interference with the androgen receptor are quite different from those for interference with the enzyme. Most notably, the 5 α -reduced carbocyclic steroids (1a, 1ar) that show good interaction with the receptor are without effect on the enzyme. The substrate testosterone (2a) is only a modest enzyme inhibitor, while the 4-cyano compound 17x, which interacts poorly with the receptor, is the most potent enzyme inhibitor of the group.

For the azasteroids, the 5 α -reduced system affords optimal activity with the enzyme. The difference between the activity of 4-methyl and 4-unsubstituted azasteroids in the enzyme assay is not as dramatic as that seen with the androgen receptor. Except for a few cases, the 4-methyl azasteroids are slightly more active than the unsubstituted analogues when the A ring is saturated (Table II); the reverse is true for the Δ^1 derivatives (Table IV). There were no activity-enhancing modifications found with the A-ring analogues of the standard 10x investigated (Table III), although permissive effects were found with the 1 α -methyl (24), 2 β -methyl (90), 1 α ,2 α -methylene (25), and 4-amino- Δ^5 (7x) derivatives.

Unsaturation at C₁₂ or C₁₅ of the azasteroids resulted in reduced 5 α -reductase inhibitory activity (cf. Table II to Table IV). The addition of a 7 β -methyl group increased activity (10ar vs. 69) as did the incorporation of a 16 α - or 16 β -methyl group (10d vs. 62 or 63). Hydrogen-bonding groups at the 17 α -position (10e, 10ba) appeared to enhance activity.

Modification of the side chain at C-17 of the azasteroids has afforded a series of compounds with a broad range of activity (Table II). As has been noted previously,^{8,31} the testosterone analogues 9a and 10a are relatively weak inhibitors while side chains composed of a semipolar group with nearby lipophilicity show high activity. The most potent inhibitors included the secondary amides 10zn, 10o, and 9o, which have IC₅₀ values at the subnanomolar level. Trigonal geometry exocyclic to C-17 (i.e., 10af) permits high activity.

The K_i data for a number of these compounds have appeared.^{9-11,28} The apparent K_i values (in parentheses)

reported for 9x (29 nM), 9y (13 nM), 10x (5 nM), 10ah (1.7 nM), 10ar (24 nM), 13m (6 nM), 13x (133 nM), and 14x (165 nM) as inhibitors of rat prostatic 5 α -reductase correspond closely to the IC₅₀ values obtained in this assay.

Human Prostatic 5 α -Reductase. The reference standard in this assay, compound 10x, has been reported to have an IC₅₀ value of 8.6×10^{-9} M.¹⁰ Thus, the units expressed for this assay in Tables I-V are approximately the same in moles $\times 10^{-6}$ as those listed under the rat 5 α -reductase and receptor assays.

It appears that the structural requirements for inhibition of the human enzyme are more stringent than for the rat enzyme. Of the compounds that can be compared, only a few (17x, 9x, 13y, 14y) show enhanced activity against the human enzyme while a great majority show a dramatic loss of inhibitory potency relative to the rat enzyme.

A-ring modifications (Table III), in general, decrease the activity of the standard compound 10x. However, the order of activity and the potency of these compounds appear to be approximately the same as found with the rat enzyme assay. Compounds with unsaturation at C₁₂ or C₁₅ generally have reduced potency in this enzyme assay as well (Table IV).

Modifications at C-17 (Tables II, IV) indicate that for optimum activity the attached semipolar group, preferably an amide, be linked with a compact lipophilic residue (10m,p,x,y; 13m,p,y). The primary amide 9i, as well as the long-chain substituted amides, 10q and 10z, had reduced activity. Simple esters (10h, 10ac, 10ai) and the ketone 10d were less active than the more lipophilically substituted analogues (10aw and 10at, 10au, respectively). The pyrrole and diazo ketones (10av and 10ay) show higher activity than might be expected for such polar-appearing derivatives whereas substitutions at the 17 α -position would appear to interfere with optimal activity (cf. 10e, 10ar). Methyl substitution at the 7 β -position was favored over the 7 α -position in the Δ^5 compounds 68 and 72.

Conclusion. These data reinforce our earlier concepts of 5 α -reductase specificity and of the structural characteristics of good inhibitors. The preferred natural substrate of the prostatic enzyme of the rat and, most likely, of the human as well is not testosterone but another 3-keto- Δ^4 steroid that possesses a less polar side chain, such as progesterone. This selectivity apparently does not change with enzyme isolated from different tissues of the same animal¹⁴ or from prostates of different disease states.¹⁰ However, there are relative differences in the selectivity of 5 α -reductase between species as shown by the difference in inhibitor effects on the human and rat enzymes.¹⁰

The mechanism of action of these inhibitors is assumed to be that of transition state inhibition.^{12,32} The conformation of the A-ring lactam closely mimics that of the transition state 5 α -reduced Δ^3 -enol that occurs on the enzyme in proceeding from the Δ^4 -3-ketone to the 5 α -reduced 3-ketone. The high activities of the 4-cyano-3-keto- Δ^4 compounds 17x and 17ar fit this concept, as well, since on reduction by the enzyme they would form a stable 5 α -reduced Δ^3 -enol, which like the azasteroids would remain tightly bound to the active site. A facile enol-to-ketone isomerization of the product may be required for turnover on the enzyme.

The androgen receptor data indicate that it is possible to design an azasteroid with high receptor binding. These compounds potentially could be agonists (14a, 5a) or an-

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tagonists (14h, 14av) in their effect on androgen-sensitive tissues. The latter compounds would be expected to have a dual mode of androgen control, namely, by 5 α -reductase inhibition and receptor inhibition. Alternately, by leaving the 4-nitrogen unsubstituted it is possible to prepare 5 α -reductase inhibitors that will not interfere with receptor action and, thus, permit the study of the actions of testosterone in the absence of its potent metabolite, DHT.

Experimental Section

General Methods. Melting points are uncorrected. ¹H NMR spectra, obtained with Varian T-60 and SC-300 spectrometers, were run in CDCl₃ solution and are reported as ppm values downfield from Me₄Si. Low-resolution mass spectra were obtained from an LKB Model 9000 spectrometer equipped with GC and direct inlet systems. Analytical high-pressure LC separations were made on a Waters Associates ALC200 series chromatograph equipped with a Model 6000A pump, a 3.9 mm $\times$ 30 cm μ Porasil column, a Series 400 refractometer, and a Series 440 ultraviolet absorbance detector. Preparative high-pressure LC separations were made on a Waters Associates Prep 500 chromatograph equipped with one or two PrepPaks (325 g of silica gel each). Thin-layer chromatography (TLC) was run on Analtech silica gel coated plates in thicknesses of 250 (analytical), 1000, and 2000 μ m. All reactions were followed by TLC, and the isolated products were analyzed by TLC to verify purity. Optical rotations were measured in chloroform solution on a Perkin-Elmer Model 241 polarimeter using a 1-cm microcell.

17 β -Carboxy-5-oxo-A-nor-3,5-secoandrostan-3- α -ol Acid (3g). A solution of 3-oxo-4-androstene-17 β -carboxylic acid (2g)⁶ (200 g, 0.633 mol) in a mixture of 3.5 L of 2-methyl-2-propanol and 500 mL of 40% aqueous Na₂CO₃ was treated with a solution of 948.5 g of NaIO₄ and 6.95 g of KMnO₄ in 3.5 L of water at 80 °C and worked up as in the procedure described previously.⁶ The crude product crystallized on treatment with a Et₂O-hexane mixture to leave the diacid 3g (152.2 g), mp 188–192 °C.

Other 3-keto- Δ^4 steroids were converted to the following new seco acids: 2',3'- α -tetrahydrofuran-2'-spiro-17-(7 α -methyl-5-oxo-A-nor-3,5-secoandrostan-3- α -ol acid) (71), 2',3'- α -tetrahydrofuran-2'-spiro-17-(5-oxo-A,19-dinor-3,5-secoandrostan-3- α -ol acid) (73); 5,20-dioxo-16 α -methyl-A-nor-3,5-secopregnan-3- α -ol acid (56); mp 204–206 °C; 5,20-dioxo-16 β -methyl-A-nor-3,5-secopregnan-3- α -ol acid (57), M⁺ 420 (Me₄Si); and 17 $\alpha\beta$ -(diethylcarbamoyl)-5-oxo-D-homo-A-nor-3,5-secoandrostan-3- α -ol acid (46), mp 218–220 °C.

3-Oxo-4-aza-5-androstene-17 β -carboxylic Acid (4g). A suspension of the diacid 3g (64.7 g, 0.19 mmol) in 350 mL of cold (5 °C) ethylene glycol was treated with 80 mL of liquid ammonia. The solution was then gradually heated (3 °C/min) to 180 °C and was held at 180 °C for 15 min. Dilution of the cooled mixture with water and acidification to pH 1.5 precipitated the desired product. Filtration, water washing, and vacuum drying afforded 57.5 g of 4g, mp 310 °C.

The following are other new Δ^5 -azasteroids prepared by this method: 4-aza-5-pregnene-3,20-dione (4d), mp 290–292 °C; N-methyl-4-methyl-3-oxo-4-aza-5-androstene-17 β -carboxamide (5j), mp 247–249 °C (a byproduct of the condensation of methylamine with the corresponding secosteroid 17 β -methyl ester); N,N-diethyl-3-oxo-4-aza-D-homo-5-androstene-17 $\alpha\beta$ -carboxamide (46), mp 198–199 °C; N,N-diethyl-4-methyl-3-oxo-4-aza-D-homo-5-androstene-17 $\alpha\beta$ -carboxamide (47), M⁺ 400; N,N-diisopropyl-3-oxo-4-aza-5-androstene-17 β -carboxamide (4y), mp 278–279 °C; 3-oxo-4-aza-5-pregnene-20 α -carboxylic acid (4ab), mp >300 °C; 4,16 α -dimethyl-4-aza-5-pregnene-3,20-dione (58), mp 160–162 °C; 4,16 β -dimethyl-4-aza-5-pregnene-3,20-dione (59), mp 145–147 °C; 2',3'- α -tetrahydrofuran-2'-spiro-17-(4,7 α -dimethyl-4-aza-5-androsten-3-one) (72), mp 145–147 °C; 2',3'- α -tetrahydrofuran-2'-spiro-17-(4-methyl-4-aza-19-nor-5-androsten-3-one) (74), mp 99–101 °C; and 2',3'- α -tetrahydrofuran-2'-spiro-17-(4-methyl-4-aza-19-nor-5(10)-androsten-3-one) (75), mp 142–144 °C. These latter two compounds were found together and were separated by chromatography (HPLC) on silica gel eluted with 3:1 cyclohexane-EtOAc.

N,N-Diethyl-4-hydroxy-3-oxo-4-aza-5-androstene-17 β -carboxamide (8x). A solution of the seco acid 3x⁶ (0.5 g, 1.3 mmol), 10 mL of 5% KOH solution, and 0.15 g of NH₂OH-HCl

in 15 mL of ethanol was refluxed for 2 h. Acetic acid was added to the cooled mixture, and dilution with water separated 365 mg of the intermediate oxime, mp 217–219 °C.

A mixture of the oxime and 560 mg of zinc dust in 10.4 mL of HOAc was heated at 90–95 °C for 1 h. The mixture was cooled and filtered. The filtrate was diluted with water, and the separated solid (180 mg) was washed with water and dried. The product 8x was isolated by preparative TLC on silica gel plates (two plates, 20 cm $\times$ 20 cm $\times$ 1000 μ m) eluted with 4% CH₃OH in CHCl₃. Isolated was 78 mg, mp 223–225 °C.

3-Oxo-4-aza-5 α -androstane-17 β -carboxylic Acid (9g). Hydrogenation at 60 °C of 126 g (0.43 mol) of the above Δ^5 -azasteroid 4g in 1630 mL of HOAc in the presence of PtO₂ (18.3 g) at 40 psig for 3 h gave, after filtration, evaporation, and water wash, 125 g of the desired 5 α -reduced product 9g, mp >310 °C.

In addition, the following 5 α -4-azasteroids have been prepared by a similar procedure: 20-hydroxy-4-aza-5 α -pregnan-3-one (5c), mp 300–302 °C; N-methyl-4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carboxamide (10j), mp 265–268 °C; N,N-di-2-propyl-3-oxo-4-aza-5 α -androstane-17 β -carboxamide (9y), mp 298–298 °C; 3-oxo-4-aza-5 α -pregnane-20 α -carboxylic acid (9ab), mp 313–315 °C; N,N-diethyl-3-oxo-4-aza-D-homo-5 α -androstane-17 $\alpha\beta$ -carboxamide (48), mp 264–265 °C dec; 4,16 α -dimethyl-20-hydroxy-4-aza-5 α -pregnan-3-one (50), mp 218–220 °C; 4,16 β -dimethyl-20-hydroxy-4-aza-5 α -pregnan-3-one (51), mp 206–208 °C; 2',3'- α -tetrahydrofuran-2'-spiro-17-(4,7 β -dimethyl-4-aza-5 α -androsten-3-one) (69), mp 115–119 °C; and 2',3'- α -tetrahydrofuran-2'-spiro-17-(4-methyl-4-aza-19-nor-5 α -androsten-3-one) (76), mp 168–167 °C, predominant isomer, isolated by HPLC. Minor isomers obtained in the latter preparation were 2',3'- α -tetrahydrofuran-2'-spiro-17-(4-methyl-4-aza-19-nor-5 α -androsten-3-one) (77), mp 95–97 °C, and 2',3'- α -tetrahydrofuran-2'-spiro-17-(4-methyl-4-aza-19-nor-5 α ,19 α -androsten-3-one) (78), mp 139–140 °C.³³

The 5 β -reduced isomers, N,N-diethyl-3-oxo-4-aza-5 β -androstane-17 β -carboxamide (79), mp 186–188 °C, and N,N-diisopropyl-4-methyl-3-oxo-4-aza-5 β -androstane-17 β -carboxamide (80), mp 177–179 °C, were isolated as minor components in scaled-up reductions of the corresponding Δ^5 -precursors.

Methyl 3-Oxo-4-aza-5 α -androstane-17 β -carboxylate (9h). A suspension of the acid 9g (105.6 g, 0.33 mol) in a mixture of 42 mL of 2,2-dimethoxypropane and 1.0 L of CH₃OH was treated with a slow stream of HCl gas with stirring for 4 h. The mixture was heated at reflux for 2 h and then allowed to stand at 24 °C for 16 h. The separated product was removed by filtration and was washed with a small amount of CH₃OH to leave 72.6 g of the ester 9h, mp 294–297 °C. Concentration of the filtrates left 43 g of a dark solid, which was extracted with hot EtOAc. On cooling additional 9h separated and was removed by filtration. After the product was washed with cold Et₂O-EtOAc, the yield amounted to 11.1 g, mp 286–289 °C. The filtrate contained (TLC) primarily nonpolar byproducts.

In a similar fashion, methyl 3-oxo-4-aza-5 α -pregnane-20 α -carboxylate (9al), mp 268–270 °C, was prepared from its corresponding acid.

Methyl 3-Oxo-4-aza-5 α -androst-1-ene-17 β -carboxylate (18h). A suspension of the saturated azasteroid 9h (83.7 g, 0.25 mol) and 126.5 g (0.35 mol) of benzeneseleninic anhydride in 2.1 L of chlorobenzene was heated at reflux for 4 h with slow removal of solvent and formed water. The mixture was concentrated to near dryness. The residue in CH₂Cl₂ was washed successively with saturated NaHCO₃ and NaCl solutions, then dried, and isolated by concentration. The crude product was eluted through 2.5 kg of silica gel with increasing percentages of acetone in CH₂Cl₂. After elution of nonpolar aromatic byproducts, the desired product (53.4 g) was eluted with 20% acetone. The isolated product was rinsed with 3 $\times$ 100 mL of Et₂O to give 49.5 g of 18h, mp 278–280 °C.

In a similar fashion, the following Δ^1 -azasteroids have been prepared from the corresponding saturated precursors: N-

(33) The assignment of A-B ring configuration for 76–78 was based on a comparison of the NMR shifts of the C-5 hydrogens (2.90, 3.56, and 3.17 ppm, respectively) with those of the corresponding 17 β -hydroxy analogues (ref. 8 and E. Walton, unpublished data).

ethyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide (13k), mp 265–267 °C; *N*-(2-methyl-2-propyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide (13m), mp 251–253 °C; *N*-(2,4,4-trimethyl-2-pentyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide (13p), mp 224–226 °C; *N,N*-di-2-propyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide (13q), mp 280–282 °C; methyl 3-oxo-4-aza-5 α -pregn-1-ene-20 α -carboxylate (13af), mp 259–261 °C; 23-methyl-4-aza-21-nor-5 α -chol-1-ene-3,20-dione (13at), mp 283–286 °C (darkens); 22-methyl-4-aza-21-nor-5 α -chol-1-ene-3,20-dione (13au), mp 239–241 °C; 2,3 α -tetrahydrofuran-2'-spiro-17-(4-aza-5 α -androst-1-en-3-one) (13ax), mp 271–272 °C; and 17 β -[(*tert*-butyldimethylsilyl)oxy]-4-aza-5 α -androst-1-en-3-one (13bk), mp 285 °C dec.

N,N-Diethyl-4-formamido-3-oxo-4-aza-5 α -androstane-17 β -carboxamide (12x). A solution of 2.0 g (6.1 mmol) of the seco acid 3x and 5 mL of hydrazine hydrate in 22 mL of HOAc was heated at 100 °C for 30 min. The solution was evaporated to dryness under reduced pressure. The residue was chromatographed by HPLC (Waters Prep-pak) on silica gel eluted with EtOAc to give 880 mg of crystalline *N,N*-diethyl-4-amino-3-oxo-4-aza-5 α -androstane-17 β -carboxamide (7x). Recrystallization from Et₂O gave material, mp 168–170 °C (softens 162–164 °C).

To a solution of the 4-amino- Δ^1 steroid 7x (100 mg, 0.25 mmol) in 2 mL of formic acid was added, with ice cooling, 100 mg of sodium cyanoborohydride. After the mixture was stirred at 23 °C for 60 min, CH₃OH was added and the mixture was concentrated to dryness. The residue was extracted with CHCl₃, and the CHCl₃ layer was washed with 5% NaHCO₃ and NaCl solutions, then dried, and evaporated to an oil (112 mg). The major product was separated from a less polar material by TLC on a 20 cm $\times$ 20 cm $\times$ 1000 μ m silica gel plate eluted with 4% CH₃OH in CHCl₃. Isolated was 15 mg of 12x, mp 248–250 °C.

N,N-Di-2-propyl-4-methyl-3-oxo-4-aza-1,5-androstadiene-17 β -carboxamide (81). Lithium diisopropylamide was prepared at –70 °C by addition of 1.64 mL of 2.2 M butyllithium (hexane) to a solution of 364 mg of diisopropylamine in 20 mL of THF. After 15 min, a solution of 8y⁸ (747 mg, 1.8 mmol) in 5 mL of THF was added, and the solution was stirred for 30 min at –70 °C. A solution of methyl benzenesulfonate²⁴ (562 mg, 3.6 mmol) in 5 mL of THF was added, and the solution was allowed to come to 23 °C. The solvent was evaporated, and the residue in EtOAc was washed with 5% NaHCO₃ solution, water, and saturated NaCl solution. Evaporation left 1.4 g of a residue, which by TLC analysis contained a mixture of starting material and the more polar phenylsulfonyl derivative. The crude product in 15 mL of toluene was refluxed for 2 h. The solution was placed directly on a column of 225 g of silica gel and was eluted with increasing amounts of EtOAc in hexane. The desired Δ^1 compound 81 (328 mg), which eluted with 22% EtOAc, had mp 169–170 °C. Continued elution afforded 168 mg of starting material 5g (NMR).

N,N-Diisopropyl-4-methyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide (14y), mp 171–173 °C; 2,3 α -tetrahydrofuran-2'-spiro-17-(4-methyl-4-aza-5 α -androst-1-en-3-one) (14az), mp 129–131 °C; and 17 β -[(*tert*-butyldimethylsilyl)oxy]-4-methyl-4-aza-5 α -androst-1-en-3-one (14bk), mp 127–128 °C, were prepared by a three-step sequence (2-phenylsulfonylation, NaIO₄ oxidation to phenylsulfonyl steroid, and pyrolysis) starting from the corresponding saturated precursors according to the previously described procedure.⁸

Methyl 4-methyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxylate (14b). A suspension of the 4-azasteroid 13h (25 g, 75 mmol) and 3.35 g of oil-free NaH in 500 mL of anhydrous DMF was stirred at 24 °C for 15 min. Methyl iodide (15 mL) was added dropwise, and the mixture was stirred at 24 °C for 30 min. Additional CH₃I (5 mL) was added, and the reaction mixture was heated at 50 °C for 2 h. The reaction mixture was cooled and then diluted to 2 L with water. The mixture was chilled and filtered. The separated solid was washed with water and vacuum dried to leave 25.4 g of 14b, mp 169–181 °C.

In a similar fashion the following 4-methyl 4-azasteroids were prepared from the corresponding unsubstituted lactams: *N,N*-

diethyl-4-methyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide (14x), mp 200–202 °C; methyl 4-methyl-3-oxo-4-aza-5 α -pregn-1-ene-20 α -carboxylate (14af), mp 166–167 °C; *N*-(2,4,4-trimethyl-2-pentyl)-4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carboxamide (10p), mp 148–150 °C; *N*-(2-methyl-2-propyl)-4-methyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide (14m), mp 154–156 °C; and *N,N*-diethyl-4-methyl-3-oxo-4-aza-*D*-homo-5 α -androstane-17 β -carboxamide (49), mp 175–176 °C.

3-Oxo-4-aza-5 α -androst-1-ene-17 β -carboxylic Acid (13g). A suspension of the ester 13b (25 g, 75 mmol) in a solution prepared from 12.5 g of KOH in 150 mL of 5:1 CH₃OH–H₂O was heated at reflux until TLC analysis indicated complete hydrolysis (4h). The mixture was cooled to 25 °C and acidified to pH < 2. Water (175 mL) was added gradually with stirring to leave a crystalline precipitate, which was removed and washed with water. After drying, the product amounted to 25 g, mp 313–315 °C with decomposition. NMR analysis indicated the product to be a roughly 1:1 mixture of the desired Δ^1 acid 13g and the corresponding CH₃OH addition product 1 α -methoxy-3-oxo-4-aza-5 α -androstane-17 β -carboxylic acid. This mixture could not be resolved at this stage, but derivatization of the carboxyl group as the pyridyl thio ester (vide infra) allowed a chromatographic separation at that point.

Similarly, saponification of methyl 4-methyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxylate (14h) led to a mixture of the Δ^1 acid and its methanol addition product. The following saponification procedure afforded the acid with no indication of involvement of the Δ^1 double bond.

4-Methyl-3-oxo-4-aza-5 α -pregn-1-ene-20 α -carboxylic Acid (14ah). A suspension of the Δ^1 ester 14aj (2.7 g, 7.2 mmol) in a mixture of 6 mL of 20% tetraethylammonium hydroxide and 100 mL of tetrahydrofuran was heated at reflux for 4 days under nitrogen. The mixture was concentrated and diluted with water. The aqueous phase was extracted with CHCl₃ and acidified. The separated solid was removed, washed well with water, and then dried. The solid was extracted with hot CH₃OH, and the solution was filtered and then diluted with an equal volume of water. After cooling, the product 14ah was separated and dried, mp 277–279 °C with decomposition.

Similarly prepared was 3-oxo-4-aza-5 α -pregn-1-ene-20 β -carboxylic acid (13ah), mp 310–312 °C with decomposition.

4,23-Dimethyl-4-aza-21-nor-5 α -cholane-3,20-dione (10at). A solution of the Δ^1 azasteroid 14at (800 mg, 2.14 mmol) in 15 mL of THF was hydrogenated at 40 psig at 24 °C for 6 h in the presence of 100 mg of 5% Pd on charcoal catalyst. After filtration and concentration, the residue was crystallized by treatment with hexane to afford 560 mg of 10at, mp 104–106 °C.

N,N-Diethyl-4-acetyl-3-oxo-4-aza-5 α -androstane-17 β -carboxamide (82). A solution of 9x (0.50 g, 1.3 mmol) in a mixture of 7 mL of pyridine and 2.5 mL of Ac₂O was heated at 100 °C for 2 h. The solution was added to ice water, stirred, and filtered. The solid was washed well with water and then dried. Elution of this material through 30 g of silica gel with EtOAc gave 466 mg (mp 186–188 °C) of 82 after evaporation and trituration with Et₂O.

N-(1-Hydroxy-2-methyl-2-propyl)-4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carboxamide (10s). Acid Chloride Procedure. A suspension of 4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carboxylic acid (10g) (0.50 g, 1.5 mmol)⁸ in 6.5 mL of toluene was treated at 24 °C with 1.2 mL of oxalyl chloride. After the mixture was stirred for 20 min, the solvent was removed under reduced pressure and the residue (10bb) was redissolved in 8 mL of anhydrous THF. A solution of 1.0 mL of 2-methyl-2-amino-propanol in 5 mL of THF was added, and the mixture was allowed to stand for 1 h. Ice water was added, and the mixture was extracted with CH₂Cl₂. The organic layer was washed with 2 N HCl and water and then dried (Na₂SO₄). Concentration left 716 mg of a noncrystalline solid. The material was passed through a column of silica gel by elution with 1:1 acetone–EtOAc to afford the desired product 10s, which crystallized from Et₂O to give 219 mg, mp 151–153 °C.

A similar amidation procedure was used to prepare the following 17 β -carboxamides from the same starting acid: *N*-2-propyl 10l, mp 221–224 °C; *N*-pentyl 10n, amorphous solid, *M*⁺ 402; *N*-cleyl (C₁₈H₃₅) 10q, oil, *M*⁺ 582; *N*-(2-hydroxyethyl) 10r, mp 119–121 °C; *N*-(2,2-dimethoxyethyl) 10w, amorphous solid, *M*⁺ 421; *N*-

(34) Field, L.; Locke, J. M. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 723.

N-dioctyl 10z, oil, *M*⁺ 556; *N*-(2-hydroxyethyl)-*N*-ethyl 10aa, mp 176–178 °C; and morpholine 10ab, mp 198–200 °C. From 4-methyl-3-oxo-4-aza-5 α -pregnane-20 α -carboxylic acid (10ah) was obtained 4-methyl-3-oxo-4-aza-5 α -pregnane-20 α -carboxamide (10am), mp 260–262 °C.

Benzotriazol-1-yl 3-Oxo-4-aza-5 α -androstane-17 β -carboxylate (9bd) and Its Conversion to *N*-1-Octyl-3-oxo-4-aza-5 α -androstane-17 β -carboxamide (9o). A solution of the acid 9g (500 mg, 1.57 mmol), *N,N*-dicyclohexylcarbodiimide (835 mg), and *N*-hydroxybenzotriazole (318 mg) in 50 mL of CH₂Cl₂ was sealed under nitrogen and stored at 4 °C for 16 h.

The reaction mixture was separated into two parts. Part one was evaporated to dryness, and the residue was chromatographed by TLC (four plates, 20 cm $\times$ 20 cm $\times$ 1000 μ m, silica gel) eluted with 4% CH₃OH in CHCl₃. The major UV absorbing band was extracted, and the isolated product was washed with ether to give 192 mg of the active ester 9bd, mp 217–219 °C with decomposition.

Part two was filtered, and the filtrate was treated with 500 μ L of *n*-octylamine. After standing at 4 °C for 16 h, the mixture was washed successively with saturated NaHCO₃, 1 N HCl, and saturated NaCl solutions. The organic solution was dried (Na₂SO₄) and evaporated. The residue was chromatographed (TLC, four plates, 20 cm $\times$ 20 cm $\times$ 1000 μ m, silica gel) by elution with 1:1 hexane-acetone. The major water opaque band was extracted, and the isolated product was crystallized with Et₂O to give 60 mg of 9o, mp 185–187 °C.

By utilization of in situ generated hydroxybenzotriazole esters of the corresponding acids, the following amides have also been prepared by the addition of the appropriate amines: *N*-(2,4,4-trimethyl-2-pentyl)-3-oxo-4-aza-5 α -androstane-17 β -carboxamide (9p), mp 250–251 °C; *N*-(carbomethoxymethyl)-4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carboxamide (10t), mp 217–219 °C; *N*-(2-methyl-2-propyl)-3-oxo-4-aza-5 α -androstane-17 β -carboxamide (9m), mp 275–276 °C; *N,N*-diethyl-4-methyl-3-oxo-4-aza-5 α -pregn-20-ene-21-carboxamide (10bj), mp 174–176 °C; and *N*-[(*N,N*-diethylcarbamoyl)methyl]-4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carboxamide (10v), mp 174–176 °C.

S-2-Pyridyl 3-Oxo-4-aza-5 α -androstane-17 β -thiocarboxylate (9bc). A solution of the acid 9g (35 g, 0.11 mol), triphenylphosphine (56 g, 0.22 mol), and 2,2'-dipyridyl disulfide (48.3 g, 0.22 mol) in 210 mL of toluene was stirred at 24 °C for 6 h. The reaction mixture was placed on a column of silica gel (1.3 kg) and was eluted with 1:1 acetone-CH₂Cl₂. The desired thio ester 9bc eluted slowly and, after rinsing with Et₂O, amounted to 36.8 g, mp 232–235 °C.

In a similar manner the following pyridyl thio esters were prepared from the corresponding carboxylic acids: S-2-pyridyl 4-methyl-3-oxo-4-aza-5 α -androstane-17 β -thiocarboxylate (10ba), mp 207–208 °C; S-2-pyridyl 3-oxo-4-aza-5 α -androst-1-ene-17 β -thiocarboxylate (13bc), mp 230–232 °C; S-2-pyridyl 4-methyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -thiocarboxylate (14bc), mp 218–220 °C; and S-2-pyridyl 1 α -methoxy-3-oxo-4-aza-5 α -androstane-17 β -thiocarboxylate (88), mp 196–198 °C.

Reaction of Amines with Thiopyridyl Esters. *N*-(2-Methyl-2-propyl)-3-oxo-4-aza-5 α -androstane-17 β -carboxamide (9m). A suspension of the thiopyridyl ester 9bc (883 mg, 2.16 mmol) in a mixture of 1.7 mL of *tert*-butylamine and 21 mL of THF was stirred at 24 °C for 16 h. The solution was concentrated and the residue passed through 60 g of silica gel with 3:1 CH₂Cl₂-acetone to give the desired product, which was eluted after a colored nonpolar material. The isolated product 9m after rinsing with Et₂O amounted to 700 mg, mp 275–278 °C.

The following amides were similarly prepared from the respective precursor 2-pyridyl thio esters: *N*-(2-methyl-2-propyl)-4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carboxamide (10m), mp 198–200 °C; 3-oxo-4-aza-5 α -androstane-17 β -carboxamide (9i), mp 224–226 °C; 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide (13i), mp 332–333 °C; 4-methyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide (14i), mp 289–291 °C; *N*-ethyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide (13k), mp 257–259 °C; *N*-ethyl-4-methyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide (14k), mp 240–242 °C; *N*-octyl-4-methyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide (14e), mp 106–108 °C; *N*-(2,4,4-trimethyl-2-pentyl)-4-methyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide (14p), mp 188–170 °C; and 1 α -methoxy-3-oxo-4-aza-5 α -androstane-17 β -carboxamide (84), mp 205–207 °C.

Reaction of Grignard Reagents with Thiopyridyl Esters. **22-Methyl-4-aza-21-nor-5 α -chol-1-ene-3,20-dione (13au).** A suspension of the Δ^1 steroid thiol ester 13bc (7.2 g, 17.6 mmol) in 288 mL of THF was treated dropwise at –78 °C with 81 mL of 1.3 M *sec*-butylmagnesium chloride in Et₂O (Alfa). After the mixture was stirred at –78 °C for 30 min, the temperature was allowed to rise to 0 °C. Saturated NaCl solution was added dropwise with stirring until the inorganic salts separated as a granular precipitate. The salts were removed by filtration and rinsed with THF and then CH₂Cl₂. The combined filtrates were concentrated to a residue, which was dissolved in CH₂Cl₂, washed with 10% NaOH and saturated NaCl solutions, and then dried and concentrated to 6.1 g. This material was passed through 360 g of silica gel with 10% acetone in CH₂Cl₂. The major eluted product was isolated and rinsed with ether to give 4.6 g of 13au, mp 246–249 °C. NMR analysis indicated this product to be a mixture (55:45) of diastereoisomers (isomeric at the 22-position). The more polar isomer could be obtained in >90% purity by 7-fold recrystallization from CH₃CN. The less polar isomer was obtained about 90% pure by peak shaving on HPLC of the first mother liquor material. The bioactivity of these isomers in the human enzyme 5 α -reductase assay were essentially equal.

In a similar fashion the following 20-keto azasteroids were prepared from precursor thiopyridyl esters: 23-methyl-4-aza-21-nor-5 α -cholane-3,20-dione (9at), mp 220–222 °C; 22-methyl-4-aza-21-nor-5 α -cholane-3,20-dione (9au), mp 223–225 °C; 4,22-dimethyl-4-aza-21-nor-5 α -cholane-3,20-dione (10au), mp 139–140 °C; 17 β -(2-pyrrylcarbonyl)-4-aza-5 α -androst-3-one (9av), mp 267–270 °C; 4-methyl-17 β -(2-pyrrylcarbonyl)-4-aza-5 α -androst-3-one (10av), mp 222–224 °C; 4,23-dimethyl-4-aza-21-nor-5 α -chol-1-ene-3,20-dione (14at), mp 147–149 °C; 4,22-dimethyl-4-aza-21-nor-5 α -chol-1-ene-3,20-dione (14au), mp 134–136 °C; 17 β -(2-pyrrylcarbonyl)-4-aza-5 α -androst-1-en-3-one (13av), mp 294–296 °C; and 4-methyl-17 β -(2-pyrrylcarbonyl)-4-aza-5 α -androst-1-en-3-one (14av), mp 247–248 °C.

***tert*-Butyl 4-Methyl-3-oxo-4-aza-5 α -androstane-17 β -carboxylate (10aw).** A solution of 129 mg (0.5 mmol) of silver trifluoromethanesulfonate in 1.0 mL of warm toluene was added to a stirred suspension of the thiopyridyl ester 10bc (213 mg, 0.5 mmol) in a mixture of 100 μ L of *t*-BuOH and 2.5 mL of toluene with vigorous stirring. A gummy residue separated, which after 2 h was triturated to give a freely suspended solid. After 80 min of additional stirring, the mixture was diluted to 8 mL with CH₂Cl₂. The solution was washed successively with H₂O, 5% NH₄OH solution, and saturated NaCl solution, and then it was dried and concentrated to a gum (240 mg). This material was chromatographed by TLC on silica gel plates (four plates, 20 cm $\times$ 20 cm $\times$ 1000 μ m) eluted with 2:1 acetone-EtOAc-CH₂Cl₂. The major non-UV-absorbing band was extracted to give crystalline 10aw. Recrystallization from heptane-ethyl acetate gave 113 mg, mp 162–170 °C (crystal change during melting). A portion from aqueous methanol had mp 164–172 °C.

In a similar fashion, the thiopyridyl ester 9bc was converted to *tert*-butyl 3-oxo-4-aza-5 α -androstane-17 β -carboxylate (9aw), mp 230–250 °C with decomposition.

S-2-Methyl-2-propyl 4-Methyl-3-oxo-4-aza-5 α -androstane-17 β -thiocarboxylate (10ax). After standing at 23 °C for 16 h, a solution of the 17-carboxylic acid 10g (167 mg, 0.5 mmol) and *N,N*-carbonyldiimidazole (162 mg, 1.0 mmol) in 2 mL of DMF was treated with 1.07 mL of *tert*-butyl mercaptan and 9 mg of magnesium ethoxide. The mixture was stirred for 16 h and then was concentrated to near dryness. The residue in CH₂Cl₂ was washed with water, saturated NaHCO₃ solution, and saturated NaCl solution. The residue after drying and evaporation was chromatographed on 18 g of silica gel. The thiol ester 10ax, which eluted with 10% acetone in CH₂Cl₂, amounted to 119 mg, mp 188–189 °C.

***N,N*-Diethyl-4-cyano-3-oxo-4-androstene-17 β -carboxamide (17x).** A solution of *N,N*-diethyl-3-oxo-4-androstene-17 β -carboxamide⁸ (2x) (1.25 g, 3.37 mmol) in 28 mL of CH₃OH was treated at 0 °C with 30% H₂O₂ (2.24 mL, 22 mmol) and 2.5 N NaOH (0.9 mL in 1.35 mL of CH₃OH). The solution was stirred at 0–10 °C for 6 h. The solution was poured into ice water and was extracted with EtOAc-Et₂O with use of NaCl to break the emulsion. The organic layer was washed with water, dried with Na₂SO₄, and evaporated to leave *N,N*-diethyl-4,5-epoxy-3-oxo-

202

213

androstene-17 β -carboxamide (15x) as a mixture of isomers (oil, 1.0 g).

A solution of this epoxide 15x (1.0 g, 2.56 mmol) in 52 mL of ethanol was treated with a solution of NaCN (1.25 g, 25.9 mmol) in 15 mL of water and then was refluxed for 21 h. The solvent was removed and the residue was treated with excess dilute NaOH solution. The aqueous solution was extracted with Et₂O and then acidified with 6 N HCl. The separated solid was dissolved in EtOAc, and the solution was washed with water, then dried (Na₂SO₄), and concentrated. The residue was recrystallized from CH₃OH-EtOAc to leave 537 mg of *N,N*-diethyl-4,5-dicyano-8-hydroxy-3-androstene-17 β -carboxamide (16x), mp 223–225 °C dec.

The cyano compound 16x (537 mg, 1.27 mmol) was heated under reduced pressure (10 mmHg) at 235 °C until gas evolution ceased (2–3 min). The residue was cooled and recrystallized from EtOAc to give 392 mg of 17x, mp 240–242 °C with slight discoloration at 230 °C.

In a similar fashion, 2',3'- α -tetrahydrofuran-2'-spiro-17-(4-androsten-3-one) (2ar)³⁵ was converted sequentially to the corresponding epoxide 15ar, 4,5-dicyano compound 16ar, and 4-cyano-3-oxo derivative 17ar, mp 180–181 °C.

20 α -Cyano-4-methyl-4-aza-5 α -pregnan-3-one (10an). To a 0 °C solution of the amide 10am (180 mg, 0.53 mmol) in 1.0 mL of pyridine was added 0.13 mL of POCl₃. After 45 min at 0 °C, the solution was poured into 40 mL of ice water containing 0.5 mL of pyridine. The separated product was dissolved in CHCl₃ and was washed with saturated NaCl solution, dried, and isolated by concentration. A small amount of polar material was removed by passing an acetone solution through a short column of silica gel. Crystallization from Et₂O afforded 100 mg of the nitrile 10an, mp 223–225 °C.

In a similar fashion, the 17 β -carboxamide 16i was converted into 17 β -cyano-4-methyl-4-aza-5 α -androstan-3-one (10ao), mp 248–250 °C.

17 β -(4,4-Dimethyloxazin-2-yl)-4-methyl-4-aza-5 α -androstan-3-one (10aq). A solution of the amide 10a (180 mg, 0.4 mmol) and 114 mg of *p*-toluenesulfonyl chloride in 5 mL of pyridine was kept at 24 °C for 24 h. The solution was concentrated under reduced pressure, and the residue was stirred with 7 mL of 10% NaHCO₃ solution for 3 h. The product was extracted into CHCl₃, washed with water, and dried. The product isolated on evaporation was eluted by HPLC through a Whatman M9 silica column with 1:1 EtOAc-acetone. The product was isolated and crystallized from hexane to give 55 mg of 10aq, mp 144–147 °C.

A similar reaction carried out with the hydroxyethyl amide 10r led to a mixture of the terminal tosylate and 17 β -oxazin-2-yl-4-methyl-4-aza-5 α -androstan-3-one (10ap), mp 212–214 °C, isolate by preparative HPLC.

17 β -Hydroxy-4-methyl-3-oxo-4-aza-5 α -pregnane-21-carboxylic Acid Lactone (10as).³⁶ Disodium chromate tetrahydrate was dried at 100 °C at 1 mmHg for 16 h over P₂O₅. To a solution of 2',3'- α -tetrahydrofuran-2'-spiro-17-(4-methyl-4-aza-5 α -androstan-3-one) (10ar) (0.50 g, 1.45 mmol) in a mixture of 3.79 mL of HOAc and 2.2 mL of Ac₂O was added Na₂CrO₄ (472 mg, 2.9 mmol). The solution was heated at 38 °C for 18 h, then cooled, and added dropwise to a solution of 1.7 g of oxalic acid in 20 mL of water. The separated product (about 1:1 single product to starting material by TLC) was extracted into CH₂Cl₂, washed with 5% NaHCO₃ water, and saturated NaCl, then dried (Na₂SO₄), and isolated by evaporation. This residue (425 mg) was chromatographed by HPLC, eluting a Whatman M9 silica column with EtOAc. The polar lactone 10as was recrystallized from Et₂O to afford 185 mg, mp 202–204 °C.

***N,N*-Diethyl-4-methyl-3-oxo-2-(phenylsulfinyl)-4-aza-5 α -androsten-1-ene-17 β -carboxamide (19).** A solution of 1.067 g (5.0 mmol) of NaIO₄ in 8 mL of water was added to a solution of 1.0 g (1.65 mmol) of *N,N*-diethyl-2,2-bis(phenylsulfinyl)-4-methyl-3-oxo-4-aza-5 α -androsten-17 β -carboxamide (18)⁶ in 24 mL of CH₃OH. The mixture was stirred at 23 °C for 43 h. The mixture

was concentrated under reduced pressure to remove the CH₃OH and then was extracted with EtOAc. The organic layer was worked up to leave a gummy residuum. The material was eluted through 100 g of silica gel with EtOAc to give *N,N*-diethyl-4-methyl-3-oxo-2-(phenylsulfinyl)-4-aza-5 α -androsten-1-ene-17 β -carboxamide⁸ (A) (160 mg) in the early fractions. The crystalline title compound 19 (407 mg) eluted next, followed by 130 mg of material having no aromatic ring as analyzed by NMR. Recrystallization of 19 from EtOAc gave 200 mg, mp 250–265 °C, the broad melting point indicating contamination of one sulfoxide isomer with the other (vide infra).

Oxidation of the phenylsulfinyl compound A (346 mg) with NaIO₄ (255 mg) in a similar fashion for 24 h afforded 285 mg of 19 as an isomeric mixture of sulfoxides. Recrystallization from EtOAc gave 108 mg, mp 255–267 °C.

The above oxidation was carried out with 7.4 g of the bis(phenylsulfinyl) compound 18 and 7.4 g of NaIO₄ in refluxing aqueous methanol for 2 h. Chromatographic isolation afforded 2.9 g of the sulfoxide 19 as well as the 2-oxo compound 85,⁸ mp 186–188 °C (softens 170 °C), and *N,N*-diethyl-2,2-dimethoxy-4-methyl-3-oxo-4-aza-5 α -androsten-17 β -carboxamide (86), mp 130–138 °C dec.

***N,N*-Diethyl-1-cyano-4-methyl-3-oxo-4-aza-5 α -androsten-1-ene-17 β -carboxamide (21).** A mixture of NaCN (55 mg, 1.1 mmol), the sulfinyl olefin 19 (30 mg, 0.06 mmol), and water (0.2 mL) in 1.5 mL of THF was heated at reflux for 2.5 h. The cooled reaction mixture was diluted with EtOAc and worked up to leave 29 mg of a gum. Chromatography (TLC, 20 cm $\times$ 20 cm $\times$ 500 μ m; acetone-hexane, 3:5) afforded 21 mg of crystalline 21. Recrystallization from Et₂O-heptane gave 15 mg, mp 162–165 °C.

***N,N*-Diethyl-1 α -cyano-4-methyl-3-oxo-4-aza-5 α -androsten-17 β -carboxamide (23).** A mixture of NaCN (105 mg, 2.1 mmol), the sulfinyl olefin 19 (76 mg, 0.16 mmol), and 0.4 mL of water in 3.0 mL of THF was stirred at 23 °C for 2.5 h. The reaction mixture was diluted with EtOAc, washed with saturated aqueous NaCl solution, and dried. Concentration at <28 °C gave 78 mg of a slowly crystallizing residue. Trituration with ether afforded 34 mg of the cyano sulfinyl steroid 22, mp 140–145 °C to a gel, which crystallized and melted 178–180 °C.

A solution of the above product 22 (25 mg) in 1.0 mL of ethanol and 0.5 mL of Raney nickel was stirred at 23 °C for 16 h and then was heated at reflux for 30 min. Ethyl acetate was added and the catalyst was removed. Evaporation left a clear gum, which was chromatographed by TLC (20 cm $\times$ 20 cm $\times$ 500 μ m; acetone-hexane, 1:1). The major component (23) was isolated and crystallized from Et₂O to give 10 mg, mp 217–219 °C.

***N,N*-Diethyl-4-methyl-1 α ,2 α -methylene-3-oxo-2-(phenylsulfinyl)-4-aza-5 α -androsten-17 β -carboxamide (20).** A 60% NaH suspension in mineral oil (30 mg) was rinsed with hexane and then was suspended in 3.0 mL of dry dimethyl sulfoxide. Trimethylsulfoxonium iodide (220 mg, 1.0 mmol) was added to the stirred mixture. When the mixture became clear, a solution of crystalline phenylsulfinyl olefin 19 (150 mg, 0.29 mmol) in 3 mL of THF was added. After 24 h at 23 °C, the solution was partially concentrated under reduced pressure and then diluted with water. The solid was separated, washed with water, and vacuum dried. Crystallization from ethyl acetate gave 80 mg of the cyclopropyl compound 20, mp 275–277 °C. The C-19 methyl singlet in the NMR spectrum of this material is observed at 0.07 ppm.

However, when noncrystalline phenylsulfinyl olefin 19 (425 mg) obtained from the mother liquor of the crystallization was reacted with dimethylsulfoxonium methylide (from 1.026 g of (CH₃)₂SO) as described above, a different (melting point and NMR) cyclopropyl compound (20) (362 mg) was obtained, mp 120–126 °C to a gel, which became free flowing at 150 °C; the C-19 methyl shift is observed at 1.00 ppm of the NMR spectrum. The isomeric origin proved to be at the sulfoxide moiety as the desulfurization reaction described below afforded the same products with each isomer.

***N,N*-Diethyl-4-methyl-1 α ,2 α -methylene-3-oxo-4-aza-5 α -androsten-17 β -carboxamide (25) and *N,N*-Diethyl-1 α ,4-dimethyl-3-oxo-4-aza-5 α -androsten-17 β -carboxamide (24).** Raney nickel (under EtOH, 0.5 mL solid volume) was added to a solution of 350 mg (0.67 mmol) of the low-melting sulfinyl methylene steroid 20 in 12 mL of EtOH. The mixture was heated

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(36) This procedure is a modification of one previously described (Reynolds, G. F., et al. *Tetrahedron Lett.* 1970, 5057). It was developed in these laboratories by G. Gal.

at reflux with stirring for 30 min. After dilution with EtOAc, the catalyst was removed and washed with EtOAc. The combined organic layers were concentrated to dryness and chromatographed by TLC (two plates, 20 cm × 20 cm × 1000 μm, EtOAc). The major zone was acetone extracted to give 244 mg of crystalline material. Recrystallization two times from Et₂O-hexane gave 89 mg of the 1α,2α-methylene steroid 25, mp 166–168 °C. The mother liquor material was eluted by HPLC (silica gel, 40 cm × 12 mm, acetone:hexane 1:2) to give a minor, faster moving component and the major component. The major component was recrystallized from ether-hexane to give an additional 86 mg of 25, mp 165–167 °C. The minor component separated from heptane-Et₂O to give 28 mg of the 1α-methyl steroid 24, mp 175–178 °C.

A similar experiment with 26 mg of the higher melting sulfinyl methylene steroid 20 and Raney nickel afforded 10 mg of the 1α,2α-methylene steroid 25, mp 167–169 °C, and 3 mg of the 1α-methyl compound 24, mp 172–175 °C.

N,N-Diethyl-2β-fluoro-4-methyl-3-oxo-4-aza-5α-androstane-17β-carboxamide (29). To a solution of N,N-diethyl-4-methyl-3-oxo-4-aza-5α-androstane-17β-carboxamide (10x) (20 g, 51.6 mmol) in 520 mL of THF was added at -78 °C 191 mL of a solution of 0.54 N lithium diisopropylamide in hexane-pentane.³⁷ After stirring for 20 min at -78 °C, this solution was added to a solution of dimethyl oxalate (12.16 g, 103 mmol) in 180 mL of THF cooled at 0 °C. The reaction mixture was allowed to come to and remain at 23 °C for 1 h. The mixture was diluted with water, acidified with 2 N HCl, and then extracted with EtOAc. The organic layer was washed with saturated NaCl solution, dried (Na₂SO₄), and evaporated to 32 g of a foam. Chromatography on 2 kg of silica gel eluted with 3:1 hexane-acetone gave 19.6 g of the noncrystalline 2-methoxalyl intermediate 28.

Perchloryl fluoride was bubbled through a solution of the above methoxalyl steroid (19.6 g, 41.3 mmol) in 588 mL of pyridine as the temperature was raised from 15 to 23 °C. Bubbling was continued for 4 h, and the solution then was allowed to stand for 2½ days. The mixture was concentrated under reduced pressure to a small volume. The residue was diluted with water, acidified with 6 N HCl solution, and extracted with Et₂O. The Et₂O layer was washed with water and saturated NaCl solution, then dried, and evaporated. The product was purified by preparative HPLC (Waters Prep-pak) on silica gel eluted with 1:1 EtOAc-hexane. The 2-fluoro-2-methoxalyl steroid 27 separated as the major component, 14.6 g, mp 150–160 °C.

A solution of the above product (14.6 g, 29.7 mmol) and 15 g of potassium acetate in 300 mL of CH₃OH was heated at reflux for 48 h. The solution was evaporated, and the residue was treated with water and Et₂O. The Et₂O layer was washed with water and saturated NaCl solution, then dried, and concentrated. The residue was chromatographed by HPLC (Waters Prep-pak) on silica gel eluted with 3:1 EtOAc-hexane. Three components in their order of elution were identified: 1.7 g of starting 2-fluoro-2-methoxalyl compound 27; 4.15 g of 2-methoxy-2-methoxalyl steroid 28, mp 175–178 °C; and 2.6 g of the desired 2-fluoro steroid 29, mp 158–165 °C.

Acidification of the aqueous phase separated a solid, which when worked up amounted to 1.8 g, mp 234–235 °C dec. This material analyzed for C₂₈H₄₈N₂O₃·F·H₂O and was probably the acid corresponding to hydrolyzed starting ester.

N,N-Diethyl-2α- and -2β-methoxy-4-methyl-3-oxo-4-aza-5α-androstane-17β-carboxamides (31 and 30). A solution of the methoxy methoxalyl steroid 28 (250 mg, 0.5 mmol) and 500 mg of NaOCH₃ in 10 mL of CH₃OH was allowed to stand at 23 °C for 3 days. The solution was treated with water and EtOAc. The organic layer was washed with water and saturated NaCl solution, then dried, and evaporated to a crystalline solid (142 mg). TLC on silica gel (EtOAc) indicated it to be a mixture of two components. These were separated by HPLC (Whatman M9-semiprep) on silica gel eluting with EtOAc. The first component eluted, 2β-methoxy isomer 30, had mp 141–142 °C. The second component eluted, 2α-methoxy isomer 31, had mp 139–140 °C. The

assignment of stereochemistry was based on the NMR shift of the 19-methyl groups (2β-methoxy ~0.88 ppm; 2α-methoxy ~0.83 ppm).

N,N-Diethyl-3,8-(ethylenedithio)-4-androstene-17β-carboxamide (32). Redistilled boron trifluoride etherate (1.0 mL) was added at 10 °C with stirring to a solution of N,N-diethyl-3-oxo-4-androstene-17β-carboxamide (2x) (2.5 g, 6.7 mmol) and 1.5 mL of ethanedithiol in 12.5 mL of HOAc. After stirring for 1.5 h at 23 °C, the mixture was diluted with water (30 mL). The separated solid was triturated and then removed by filtration. Crystallization from aqueous CH₃OH gave 2.524 g of 32, mp 130–133 °C.

N,N-Diethyl-4-androstene-17β-carboxamide (33). A solution of the thioketal 32 (1.0 g, 2.2 mmol) in 1.0 mL of anhydrous THF was added to a solution prepared from 1.2 g of sodium in 80 mL of refluxing ammonia. After 20 min, the mixture was treated dropwise with EtOH until the blue color was quenched. The mixture was allowed to evaporate, and the residue was worked up in methylene chloride to leave 0.808 g of crystalline 33. A portion recrystallized from hexane had mp 115–116 °C.

N,N-Diethyl-4α-hydroxy-5α-androstene-17β-carboxamide (34). Borane-dimethyl sulfide complex (190 μL) was added at 0 °C to a solution of 535 mg (1.49 mmol) of the olefinic steroid 33 in 3.5 mL of anhydrous THF. The reaction mixture was stirred at 0 °C for 40 min and then at 23 °C for 3.5 h. It was cooled to 0 °C and was treated dropwise with 3 N NaOH solution (1.0 mL). When the foaming subsided, 1.0 mL of 30% H₂O₂ was added and the mixture was allowed to come to 23 °C. Tetrahydrofuran (8 mL) was added, and the organic layer was separated and washed successively with saturated NaCl solution (two times), 5% NaHSO₃ solution, and saturated NaCl solution. After drying and concentration of the solution, the residue (530 mg) was recrystallized twice from EtOAc-hexane to give 110 mg of the α-hydroxy steroid 34, mp 178–180 °C. The mother liquors on TLC analysis (hexane-EtOAc, 1:1) indicated a trace of starting olefin with only one other spot, which represented a mixture of the 4α- and 4β-hydroxy steroids (see below).

N,N-Diethyl-4-oxo-5α-androstane-17β-carboxamide (35). Jones reagent³⁸ was added at 0 °C with vigorous agitation to a suspension of the pure 4α-hydroxy steroid 34 (130 mg, 0.36 mmol) in 4 mL of acetone until a definite orange color persisted. After stirring for 15 min at 0 °C, the mixture was treated with isopropyl alcohol until the supernatant was colorless. The layers were separated. The inorganic layer was diluted with water and was extracted with EtOAc. The organic layers were combined and dried. Concentration afforded 120 mg of crystalline product. Recrystallization from hexane gave 60 mg of 35 as prisms, mp 130–134 °C.

When the material (400 mg, 1.08 mmol) obtained from the mother liquors of the crystallization of 34 was carried through the oxidation procedure, 378 mg of a ketone mixture was obtained. TLC analysis (1:1 hexane-EtOAc) indicated a slight predominance of the 5β-isomer.

A solution of the ketone mixture (378 mg) with 160 mg of sodium methoxide in 15 mL of CH₃OH was heated at reflux for 45 min. The solvent was evaporated, and the residue was extracted with water and EtOAc. Workup of the organic layer gave a residue in which the 5α-isomer predominated. Crystallization from hexane afforded 232 mg of 35, mp 128–133 °C. The residue from the mother liquor was eluted through a 40 cm × 12 mm silica column (HPLC) with 4:1 hexane-EtOAc to give Δ⁴-steroid 33 (13 mg), the 5β-ketone (42 mg, mp 154–156 °C), and 5α-ketone 35 (43 mg).

A solution of 270 mg (0.72 mmol) of the 5α-ketone 35, 100 mg of NH₄OH-HCl, and 4 drops of diethylamine in 6 mL of CH₃OH stood at 28 °C for 60 min. Water (8 mL) was added, and the solid

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215

T2

was separated, washed, and air-dried. Crystallization from CH_3OH gave 206 mg of the oxime 36, mp 219–226 °C. A sample recrystallized from heptane–EtOAc had a crystal change at >210 °C with mp 226–230 °C.

N,N-Diethyl-4-oxo-4a-aza-*A*-homo-5 α -androsterane-17 β -carboxamide (37). *p*-Toluenesulfonyl chloride (300 mg, 1.58 mmol) was added at 0 °C to a solution of 270 mg (0.70 mmol) of the oxime 36 in 5.5 mL of pyridine. After standing at 5 °C for 16 h, the stirred solution was treated with saturated NaHCO_3 solution. Water was added after 3 h, and the product was extracted with EtOAc. The organic layer was washed with 5% HCl solution and then worked up to leave a solid residue. Crystallization from ethyl acetate afforded 207 mg of the *A*-homo-azasteroid 37, mp 202–204 °C. A portion separated from heptane–EtOAc gave prisms, mp 205.5–207 °C.

N,N-Diethyl-4a-methyl-4-oxo-4a-aza-*A*-homo-5 α -androsterane-17 β -carboxamide (38). Oil-free sodium hydride (8.0 mg, 0.4 mmol) was added to a solution of 60 mg (0.16 mmol) of the steroidal lactam 37 in 1.0 mL of toluene. The solution was refluxed gently while methyl iodide was added in 0.2-mL aliquots every 3 h over a 9-h period. Reflux was continued for 3 h before the reaction mixture was cooled to 23 °C and treated with water. The organic layer was diluted with EtOAc and worked up to leave an oil. Chromatography (HPLC) on a 40 cm $\times$ 12 mm silica gel column with 2:1 EtOAc–acetone afforded 49 mg of 38 and a trace of starting lactam. Recrystallization of 38 from EtOAc–heptane gave 41 mg, mp 183–189 °C.

17 α -Methylene-*D*-homo-5-androsten-3 β -ol (40) and Its THP Ether. To a suspension of 482 mg of 60% sodium hydride (suspended in mineral oil, 11.5 mmol) in 8.5 mL of dimethyl sulfoxide (Me_2SO) was added at 24 °C with vigorous stirring a solution of methyltriphenylphosphonium bromide in 12.6 mL of Me_2SO . After 2 h, the resulting clear solution was treated with a solution of 1.0 g of *D*-homodehydroisandrosterone²¹ 39 (3.3 mmol) in 12 mL of THF, and the reaction mixture was heated at 50–55 °C for 16 h. The mixture was cooled and diluted with water. The product, extracted with EtOAc, was washed with water and saturated NaCl solution, then dried, and isolated by evaporation to leave 1.6 g of crude residue. The desired 17-methylene steroid 40 ($R = \text{H}$) was purified by chromatography on silica gel (250 g, eluted with 70:30 cyclohexane–EtOAc) to give 900 mg of 40 ($R = \text{H}$), mp 140–142 °C.

A solution of 900 mg (3.0 mmol) of the above methylene steroid and 50 mg of *p*-TbCl in 8.0 mL of dihydropyran was stirred at 24 °C for 2 h. Pyridine (1 mL) was added followed by dilution with water. The layers were mixed well; EtOAc was added, and the layers were separated. The organic layer was washed with water and saturated NaCl solution, then dried, and concentrated. Recrystallization of the residue from EtOAc gave 487 mg of the tetrahydropyranyl ether 40 ($R = \text{THP}$), mp 139–140 °C.

17 $\alpha\beta$ -(Hydroxymethyl)-*D*-homo-5-androsten-3 β -ol (41). To a solution of the above tetrahydropyranyl ether 40 (5.39 g, 14 mmol) in THF was added at 24 °C a solution of 9-borabicyclo-[3.3.1]nonane, 0.5 N in THF (100 mL, 50 mmol). After standing for 16 h, the solution was cooled to 0 °C and was treated dropwise with 89 mL of 2.5 N NaOH and then 32 mL of 30% hydrogen peroxide. The mixture was allowed to warm to 24 °C and stood for 20 h. Saturated NaCl solution and EtOAc were added. The organic layer was worked up to leave the crude product. This material was purified by preparative HPLC (Waters, Prep-pak) on silica gel eluted with 60:40 hexane–EtOAc. The isolated product, 3 β -(tetrahydropyranyloxy)-*D*-homo-5-androsten-17 β -ylmethanol, amounted to 3.4 g, mp 130–132 °C.

A solution of the above material (6.4 g, 15.8 mmol) and 1.4 g of *p*-toluenesulfonic acid in a mixture of 182 mL of CH_3OH and 9.2 mL of water was kept at 24 °C for 16 h. The solution was neutralized with 2 N NaOH and then concentrated. The residue was extracted into EtOAc. The organic solution was washed with water, 5% NaHCO_3 , and saturated NaCl solution, then dried, and concentrated to a crystalline residue. Recrystallization from EtOAc gave 3.38 g of 41, mp 208–210 °C.

17 $\alpha\beta$ -(Hydroxymethyl)-*D*-homo-4-androsten-3-one (42). A solution of the dihydroxy compound 41 (7.6 g, 24 mmol) in a mixture of 442 mL of toluene and 45 mL of cyclohexanone was distilled until 100 mL of solution remained. A slurry of 5.2 g of aluminum isopropoxide in 76 mL of toluene was added, and the

mixture was heated at reflux for 1.5 h. The mixture was concentrated to about one-half of its initial volume and was treated with 3.9 g of diatomaceous earth (Supercel) and 7.8 mL of water. After mixing, the mixture was filtered and the filter cake was washed well with EtOAc. The combined filtrates were concentrated to an oily residue. This residue was submitted to steam distillation to remove cyclohexanone. The residue in EtOAc was washed with water and saturated NaCl solution, then dried, and isolated by evaporation. Recrystallization of the residue from EtOAc afforded 2.83 g of 42, mp 152–153 °C.

The material in the mother liquor was chromatographed by HPLC (Waters Prep-pak) on silica gel eluted with 1:1 EtOAc–hexane. Early fractions afforded 2.47 g of 3-oxo-*D*-homo-4-androstene-17 $\alpha\beta$ -carboxaldehyde, ^1H NMR (CDCl_3) δ 0.98 (18- CH_3), 1.00 (19- CH_3), 4.72 (4-H), and 9.33 (d, $J = 2$ Hz, 17 α -CHO). Additional 17 α -carbinol 42 (1.96 g, mp 152–153 °C) was isolated from later fractions.

3-Oxo-*D*-homo-4-androstene-17 $\alpha\beta$ -carboxylic Acid (43) and the Corresponding Diethyl Amide (44). To a solution of the 17 $\alpha\beta$ -hydroxymethyl steroid 42 (2.83 g, 8.3 mmol) in 78 mL of HOAc was added CrO_3 (1.98 g, 19.8 mmol) portionwise with stirring. After 18 h at 24 °C, water (160 mL) was added with stirring. The mixture was cooled at 4 °C for 14 h. The crystalline solid was removed and washed with water to leave 1.78 g of 43 ($R = \text{OH}$) after drying, mp 228–230 °C dec.

The combined filtrates were extracted with EtOAc. After washing with water, the organic layer was evaporated. The residue was extracted with 2.5 N NaOH solution. The aqueous solution was acidified and extracted with EtOAc. Workup of the organic layer afforded 538 mg of additional 43.

The *N,N*-diethyl amide 44 (mp 169–171 °C) was prepared via the acid chloride procedure as previously described for 2x.⁵

N,N-Diethyl-1-oxo-8-aza-1,2-seco-*A*-nor-5 α -androsterane-17 β -carboxamide (50). Cerium tetrachloride (40 mg) was added to a mixture of *N,N*-diethyl-4-methyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide (14x)⁸ (500 mg, 1.5 mmol), 2.5 g of $\text{Pb}(\text{OAc})_4$, and 0.75 mL of water in 5.0 mL of HOAc. After standing for 16 h at 23 °C, the mixture was diluted with toluene and the layers were separated. The organic layer was extracted successively with water, 5% aqueous HCl, water, and saturated NaCl solution. The aqueous layers were combined and separated from the precipitated lead salts. The solution was made alkaline with K_2CO_3 and was extracted with CHCl_3 . This solution was washed with water and saturated NaCl solution, dried over CaSO_4 , and concentrated to 300 mg of a crystalline residue. Chromatography by elution through 30 g of silica gel afforded 268 mg of pale yellow product 50. An analytical sample prepared by trituration with Et₂O had mp 143–145 °C.

This material (100 mg) was converted to the corresponding oxime 51 by reaction with 30 mg of $\text{NH}_2\text{OH}\cdot\text{HCl}$ in 2 mL of CH_3OH at 23 °C for 16 h. Concentration of the reaction mixture and extraction of the residue with CH_2Cl_2 led to 85 mg of the oxime 51 after workup. Recrystallization from EtOAc gave material of mp 167–169 °C.

N,N-Diethyl-4-methyl-3-oxo-2,4-diaza-5 α -androsterane-17 β -carboxamide (54). The oxime 51 (80 mg) in 1.5 mL of HOAc was hydrogenated in the presence of 50 mg of PtO_2 at 40 psig at 23 °C for 6 h. The catalyst was removed and the solution was concentrated to dryness. The product was treated with 5% aqueous NaOH solution and extracted with CHCl_3 . Workup afforded 62 mg of the crude 1-amino compound 52.

A solution of the amino compound 52 (56 mg) in 1.5 mL of dry THF was treated with 85 mg of carbonyldiimidazole. After standing for 16 h, the solution was concentrated to a gum, which solidified on trituration in water. This solid was crystallized from EtOAc–heptane (3 mL) by distillation to leave 34 mg of the diazasteroid 54, mp 212–217 °C. Recrystallization from EtOAc gave plates, mp 217–218 °C.

N,N-Diethyl-4-methyl-3-oxo-4-aza-2-oxa-5 α -androsterane-17 β -carboxamide (55). Sodium borohydride (40 mg) was added in portions at 0 °C to a solution of the aminoaldehyde 50 (145 mg, 0.4 mmol) in 2.5 mL of CH_3OH . After stirring at 0 °C for 30 min and at 23 °C for 1.5 h, the solution was treated with water. The precipitate was collected, washed with water, dried, and crystallized from aqueous CH_3OH to give 84 mg of the amino alcohol 53, mp 116–125 °C.

A solution of the amino alcohol 53 (75 mg, 0.2 mmol) in dry THF was treated at 0 °C with 90 mg of carbonyldiimidazole. The solution was concentrated, and the residue was chromatographed on TLC (two plates, 20 cm × 20 cm × 1000 μm, 10% acetone-EtOAc). The major product amounted to 58 mg. Recrystallization from EtOAc gave 55 (47 mg), mp 183–185 °C.

4,16α- and 4,16β-Diethyl-4-aza-5α-androstane-3,20-diones (62 and 63). Oxidation of the 20-hydroxy steroids 60 and 61 in acetone according to the Jones procedure³⁸ (see preparation of 35 above) afforded, respectively, the corresponding 20-ketones 62, mp 178–181 °C, and 63, mp 128–132 °C with coloration.

4-Methyl-3-oxo-4-aza-5α-pregn-20-ene-21-carboxylic Acid (10bi). Raney nickel under ethanol (volume of solid about 175 mL) was washed free of ethanol by treatment with Et₂O followed by decantation (three times) and then was suspended in DMF by the same procedure. A solution of the thiopyridyl ester 10bc (18.4 g, 43.2 mmol) with the above Raney nickel in 450 mL of DMF was heated at 115 °C for 4 h. The solid was removed and rinsed with CH₂Cl₂ and CH₃OH. The combined filtrates were concentrated to a white solid. The solid was suspended in 1:1 Et₂O-hexane and filtered. The crystalline solid was washed with hexane to give 13.7 g of 4-methyl-17β-(hydroxymethyl)-4-aza-5α-androstan-3-one (10bf), mp 224–227 °C (acetate, mp 95–97 °C).

A solution of the above alcohol 10bf (14.5 g, 45.5 mmol) in 125 mL of CH₂Cl₂ was added rapidly to a stirred solution of pyridinium chlorochromate (14.9 g, 68.2 mmol) in 100 mL of CH₂Cl₂. After 1.5 h, isopropyl alcohol was added. Addition of 2.5 N HCl served to solubilize the black tar. Additional CH₂Cl₂ was added, and the phases were separated. The CH₂Cl₂ layer was washed with water and saturated NaCl solution, then dried, and concentrated to leave 11.0 g of crystalline aldehyde 10bg. Color was removed from the product by eluting it through 30 g of silica gel with 5% CH₃OH-CH₂Cl₂ to leave, after crystallization from Et₂O, 9.4 g of pure 10bg, 216–219 °C.

A solution of the above aldehyde 10bg (9.4 g, 30 mmol) and methyl (triphenylphosphoranylidene)acetate (12.1 g, 35.6 mmol) in 395 mL of CH₂Cl₂ was refluxed for 24 h. The reaction mixture was concentrated to an oil, which was purified by HPLC (Waters Prep-pak) on silica gel eluted with EtOAc.

The methyl ester 10bh obtained above (10.7 g, 28.7 mmol) was saponified with 8.0 g of K₂CO₃ in 440 mL of 10:1 CH₃OH-water at reflux for 16 h. The reaction mixture was concentrated and the residue was dissolved in water. The aqueous solution was washed with CHCl₃ and then acidified. The separated solid was dissolved in CHCl₃, washed with saturated NaCl solution, and then dried and isolated to give 7.62 g of the acid 10bi, mp 260–263 °C.

This acid was converted to the *N,N*-diethyl amide 10bj via the hydroxybenzotriazole procedure described above.

2',3'-Tetrahydrofuran-2'-spiro-17-(4,7β-dimethyl-4-aza-5-androsten-3-one) (68). Ozone was passed through a solution of 2',3'-α-tetrahydrofuran-2'-spiro-17-(6,7β-methylene-4-androsten-3-one) (64)²⁷ (1.0 g, 2.9 mmol) in a mixture of 12 mL of CH₂Cl₂ and 2 mL of CH₃OH at -70 °C until the blue color of the solution persisted for 20 min. The solution was purged with nitrogen, and the temperature was allowed to rise. The mixture was concentrated to dryness and treated with 6% methanolic NaOH. After stirring for 15 min, the mixture was concentrated and the residue was washed with Et₂O. The residue was dissolved in water, and the resulting solution was acidified with 2.5 N HCl. The product was extracted into EtOAc and washed with water and saturated NaCl solution; it was then dried and isolated by concentration under reduced pressure. The glassy seco acid 65 (750 mg) on TLC eluted as a single spot with 0.5% HCOOH in Et₂O.

The seco acid 65 (750 mg) in 10 mL of 88% HCOOH was treated with 3.2 g of potassium iodide. Water was added to the mixture after stirring for 3 h at 23 °C. The gummy product was dissolved in CH₂Cl₂ and washed with 5% Na₂S₂O₃ solution and water to give, after drying and concentration, the iodomethyl compound 66 as an amber foam. The NMR spectrum has a broad doublet at 3.27 ppm (*J* = 4.0).

This foam in 200 mL of 70% aqueous HOAc was treated portionwise with 1.0 g of granular zinc. After the mixture was stirred at 23 °C for 16 h, 1.5 g of zinc powder was added and the mixture was heated at 80 °C for 15 min. The mixture was con-

centrated to near dryness and was diluted with EtOAc and 40 mL of 1.5 N HCl. After the mixture was stirred for 30 min, the EtOAc layer was separated, washed with water and saturated NaCl solution, dried, and concentrated to leave 530 mg of the crude 7β-methyl seco acid 67.

A solution of this material in 5 mL of EtOH and 1.0 g of CH₃NH₂ was sealed in a tube and heated at 180 °C for 8 h. The cooled reaction mixture was evaporated, and the residue was worked up in EtOAc. The residue (520 mg) was purified by TLC (four plates, 20 cm × 20 cm × 1000 μm, 2% CH₃OH-CHCl₃) to give 283 mg of crystalline product 68. Recrystallization from Et₂O-hexane gave 126 mg of 68, mp 132–133 °C.

4-Methyl-4-aza-5-androstene-3,17-dione (5b). A solution of 17β-hydroxy-4-methyl-4-aza-5-androsten-3-one (5a)²⁰ (1.0 g, 3.3 mmol) in 6 mL of CH₂Cl₂ was added at 23 °C to a suspension of pyridinium chlorochromate (1.29 g, 6 mmol) in 8 mL of CH₂Cl₂. After 30 min, 50 mL of ether was added with stirring. The phases were separated, and the solid was extracted again with Et₂O. The combined organic layers were filtered through Florisil (20 g) and concentrated to a crystalline residue. Recrystallization from EtOAc-heptane gave 631 mg of 5b, mp 158–157 °C (unchanged on further crystallization).

Ethyl 4-Methyl-3-oxo-4-aza-5,17(20)-pregnadien-21-oate (5ac). The ketone 5b (525 mg, 1.74 mmol) was reacted with methyl (diethylphosphono)acetate in ethanolic sodium ethoxide by a procedure described previously.⁸ The crude product was purified by HPLC (Whatman M9) on silica gel eluted with 1:1 EtOAc-hexane to give 466 mg of 5ac, mp 136–138 °C, on crystallization from EtOAc-heptane.

17β-[(*tert*-Butyldimethylsilyloxy)]-4-aza-5α-androstan-3-one (9bk). To a solution of the azadihydrotestosterone 9a (16.3 g, 55 mmol) in 350 mL of DMF was added 15.6 mL of triethylamine and 16.9 g (0.11 mol) of *tert*-butyldimethylsilyl chloride. After stirring at 23 °C for 18 h, the mixture was filtered to remove the precipitated product. The solid was rinsed with DMF and then taken up in CH₂Cl₂. After washing with water and saturated NaCl solution, the solution was dried and evaporated to leave 9.2 g of 9bk, mp >300 °C.

In a similar fashion, 17β-[(*tert*-butyldimethylsilyloxy)]-4-methyl-4-aza-5α-androstan-3-one (10bk), mp 126–127 °C, was prepared from 10a. This material remained in solution and was isolated by workup of the residue obtained on evaporation of the initial reaction mixture.

17β-Hydroxy-4-methyl-4-aza-5α-androst-1-en-3-one (14a). To a solution of the Δ¹ silyloxy compound 14bk (1.8 g, 3.1 mmol) in 90 mL of THF was added 3.75 mL of 1.0 M tetrabutylammonium fluoride. After 8 h at 24 °C, the solvent was evaporated and the residue was extracted with EtOAc. The organic solution was washed with water, dried, and evaporated. The residue was chromatographed on TLC silica gel plates (five plates, 20 cm × 20 cm × 2000 μm) eluted with EtOAc. The starting material (*R*_f 0.79, 20 mg) and desired Δ¹-17-hydroxy steroid 14a (*R*_f 0.48, 800 mg) were isolated. Recrystallization of 14a from EtOAc gave 455 mg, mp 133–134 °C.

In a similar fashion, 17β-hydroxy-4-aza-5α-androst-1-en-3-one (13a), mp 267–268 °C, was prepared from 13bk.

Bioassays. Rat Prostatic 5α-Reductase. This assay was carried out as described previously.^{11,28} A range of concentrations (10⁻⁸–10⁻⁵ M) of the test steroid was incubated in duplicate with radioactive T and an excess of NADPH in a medium containing the crude, cell-free enzymes. The radioactive DHT was measured and compared with that of a control incubation to determine inhibitory activity. The IC₅₀ data reported in Tables I–V were estimated from plots of the inhibitory activities at various concentrations of the inhibitors. The results shown are a composite of many assays performed over a period of several years and, as such, should be regarded qualitatively.

Rat Prostatic Androgen Receptor Binding Assay. Prostate cytosol was prepared from rats that had been castrated 20 h prior to sacrifice. The assay was carried out as previously described^{11,28} with use of a combination of ammonium sulfate fractionation and dextran-coated charcoal treatment to separate receptor bound [³H]-5α-DHT from free and from that bound to a nonreceptor protein. Aliquots of cytosol were incubated in duplicate with the radioactive steroid in the presence or absence of competitors. The IC₅₀ values reported in Tables I–V were estimated from plots of

inhibition at various concentrations of inhibitor. Compounds were tested in batches of 3-20 per assay, and the results shown were obtained over a period of several years.

Human Prostatic 5 α -Reductase. This assay was performed by modification of a previous procedure²² that utilized rat prostate tissue. Human benign prostatic hypertrophy tissue that had been obtained by surgery and quickly frozen and stored at -70 °C served as the source of the enzyme. Typically, a 1.8-g portion was thawed, minced, and homogenized in 0.25 M sucrose buffer. The homogenate was centrifuged at 1200 rpm for 10 min, and the supernate was discarded. After the pellet was washed three times in buffer, it was suspended in buffer so that 1.0 mL contained about 300 mg of homogenized tissue. This suspension (0.1 mL) was incubated with 0.01 mL of inhibitor and 0.1 mL of a mixture containing [³H]testosterone, unlabeled testosterone and dihydrotestosterone, glucose 6-phosphate, glucose-6-phosphate dehydrogenase, and NADP for 30 min at 37 °C. After the incubation, the steroids were extracted with 3.0 mL of ethyl acetate, and the organic phase was separated and evaporated under N₂. This extract was spotted onto TLC plates. After the TLC plates were developed in ethyl acetate-cyclohexane (1:1), the [³H]DHT zone was scraped from the plate and counted. A control incubation without inhibitor

and incubations with the standard inhibitor 10 $\times$ were run with each assay. The number of compounds run per assay ranged from one to 12. Generally, IC₅₀ values were estimated from plots of inhibitory activity and then were compared to that obtained with 10 $\times$ in the same assay. These data are reported in Tables I-V.

Acknowledgment. We are indebted to Dr. Byron Arison and Herman Flynn for obtaining the 300-MHz NMR spectra and to Jack L. Smith for the mass spectra. Microanalytical data were obtained by the Analytical Research Department of Merck Sharp & Dohme Research Laboratories. We also acknowledge the helpful comments and encouragement of Dr. R. L. Tolman, Dr. B. G. Christensen, Dr. M. S. Glitzer, and Dr. E. H. Cordes. A special note of thanks to MaryAnn Haas, who prepared the manuscript.

Supplementary Material Available: A table listing additional physical, analytical, and spectral (NMR, UV, and MS) data for compounds described in this paper (29 pages). Ordering information is given on any current masthead page.

Synthesis and Renal Vasodilator Activity of Some Dopamine Agonist 1-Aryl-2,3,4,5-tetrahydro-1H-3-benzazepine-7,8-diols: Halogen and Methyl Analogues of Fenoldopam

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Certain 6-halo-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepines were found to be potent D-1 dopamine agonists. The 1-(4-hydroxyphenyl) analogues did not have central nervous system activity because their high polarity inhibited entry into the brain. However, these compounds were potent renal vasodilators. Fenoldopam, the 6-chloro analogue, is an especially significant member of the series, and its synthesis, pharmacology, and clinical properties have been studied extensively. The 6-methyl and 6-iodo congeners were potent renal vasodilators, but nonpotent partial D-1 agonists as measured by stimulation of rat caudate adenylate cyclase. A possible rationalization suggests different receptor reserves for these activities. The 9-substituted benzazepines were either inactive or of low potency as dopamine agonists, while the N-methyl analogues had significant antagonist potency as measured by inhibition of dopamine stimulation of rat caudate adenylate cyclase.

Elevated renal vascular resistance is found in most patients with essential hypertension^{1,2} and is strongly implicated in both the pathogenesis and maintenance of this disease.³ This suggested that selective renal vasodilators might be useful antihypertensive agents.² An approach to this type of agent via stimulation of renal dopamine receptors was suggested by the work of Goldberg^{4,5} on the effects of dopamine on renal blood flow in α -adrenergic blocked dogs.

Dopamine is not suitable for general use as an antihypertensive agent. Its limitations include lack of oral absorption and its lack of selectivity because of activity at both D-1 and D-2 receptors as well as at norepinephrine receptors, which mediate both α - and β -adrenergic responses. Furthermore, although dopamine itself does not cross the blood-brain barrier, other dopamine agonists such as apomorphine and bromocriptine do pass the blood-brain barrier and cause biochemical and behavioral changes characteristic of central dopamine receptor activation.

The objective of our research in this area was the discovery of orally active dopamine agonist renal vasodilators selective for increasing renal blood flow without inducing central nervous system effects or responses due to activation of α - or β -adrenergic receptors. While this work was in progress, the concept of dopamine D-1 and D-2 receptor subtypes was developed⁶ and a further objective that desirable compounds be D-1 agonists without significant D-2 activity was added. A major reason for this was to avoid the possibility of D-2-induced emesis. Apart

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ALICIA LLOREDA RICAURTE

ASUNTO	Radicación	04088823
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	Nº 9 2 1 6
	Folios	006

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒ Cap. I ☐ Cap. II ☒

No. Sol. Internacional PCT/US03/08277
Fecha de Presentación Interna. 07 de Marzo de 2003

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

1.1. Descripción: Folios: 59 a 128 (como se radicó inicialmente)

1.2. Reivindicaciones: Folios: 18 a 31 (como se radicó inicialmente)
Folios: 129 a 140 primera modificación.
Folios: 163 a 175 segunda modificación.

1.3. Prioridad: Folio 1 (US60/363,822 , 13 de Marzo de 2002.)

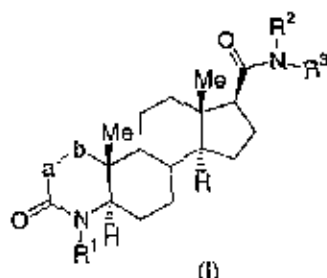
Se acepta para estudio el capítulo reivindicatorio de los folios 163 a 175.

2. Objeto de la invención

Título de la solicitud . Derivados de 4-azasteroides fluorados como moduladores del receptor de andrógenos.

El objeto de la presente solicitud de patente de invención consiste en:
Derivados de 4-azasteroides fluorados

Reivindicaciones 1-20,30-36 : Compuesto de la fórmula I :



Reivindicación 21,28 : Composición farmacéutica del compuesto de fórmula I.

Reivindicaciones 22-27 : Composición farmacéutica del compuesto de fórmula I con otros activos.

Reivindicación 29 : Un procedimiento para preparar la composición farmacéutica del compuesto de fórmula I.

El problema planteado en esta solicitud es la necesidad de derivados de azasteroides que sean moduladores del receptor de andrógenos de una forma selectiva de tejido y son útiles como agonistas del receptor de andrógenos en el tejido óseo y / o muscular que a la vez antagonizan el AR en la próstata de un paciente varón o en el útero de una paciente mujer.

Para solucionar este problema técnico la solicitud en estudio proporciona derivados de azasteroides fluorados , procedimientos para su preparación y formulaciones farmacéuticas que emplean dichos compuestos.

El objeto de la invención definido anteriormente se clasificó de acuerdo con la Clasificación Internacional de Patentes (IPC) : C07D221/18; A61K31/473 ;

3. De la solicitud de Patente

3.1. Descripción (artículo 28 D. 486)

- Teniendo en cuenta la definición de los compuestos de fórmula I de los folios (163 a 175) , esta Dependencia se permite señalar que dentro del aparte descriptivo se encuentra que se habla que los compuestos de fórmula I pueden ser administrados con otros agentes en composiciones farmacéuticas o pueden administrarse por separado (Folios 87-100) , pero estas composiciones o combinaciones no muestran ninguna ventaja técnica inesperada ya que no se encuentran datos que las respalden.

- En cuanto a los resultados obtenidos , son datos muy generales, y no son representativos para todas las variables en R3 con los sustituyentes respectivos con reivindicadas en 1.

En consecuencia, las reivindicaciones 1-36 no encuentran sustento dentro del aparte descriptivo de la solicitud

Se requiere al solicitante ajustar su capítulo descriptivo y reivindicatorio de acuerdo a aquellas modalidades que son objeto de la invención y a las observaciones realizadas, teniendo cuidado de no ampliar la materia más allá de cómo se estableció originalmente.

3.2. Reivindicaciones (artículo 30 D 486)

- Las reivindicaciones 1,13,15 no son claras ni concisas ya que resultan amplias y especulativas en el sentido que existen múltiples posibilidades de sustitución a nivel del compuesto de fórmula I para el sustituyente R3, cuando se habla "...de cicloheteroalquilo ...del cual no se especifica el número de carbonos que lo conforma , no se define su tamaño, el número y clase de heteroátomos que lo conforman , y por este motivo la característica esencial de las moléculas que corresponden a la estructura de la fórmula (I) no es representativa, ni define todas las posibilidades de los compuestos que se pueden obtener una vez se procede a realizar las sustituciones respectivas en dicha estructura. Se le requiere al interesado definir o especificar los grupos cicloheteroalquilo en lo posible (por ejemplo si es piperidina , piperazina ..) y que son relevantes para la invención.
- Para la reivindicación 3 , se habla de " ... donde el grupo alquilo o el **grupo cicloheteroalquilo**, pero este grupo ya no se encuentra dentro del alcance de esta reivindicación.
- La reivindicación 22 y en consecuencia sus dependientes no son claras ni concisas ya que resultan amplias y especulativas en el sentido que existen múltiples posibilidades de composiciones farmacéuticas obtenidas de la combinación de "el compuesto de formula I con un estrógeno, un bifosfonato, un inhibidor de captésina K etc... .. Se le requiere al interesado definir o especificar las composiciones farmacéuticas del compuesto de formula I con otros ingredientes activos y que son relevantes para la invención.
- La reivindicación 28 no es clara y resulta amplia y especulativa , ya que se reclama nuevamente la composición reivindicada en 22, sin aportar ninguna característica técnica adicional.

4. Unidad de invención (artículo 25 D 486)

Se aclara que, de acuerdo al Art 25, las reivindicaciones 1-36 carecen de unidad de invención por lo siguiente:

Se distinguen los siguientes grupos de invención (no limitantes):

- Grupo I : Reivindicaciones 1-21,28-36 . Compuestos de fórmula I, sus composiciones farmacéuticas y procedimiento para preparar dicha composición.
- Grupo II. Reivindicaciones 22-27, composiciones que comprenden un compuesto de fórmula I con ingredientes activos adicionales.

Cada una de estas invenciones, es una invención distinta caracterizada por su propia característica técnica y no se encuentran tan unidas como para formar un concepto general inventivo único.

En especial la patentabilidad de grupo II depende del tipo y cantidad de los múltiples ingredientes activos que lo conforman, su interacción, co-acción, por ejemplo si crean sinergismo etc., y lo hace distinto de las composiciones del grupo I de invención que contienen sólo un solo ingrediente activo del compuesto de fórmula I.

En consecuencia, dado que las realizaciones preferidas de la invención reivindicada, manifiestan una falta evidente de un concepto inventivo común a todas ellas, toda vez que en el desarrollo y caracterización de la composición farmacéutica del compuesto de fórmula I se identifican núcleos estructuralmente diferentes, esta Dependencia recomienda realizar las modificaciones correspondientes.

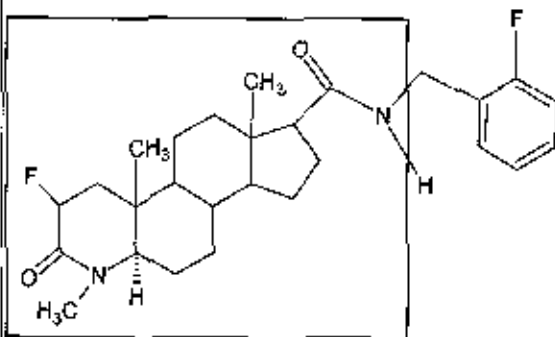
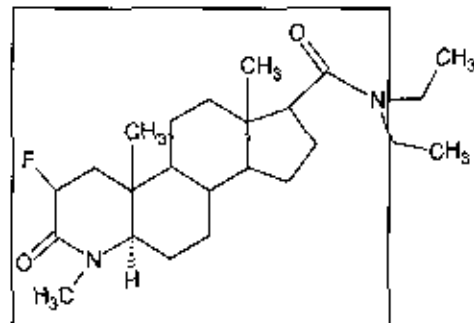
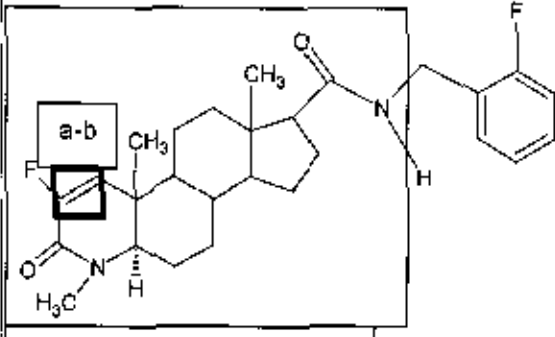
5. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es 13 de Marzo del 2002, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud :

Nº	Documento	Título	Fecha de Publicación*
D1	JOURNAL MEDICAL CHEMISTRY VOL 29 págnas 2298- 2315, RASMUSSEN , GARY.	AZASTETORIDS: STRUCTURE- ACTIVITY RELATION SHIPS FOR INHIBITION OF 5 α - REDUCTASE AND ANDROGEN RECEPTOR BINDING.	1986

6. Análisis de patentabilidad (artículo 14 D486)

Para entender mejor el concepto se realizará el siguiente cuadro comparativo.

SOLICITUD	D1
 Grupo farmacofórico Compuesto 51 de la actual solicitud	 Grupo farmacofórico Compuesto 29, tabla III, página 2301
 Grupo farmacofórico Compuesto 5.1 de la actual solicitud	

6.1 . Nivel inventivo (artículo 18 D486)

El documento del estado de la técnica más cercano es D1 (folios 197-214) que enseña derivados azasteroides , caracterizados por ser inhibidores de la 5 α -reductasa la y de la unión al receptor androgénico, las cuales sirven como reguladores importantes de la acción de la hormona en células andrógeno-sensibles.

La diferencia con D1 son las sustituciones sobre el nitrógeno de la carboxamida del grupo farmacofórico y el doble enlace sobre el carbono que contiene el F (a-b) (derivados de azasteroides fluorados) .

Esta diferencia no parece conceder un efecto técnico inesperado ò una ventaja a los compuestos reivindicados en comparación con los compuestos del Estado de la Técnica más cercano (Ver folio 200 , Compuesto 29, tabla III, página 2301) ; porque estos compuestos **no presentan un mayor efecto modulador del receptor de andrógenos** Ver folios 122-125).

Así que el Problema Técnico planteado en esta solicitud que consiste en la necesidad de derivados de azasteroides que sean moduladores del receptor de andrógenos de una forma selectiva de tejido y son útiles como agonistas del receptor de andrógenos en el tejido óseo y / o muscular que a la vez antagonizan el AR en la próstata de un paciente varón o en el útero de una paciente mujer, se había solucionado previamente mediante compuestos muy similares derivados de azasteroides, sin tener otras sustituciones sobre el nitrógeno de la carboxamida del grupo farmacofórico. De manera que los nuevos compuestos **son una alternativa a los compuestos conocidos porque no presentan un mayor efecto modulador del receptor de andrógenos.**

El experto en la materia en vista del Estado de la Técnica en su totalidad, es decir en vista de D1, hubiera sugerido sin mucho esfuerzo de su parte, modificar los sustituyentes sobre el nitrógeno de la carboxamida del grupo farmacofórico, (por ejemplo por hidrógeno y un grupo arilalquilo) , lo cual es una práctica común en el campo técnico y así lograr los derivados de azasteroides fluorados reivindicados que no parecen **presentar un mayor efecto modulador del receptor de andrógenos.**

Por lo cual se consideran obvios para el experto en la materia. En consecuencia, carecen de nivel inventivo.

La composición farmacéutica de las reivindicaciones 21-28 no tiene nivel inventivo porque el compuesto que la caracteriza no es inventivo.

7. . Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D1	JOURNAL MEDICAL CHEMISTRY VOL 29 páginas 2298- 2315, RASMUSSEN , GARY.	1-36	Nivel inventivo.

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 11 JUL 2008

CONCEPTO TÉCNICO No. 1260	EXAMINADOR TÉCNICO Código No. 202075
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VPC/2008