Azasteroids: Structure–Activity Relationships for Inhibition of 5α-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 5α-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 1α-CN, 1α-CH_3, 1α,2α-CH_2, 2β-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-16 (α and β) were prepared. The majority of the C-17 substituents were prepared from reactive intermediates derived from the 17β-COOH. Enhanced 5α-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-5α-androstane 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 17β-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 5α-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 5α-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 5α-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 5α-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 5α-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 5α-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.

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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 5α-4-azasteroids **9–11** (Scheme I; see the Experimental Section, preparation of **9g**, and ref 8 for applicable R and R_1). 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.

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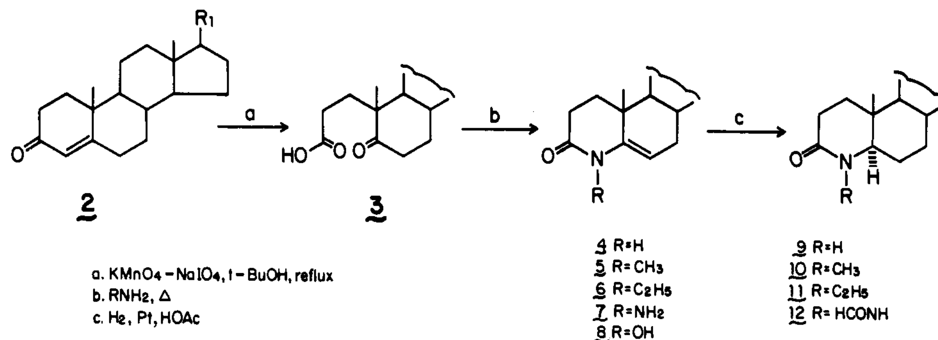
Scheme I



Scheme II

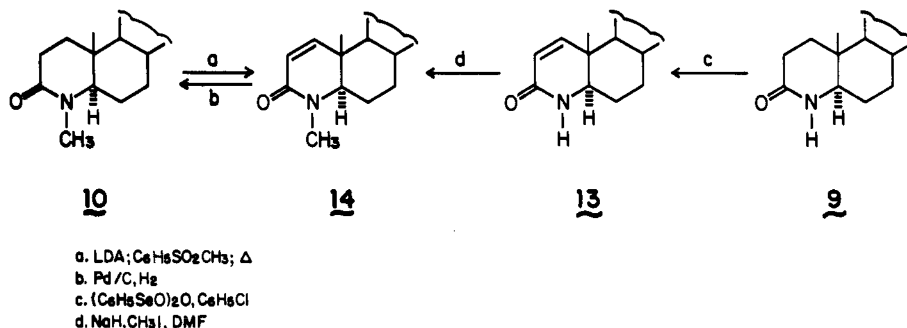


Table I. In Vitro Activities of Substituted Androstan-3-ones[a]

	substituents			in vitro bioactivity		
no.	R	other	ref[b]	human 5α-R: IC_{50}/IC_{50} **10x**	rat 5α-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		190	0.32
1b	=O		39			2.00
2b	=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-$CON(C_2H_5)_2$	Δ^4	8	44	76	34
17x	β-$CON(C_2H_5)_2$	Δ^4, 4-CN		0.83	2.9	130
1ar	α-$CH_2CH_2CH_2O$-β		11		≫100	2.3
2ar	α-$CH_2CH_2CH_2O$-β	Δ^4	35		110	8.9
94	α-$CH_2CH_2CH_2O$-β	Δ^4, 19-nor	35		150	3.0
17ar	α-$CH_2CH_2CH_2O$-β	Δ^4, 4-CN		13		
88	α-$OCOCH_3$, β-$COCH_3$	Δ^4, 6-=CH_2	40	>160	16	1.2
89	β-$COCH_3$	Δ^4, 11α-OH	39	≫30		33

[a] Unless otherwise indicated, 17β-substituted 5α-androstane 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 5α- and 5β-isomers.

Because of the enhanced in vivo activity[19] 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 dehydrogenation[20] of the unsubstituted lactams **9** in refluxing 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^5, 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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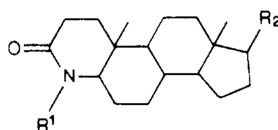
Table II. In Vitro Activities of 17-Substituted-4-azaandrostan-3-ones



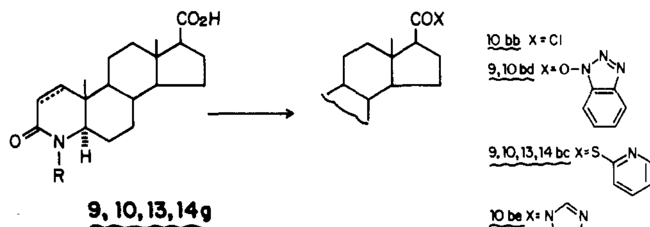
no.	substituents		ref	in vitro bioactivity		
	R_1	R_2		human 5α-R: IC_{50}/IC_{50} **10x**	rat 5α-R: IC_{50}, 10^{-8} M	rat receptor: IC_{50}, 10^{-8} M
9a	H	β-OH	41		25	93
10a	CH$_3$	β-OH	8	>50	15	1.9
9d	H	β-COCH$_3$	8		5	6800
10d	CH$_3$	β-COCH$_3$	8	27	2.3	21
9c	H	β-CHOHCH$_3$		>500	4.5	930
10c	CH$_3$	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			2.5	>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	9.4	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	0.056	68
10n	CH$_3$	β-CONH(CH$_2$)$_4$CH$_3$		2.4		25
9o	H	β-CONH(CH$_2$)$_7$CH$_3$		2.4	0.013	520
10o	CH$_3$	β-CONH(CH$_2$)$_7$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$_{18}$H$_{35}$ (oleyl)		25	2	1700
10r	CH$_3$	β-CONHCH$_2$CH$_2$OH		>62.5	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$_3$H$_7$)$_2$		1.5	1.1	>10000
10y	CH$_3$	β-CON(i-C$_3$H$_7$)$_2$	8	0.82	0.35	1400
10z	CH$_3$	β-CON(n-C$_8$H$_{17}$)$_2$		>125	3.3	4600
10aa	CH$_3$	β-CON(C$_2$H$_5$)CH$_2$CH$_2$OH		3		
10ab	CH$_3$	β-CON(C$_2$H$_4$)$_2$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	96
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	0.34	43
10an	CH$_3$	β-CH(CH$_3$)CN		>62	0.76	29
10ao	CH$_3$	β-CN		83		
10ap	CH$_3$	β-(2-oxazolinyl)		11		
10aq	CH$_3$	β-(4,4-dimethyl-2-oxazolinyl)		125		
9ar	H	α-CH$_2$CH$_2$CH$_2$O-β	8	735	9.3	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-COSC(CH$_3$)$_3$		47		
10ay	CH$_3$	β-COCHN$_2$	43	<6		58
10az	CH$_3$	β-NHCOCH$_3$	8	>330	27	140
10ba	CH$_3$	α-NHCOCH$_3$	8	>500	5.8	4000

in two steps as described previously[8] 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**)

no.	substituents: R_1	substituents: other	ref	in vitro bioactivity: human 5α-R: IC_{50}/IC_{50} **10x**	in vitro bioactivity: rat 5α-R: IC_{50}, 10^{-8} M	in vitro bioactivity: 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_2H_5		8	>125		3200
82	CH_3CO			$\gg$150		
12x	HCONH			>6	40	$\gg$1000
79	H	5β-H		>125	>100	$\gg$1000
23	CH_3	1α-CN		$\gg$150	$\gg$100	$\gg$1000
24	CH_3	1α-CH_3		7	8.6	1600
90	CH_3	2β-CH_3	8	3.6	2.0	610
25	CH_3	1α,2α-CH_2		1.3	2.0	270
91	CH_3	1α,2α-O	8	63		71
29	CH_3	2β-F		5.0		180
92	CH_3	2α-OH	8		46	320
31	CH_3	2α-OCH_3		$\gg$30		>1000
30	CH_3	2β-OCH_3		15		>1000
86	CH_3	2-$(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		60
48	H	D-homo		5.4		
49	CH_3	D-homo		1.6		710
54	CH_3	2-aza		44	50	160
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 esters[22] 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 spirolactone **10as** was conveniently prepared by reaction of the corresponding spiroether **10ar** with disodium chromate in acetic anhydride–acetic acid (Scheme VI).

Early attempts to react the Δ^1-azasteroid **14x** with dimethyloxosulfonium 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

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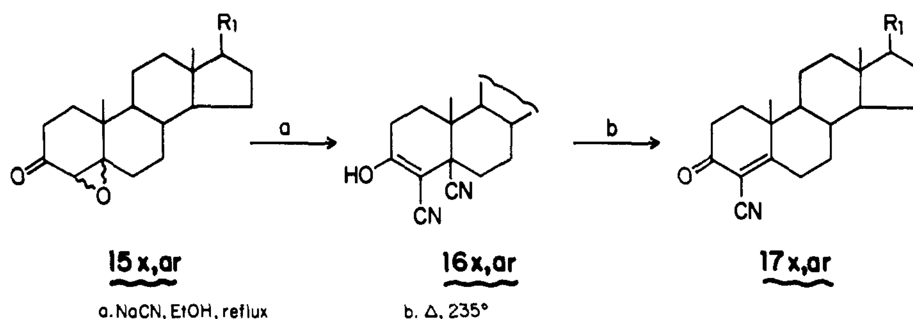
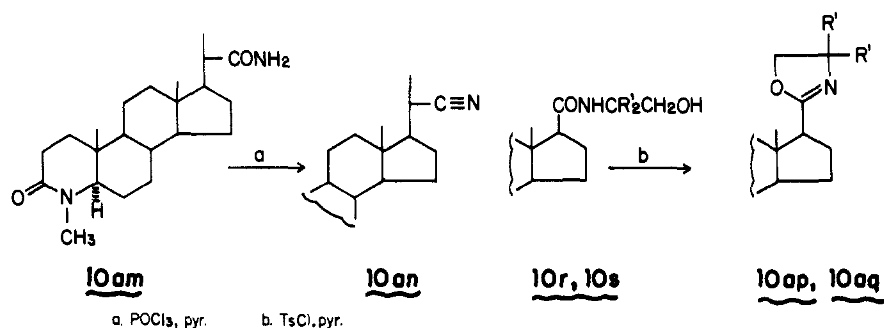
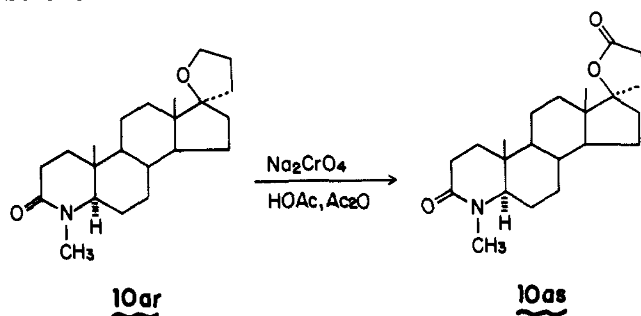
Scheme IV



Scheme V



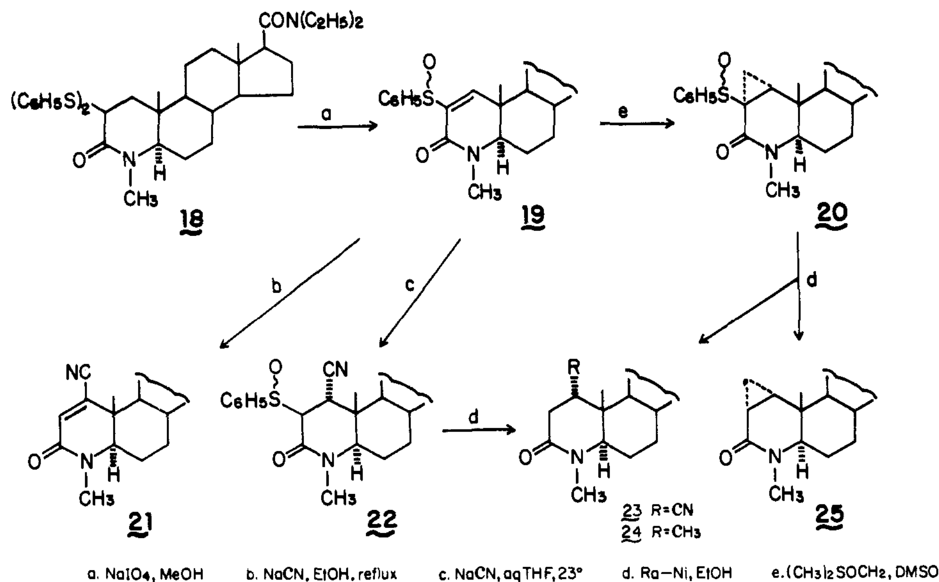
Scheme VI



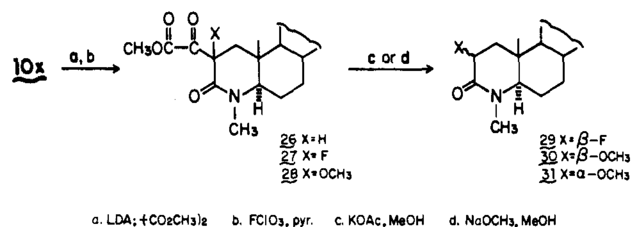
phenylsulfinyl compound 19 (Scheme VII). This material reacted smoothly in refluxing ethanolic sodium cyanide to give the 1-cyano-Δ^1-azasteroid 21. At room temperature, a saturated cyano compound (22) was obtained from this reaction. Raney nickel desulfurization of 22 gave the 1α-cyano compound 23. The sulfinyl compound 19 (a mixture of isomers at sulfur) reacted with DMSM to give a mixture of 1α,2α-methylene products (20). Desulfurization of 20 gave a single 1α,2α-methylene azasteroid (25) and the 1α-methyl compound 24.

To introduce a fluorine at the 2-position, the enolate generated from LDA and **10x** was condensed 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 2α- and 2β-methoxy analogues, 31 and 30, which were separated and identified by the NMR shifts of the angular 19-CH_3 (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-CH_3, which appeared as

Scheme VII



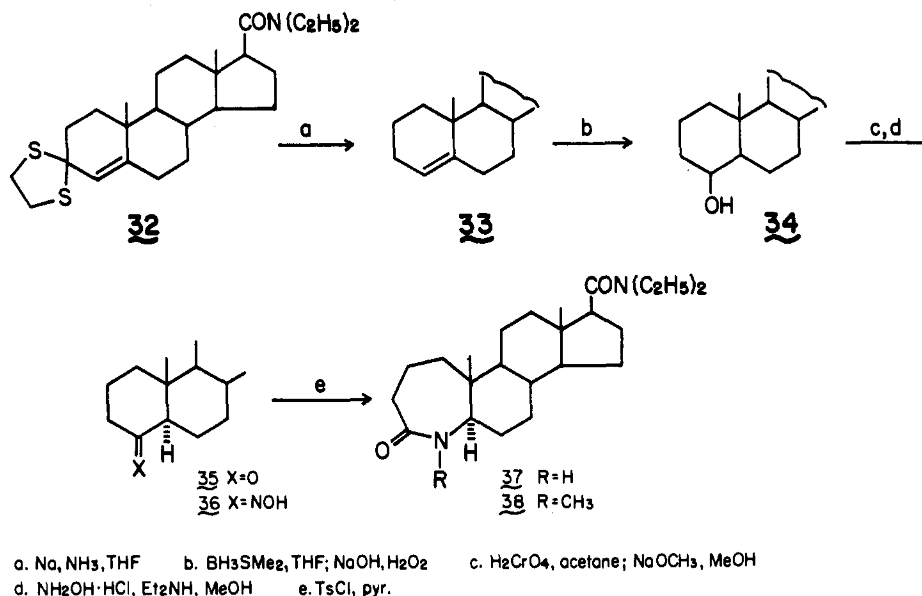
Scheme VIII



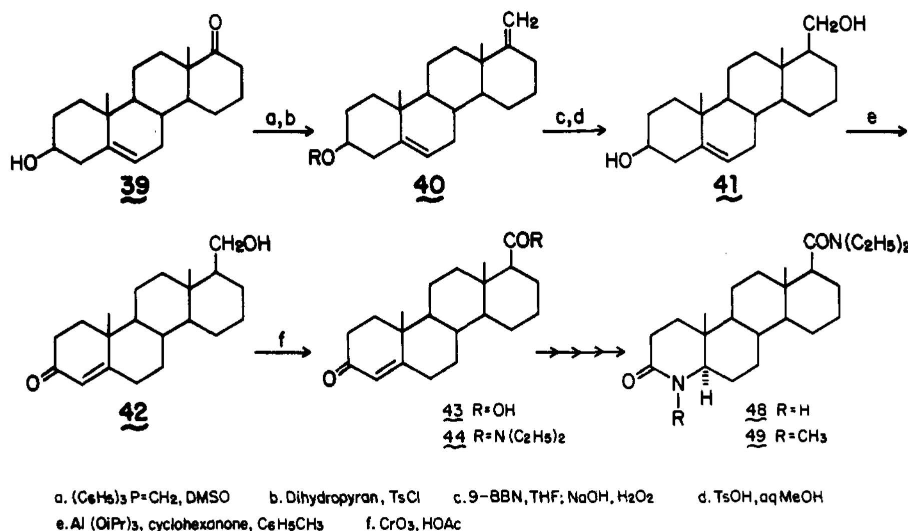
a doublet (J = 1 Hz) at 0.94 ppm.

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

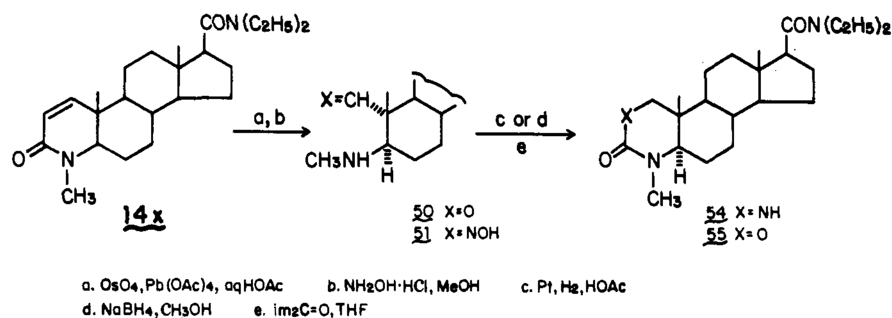
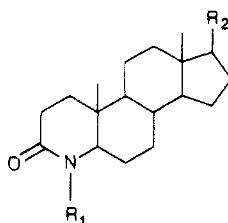


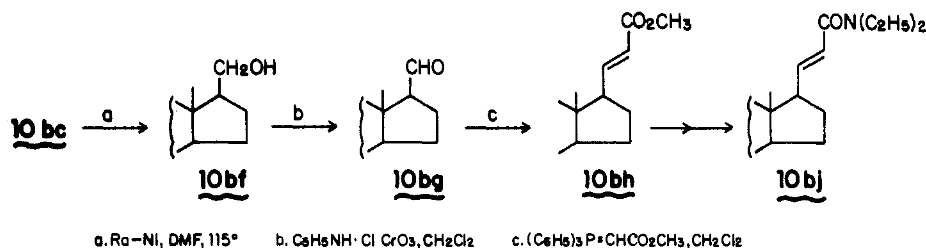
Table IV. In Vitro Activities of Unsaturated 4-Azasteroids



no.	substituents: R_1	substituents: R_2	unsaturation	in vitro bioactivity: human 5α-R: IC_{50}/IC_{50} **10x**	in vitro bioactivity: rat 5α-R: IC_{50} 10^{-8} M	in vitro bioactivity: rat receptor: IC_{50} 10^{-8} M
13a	H	β-OH	Δ^1	100		17
14a	CH_3	β-OH	Δ^1	≫30		0.24
13h	H	β-CO_2CH_3	Δ^1	36		320
14h	CH_3	β-CO_2CH_3	Δ^1	>150		1.3
13i	H	β-$CONH_2$	Δ^1	83		>1000
14i	CH_3	β-$CONH_2$	Δ^1	>150		15
13k	H	β-$CONHC_2H_5$	Δ^1	15		>1000
14k	CH_3	β-$CONHC_2H_5$	Δ^1	150		8.3
14o	CH_3	β-$CONH(CH_2)_7CH_3$	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	15
13p	H	β-$CONHC(CH_3)_2CH_2C(CH_3)_3$	Δ^1	1.2		≫10000
14p	CH_3	β-$CONHC(CH_3)_2CH_2C(CH_3)_3$	Δ^1	3.0		
13x[a]	H	β-$CON(C_2H_5)_2$	Δ^1	6.1	14	>10000
14x[a]	CH_3	β-$CON(C_2H_5)_2$	Δ^1	22	29	45
13y	H	β-$CON(i\text{-}C_3H_7)_2$	Δ^1	1.6	7.9	1800
14y	CH_3	β-$CON(i\text{-}C_3H_7)_2$	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-$CH(CH_3)CO_2CH_3$	Δ^1	30		>10000
14ai	CH_3	β-$CH(CH_3)CO_2CH_3$	Δ^1	150		27
13ah	H	β-$CH(CH_3)CO_2Na$	Δ^1	4.5		>10000
14ah	CH_3	β-$CH(CH_3)CO_2Na$	Δ^1	>25		>10000
13at	H	β-$COCH_2CH(CH_3)_2$	Δ^1	1.8		≫10000
14at	CH_3	β-$COCH_2CH(CH_3)_2$	Δ^1	30		
13au	H	β-$COCH(CH_3)C_2H_5$	Δ^1	7.6	5.0	>10000
14au	CH_3	β-$COCH(CH_3)C_2H_5$	Δ^1	50	12	6.4
13ay	H	β-CO(2-pyrrolyl)	Δ^1	10		800
14av	CH_3	β-CO(2-pyrrolyl)	Δ^1	33		1.5
13ar	H	α-$CH_2CH_2CH_2O$-β	Δ^1	1000	43	150
14ar	CH_3	α-$CH_2CH_2CH_2O$-β	Δ^1	1250	43	11
5a[a]	CH_3	β-OH	Δ^5			0.74
5j	CH_3	β-$CONHCH_3$	Δ^5	37	14	40
5x[a]	CH_3	β-$CON(C_2H_5)_2$	Δ^5	4.5		
4y	H	β-$CON(i\text{-}C_3H_7)_2$	Δ^5	4.0	8.6	1400
5y[a]	CH_3	β-$CON(i\text{-}C_3H_7)_2$	Δ^5	1.6		1000
81	CH_3	β-$CON(i\text{-}C_3H_7)_2$	$\Delta^{1,5}$	27		640
5ah[a]	CH_3	β-$CH(CH_3)CO_2Na$	Δ^5	5.2	1.3	2500
5ae	CH_3	$=CHCO_2C_2H_5$ (*E*)	$\Delta^{5,17(20)}$	100		
10bj	CH_3	β-$CH{=}CHCON(C_2H_5)_2$ (*E*)	Δ^{20}	2.0		

[a] These 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 17a-ketone of *D*-homodehydroisoandrosterone[25] 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 17a-carboxaldehyde accounted for 30% of the reaction product. Chromic acid oxidation of **42** gave the

(25) Kirk, D. N.; Wilson, M. A. *J. Chem. Soc. C* 1971, 414.

Scheme XIII

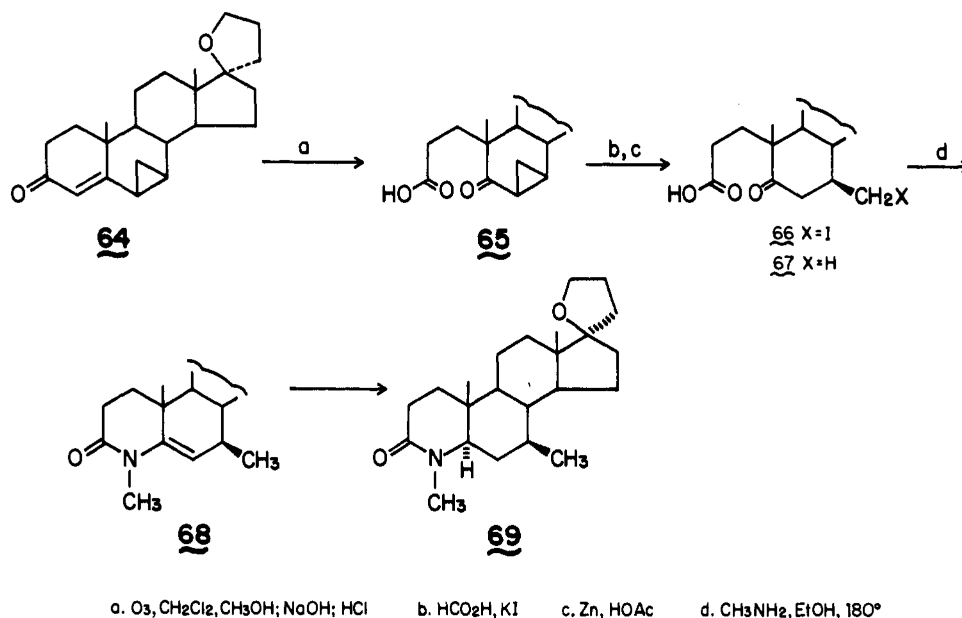


Table V. In Vitro Activities of Other 4-Azasteroid Derivatives

	substituents			in vitro bioactivity		
no.	R_1	R_2	other	human 5α-R: IC_{50}/IC_{50} **10x**	rat 5α-R: IC_{50}, 10^{-8} M	rat receptor: IC_{50}, 10^{-8} M
62	CH_3	β-$COCH_3$	16α-CH_3	22	0.34	29
63	CH_3	β-$COCH_3$	16β-CH_3		1.6	860
60	CH_3	β-$CHOHCH_3$	16α-CH_3	250	0.28	17
80	CH_3	β-$CON(i\text{-}C_3H_7)_2$	5β-H	>30	100	≫1000
69	CH_3	α-$CH_2CH_2CH_2O$-β	7β-CH_3		0.46	50
68	CH_3	α-$CH_2CH_2CH_2O$-β	Δ^5, 7β-CH_3	100		
72	CH_3	α-$CH_2CH_2CH_2O$-β	$\Delta,^5$ 7α-CH_3	>150		
76	CH_3	α-$CH_2CH_2CH_2O$-β	19-nor	>150		200
74	CH_3	α-$CH_2CH_2CH_2O$-β	$\Delta,^5$ 19-nor	>30		24
75	CH_3	α-$CH_2CH_2CH_2O$-β	$\Delta^{5(10)}$, 19-nor	>30		15
7x	NH	β-$CON(C_2H_5)_2$	Δ^5		3.6	540
8x	OH	β-$CON(C_2H_5)_2$	Δ^5		22	19
84	H	β-$CONH_2$	1α-OCH_3	>150		>10000
21	CH_3	β-$CON(C_2H_5)_2$	$\Delta,^1$ 1-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 $Pb(OAc)_4$–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 **10bj** was obtained after saponification and amidation by using the hydroxybenzotriazole activation procedure.

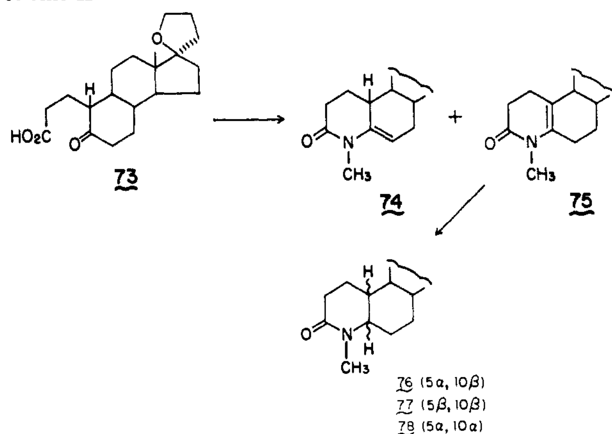
To provide a precursor for a 7β-methyl-substituted azasteroid, the 6β,7β-methylene steroid **64**[27] was ozonized to give the seco acid **65** (Scheme XIII). The cyclopropane ring of **65** was cleaved by hydroiodic acid, and the intermediate iodomethyl compound was reduced with zinc to give a methyl 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 **73** 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*, 831.

(27) Arth, G. E.; Reynolds, G. F.; Rasmusson, 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 those 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 Δ^1 double bond results in a compound (**87**) of equal or slightly increased binding activity whereas a Δ^4 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 Δ^4 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-CO_2CH_3, 17β-$CON(C_2H_5)_2$, and 17β-COOH. The progesterone analogues, **88** and **89**, reported as 5α-reductase inhibitors with antiprostatic[30] and antisebotrophic[31] 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 (R_1 = H), receptor activity was greatly diminished relative to the parent carbocyclic steroid or to the corresponding methyl derivative (R_1 = CH_3). Except for the 4-hydroxy-Δ^5 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 Δ^1 (**14x**), 3-oximino (**93**), A-homo (**38**), and 1α,2α-epoxy (**91**) 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**, **30**), 1-cyano-Δ^1 (**21**), and 1α-cyano (**23**) functionalities.

Unsaturation of the azasteroids at $C_{5,6}$ increased receptor activity (**5j**, **5y**, **5ah**, **74**, **81**). Other activity-decreasing modifications of the ring system include the 7β-methyl (**69**), 16β-methyl (**63**), 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

Table VI. 17-Side-Chain Substituents (Schemes I–IV)

a	β-OH	af	=$CHCON(C_2H_5)_2$ (*E*)
b	=O	ah	β-$CH(CH_3)CO_2H$ (Na)
c	β-$CHOHCH_3$	ai	β-$CH(CH_3)CO_2CH_3$
d	β-$COCH_3$	aj	β-$CH(CH_3)CON(C_2H_5)_2$
e	α-OH,β-$CHOHCH_3$	ak	β-$CH(CH_3)(CH_2)_2CO_2H$ (Na)
f	β-$CH(CH_3)CH_2OH$	al	β-$CH(CH_3)(CH_2)_2CON(C_2H_5)_2$
g	β-CO_2H(K)	am	β-$CH(CH_3)CONH_2$
h	β-CO_2CH_3	an	β-$CH(CH_3)CN$
i	β-$CONH_2$	ao	β-CN
j	β-$CONHCH_3$	ap	β-(2-oxazolinyl)
k	β-$CONHC_2H_5$	aq	β-(4,4-dimethyl-2-oxazolinyl)
l	β-$CONHCH(CH_3)_2$	ar	α-$CH_2CH_2CH_2O$-β
m	β-$CONHC(CH_3)_3$	as	α-$CH_2CH_2CO_2$-β
n	β-$CONH(CH_2)_4CH_3$	at	β-$COCH_2CH(CH_3)_2$
o	β-$CONH(CH_2)_7CH_3$	au	β-$COCH(CH_3)C_2H_5$
p	β-$CONHC(CH_3)_2CH_2C$-$(CH_3)_3$	av	β-CO(2-pyrrolyl)
q	β-$CONHC_{18}H_{35}$ (oleyl)	aw	β-$CO_2C(CH_3)_3$
r	β-$CONHCH_2CH_2OH$	ax	β-$COSC(CH_3)_3$
s	β-CONHC-$(CH_3)_2CH_2OH$	ay	β-$COCHN_2$
t	β-$CONHCH_2CO_2CH_3$	az	β-$NHCOCH_3$
u	β-$CONHCH_2CO_2H$	ba	α-$NHCOCH_3$
v	β-$CONHCH_2CON$-$(C_2H_5)_2$	bb	β-COCl
w	β-$CONHCH_2CH$-$(OCH_3)_2$	bc	β-COS(2-pyridinyl)
x	β-$CON(C_2H_5)_2$	bd	β-CO_2(1-benzotriazolyl)
y	β-$CON(i$-$C_3H_7)_2$	be	β-CO(1-imidazolyl)
z	β-$CON(n$-$C_8H_{17})_2$	bf	β-CH_2OH
aa	β-$CON(C_2H_5)$-CH_2CH_2OH	bg	β-CHO
ab	β-$CON(C_2H_4)_2O$	bh	β-$CH{=}CHCO_2CH_3$
ac	β-$CH_2CO_2C_2H_5$	bi	β-$CH{=}CHCO_2H$
ad	β-$CH_2CON(C_2H_5)_2$	bj	β-$CH{=}CHCON(C_2H_5)_2$
ae	=$CHCO_2C_2H_5$	bk	β-$OSi(CH_3)_2C(CH_3)_3$

(28) Liang, T.; Heiss, C. E. *J. Biol. Chem.* 1981, *256*, 7998.
(29) Brooks, J. R.; Baptista, E. M.; Berman, C.; Ham, E. A.; Hichens, M.; Johnston, D. B. R.; Primka, R. L.; Rasmusson, G. H.; Reynolds, G. F.; Schmitt, S. M.; Arth, G. E. *Endocrinology (Baltimore)* 1981, *109*, 830.
(30) Petrow, V.; Lack, L. *The Prostatic Cell: Structure and Function*, Alan R. Liss: New York, 1981; Part B, pp 283–297.
(31) Tamm, J.; Seckelmann, M.; Volkwein, U.; Ludwig, E. *Br. J. Dermatol.* 1982, *107*, 63.

carbocyclic system. Thus, in decreasing order of receptor activity are active compounds with the following side chains: 17β-OH (**10a**), 17β-$CH_2CO_2C_2H_5$ (**10ac**), 17β-$CHOHCH_3$ (**10c**), the spirolactone (**10as**), the ketopyrrole (**10av**), 17β-CO_2CH_3 (**10h**), 17β-$CONH(CH_2)_7CH_3$ (**10o**), 17-spiro THF (**10ar**), 17β-$COCH_3$ (**10d**), 17β-$CONH(CH_2)_4CH_3$ (**10n**), 17β-$CH(CH_3)CN$ (**10an**), and 17β-$CONH_2$ (**10i**).

Carboxyl-containing side chain analogues were very weak antagonists (**10g**, **10ah**, **10ak**), as were analogues with hydrogen-bonding groups in the 17α-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 cholanic 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 5α-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 5α-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 5α-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 1α-methyl (**24**), 2β-methyl (**90**), 1α,2α-methylene (**25**), and 4-amino-Δ^5 (**7x**) derivatives.

Unsaturation at $C_{1,2}$ or $C_{5,6}$ of the azasteroids resulted in reduced 5α-reductase inhibitory activity (cf. Table II to Table IV). The addition of a 7β-methyl group increased activity (**10ar** vs. **69**) as did the incorporation of a 16α- or 16β-methyl group (**10d** vs. **62** or **63**). Hydrogen-bonding groups at the 17α-position (**10e**, **10ba**) appeared to enhance activity.

Modification of the side chain at C-17 of the azaandrostanes has afforded a series of compounds with a broad range of activity (Table II). As has been noted previously,[8,11] 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 **10m**, **10o**, and **9o**, which have IC_{50} 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 5α-reductase correspond closely to the IC_{50} values obtained in this assay.

Human Prostatic 5α-Reductase. The reference standard in this assay, compound **10x**, has been reported to have an IC_{50} 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 $\times 10^{-8}$ as those listed under the rat 5α-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 $C_{1,2}$ or $C_{5,6}$ 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 pyrrolo and diazo ketones (**10av** and **10ay**) show higher activity than might be expected for such polar-appearing derivatives whereas substitutions at the 17α-position would appear to interfere with optimal activity (cf. **10e**, **10ar**). Methyl substitution at the 7β-position was favored over the 7α-position in the Δ^5 compounds **68** and **72**.

Conclusion. These data reinforce our earlier concepts of 5α-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 animal[14] or from prostates of different disease states.[10] However, there are relative differences in the selectivity of 5α-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 5α-reduced Δ^3-enol that occurs on the enzyme in proceeding from the Δ^4-3-ketone to the 5α-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 5α-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-

(32) Rasmusson, G. H.; Liang, T.; Brooks, J. R. In *Gene Regulation by Steroid Hormones II*, Roy, A. K., Clark, J. H., Eds.; Springer-Verlag: New York, 1983; Chapter 19.

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 5α-reductase inhibition and receptor inhibition. Alternately, by leaving the 4-nitrogen unsubstituted it is possible to prepare 5α-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 $CDCl_3$ solution and are reported as ppm values downfield from Me_4Si. 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 × 30 cm μPorasil 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 μm. 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.

17β-Carboxy-5-oxo-*A*-nor-3,5-secoandrostan-3-oic Acid (3g). A solution of 3-oxo-4-androstene-17β-carboxylic acid (**2g**)[8] (200 g, 0.633 mol) in a mixture of 3.5 L of 2-methyl-2-propanol and 500 mL of 40% aqueous Na_2CO_3 was treated with a solution of 948.5 g of $NaIO_4$ and 6.95 g of $KMnO_4$ in 3.5 L of water at 80 °C and worked up as in the procedure described previously.[8] The crude product crystallized on treatment with a Et_2O-hexane mixture to leave the diacid **3g** (152.2 g), mp 189–192 °C.

Other 3-keto-Δ^4 steroids were converted to the following new seco acids: 2′,3′α-tetrahydrofuran-2′-spiro-17-(7α-methyl-5-oxo-*A*-nor-3,5-secoandrostan-3-oic acid) (**71**); 2′,3′α-tetrahydrofuran-2′-spiro-17-(5-oxo-*A*,19-dinor-3,5-secoandrostan-3-oic acid) (**73**); 5,20-dioxo-16α-methyl-*A*-nor-3,5-secopregnan-3-oic acid (**56**); mp 204–206 °C; 5,20-dioxo-16β-methyl-*A*-nor-3,5-secopregnan-3-oic acid (**57**), M^+ 420 (Me_3Si); and 17aβ-(diethylcarbamoyl)-5-oxo-*D*-homo-*A*-nor-3,5-secoandrostan-3-oic acid (**45**), mp 218–220 °C.

3-Oxo-4-aza-5-androstene-17β-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-17β-carboxamide (**5j**), mp 247–249 °C (a byproduct of the condensation of methylamine with the corresponding secosteroid 17β-methyl ester); *N*,*N*-diethyl-3-oxo-4-aza-*D*-homo-5-androstene-17aβ-carboxamide (**46**), mp 198–199 °C; *N*,*N*-diethyl-4-methyl-3-oxo-4-aza-*D*-homo-5-androstene-17aβ-carboxamide (**47**), M^+ 400; *N*,*N*-diisopropyl-3-oxo-4-aza-5-androstene-17β-carboxamide (**4y**), mp 276–279 °C; 3-oxo-4-aza-5-pregnene-20α-carboxylic acid (**4ah**), mp >300 °C; 4,16α-dimethyl-4-aza-5-pregnene-3,20-dione (**58**), mp 160–162 °C; 4,16β-dimethyl-4-aza-5-pregnene-3,20-dione (**59**), mp 145–147 °C; 2′,3′α-tetrahydrofuran-2′-spiro-17-(4,7α-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-17β-carboxamide (8x).** A solution of the seco acid **3x**[8] (0.5 g, 1.3 mmol), 10 mL of 5% KOH solution, and 0.15 g of NH_2OH–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 × 20 cm × 1000 μm) eluted with 4% CH_3OH in $CHCl_3$. Isolated was 78 mg, mp 223–225 °C.

3-Oxo-4-aza-5α-androstane-17β-carboxylic Acid (9g). Hydrogenation at 60 °C of 136 g (0.43 mol) of the above Δ^5-azasteroid **4g** in 1630 mL of HOAc in the presence of PtO_2 (16.3 g) at 40 psig for 3 h gave, after filtration, evaporation, and water wash, 125 g of the desired 5α-reduced product **9g**, mp >310 °C.

In addition, the following 5α-4-azasteroids have been prepared by a similar procedure: 20-hydroxy-4-aza-5α-pregnan-3-one (**9c**), mp 300–302 °C; *N*-methyl-4-methyl-3-oxo-4-aza-5α-androstane-17β-carboxamide (**10j**), mp 265–268 °C; *N*,*N*-di-2-propyl-3-oxo-4-aza-5α-androstane-17β-carboxamide (**9y**), mp 296–298 °C; 3-oxo-4-aza-5α-pregnane-20α-carboxylic acid (**9ah**), mp 313–315 °C; *N*,*N*-diethyl-3-oxo-4-aza-*D*-homo-5α-androstane-17aβ-carboxamide (**48**), mp 264–265 °C dec; 4,16α-dimethyl-20-hydroxy-4-aza-5α-pregnan-3-one (**60**), mp 218–220 °C; 4,16β-dimethyl-20-hydroxy-4-aza-5α-pregnan-3-one (**61**), mp 206–208 °C; 2′,3′α-tetrahydrofuran-2′-spiro-17-(4,7β-dimethyl-4-aza-5α-androstan-3-one) (**69**), mp 115–119 °C; and 2′,3′α-tetrahydrofuran-2′-spiro-17-(4-methyl-4-aza-19-nor-5α-androstan-3-one) (**76**), mp 166–167 °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-5β-androstan-3-one) (**77**), mp 95–97 °C, and 2′,3′α-tetrahydrofuran-2′-spiro-17-(4-methyl-4-aza-19-nor-5α,19α-androstan-3-one) (**78**), mp 139–140 °C.[33]

The 5β-reduced isomers, *N*,*N*-diethyl-3-oxo-4-aza-5β-androstane-17β-carboxamide (**79**), mp 186–188 °C, and *N*,*N*-diisopropyl-4-methyl-3-oxo-4-aza-5β-androstane-17β-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-5α-androstane-17β-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 CH_3OH 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 CH_3OH 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 Et_2O–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-5α-pregnane-20α-carboxylate (**9ai**), mp 268–270 °C, was prepared from its corresponding acid.

Methyl 3-Oxo-4-aza-5α-androst-1-ene-17β-carboxylate (13h). 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 CH_2Cl_2 was washed successively with saturated $NaHCO_3$ and NaCl solutions, then dried, and reisolated by concentration. The crude product was eluted through 2.5 kg of silica gel with increasing percentages of acetone in CH_2Cl_2. After elution of nonpolar aromatic byproducts, the desired product (53.4 g) was eluted with 20% acetone. The isolated product was rinsed with 3 × 100 mL of Et_2O to give 49.5 g of **13 h**, 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 17β-hydroxy analogues (ref. 8 and E. Walton, unpublished data).

ethyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide (**13k**), mp 265–267 °C; *N*-(2-methyl-2-propyl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide (**13m**), mp 251–253 °C; *N*-(2,4,4-trimethyl-2-pentyl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide (**13p**), mp 224–226 °C; *N*,*N*-di-2-propyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide (**13y**), mp 290–292 °C; methyl 3-oxo-4-aza-5α-pregn-1-ene-20α-carboxylate (**13ai**), mp 259–261 °C; 23-methyl-4-aza-21-nor-5α-chol-1-ene-3,20-dione (**13at**), mp 283–286 °C (darkens); 22-methyl-4-aza-21-nor-5α-chol-1-ene-3,20-dione (**13au**), mp 239–241 °C; 2′,3′α-tetrahydrofuran-2′-spiro-17-(4-aza-5α-androst-1-en-3-one (**13ar**), mp 271–272 °C; and 17β-[(*tert*-butyldimethylsilyl)oxy]-4-aza-5α-androst-1-en-3-one (**13bk**), mp 285 °C dec.

***N*,*N*-Diethyl-4-formamido-3-oxo-4-aza-5α-androstane-17β-carboxamide (12x).** A solution of 2.0 g (5.1 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 860 mg of crystalline *N*,*N*-diethyl-4-amino-3-oxo-4-aza-5-androstene-17β-carboxamide (**7x**). Recrystallization from Et_2O gave material, mp 168–170 °C (softens 162–164 °C).

To a solution of the 4-amino-Δ^5 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, CH_3OH was added and the mixture was concentrated to dryness. The residue was extracted with $CHCl_3$, and the $CHCl_3$ layer was washed with 5% $NaHCO_3$ 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 × 20 cm × 1000 μm silica gel plate eluted with 4% CH_3OH in $CHCl_3$. Isolated was 15 mg of **12x**, mp 248–250 °C.

***N*,*N*-Di-2-propyl-4-methyl-3-oxo-4-aza-1,5-androstadiene-17β-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 **5y**[8] (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 benzenesulfinate[34] (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% $NaHCO_3$ 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 phenylsulfinyl 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-5α-androst-1-ene-17β-carboxamide (**14y**), mp 171–173 °C; 2′,3′α-tetrahydrofuran-2′-spiro-17-(4-methyl-4-aza-5α-androst-1-en-3-one) (**14ar**), mp 129–131 °C; and 17β-[(*tert*-butyldimethylsilyl)oxy]-4-methyl-4-aza-5α-androst-1-en-3-one (**14bk**), mp 127–128 °C, were prepared by a three-step sequence (2-phenylsulfenylation, $NaIO_4$ oxidation to phenylsulfinyl steroid, and pyrolysis) starting from the corresponding saturated precursors according to the previously described procedure.[8]

Methyl 4-Methyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxylate (14h). 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 CH_3I (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 **14h**, mp 159–161 °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-5α-androst-1-ene-17β-carboxamide (**14x**), mp 200–202 °C; methyl 4-methyl-3-oxo-4-aza-5α-pregn-1-ene-20α-carboxylate (**14ai**), mp 166–167 °C; *N*-(2,4,4-trimethyl-2-pentyl)-4-methyl-3-oxo-4-aza-5α-androstane-17β-carboxamide (**10p**), mp 148–150 °C; *N*-(2-methyl-2-propyl)-4-methyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide (**14m**), mp 154–156 °C; and *N*,*N*-diethyl-4-methyl-3-oxo-4-aza-*D*-homo-5α-androstane-17aβ-carboxamide (**49**), mp 175–176 °C.

3-Oxo-4-aza-5α-androst-1-ene-17β-carboxylic Acid (13g). A suspension of the ester **13h** (25 g, 75 mmol) in a solution prepared from 12.5 g of KOH in 150 mL of 5:1 CH_3OH–H_2O 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 CH_3OH addition product 1α-methoxy-3-oxo-4-aza-5α-androstane-17β-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-5α-androst-1-ene-17β-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-5α-pregn-1-ene-20α-carboxylic Acid (14ah). A suspension of the Δ^1 ester **14ai** (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 $CHCl_3$ and acidified. The separated solid was removed, washed well with water, and then dried. The solid was extracted with hot CH_3OH, 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-5α-pregn-1-ene-20β-carboxylic acid (**13ah**), mp 310–312 °C with decomposition.

4,23-Dimethyl-4-aza-21-nor-5α-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 550 mg of **10at**, mp 104–106 °C.

***N*,*N*-Diethyl-4-acetyl-3-oxo-4-aza-5α-androstane-17β-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 Ac_2O 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 456 mg (mp 186–188 °C) of **82** after evaporation and trituration with Et_2O.

***N*-(1-Hydroxy-2-methyl-2-propyl)-4-methyl-3-oxo-4-aza-5α-androstane-17β-carboxamide (10s). Acid Chloride Procedure.** A suspension of 4-methyl-3-oxo-4-aza-5α-androstane-17β-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 CH_2Cl_2. The organic layer wa washed with 2 N HCl and water and then dried (Na_2SO_4). 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 Et_2O to give 219 mg, mp 151–153 °C.

A similar amidation procedure was used to prepare the following 17β-carboxamides from the same starting acid: *N*-2-propyl **10l**, mp 221–224 °C; *N*-pentyl **10n**, amorphous solid, M^+ 402; *N*-oleyl ($C_{18}H_{35}$) **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 morpholide **10ab**, mp 198–200 °C. From 4-methyl-3-oxo-4-aza-5α-pregnane-20α-carboxylic acid (**10ah**) was obtained 4-methyl-3-oxo-4-aza-5α-pregnane-20α-carboxamide (**10am**), mp 260–262 °C.

Benzotriazol-1′-yl 3-Oxo-4-aza-5α-androstane-17β-carboxylate (9bd) and Its Conversion to *N*-1-Octyl-3-oxo-4-aza-5α-androstane-17β-carboxamide (9o). A solution of the acid **9g** (500 mg, 1.57 mmol), *N,N′*-dicyclohexylcarbodiimide (335 mg), and *N*-hydroxybenzotriazole (318 mg) in 50 mL of CH_2Cl_2 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 × 20 cm × 1000 μm, silica gel) eluted with 4% CH_3OH in $CHCl_3$. 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 μL of *n*-octylamine. After standing at 4 °C for 16 h, the mixture was washed successively with saturated $NaHCO_3$, 1 N HCl, and saturated NaCl solutions. The organic solution was dried (Na_2SO_4) and evaporated. The residue was chromatographed (TLC, four plates, 20 cm × 20 cm × 1000 μm, silica gel) by elution with 1:1 hexane–acetone. The major water opaque band was extracted, and the isolated product was crystallized with Et_2O to give 80 mg of **9o**, mp 165–167 °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-5α-androstane-17β-carboxamide (**9p**), mp 250–251 °C; *N*-(carbomethoxymethyl)-4-methyl-3-oxo-4-aza-5α-androstane-17β-carboxamide (**10t**), mp 217–219 °C; *N*-(2-methyl-2-propyl)-3-oxo-4-aza-5α-androstane-17β-carboxamide (**9m**), mp 275–276 °C; *N,N*-diethyl-4-methyl-3-oxo-4-aza-5α-pregn-20-ene-21-carboxamide (**10bj**), mp 174–176 °C; and *N*-[(*N′,N′*-diethylcarbamoyl)methyl]-4-methyl-3-oxo-4-aza-5α-androstane-17β-carboxamide (**10v**), mp 174–176 °C.

***S*-2-Pyridyl 3-Oxo-4-aza-5α-androstane-17β-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–CH_2Cl_2. The desired thio ester **9bc** eluted slowly and, after rinsing with Et_2O, 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-5α-androstane-17β-thiocarboxylate (**10bc**), mp 207–209 °C; *S*-2-pyridyl 3-oxo-4-aza-5α-androst-1-ene-17β-thiocarboxylate (**13bc**), mp 230–232 °C; *S*-2-pyridyl 4-methyl-3-oxo-4-aza-5α-androst-1-ene-17β-thiocarboxylate (**14bc**), mp 218–220 °C; and *S*-2-pyridyl 1α-methoxy-3-oxo-4-aza-5α-androstane-17β-thiocarboxylate (**83**), mp 196–198 °C.

Reaction of Amines with Thiopyridyl Esters. *N*-(2-Methyl-2-propyl)-3-oxo-4-aza-5α-androstane-17β-carboxamide (9m). A suspension of the thiopyridyl ester **9bc** (883 mg, 2.15 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 CH_2Cl_2–acetone to give the desired product, which was eluted after a colored nonpolar material. The isolated product **9m** after rinsing with Et_2O amounted to 700 mg, mp 275–276 °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-5α-androstane-17β-carboxamide (**10m**), mp 198–200 °C; 3-oxo-4-aza-5α-androstane-17β-carboxamide (**9i**), mp 224–226 °C; 3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide (**13i**), mp 332–333 °C; 4-methyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide (**14i**), mp 289–291 °C; *N*-ethyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide (**13k**), mp 257–259 °C; *N*-ethyl-4-methyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide (**14k**), mp 240–242 °C; *N*-octyl-4-methyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide (**14o**), mp 106–108 °C; *N*-(2,4,4-trimethyl-2-pentyl)-4-methyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide (**14p**), mp 168–170 °C; and 1α-methoxy-3-oxo-4-aza-5α-androstane-17β-carboxamide (**84**), mp 205–207 °C.

Reaction of Grignard Reagents with Thiopyridyl Esters. 22-Methyl-4-aza-21-nor-5α-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 Et_2O (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 CH_2Cl_2. The combined filtrates were concentrated to a residue, which was dissolved in CH_2Cl_2, 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 CH_2Cl_2. The major eluted product was isolated and rinsed with ether to give 4.5 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 CH_3CN. 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 5α-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-5α-cholane-3,20-dione (**9at**), mp 220–222 °C; 22-methyl-4-aza-21-nor-5α-cholane-3,20-dione (**9au**), mp 223–225 °C; 4,22-dimethyl-4-aza-21-nor-5α-cholane-3,20-dione (**10au**), mp 138–140 °C; 17β-(2-pyrrylcarbonyl)-4-aza-5α-androstan-3-one (**9av**), mp 267–270 °C; 4-methyl-17β-(2-pyrrylcarbonyl)-4-aza-5α-androstan-3-one (**10av**), mp 222–224 °C; 4,23-dimethyl-4-aza-21-nor-5α-chol-1-ene-3,20-dione (**14at**), mp 147–149 °C; 4,22-dimethyl-4-aza-21-nor-5α-chol-1-ene-3,20-dione (**14au**), mp 134–136 °C; 17β-(2-pyrrylcarbonyl)-4-aza-5α-androst-1-en-3-one (**13av**), mp 294–296 °C; and 4-methyl-17β-(2-pyrrylcarbonyl)-4-aza-5α-androst-1-en-3-one (**14av**), mp 247–248 °C.

***tert*-Butyl 4-Methyl-3-oxo-4-aza-5α-androstane-17β-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 μL 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 60 min of additional stirring, the mixture was diluted to 8 mL with CH_2Cl_2. The solution was washed successively with H_2O, 5% NH_4OH 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 × 20 cm × 1000 μm) eluted with 2:2:1 acetone–EtOAc–CH_2Cl_2. 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-5α-androstane-17β-carboxylate (**9aw**), mp 230–250 °C with decomposition.

***S*-2-Methyl-2-propyl 4-Methyl-3-oxo-4-aza-5α-androstane-17β-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 CH_2Cl_2 was washed with water, saturated $NaHCO_3$ 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 CH_2Cl_2, amounted to 119 mg, mp 188–189 °C.

***N,N*-Diethyl-4-cyano-3-oxo-4-androstene-17β-carboxamide (17x).** A solution of *N,N*-diethyl-3-oxo-4-androstene-17β-carboxamide[8] (**2x**) (1.25 g, 3.37 mmol) in 28 mL of CH_3OH was treated at 0 °C with 30% H_2O_2 (2.24 mL, 22 mmol) and 2.5 N NaOH (0.9 mL in 1.35 mL of CH_3OH). The solution was stirred at 0–10 °C for 6 h. The solution was poured into ice water and was extracted with EtOAc–Et_2O with use of NaCl to break the emulsion. The organic layer was washed with water, dried with Na_2SO_4, and evaporated to leave *N,N*-diethyl-4,5-epoxy-3-oxo-

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

A solution of this epoxide **15x** (1.0 g, 2.59 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 Et_2O and then acidified with 6 N HCl. The separated solid was dissolved in EtOAc, and the solution was washed with water, then dried (Na_2SO_4), and concentrated. The residue was recrystallized from CH_3OH–EtOAc to leave 537 mg of *N*,*N*-diethyl-4,5-dicyano-3-hydroxy-3-androstene-17β-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 160–161 °C.

20α-Cyano-4-methyl-4-aza-5α-pregnan-3-one (10an). To a 0 °C solution of the amide **10am** (190 mg, 0.53 mmol) in 1.0 mL of pyridine was added 0.13 mL of $POCl_3$. 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 $CHCl_3$ 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 Et_2O afforded 100 mg of the nitrile **10an**, mp 223–225 °C.

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

17β-(4,4-Dimethyloxazin-2-yl)-4-methyl-4-aza-5α-androstan-3-one (10aq). A solution of the amide **10s** (160 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% $NaHCO_3$ solution for 3 h. The product was extracted into $CHCl_3$, 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 17β-oxazin-2-yl-4-methyl-4-aza-5α-androstan-3-one (**10ap**), mp 212–214 °C, isolate by preparative HPLC.

17β-Hydroxy-4-methyl-3-oxo-4-aza-5α-pregnane-21-carboxylic Acid Lactone (10as).[36] Disodium chromate tetrahydrate was dried at 100 °C at 1 mmHg for 16 h over P_2O_5. To a solution of 2′,3′α-tetrahydrofuran-2′-spiro-17-(4-methyl-4-aza-5α-androstan-3-one) (**10ar**) (0.50 g, 1.45 mmol) in a mixture of 3.79 mL of HOAc and 2.2 mL of Ac_2O was added Na_2CrO_4 (472 mg, 2.9 mmol). The solution was heated at 39 °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 CH_2Cl_2, washed with 5% $NaHCO_3$, water, and saturated NaCl, then dried (Na_2SO_4), 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 Et_2O to afford 185 mg, mp 202–204 °C.

***N*,*N*-Diethyl-4-methyl-3-oxo-2-(phenylsulfinyl)-4-aza-5α-androst-1-ene-17β-carboxamide (19).** A solution of 1.067 g (5.0 mmol) of $NaIO_4$ in 8 mL of water was added to a solution of 1.0 g (1.65 mmol) of *N*,*N*-diethyl-2,2-bis(phenylsulfenyl)-4-methyl-3-oxo-4-aza-5α-androstane-17β-carboxamide (**18**)[8] in 24 mL of CH_3OH. The mixture was stirred at 23 °C for 48 h. The mixture was concentrated under reduced pressure to remove the CH_3OH and then was extracted with EtOAc. The organic layer was worked up to leave a gummy residue. The material was eluted through 100 g of silica gel with EtOAc to give *N*,*N*-diethyl-4-methyl-3-oxo-2-(phenylsulfenyl)-4-aza-5α-androst-1-ene-17β-carboxamide[8] (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 phenylsulfenyl compound A (346 mg) with $NaIO_4$ (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(phenylsulfenyl) compound **18** and 7.4 g of $NaIO_4$ 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-5α-androstane-17β-carboxamide (**86**), mp 130–133 °C dec.

***N*,*N*-Diethyl-1-cyano-4-methyl-3-oxo-4-aza-5α-androst-1-ene-17β-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 × 20 cm × 500 μm; acetone–hexane, 3:5) afforded 21 mg of crystalline **21**. Recrystallization from Et_2O–heptane gave 15 mg, mp 162–165 °C.

***N*,*N*-Diethyl-1α-cyano-4-methyl-3-oxo-4-aza-5α-androstane-17β-carboxamide (23).** A mixture of NaCN (105 mg, 2.1 mmol), the sulfinyl olefin **19** (75 mg, 0.15 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 <23 °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 × 20 cm × 500 μm; acetone–hexane, 1:1). The major component (**23**) was isolated and crystallized from Et_2O to give 10 mg, mp 217–219 °C.

***N*,*N*-Diethyl-4-methyl-1α,2α-methylene-3-oxo-2-(phenylsulfinyl)-4-aza-5α-androstane-17β-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 $(CH_3)_3SOI$) 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 isomerism 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-1α,2α-methylene-3-oxo-4-aza-5α-androstane-17β-carboxamide (25) and *N*,*N*-Diethyl-1α,4-dimethyl-3-oxo-4-aza-5α-androstane-17β-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 Et_2O–hexane gave 69 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–Et_2O to give 28 mg of the 1α-methyl steroid **24**, mp 175–178 °C.

A similar experiment with 25 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 173–175 °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 160 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 (Na_2SO_4), 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 **26**.

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 $2^1/_2$ 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 Et_2O. The Et_2O 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 CH_3OH was heated at reflux for 48 h. The solution was evaporated, and the residue was treated with water and Et_2O. The Et_2O 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 2.5 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 $C_{26}H_{39}N_2O_5F{\cdot}H_2O$ 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-carboxamide (31 and 30).** A solution of the methoxy methoxalyl steroid **28** (250 mg, 0.5 mmol) and 500 mg of $NaOCH_3$ in 10 mL of CH_3OH 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-3,3-(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 CH_3OH 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 60 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 0.806 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% H_2O_2 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% $NaHSO_3$ solution, and saturated NaCl solution. After drying and concentration of the solution, the residue (530 mg) was recrystallized twice from EtOAc–heptane 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 reagent[38] was added at 0 °C with vigorous agitation to a suspension of the pure 4α-hydroxy steroid **34** (130 mg, 0.35 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, 1.06 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 150 mg of sodium methoxide in 15 mL of CH_3OH 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 Δ^4-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 $NH_2OH{\cdot}HCl$, and 4 drops of diethylamine in 6 mL of CH_3OH stood at 23 °C for 60 min. Water (8 mL) was added, and the solid

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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 225–230 °C.

***N,N*-Diethyl-4-oxo-4a-aza-*A*-homo-5α-androstane-17β-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-5α-androstane-17β-carboxamide (38).** Oil-free sodium hydride (9.0 mg, 0.4 mmol) was added to a solution of 60 mg (0.15 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 × 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 188–189 °C.

17a-Methylene-*D*-homo-5-androsten-3β-ol (40) and Its THP Ether. To a suspension of 462 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 12.5 mL of Me_2SO. After 2 h, the resulting clear solution was treated with a solution of 1.0 g of *D*-homodehydroisoandrosterone[25] **39** (3.3 mmol) in 13 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 = H) was purified by chromatography on silica gel (250 g, eluted with 70:30 cyclohexane–EtOAc) to give 900 mg of **40** (R = H), mp 140–142 °C.

A solution of 900 mg (3.0 mmol) of the above methylene steroid and 50 mg of *p*-TsCl 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 = THP), mp 139–140 °C.

17aβ-(Hydroxymethyl)-*D*-homo-5-androsten-3β-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 39 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, 3β-(tetrahydropyranyloxy)-*D*-homo-5-androsten-17β-ylmethanol, amounted to 3.4 g, mp 130–132 °C.

A solution of the above material (6.4 g, 15.9 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.

17aβ-(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 2.63 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-17aβ-carboxaldehyde, ^1H NMR ($CDCl_3$) δ 0.98 (18-CH_3), 1.00 (19-CH_3), 4.72 (4-H), and 9.83 (d, *J* = 2 Hz, 17a-CHO). Additional 17a-carbinol **42** (1.96 g, mp 152–153 °C) was isolated from later fractions.

3-Oxo-*D*-homo-4-androstene-17aβ-carboxylic Acid (43) and the Corresponding Diethyl Amide (44). To a solution of the 17aβ-hydroxymethyl steroid **42** (2.63 g, 8.3 mmol) in 76 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 = 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**.[8]

***N,N*-Diethyl-1-oxo-3-aza-1,2-seco-*A*-nor-5α-androstane-17β-carboxamide (50).** Osmium tetraoxide (40 mg) was added to a mixture of *N,N*-diethyl-4-methyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide (**14x**)[8] (500 mg, 1.3 mmol), 2.5 g of $Pb(OAc)_4$, and 0.75 mL of water in 6.0 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 Et_2O had mp 143–145 °C.

This material (100 mg) was converted to the corresponding oxime **51** by reaction with 30 mg of $NH_2OH{\cdot}HCl$ 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-5α-androstane-17β-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** (55 mg) in 1.5 mL of dry THF was treated with 35 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-5α-androstane-17β-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 115–125 °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 59 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 accordine to the Jones procedure[38] (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 Et_2O 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 460 mL of DMF was heated at 115 °C for 4 h. The solid was removed and rinsed with CH_2Cl_2 and CH_3OH. The combined filtrates were concentrated to a white solid. The solid was suspended in 1:1 Et_2O–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 CH_2Cl_2 was added rapidly to a stirred solution of pyridinium chlorochromate (14.9 g, 68.2 mmol) in 100 mL of CH_2Cl_2. After 1.5 h, isopropyl alcohol was added. Addition of 2.5 N HCl served to solubilize the black tars. Additional CH_2Cl_2 was added, and the phases were separated. The CH_2Cl_2 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% CH_3OH–CH_2Cl_2 to leave, after crystallization from Et_2O, 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 335 mL of CH_2Cl_2 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 K_2CO_3 in 440 mL of 10:1 CH_3OH–water at reflux for 16 h. The reaction mixture was concentrated and the residue was dissolved in water. The aqueous solution was washed with $CHCl_3$ and then acidified. The separated solid was dissolved in $CHCl_3$, 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′α-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 CH_2Cl_2 and 2 mL of CH_3OH 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 Et_2O. 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 Et_2O.

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 CH_2Cl_2 and washed with 5% $Na_2S_2O_3$ 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 concentrated 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 CH_3NH_2 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% CH_3OH–$CHCl_3$) to give 263 mg of crystalline product **68**. Recrystallization from Et_2O–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 CH_2Cl_2 was added at 23 °C to a suspension of pyridinium chlorochromate (1.29 g, 6 mmol) in 8 mL of CH_2Cl_2. After 60 min, 50 mL of ether was added with stirring. The phases were separated, and the solid was extracted again with Et_2O. The combined organic layers were filtered through Florisil (20 g) and concentrated to a crystalline residue. Recrystallization from EtOAc–heptane gave 631 mg of **56**, mp 158–167 °C (unchanged on further crystallization).

Ethyl 4-Methyl-3-oxo-4-aza-5,17(20)-pregnadien-21-oate (5ae). The ketone **56** (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 **5ae**, mp 136–138 °C, on crystallization from EtOAc–heptane.

17β-[(*tert*-Butyldimethylsilyl)oxy]-4-aza-5α-androstan-3-one (9bk). To a solution of the azadihydrotestosterone **9a** (16.3 g, 56 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 CH_2Cl_2. 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*-butyldimethylsilyl)oxy]-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 Δ^1 silyloxy compound **14bk** (1.3 g, 3.1 mmol) in 90 mL of THF was added 3.75 mL of 1.0 M tetrabutylammonium fluoride. After 6 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 Δ^1-17-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^{-9}–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 enzyme. The radioactive DHT was measured and compared with that of a control incubation to determine inhibitory activity. The IC_{50} 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 [^{3}H]-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 IC_{50} 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 5α-Reductase. This assay was performed by modification of a previous procedure[29] 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 [^{3}H]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 N_2. This extract was spotted onto TLC plates. After the TLC plates were developed in ethyl acetate–cyclohexane (1:1), the [^{3}H]DHT zone was scraped from the plate and counted. A control incubation without inhibitor and incubations with the standard inhibitor **10x** were run with each assay. The number of compounds run per assay ranged from one to 12. Generally, IC_{50} values were estimated from plots of inhibitory activity and then were compared to that obtained with **10x** in the same assay. These data are reported in Tables I–V.

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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-1*H*-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-1*H*-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.[6] 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 developed[7] 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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