of H_2 at 60 °C on a Parr apparatus for 8 h. The catalyst was removed by filtration and the filtrate was concentrated to 50 mL and then diluted with 200 mL of acetone. The resulting hydrochloride salt, 9.6 g, was filtered.

Biological Methods. Carrageenin Edema Assay. Male rats (Charles River, Sprague–Dawley strain) weighing 100–110 g were divided into groups of eight, fasted for 18 h, and administered by gavage, a placebo, or the drug suspended in 1% gum tragacanth or in a corn oil–water emulsion. One hour after medication, 0.05 mL of a 1% suspension of carrageenin in 0.9% saline was injected into the plantar tissue of the left hind paw. Three hours later, the increase in paw volume (difference between the left hind paw and the uninjected right hind paw) was measured by mercury displacement. The mean increase in paw volume was compared between drug treated groups and placebo to calculate the percent inhibition.

Standard Adjuvant Arthritis Assay. Male rats (Charles River, Sprague–Dawley strain) weighing 200–230 g in groups of eight had adjuvant (*M. butyricum*) 0.1 mL of a 0.6% suspension in heavy mineral oil or a mineral oil placebo, injected into the plantar tissue of one hind paw. Nine days after adjuvant injection, a 12-day daily medication by gavage routine was begun. The test compound was suspended in 1% gum tragacanth or in a corn oil–water emulsion. Negative control and adjuvant injected control animals received the vehicle only. Twenty-four hours after the last medication, the animals were weighed, and the increase in total hind paw volume was determined by mercury displacement. The percent inhibition was calculated from the average differences in hind paw volume between the adjuvant injected controls and the adjuvant-injected medicated rats.

Adjuvant Arthritis Assay. 21-Day Medication. The procedure was similar to the standard adjuvant arthritis assay except that medication was begun on the day of adjuvant injection. At the conclusion of the experiment, the animals were weighed, total hind paw volume was measured by mercury displacement, and the animals were sacrificed. The small intestines and stomachs of the animals were examined for ulceration.

Registry No. 1, 92365-90-7; 1·HCl, 60695-27-4; **2**, 60695-51-4; **2a**, 60695-54-7; **3**, 60695-55-8; **3**·$C_6H_{13}NO_3S$, 60695-56-9; **4**, 92365-91-8; **4**·2HCl, 60695-28-5; **5**, 60695-41-2; **6**, 92365-92-9; **6**·HCl, 81598-09-6; **7**, 60695-63-8; **8**, 60695-46-7; **9**, 60695-78-5; **10**, 60695-62-7; 11, 60695-81-0; **12**, 60695-79-6; **13**, 60695-77-4; **14**, 60695-80-9; **15**, 60695-43-4; **16**, 60991-10-8; **17**, 60695-59-2; **18**, 60695-60-5; **19**, 60695-44-5; **20**, 92365-93-0; **20**·HCl, 81311-09-3; **21**, 60695-48-9; **22**, 60695-45-6; **23**, 60695-64-9; **24**, 60695-68-3; **25**, 60695-34-3; **26**, 60695-25-2; **27**, 60695-24-1; **28**, 60695-22-9; **29**, 60695-33-2; **30**, 60695-39-8; **31**, 60731-07-9; **32**, 60695-32-1; **33**, 60695-38-7; **34**, 60695-40-1; **35**, 60695-37-6; **36**, 92365-94-1; **36**·2HCl, 60695-69-4; **37**, 92365-95-2; **37**·2HCl, 60695-71-8; **38**, 92365-96-3; **38**·2HCl, 60695-67-2; **39**, 60695-72-9; **40**, 60695-61-6; 41, 60731-06-8; **42**, 59452-90-3; **43**, 60601-82-3; **44**, 22071-22-3; 3-bromoacetophenone, 2142-63-4; ethyl chloroacetate, 105-39-5; ethyl 3′-bromo-3-methyl-2,3-epoxybenzenepropanoic acid, 81606-42-0; 2-(cyclohexylmethyl)piperidine, 51523-49-0; 3-methylbenzophenone, 643-65-2; 3-(bromomethyl)benzophenone, 22071-24-5; 3-(cyanomethyl)benzophenone, 21288-34-6; benzonitrile, 100-47-0; 4-chlorobenzaldehyde, 104-88-1; *p*-chloro-*m*′-[2-[2-(cyclohexylmethyl)-1-piperidinyl]-1-methylethyl]benzophenone, 60695-77-4; 4-[2-(3-benzoylphenyl)-1-oxoethyl]morpholine, 81597-82-2; 3-(2-chloro-2-oxoethyl)benzophenone, 41652-38-4; 2,6-dimethylpiperidine, 504-03-0; *N*-[2-(3-benzoylphenyl)acetyl]-2,6-dimethylpiperidine, 92365-98-5; 3-[2-morpholino-2-oxoethyl]-benzophenone cyclic ethylene acetal, 92365-97-4.

Azasteroids as Inhibitors of Rat Prostatic 5α-Reductase

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Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065. *Received March 26, 1984*

A series of A-ring heterocyclic steroids has been prepared and tested for inhibition of rat prostatic steroid 5α-reductase in vitro. Strikingly high inhibitory activity was found with a group of 17β-substituted 4-methyl-4-aza-5α-androstan-3-ones. These compounds were prepared from 3-keto-Δ^4-precursors by oxidative (O_3 or $NaIO_4$–$KMnO_4$) A-ring cleavage followed, in turn, by ring closure with an amine and hydrogenation over platinum catalyst. Other A-ring azasteroids were made by Beckmann rearrangement of oximes of 2-oxo-*A*-nor-, 3-oxo- and 4-oxo-5α-androstanes. An *A*-nor-2-oxo-3-azasteroid was prepared by oxidative decarbonylation of a precursor 2,3-dioxo-4-azasteroid with *m*-chloroperbenzoic acid. A-ring modifications of the 4-azasteroids included Δ^1-unsaturation, 2- and 4-substituents, and 3-carbonyl replacements. Side chains at the 17-position were varied with an emphasis on carboxylate derivatives (salts, esters, and amides).

The enzyme 5α-reductase serves an important function in many androgen-sensitive cells by converting the major circulating androgenic hormone, testosterone (T) irreversibly into the more potent intracellular hormone, 5α-dihydrotestosterone (DHT) (Figure 1). The quantity of this enzyme and its product, DHT, is elevated in the affected tissues of such conditions as benign prostatic hypertrophy,[1] acne, certain forms of hirsutism, and male pattern baldness.[2] Selective inhibition of this enzyme might thus provide a means of therapy for these androgen-related disorders.

In the past, control of androgen action has usually been via interference with the interaction of the androgenic hormones with their intracellular receptor.[3] This receptor, which in its free form is found in the cytosol of sensitive cells, serves to concentrate the active androgens in the cell and, after activation and transport, binds to intranuclear components to initiate the formation of mRNA and subsequent protein synthesis. Compounds such as flutamide (Figure 1), which specifically interfere with androgen–receptor interaction, thus deplete the cell of total androgen (DHT and T), although circulating levels remain the same or may even be elevated due to an interference with receptor action at the hypothalamo-pituitary axis where androgen hormone(s) regulate their own production by a negative feedback effect on the secretion of LH.[4]

Selective blockage of the conversion of T into DHT would allow T to accumulate in the androgen-sensitive cell and attenuate only those responses attributable to DHT and its metabolites. Direct action of T via the receptor as well as its metabolism to estrogen or other metabolites could proceed, thus affording a means to study the actions

(1) Siiteri, P. K.; Wilson, J. D. *J. Clin. Invest.* **1970**, *49*, 1737.
(2) Price, V. H. *Arch. Dermatol.* **1975**, *111*, 1496.
(3) Neri, R.; Kassem, N. In "Hormone Antagonists"; Agarwal, M. K.; Ed.; Walter de Gruyter Co.: New York, 1982; p 247.
(4) (a) Geller, J.; Albert, J.; Nachtsheim, D. A.; Loza, D.; Geller, S. *Prostate (N.Y.)* **1981**, *2*, 309. (b) Viguier-Martinez, M. C.; Hochereau de Reviers, M. T.; Barenton, B.; Perreau, C. *Acta Endocrinol.* **1983**, *102*, 299.

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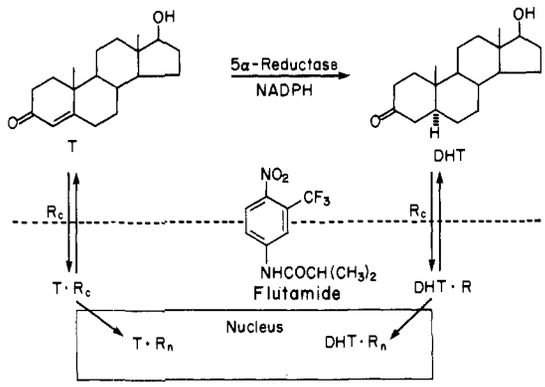


Figure 1. Intracellular events of testosterone action.

and conversions of T in the absence of its 5α-reduced metabolites.

Early studies in these laboratories screened numerous steroids for their ability to block the conversion of T to DHT by a crude, cell-free enzyme system isolated from rat ventral prostate. A series of inhibitors was found, all of which could be regarded as substrates of the enzyme, i.e., 3-keto-Δ^4-steroids.

The enzyme tolerated a wide variety of side chains at the 17β-position, thus allowing a number of nonandrogenic, even nonhormonal agents, to be considered for further evaluation as selective antiandrogens. However, none of these 3-keto-Δ^4 compounds, when given systemically to rats or hamsters, could be shown to interfere with the in vivo conversion of T to DHT. Their metabolic conversion to inactive 5α- or 5β-reduced metabolites must be so facile as to prevent expression of any reductase-inhibiting ability at target organs.

In the course of a search for nonreducible inhibitors of 5α-reductase, a 4-aza-3-ketosteroid was prepared and found to have appreciable inhibitory activity. In addition, certain members of this group of steroids have shown this activity in vivo.[5] Described below are the results of a structure–activity study of these compounds with respect to their in vitro inhibition of rat prostate 5α-reductase.

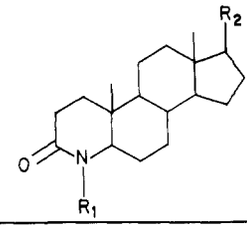
Results and Discussion

Bioassay. The in vitro inhibition of rat 5α-reductase by various steroids is listed in Tables I and II. The enzyme assay was carried out as previously described,[5] where a standard amount of steroid (150 ng) was incubated with radioactive T and an excess of NADPH in 0.21 mL of medium containing the rat prostatic enzyme. Since the molecular weight of the steroids generally ranges between 300 and 400, the approximate molar concentration of inhibitor was 2 μM. The steroids were assayed in duplicate and with progesterone (150 ng/ca. 75% inhibition) or compound **4p** (25 ng/ca. 80% inhibition) as positive control inhibitors. The inhibition was measured as the percent effectiveness in preventing the conversion of [^{3}H]T to [^{3}H]DHT as determined vs. a control incubation without inhibitor. The inhibitions tabulated should be regarded as approximate, as most of the values shown are the result of single and separate determinations. Many of the more active compounds have been tested at several dose levels and their inhibitory activity will be expressed as an ED_{50} in a subsequent paper.

Structure–Activity Relationships. It is apparent from Tables I and II that a 4-methyl-4-aza-3-oxo steroid

(5) Brooks, J. R.; Baptista, E. M.; Berman, C.; Ham, E. A.; Hichens, M. H.; Johnston, D. B. R.; Primka, R. L.; Rasmusson, G. H.; Reynolds, G. F.; Schmitt, S. M.; Arth, G. E. *Endocrinology* **1981**, *109*, 830.

Table I. In Vitro Inhibition of Rat Prostatic 5α-Reductase by 4-Azasteroids

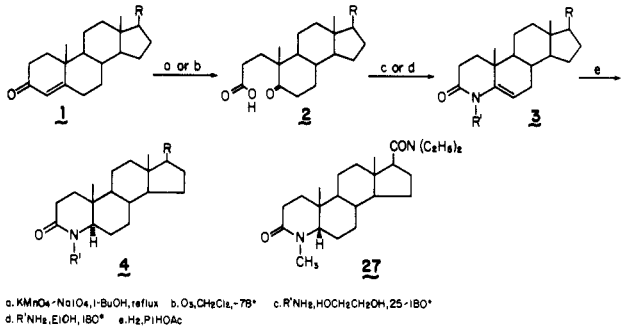


no.	R_1	R_2	% inhibtn (150 ng/tube)
4a	H	β-OH	57
4b	CH_3	β-OH	72
4c	H	β-$COCH_3$	100
4d	CH_3	β-$COCH_3$	100
4e	CH_3	β-$CHOHCH_3$	100
4f	CH_3	β-$CH(CH_3)CH_2OH$	100
4g	CH_3	α-OH, β-$CHOHCH_3$	100
4h	H	α-$CH_2CH_2CH_2O$-β	68
4i	CH_3	α-$CH_2CH_2CH_2O$-β	81
4j	C_2H_5	α-$CH_2CH_2CH_2O$-β	27
4k	CH_3	β-$C_{10}H_{21}$	7
4l	CH_3	β-CH_2NH_2	80
4m	CH_3	β-$NHCOCH_3$	76
4n	CH_3	α-$NHCOCH_3$	87
4o	H	β-$CON(C_2H_5)_2$	95
4p	CH_3	β-$CON(C_2H_5)_2$	99
4q	C_6H_5	β-$CON(C_2H_5)_2$	5
4r	CH_2CH_2OH	β-$CON(C_2H_5)_2$	0
4s	CH_3NH	β-$CON(C_2H_5)_2$	24
4t	CH_3	β-CO_2Na	90
4u	CH_3	β-$CH(CH_3)CO_2Na$	96
4v	CH_3	β-$CH(CH_3)CH_2CH_2CO_2Na$	88
4w	CH_3	β-CO_2CH_3	96
4x	CH_3	β-$CH(CH_3)CH_2CH_2CO_2CH_3$	84
4y	CH_3	β-$CONH_2$	91
4z	CH_3	β-$CONHC_2H_5$	83
4aa	CH_3	β-$CONH(CH_2)_7CH_3$	100
4bb	CH_3	β-$CON(i\text{-}C_3H_7)_2$	100
4cc	CH_3	β-$CH(CH_3)CON(C_2H_5)_2$	83
4dd	CH_3	β-$CH(CH_3)(CH_2)_2CON(C_2H_5)_2$	100
23c	CH_3	$=CHCO_2Na$	92
24	CH_3	$=CHCON(C_2H_5)_2$	100
25	CH_3	β-$CH_2CO_2C_2H_5$	88
26	CH_3	β-$CH_2CON(C_2H_5)_2$	97

unsubstituted in the 1- and 2-positions affords the optimal A-ring substitution pattern for inhibitory activity. A loss of potency for other substituents is found in the approximate order of 4-H (**4a**, **4h**, **4o**), 3 = NOH (**6d**), 2-oxo (**14**), Δ^1 (**8**), 2α-OH, 2 = CHOH (**35**, **13**), 3-thione, 3 = NCH_3 (**6c**, **6a**), 3-deoxo (**6e**), 4-C_2H_5 (**4j**), 3 = NH, 4-methylamino (**6b**, **4s**), 1α,2α-epoxy (**10**), 4-phenyl (**4q**), and 4-(2-hydroxyethyl) (**4r**). The preference of a methyl group at the 4-position over a hydrogen or an ethyl group indicates that there is a limited steric tolerance at this binding site of the enzyme that prefers the small lipophilic group. There is an indication that the reverse is true with the less active Δ^1-azasteroids (**8** vs. **9**). Other modifications of the A ring that result in compounds with retained enzyme inhibition include the 2β-methyl derivative **36**, the 19-nor analogue **4ee**, and the A-homo analogue **31** in which an additional carbon has been inserted on the carbonyl side of the lactam moiety. Other A-homo modifications (**28b**, **29b**) and shifts of the lactam moiety (**21**, **28a**, **29a**) result in a loss of activity. Oxa- and thiasteroids (**40**, **41–43**) show marginal inhibition. The A-nor system (**15**) likewise shows low activity.

The orientation of the A–B ring juncture has a 5α-H for optimal activity. A substantial loss of activity is found with

Scheme I

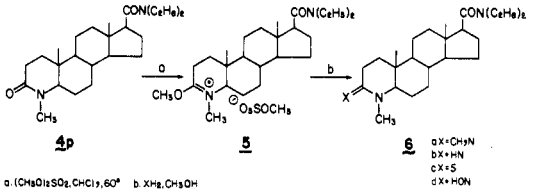


the Δ^5-analogue **3b** and almost a complete loss is observed with the 5β-compound **27**.

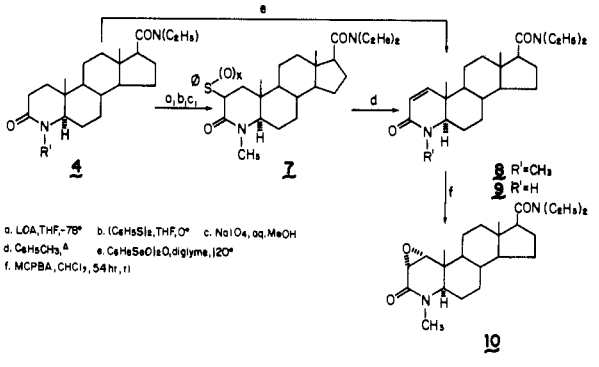
However, a great range of modifications of the side chain at C-17 is compatible with high 5α-reductase inhibition. As has been seen in the all-carbocyclic steroids,[6] the closest analogues to the natural substrate, i.e., the 17β-hydroxyandrostanes **4a** and **4b**, are not the best inhibitors. It is apparent that larger and possibly less polar functionalities, such as the pregnanes **4c–e**, interfere more effectively with the enzyme. Polarity cannot be a sole contributing factor as two of the most potent inhibitors listed, **4u** and **4aa**, differ widely in their TLC mobility. The large, nonpolar stigmastane side chain leads to a compound (**4k**) essentially devoid of activity. An analysis of the relative effectiveness of the salts, esters, and diethylamides of the etiocholanic (**4t**, **4w**, **4p**), 21-pregnanoic (**25**, **26**), bisnorcholanic (**4u**, **4cc**), and cholanic acids (**4v**, **4x**, **4dd**) indicates that no one carboxyl derivative is likely to be most effective on all steroid frameworks. Increasing the bulk and lipophilicity of the dialkylated etiocholanamides (**4y**, **4p**, **4bb**) led to a maximum activity with the diisopropyl derivative **4bb**. Trigonal geometry at C-17 is compatible with activity as shown by the effectiveness of the azapregnenamide **24**. The presence of a 17α-hydroxy group (**4g**) does not interfere with inhibitory activity, while the 17α-alkyl substitution observed by others[6a,7,8] to lower activity may explain the reduced activity found with the spirotetrahydrofurans **4h** and **4i**. Substitution of acetamido functions (**4m**, **4n**) at the 17-position leads to compounds of modest activity.

Chemistry. The 4-azasteroids described in this paper have been prepared from 3-keto-Δ^4-precursors (**1**) by the standard method of oxidative ring cleavage[9] followed by condensation with the appropriate amine (Scheme I; see Table III for R and R^1).[10] Hydrogenation of the resulting Δ^5-enlactam **3** over a platinum catalyst afforded the desired 5α-4-azasteroids **4** in high stereochemical purity.[11] Only very minor quantities of byproducts, such as the deoxo

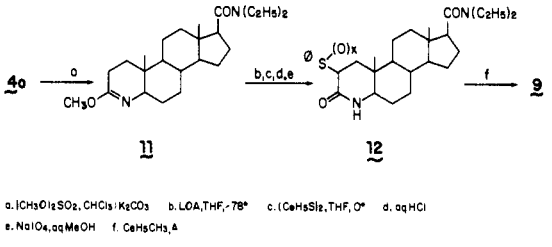
Scheme II



Scheme III



Scheme IV



compound **6e** or the 5β-isomer **27**, have been found. The oxidative ring cleavage with ozone worked well on a small scale (<10 mmol) but was of little use on a large scale. The $KMnO_4$–$NaIO_4$ reagent was preferred for large-scale preparations and was selective for the cleavage of the α,β-unsaturated ketone system such as is found in stigmasta-4,22-diene-3-one (**1k**). Under appropriate conditions ozone selectivity cleaves the Δ^{22}-double bond of the same material.[12]

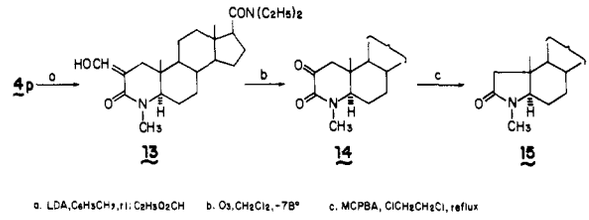
Side-chain variations could be incorporated into the steroid molecule either prior or subsequent to formation of the aza A ring depending on the precursor's availability and/or the substituent's reactivity to the ring closure and reduction conditions. Direct formation of amides from side-chain carboxy azasteroids could be carried out via the acid chloride when the 4-aza nitrogen was alkylated.

Exchanges of groups for the 3-oxo function in these azasteroids could be carried out via the reaction of appropriate nucleophiles with an O-methylated intermediate generated by reaction of the A-ring lactam with dimethyl sulfate in chloroform (Scheme II). These steps could be carried out selectively in the presence of a side-chain amide (i.e., compound **4p**).

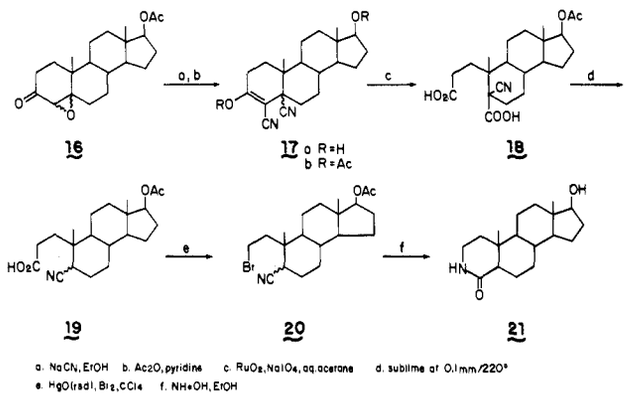
Changes made at the 1- and 2-positions of the 4-azasteroid were generally initiated by formation of the anion at the 2-position by lithium diisopropylamide (Scheme III). Reaction of the anion with diphenyl disulfide afforded the 2-phenylthio derivative **7a** with some of the corresponding 2,2-disubstituted derivative **32** as a byproduct. Oxidation of **7a** with periodate followed by pyrolysis served to convert the phenylthio compound into the Δ^1-azasteroid.[13] Re-

(6) (a) Petrow, V.; Wang, Y.; Lack, L.; Sandberg, A.; Kadohama, N.; Kendle, K. *J. Steroid Biochem.* **1983**, *19*, 1491. (b) Batzold, F. H. In "The Prostatic Cell: Structure and Function", Part B; Alan R. Liss, Inc.: New York, 1981; p 269.
(7) Dupuy, G. M.; Roberts, K. D.; Bleau, G.; Chapdelaine, A. *J. Steroid Biochem.* **1978**, *9*, 1043.
(8) Voigt, W.; Hsia, S. L. *J. Biol. Chem.* **1973**, *248*, 4280.
(9) (a) Gut, M.; Uskokovic, M. *J. Org. Chem.* **1961**, *26*, 1943. (b) Edwards, J. T.; Holder, D.; Lunn, W. H.; Puskas, I. *Can. J. Chem.* **1961**, *39*, 599.
(10) (a) Doorenbos, N. J.; Huang, C. L.; Tamorria, C. R.; Wu, M. T. *J. Org. Chem.* **1961**, *26*, 2546. (b) Singh, H.; Sharma, P. P.; Mathur, R. B. *Indian J. Chem.* **1973**, *11*, 1254. (c) Rasmusson, G. H.; Johnston, D. B. R.; Reinhold, D. F.; Utne, T.; Jobson, R. B. U.S. Patent 4 220 775 1980. (d) Rasmusson, G. H.; Johnston, D. B. R.; Arth, G. E. U.S. Patent 4 377 584, 1983.
(11) Shoppee, C. W.; Killick. R. W.; Kruger, G. *J. Chem. Soc.* **1962**, 2275.
(12) Slomp, G.; Johnson, J. L. *J. Am. Chem. Soc.* **1958**, *80*, 915.
(13) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.

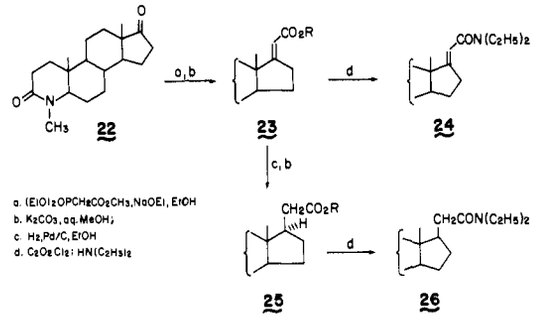
Scheme V



Scheme VI



Scheme VII



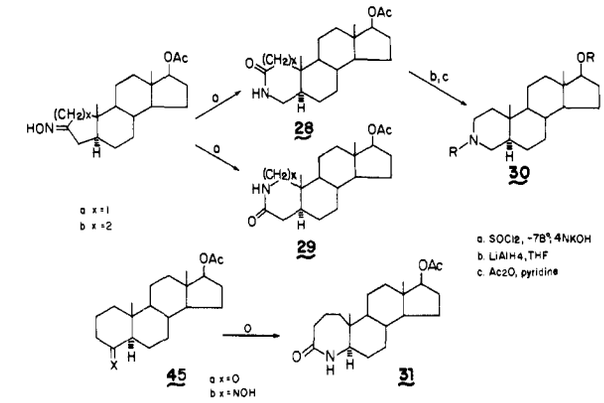
action under forcing conditions with *m*-chloroperbenzoic acid partially converted the unsaturated amide **8** into the 1α,2α-epoxy derivative **10**.

Introduction of a Δ^1-double bond into the 4-unsubstituted azasteroid **4o** could be accomplished by reaction with phenylseleninic anhydride,[14] but this reaction was not satisfactory for the preparation of Δ^1-4-alkylated azasteroids.

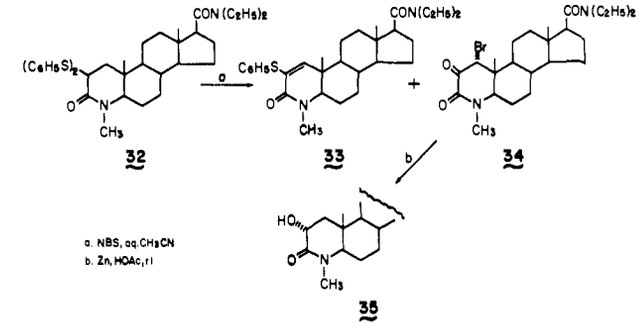
An alternate route to prepare the Δ^1-4-unsubstituted azasteroid **9** involved the phenylsulfenylation[15] of the lactim methyl ether **11** followed by sequential hydrolysis, oxidation, and pyrolysis (Scheme IV).

In the course of these studies, a method was discovered for converting the six-membered lactam ring of these azasteroids to the corresponding five-membered lactam with retained ring junction stereochemistry (Scheme V). Formylation of **4p** at C-2 followed by ozonization of **13** gave the 2-oxo lactam **14**. An attempt to ring contract this compound with periodate according to the procedure described by Rapoport[16a] was unsuccessful. However, when

Scheme VIII



Scheme IX



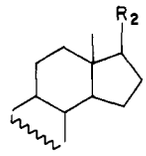
heated in ethylene dichloride with metachloroperbenzoic acid, **14** was smoothly decarbonylated to give the norcompound **15** directly.[16b]

The A-homosteroid **31** was prepared from 4-oxo-5α-androstan-17β-yl acetate (**45a**)[17] by Beckmann rearrangement (Scheme VIII). Similarly, Beckmann rearrangements of the oximes of 5α-dihydrotestosterone acetate and *A*-nor-2-oxo-5α-androstan-17β-yl acetate gave the known pairs of 5α-steroidal A-ring lactams **28a**, **29a**; **28b** and **29b**, respectively.[18] The 3-aza-4-oxoandrostanol **21** was prepared in six steps from testosterone oxide (**16**) as shown in Scheme VI. This pathway, which features a ruthenium tetraoxide ring cleavage and a modified Hunsdieker reaction, leads to a product with unknown orientation of the hydrogen at C-5. The stereochemistry has tentatively been assigned as being 5α (trans ring junction) on the basis of the NMR shift of the C-19 methyl group (0.92 ppm), which is approximately the same as that of the 2-aza-3-oxo compound **28a**, which has known 5α-stereochemistry and the C-19 methyl is in the same positional orientation to the lactam moiety. As a rule, in 5β (A–B cis) steroids with polar functionalities in the A ring, the C-19 methyl proton resonances occur at shifts >1.0 ppm.[19]

The 19-nor azasteroid **4ee** also had doubtful stereochemistry at the C-5 and C-10 positions as the ring closure of the 3,5-seco acid leads to a mixture of Δ^5- and $\Delta^{5(10)}$-4-aza compounds, hydrogenation of which could lead to three (5α,10β; 5α,10α; and 5β,10β) isomers. A mixture was obtained, but the major isomer could be separated by crystallization. By X-ray crystallography this isomer was identified as the A–B trans steroid **4ee**.[28]

(14) Back, T. G. *J. Org. Chem.* **1981**, *46*, 1442.
(15) Phenylsulfenylation of a cyclic lactim ether has been described: Zoretic, P. H.; Soja, P.; Sinha, N. D. *J. Org. Chem.* **1978**, *4*, 1379.
(16) (a) Bender, D. R.; Bjeldanes, L. F.; Kanpp, D. R.; Rapoport, H. *J. Org. Chem.* **1975**, *40*, 1264. (b) Peracid cleavage of an α-oxo imide has been utilized in the ring contraction of a D-ring azasteroid: Rakhit, S.; Gut, M. J. Org. Chem. **1964**, *29*, 859.
(17) Heusler, K.; Kalvoda, J.; Anner, G.; Wettstein, A. *Helv. Chim. Acta* **1963**, *46*, 352.
(18) Oka, K.; Hara, S. *Chem. Ind.* **1969**, 168.
(19) Bhacca, N. S.; Williams, D. H. In "Applications of NMR Spectroscopy in Organic Chemistry"; Holden Day, Inc.: San Francisco, 1966; p 19–20.

Table II. In Vitro Inhibition of Rat Prostatic 5α-Reductase by A-Ring-Modified Heterosteroids



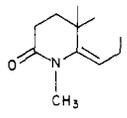
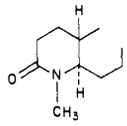
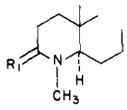
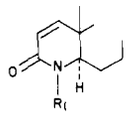
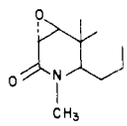
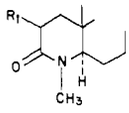
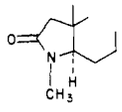
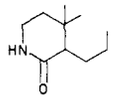
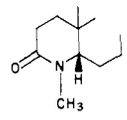
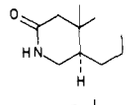
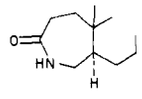
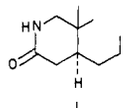
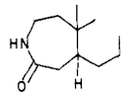
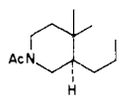
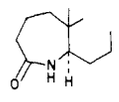
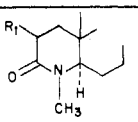
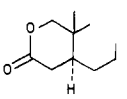
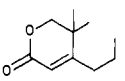
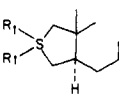
structure	no.	R_1	R_2	% inhibtn (150 ng/tube)
	**3b**		β-OH	36
	**4ee**		β-OH	81
	**6a**	$=NCH_3$	β-$CON(C_2H_5)_2$	49
	6b	=NH	β-$CON(C_2H_5)_2$	22
	6c	=S	β-$CON(C_2H_5)_2$	50
	6d	=NOH	β-$CON(C_2H_5)_2$	77
	6e	$=H_2$	β-$CON(C_2H_5)_2$	44
	8	CH_3	β-$CON(C_2H_5)_2$	63
	9	H	β-$CON(C_2H_5)_2$	74
	10		β-$CON(C_2H_5)_2$	19
	13	=CHOH	β-$CON(C_2H_5)_2$	48
	14	=O	β-$CON(C_2H_5)_2$	78
	15		β-$CON(C_2H_5)_2$	7
	21		β-OH	0
	27		β-$CON(C_2H_5)_2$	7
	**28a**		β-OAc	0
	**28b**		βOAc	0
	**29a**		β-OAc	35
	**29b**		β-OAc	0
	**30b**		β-OAc	33
	31		β-OAc	94

Table II (*Continued*)

structure	no.	R_1	R_2	% inhibtn (150 ng/tube)
	**35**	α-OH	β-$CON(C_2H_5)_2$	46
	36	β-CH_3	β-$CON(C_2H_5)_2$	99
	**40**		β-CO_2CH_3	0
	**41**		β-OH, α-CH_3	8
	**42–44**	$O_{(O-2)}$	β-OAc	0–13

The compounds containing a C17(20) double bond (**23**, **24**) were prepare via reaction of the 17-ketone **22** with the anion of triethyl phosphonoacetate. This reaction gives exclusively α,β-unsaturated esters of *E* geometry (Scheme VII).[20] Hydrogenation of **23** in the presence of palladium gave selectively the 17β-acetic ester **25**.

Bromination of the bis(phenylthio) compound **32** (Scheme IX) led to a mixture of the olefin **33** and the bromo ketone **34**. Treatment of the latter (**34**) with zinc in acetic acid afforded the 2-hydroxy analogue **35** as the major product.

The enolate of **4p** was prepared in THF with LDA and was alkylated with methyl iodide to give after isolation a single 2-methyl derivative (**36**). Refluxing sodium methoxide partially (ca. 25%) converted this material to an isomer which had proton NMR shifts of the 19-CH_3 and 2-$CHCH_3$ displaced upfield from those of **36**. Such effects would be expected for an axial (β) to equatorial (α) isomerization.[21] On this basis, the stereochemistry of the initially isolated 2-methyl compound has been tentatively assigned the β-configuration.

Bromination–dehydrobromination of methyl 3-oxo-5α-androstane-17-carboxylate afforded the corresponding Δ^1-steroid **38**. Ozonization of **38** followed by peracid workup and $NaBH_4$ reduction gave the 2-oxa analogue **40**.

The known oxasteroid **41**[22] and thiasteroids **42–44**[23] were prepared, respectively, from 1,17β-dihydroxy-17α-methyl-2-oxa-1-androsten-3-one and 5α-androst-2-en-17β-yl acetate.

Summary and Conclusions

Potent in vitro steroid 5α-reductase inhibitory activity of A-ring heterosubstituted sterids resides uniquely with 3-oxo-4-aza-5α-steroids optimally substituted with a methyl group at the 4-position. It is possible that these compounds behave as "intermediate state" inhibitors where the A-ring lactam mimics the conformation of the intermediate enol form of the 5α-reduced steroid prior to ketonization and debinding from the enzyme.[24] The activity-enhancing features of a 4-methyl group and a semipolar side chain at the 17-position indicate that the enzyme has steric and lipophilic preferences at these positions.

One of these compounds, the diethylamide **4p**, has been extensively studied both in vitro and in vivo[5,24,25] and has been found to be effective in reducing the size of the enlarged dog prostate.[26]

It is of interest that the structural requirements of the 5α-reductase enzyme and the androgen receptor differ markedly.[25a] A subsequent paper will explore these differences and will present a more extensive study of structural features necessary for optimum 5α-reductase activity.

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. High-resolution mass spectra were obtained with a Finnigan MAT212 spectrometer. 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[27] 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. X-ray data were collected on a Syntex $P2_1$ diffractometer by Jordan Hirshfield of the Department of Biophysics.[28] Optical rotations were measured in chloroform solution on a Perkin-Elmer Model 241 polarimeter using a 1-cm microcell.

Methyl 3β-Hydroxy-5-androstene-17β-carboxylate. Iodine (2.6 kg, 10.23 mol) was added portionwise over 15–30 min to an initially warm (90 °C) solution of pregnenolone (3.0 kg, 0.47 mol) in 8 L of pyridine. The exothermic reaction warmed to reflux during addition and was stirred for an additional 60 min while the temperature remained >100 °C. The mixture cooled gradually to room temperature and was filtered. The solid was washed three times with 2 L of pyridine and twice with 3 L of Et_2O. Air-drying gave 5.1 kg of crude pregnenolone 21-pyridinium iodide as a yellow-tan powder, mp 228–230 °C dec (lit.[29] mp 248–250 °C).

(20) Wicha, J.; Bal, K.; Piekut, S. *Synth. Commun.* **1977**, *7*, 215.
(21) Reference 19, pp 19–20, 37–38.
(22) Pappo, R.; Jung, C. J. *Tetrahedron Lett.* **1962**, 365.
(23) (a) Wolff, M. E.; Zanati, G.; Shanmugasundarum, G.; Gupte, S.; Aadahl, G. *J. Med. Chem.* **1970**, *13*, 531. (b) Wolff, M. E.; Zanati, G. *J. Med. Chem.* **1969**, *12*, 629.
(24) 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.
(25) (a) Liang, T.; Heiss, C. E. *J. Biol. Chem.* **1981**, *256*, 7998. (b) Brooks, J. R.; Berman, C.; Hichens, M.; Primka, R. L.; Reynolds, G. F.; Rasmusson, G. H. *Proc. Soc. Exp. Biol. Med.* **1982**, *169*, 67. (c) Liang, T.; Heiss, C. E.; Ostrove, S.; Rasmusson, G. H.; Cheung, A. *Endocrinology* **1983**, *112*, 1460.
(26) (a) Brooks, J. R.; Berman, C.; Glitzer, M. S.; Gordon, L. R.; Primka, R. L.; Reynolds, G. F.; Rasmusson, G. H. *Prostate (N.Y.)* **1982**, *3*, 35. (b) Wenderoth, U. K.; George, F. W.; Wilson, J. D. *Endocrinology* **1983**, *113*, 569.
(27) Address: 75 Blue Hen Drive, Newark, DE 19711.
(28) X-ray data will be reported separately.

The crude pyridinium iodide (5.0 kg, 9.58 mol) was added in portions (N_2) over 15 min to a refluxing solution of sodium methoxide (574 g, 10.65 mol) in 15 L of methanol. The heavy slurry gradually dissolved and the dark solution was refluxed for another hour. Upon cooling to 45 °C (2 h) the ester crystallized. Water (15 L) was added with vigorous stirring followed by neutralization with 950 mL of 6 N HCl solution. After aging for 1 h, the solids were removed by filtration and were washed four times with 6 L of 1:1 MeOH–water until the color was largely extracted. Drying in an air stream left 2.709 kg (85% from pregnenolone) of crude ester, mp 173–176 °C (lit. mp[29] 174–177 °C).

Methyl 3-Oxo-4-androstene-17β-carboxylate (1w). A solution of the above 3-hydroxysteroid (2.65 kg, 7.96 mol) in 26 L of toluene and 6.6 L of cyclohexanone was heated until 3 L of distillate was collected. A slurry of Al(*i*-PrO)$_3$ (1.46 kg, 7.15 mol) in 6 L of toluene was added and the mixture was refluxed for 1 h while 6 L of distillate was removed. After cooling to 65 °C, the mixture was treated with 660 g of Supercel, 660 g of Darco KB, and 660 mL of water. The mixture was filtered after 15 min of aging and the solid was washed several times with EtOAc (6–8 L). The combined filtrates were concentrated, and the gummy residue was flushed by removing water (3 × 500 mL) under reduced pressure. The residue was stirred with 4 L of hexane at 5 °C for 16 h and then for 1 h in an ice–methanol bath. Filtration and washing (2 × 500 mL) with cold hexane gave 1.975 kg of **1w**, mp 128–130 °C (lit.[30] mp 131 °C).

The ester **1w** (1.84 kg, 5.58 mol) was saponified in refluxing 10% KOH in methanol (9.5 L, 6 h, N_2). Dilution with aqueous acid (6 N HCl) and water followed by filtration gave on drying 1.71 kg of **3-oxo-4-androstene-17β-carboxylic acid (1t)**: mp 245–248 °C; $[\alpha]^{25}$ +143° (1%, MeOH) (lit.[31] mp 247–249 °C; $[\alpha]_D$ +156°).

***N,N*-Diethyl-3-oxo-4-androstene-17β-carboxamide (1o).** A solution of the acid **1t** (700 g, 2.21 mol) in 11.6 L of toluene was azeotropically dried (1.0 L distillate). Pyridine (221 g, 2.79 mol) was added with stirring to the cooled (10 °C) solution followed by slow (20 min) addition of a solution of oxalyl chloride (363 g, 2.86 mol) in 250 mL of toluene. The mixture was stirred at room temperature for 1 h and then cooled to 10 °C. A solution of dry diethylamine (848 g, 11.4 mol) in 1.2 L of toluene was added (N_2, stirring) at such a rate that the temperature did not exceed 40 °C. The thick slurry was stirred for 0.5 h and then quenched with 10 L of ice water. The layers were separated, and the aqueous layer was extracted three times with 4 L of EtOAc. The combined organic layers were washed with dilute HCl solution, water, and saturated NaCl solution, then dried (Na_2SO_4), and concentrated to a solid mass. Recrystallization by addition of 5 L of hexane to a solution of the residue in 500 mL of hot toluene gave **1o** (731 g, 89%), mp 123–126 °C.

In a similar fashion, the following amides were prepared from 3-oxo-4-androstene-17β-carboxylic acid:

compd	amide substituent	mp, °C
1y	unsubstituted	261–263 (lit.[32] 260–1 °C)
1z	monoethyl	174–176
1aa	mono-*n*-octyl	121–123
1bb	diisopropyl	176–179

17β-(Diethylcarbamoyl)-5-oxo-*A*-nor-3,5-secoandrostan-3-oic Acid (2o) Periodate Oxidation: Method A. To a stirred solution of the unsaturated ketone **1o** (400 g, 1.08 mol) in 6 L of *tert*-butyl alcohol was added a solution of Na_2CO_3 (168 g, 1.58 mol) in 800 mL of water. The mixture was brought to reflux and a solution of $NaIO_4$ (1600 g, 7.48 mol) and $KMnO_4$ (12 g, 0.08 mol) in warm (75 °C) water was added gradually (1 h) while the reflux temperature was maintained. The reaction was cooled to 30 °C, and after 15 min the solids were removed by filtration. The solid was washed with 1.0 L of water, and the combined filtrates were concentrated under reduced pressure to remove most of the *tert*-butyl alcohol (final volume 5 L). The aqueous residue was cooled and acidified (pH 3) with 125 mL of concentrated HCl solution. The product acid was extracted with CH_2Cl_2 (4 × 1.5 L), washed with water, dried (Na_2SO_4), and isolated by evaporation. The crude product was swished with 1.2 L of boiling EtOAc and cooled at 0 °C for 4 h to give 370 g (87%) of crystalline **2o**, mp 207–210 °C. A second crop from the mother liquor amounted to 12.5 g. See Table III for a list of other seco acids **2** prepared by this method.

17β-(Diethylcarbamoyl)-5-oxo-*A*-nor-3,5-secoandrostan-3-oic Acid (2o) Ozonation: Method B. Ozone was bubbled at −78 °C into a solution of the unsaturated ketone **1o** (15 g, 40.4 mol) in a mixture of CH_3OH (75 mL) and CH_2Cl_2 (150 mL) until a definite blue color persisted in the reaction mixture. The solution was purged with N_2 as it warmed to 30 °C and then was concentrated to dryness. The residue was taken up in benzene and extracted three times with 2.5 N NaOH solution. The aqueous layer was acidified with concentrated HCl solution and the separated acid was extracted with benzene. The organic layer was washed with water, dried, and concentrated to give 11.5 g (72.7%) of crystalline **2o**. A portion recrystallized from EtOAc had mp 205–208 °C. See Table III for a list of other seco acids **2** prepared by this method.

***N,N*-Diethyl-3-oxo-4-methyl-4-aza-5-androstene-17β-carboxamide (3p): Method I.** A suspension of the seco acid **2o** (370 g, 0.945 mol) in ethylene glycol (1850 mL) was treated with methylamine (210 g, 6.77 mol) at room temperature. The resulting solution was heated slowly (3 °C/min) up to 180 °C and held at this temperature for 15 min. The reaction was cooled to 30 °C and the product began to precipitate. Water (2.2 L) was added slowly and the slurry was cooled at 10–15 °C. The solid was separated, washed with water, and dried to give 319 g (87%) of **3p**, mp 120–123 °C.

***N,N*-Diethyl-3-oxo-4-methyl-4-aza-5-androstene-17β-carboxamide (3p): Method II.** A solution of the seco acid **2o** (26.3 g, 67.2 mol) in 190 mL of EtOH was saturated with methylamine at 0 °C and then heated in an autoclave at 180 °C for 8 h. After cooling, the solution was concentrated. The residue (22.3 g) was combined with the crude product (14.3 g) of a similar run which started with 15 g of **2o** and was eluted on 600 g of silica gel with $CHCl_3$ to give 34.5 g of crystalline **3p**. Recrystallization from ether gave **3p**, mp 120–122 °C. Table III lists 3-keto-Δ^4-steroids that have been converted to the corresponding 4-aza-Δ5-steroids **3**.

***N,N*-Diethyl-3-oxo-4-methyl-4-aza-5α-androstane-17β-carboxamide (4p).** A solution of the Δ^5-steroid **3p** (360 g, 0.93 mol) in 1800 mL of HOAc was hydrogenated in the presence of 36 g of PtO_2 at 45 psi, starting at room temperature and heated to 60 °C over 30 min. After theoretical uptake (3 h) of hydrogen, the reaction was cooled and filtered. The catalyst was washed with HOAc, and the combined filtrates were concentrated to a syrup. This material in 1500 mL of CH_2Cl_2 was washed in turn with 2 × 500 mL of 1 N H_2SO_4, 1 × 500 mL of saturated NaCl, 2 × 500 mL of saturated $NaHCO_3$, and 1 × 500 mL of saturated NaCl solutions. The organic layer was dried ($MgSO_4$), filtered, and passed through a column of 200 g of silica gel, eluting first with 4 L of CH_2Cl_2 and then with 2 L of 3% MeOH in CH_2Cl_2. Evaporation of the solvents left 348 g (96%) of crystalline **4p**, mp 163–166 °C. Recrystallization by concentration of a hot solution in 1.4 L of EtOAc to 700 mL and cooling gave 288 g of pure **4p**, mp 170–173 °C, $[\alpha]^{25}$ 16.1°. A second crop afforded 25 g of **4p**, mp 170–172 °C.

In a similar fashion, compounds **4** of Table III were prepared from their corresponding Δ^5-precursors.

Neutralization of the 1 N H_2SO_4 extract of the above reaction with NaOH solution separated a product which was extracted with CH_2Cl_2, washed with water and saturated NaCl solution, dried, and concentrated. Crystallization from EtOAc gave **6e** (X = H_2), mp 120–123 °C.

The mother liquors from the final crystallization of several runs of **4p** were combined (51 g) and eluted by preparative HPLC in four passes through two silica gel PrepPaks (Waters) with 6:3:1 cyclohexane–acetone–EtOAc. The 5β-isomer **27** (14.04 g) eluted just in front of **4p** (18.30 g). Recrystallization of **27** from EtOAc gave material with mp 164–166 °C, $[\alpha]^{25}$ 93.9°.

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Table III. Conversion of 3-Keto-Δ^4 Steroids into 4-Azasteroids

starting ketone	ring cleavage: method	ring cleavage: product (mp, °C)	ring closure: method	ring closure: amine	product (mp, °C)	hydrogenation product (mp, °C)	substituents[b]: R	substituents[b]: R^1
testosterone (1a)	A and B	2a (189–191)	I and II	NH_3	3a (289–291)[40]	4a (257–259)[42]	β-OH	H
			I and II	CH_3NH_2	3b (194–196)	4b (192–195)	β-OH	CH_3
progesterone (1c)	B	2c (169–171)	II	NH_3	3c (290–292)[40]		β-$COCH_3$	H
			II	CH_3NH_2	3d (256–259)[41]		β-$COCH_3$	CH_3
						4e (208–210)[43]	β$CHOHCH_3$	CH_3
20α-(hydroxymethyl)-4-pregnen-3-one (1f)[33]	B	2f[a]	II	CH_3NH_2	3f (181–183)	4f (194–197)	β-$CH(CH_3)CH_2OH$	CH_3
17α,20-dihydroxy-4-pregnen-3-one (1g)[34]	B	2g[a]	II	CH_3NH_3	3g[a]	4g (210–216)	α-OH, β-$CHOHCH_3$	CH_3
2′,3′α-tetrahydrofuran-2′-spiro-17-(4-androsten-3-one) (1h)[35]	A and B	2h (158–160)	I and II	NH_3	3h (239–241)	4h (283–285)	α-$CH_2CH_2CH_2O$-β	H
			I and II	CH_3NH_2	3i (174–176)	4i (138–140)	α-$CH_2CH_2CH_2O$-β	CH_3
			II	$C_2H_5NH_2$	3j (137–139)	4j (glass)	α-$CH_2CH_2CH_2O$-β	C_2H_5
4,22-stigmastadien-3-one (1k)	A	2k[a]	I	CH_3NH_2	3k (158–160)		β-$C_{10}H_{19}$	CH_3
						4k (132–133)	β-$C_{10}H_{21}$	CH_3
	B	2u[c]	I	CH_3NH_2	3u (268–270)	4u (307–309)	β-$CH(CH_3)CO_2H$	CH_3
17β-cyano-4-androsten-3-one (1l)[36]	A	2l[c]	II	CH_3NH_2	3l (222–224)		β-CN	CH_3
						4l (154–156)	β-CH_2NH_2	CH_3
17β-acetamido-4-androsten-3-one (1m)[37]	A	2m[a]	II	CH_3NH_2	3m (242–244)	4m (284–287)	β-$NHCOCH_3$	CH_3
17α-acetamido-4-androsten-3-one (1n)[37]	A	2n[a]	II	CH_3NH_2	3n (178–180)	4n (165–168)	α-$NHCOCH_3$	CH_3
N,*N*-diethyl-3-oxo-4-androstene-17β-carboxamide (1o)	A and B	2o (205–207)	I and II	NH_3	3o (250–253)	4o (263–265)	β-$CON(C_2H_5)_2$	H
			I and II	CH_3NH_2	3p (121–123)	4p (172–174)	β-$CON(C_2H_4)_2$	CH_3
			II	$C_6H_5NH_2$	3q (189–192)	4q (220–222)	β-$CON(C_2H_5)_2$	C_6H_5
			II	$HOCH_2CH_2NH_2$	3r (144–146)	4r (148–150)	β-$CON(C_2H_5)_2$	$HOCH_2CH_2$
			II	CH_3NHNH_2	3s (130–132)	4s (227–229)	β-$CON(C_2H_5)_2$	CH_3NH
methyl 3-oxo-4-androstene-17β-carboxylate (1w)[30]	A	2w (158–161)	I and II	CH_3NH_2	3w (159–161)	4w (133–135)	β-CO_2CH_3	CH_3
methyl 3-oxo-4-cholen-24-oate (1x)[38]	B	2x	II	CH_3NH_2	3x (103–105)	4x (95–97)	β-$CH(CH_3)CH_2CH_2CO_2CH_3$	CH_3
3-oxo-4-androstene-17β-carboxamide (1y)[39]	A	2y[a]	II	CH_3NH_2	3y (248–250)	4y (246–248)	β-$CONH_2$	CH_3
N-ethyl-3-oxo-4-androstene-17β-carboxamide (1z)	B	2z	II	CH_3NH_2	3z (242–246)	4z (249–251)	β-$CONHC_2H_5$	CH_3
N-octyl-3-oxo-4-androstene-17β-carboxamide (1aa)	A	2aa[a]	II	CH_3NH_2	3aa (oil)	4aa (109–111)	β-$CONH(CH_2)_7CH_3$	CH_3
N,*N*-diisopropyl-3-oxo-4-androstene-17β-carboxamide (1bb)	A	2bb (236–238)	I and II	CH_3NH_2	3bb (115–117)	4bb (181–183)	β-$CON(i\text{-}C_3H_7)_2$	CH_3
19-nortestosterone (1ee)	A and B	2ee (125–127)	I and II	CH_3NH_2	3ee (215–217)	4ee (225–228)	β-OH (19-nor)	CH_3 (19-nor)

[a] Structure verified by ^1H NMR. [b] Other substituent at C-17 is hydrogen unless otherwise specified. [c] Structure verified by mass spectrum.

17β-(Diethylcarbamoyl)-3-methoxy-4-methyl-4-azonia-5α-androst-3-ene Methosulfate (5). A solution of the azasteroid **4p** (1.00 g, 2.58 mmol) and dimethyl sulfate (0.48 g, 3.81 mmol) in 5 mL of $CHCl_3$ was refluxed (N_2) for 64 h. Evaporation left a tacky residue which was triturated with 1:1 EtOAc–toluene (15 mL). The resulting solid was filtered under N_2 and washed with 1:1 Et_2O–EtOAc to leave 875 mg of **5**, mp 120–125 °C. A portion recrystallized twice from EtOAc–CH_2Cl_2 had mp 133–134 °C.

***N*,*N*-Diethyl-3-(methylimino)-4-methyl-4-aza-5α-androstane-17β-carboxamide (6a) (X = CH_3N).** Dry, gaseous CH_3NH_2 was bubbled for 3 h into 3 mL of a refluxing methanol solution of the crude methonium salt **5** prepared as described above (from 195 mg of **4p** and 70 mg of $CH_3OSO_3CH_3$). Excess CH_3NH_2 was removed by codistillation with methanol and the mixture was concentrated to a tacky residue. EtOAc–Et_2O (1:1, 6 mL) trituration resulted in separation of a solid which was removed and rinsed with Et_2O and then washed with H_2O (2 × 4 mL). After drying, the solid was crystallized from EtOAc to leave 62 mg of **6a** as prisms, mp 184–187 °C. From the trituration supernatant was obtained 90 mg of recovered **4p** identified by NMR and TLC (yield of **6a** was 57% based on recovered **4p**).

In a similar fashion, reaction of **5** (from 388 mg of **4p**) with ammonia afforded ***N*,*N*-diethyl 3-imino-4-methyl-4-aza-5α-androstane-17β-carboxamide (6b,** X = HN) (102 mg, mp 178–184 °C).

***N*,*N*-Diethyl-3-thioxo-4-methyl-4-aza-5α-androstane-17β-carboxamide (6c, X = S).** A solution of the steroidal salt **5** (50 mg, 0.095 mmol) and $NaSH{\cdot}xH_2O$ (15 mg, ca. 0.15 mmol) in 0.8 mL of methanol stood at room temperature for 16 h. The residue obtained on concentration was worked up in CH_2Cl_2. The crude product was chromatographed by TLC (20 cm × 20 cm × 1000 μm, 2:1 EtOAc–hexane). The major UV-absorbing band was extracted and the product crystallized from EtOAc–hexane to give 20 mg of **6c**, mp 166–168 °C.

***N*,*N*-Diethyl-3-hydroximino-4-methyl-4-aza-5α-androstane-17β-carboxamide (6d, X = HON).** A solution of the steroid salt **5** (100 mg, 0.19 mmol), $HONH_2{\cdot}HCl$ (69 mg, 1.0 mmol), and 0.1 mL of pyridine in anhydrous methanol (1.0 mL) was heated at reflux (N_2) for 18 h. The solvent was largely removed at room temperature under a stream of nitrogen and the residue was dissolved in $CHCl_3$. The organic layer was washed with 5% NaOH, water, and saturated NaCl solution, dried, and concentrated. The semisolid residue crystallized from EtOAc gave 35 mg of **6d**, mp 204–212 °C dec.

Phenylsulfenylation of *N*,*N*-Diethyl-3-oxo-4-methyl-4-aza-5α-androstane-17β-carboxamide. A solution of *i*-Pr_2NLi in hexane–pentane[44] (6.0 mL, 3 mequiv) was added (N_2, −78 °C) to a solution of the azasteroid **4p** (1.164 g, 3.0 mmol) in THF (12 mL) and the solution then was allowed to come to 0 °C. This solution was added (N_2, 0 °C) to a solution of diphenyl disulfide (900 mg, 4.13 mmol) in 5 mL of THF over a period of 5 min with stirring and then was allowed to stand at room temperature for 1.5 h. The mixture was treated with water and diluted with ethyl acetate. The organic layer was washed successively with 5% NaOH, water, 2.5 N HCl, water, and saturated NaCl solution, then dried, and concentrated to 1.68 g of residue. The residue was triturated with 50 mL of hexane and the extract decanted. The residue afforded the 2-phenyl sulfide **7** (X = 0) (282 mg) when separated from 8 mL of EtOAc. Preparative TLC (silica gel, 6 × 20 cm × 20 cm × 2000 μm, 30% hexane–EtOAc) of the mother liquor afforded 713 mg additional of 2-phenyl sulfide (67% total yield) and 401 mg (22%) of the solid, noncrystalline 2,2-bis(phenyl sulfide) **32**. HPLC analysis of the 2-phenyl sulfide (2:1 EtOAc–hexane, 30 cm μPorasil) indicated it was a mixture of isomers. Recrystallization from ethyl acetate gave pure α-isomer, mp 169–170 °C. The β-isomer, eluted as the faster component on HPLC, crystallized from ether, mp 201–205 °C, and when exposed to 0.4% sodium methoxide in methanol at room temperature for 16 h was >70% converted to the α-isomer as analyzed by HPLC.

***N*,*N*-Diethyl-3-oxo-4-methyl-4-aza-5α-androst-1-ene-17β-carboxamide (8).** To a solution of crude, crystalline 2-phenylthio compound **7** (*x* = 0) (13.2 g, 26 mmol) in 160 mL of MeOH was added at 0 °C a solution of $NaIO_4$ (9.4 g, 44 mmol) in 45 mL of water. A heavy precipitate formed and after stirring for 2.5 h the mixture was diluted to 500 mL with water. The product mixture of sulfoxides (epimeric at the 2-position and the sulfur atom) was washed with water and dried to leave 12.7 g of product. Additional product slowly separated from the filtrate. Separation of the crude product from cold EtOAc gave crystalline **7** (*x* = 1), mp 149–152 °C.

A solution of the crude sulfoxide **7** (12.7 g, 24 mmol) in 150 mL of toluene was refluxed for 2.5 h. The solution was concentrated to dryness and the residue crystallized from 75 mL of EtOAc to give 6.325 g of **8** as heavy prisms, mp 202.5–204.5 °C. The filtrate was concentrated and the residue was chromatographed on 250 g of silica gel, eluting with 5% acetone in chloroform. Addition **8** was obtained, which crystallized from EtOAc to give 1.297 g, mp 200–204.5 °C [total yield from **7** (*x* = 0), 74%].

***N*,*N*-Diethyl-1α,2α-epoxy-3-oxo-4-methyl-4-aza-5α-androstane-17β-carboxamide (10).** A solution of the olefin **8** (200 mg, 0.52 mmol) and 85% *m*-chloroperbenzoic acid (200 mg, 0.98 mmol) in chloroform (3.0 mL) stood at room temperature for 42 h. Additional peracid (100 mg) was added and the reaction mixture stood at room temperature for 12 h and then at 55 °C for 4 h. Chloroform was added and the solution was washed with saturated $NaHCO_3$, water, and saturated NaCl solution. Drying and concentration left 193 mg of a semicrystalline residue. Trituration with ether left 173 mg of white solid, which crystallized from EtOAc to give **10**, mp 214–216 °C.

***N*,*N*-Diethyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide (9) via Sulfoxide Elimination.** A solution of the unsubstituted lactam **4o** (500 mg, 1.34 mmol) in a mixture of 1.5 mL of $CHCl_3$ and 1.5 mL of redistilled dimethyl sulfate was refluxed for 5 h and then in a 100 °C bath while the $CHCl_3$ was allowed to distill (1 h). The solution was concentrated at 5 mm to leave a gummy residue. The residue was treated with absolute MeOH (20 mL) containing 200 mg of anhydrous K_2CO_3 and then was diluted with 20 mL of EtOAc. The cloudy mixture was stirred for 30 min and filtered and the filtrate concentrated to leave 650 mg of residue. This was extracted with toluene (25 mL). The extract was concentrated to a solid residue, which was ether (25 mL) extracted. Evaporation of the ether left a solid residue which was primarily ***N*,*N*-diethyl-3-methoxy-4-aza-5α-androst-3-ene-17β-carboxamide** (11), mp 137–139 °C.

To a solution of the crude imino ether **11** (100 mg, 0.26 mmol) in THF (1.0 mL) was added with stirring at −78 °C a solution of 0.5 M lithium diisopropylamide (0.5 mL).[44] After 5 min the temperature was allowed to rise to 0 °C. This solution was added at 0 °C with a syringe to a solution of diphenyl disulfide (130 mg, 0.6 mmol) in 1.0 mL of THF under N_2. Excess 2.5 N HCl solution and EtOAc was added to the solution. The layers were mixed well and separated. The EtOAc layer was washed with water, 5% NaOH, water, and then saturated NaCl solution, dried, and concentrated. The residue (135 mg) was chromatographed by TLC (2 × 20 cm × 20 cm × 1000 μm silica plates, eluted with 5% MeOH in EtOAc). The major band (R_f 0.5) was isolated to give 51 mg of a gum that solidified on trituration with ether. Additional material was obtained by chromatography of a solid which slowly separated from the aqueous acid layer to give 88 mg total yield of ***N*,*N*-diethyl-3-oxo-2-(phenylthio)-4-aza-5α-androstane-**

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17β-carboxamide (12, x = 0). Crystallization from EtOAc (0.5 mL) gave 38 mg, mp 194–198°.

This crude phenylthio compound (**12**, 66 mg) was oxidized in 1.0 mL of MeOH with 48 mg of $NaIO_4$ as described for the corresponding *N*-methyl analogue **7** to give 67 mg of a mixture of sulfoxides (**12**, X = 1). A solution of this mixture in 1.0 mL of toluene was heated at reflux for 2.5 h, then cooled, and chromatographed directly on a 20 cm × 20 cm × 1000 μm silica gel plate eluting with 10% MeOH in EtOAc. The product (R_f 0.5) was isolated and recrystallized from EtOAc to give 16 mg of **9**, mp 276–278 °C.

***N,N*-Diethyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide (9). Seleninic Anhydride Oxidation.**[14] A mixture of the lactam **4o** (11.35 g, 30.3 mmol) and benzeneseleninic anhydride (15.22 g, 42.3 mmol) in 600 mL of redistilled (LAH) diglyme was heated at 120 °C for 19 h. The solvent was removed under reduced pressure and the residue was worked up in CH_2Cl_2 (2.5 N NaOH, saturated NaCl, dried, and concentrated) to leave 26.5 g of residue. This residue was chromatographed (HPLC), eluting through a preparative silica gel cartridge (Waters) with 3:1 CH_2Cl_2–acetone. After early elution of nonsteroid aromatic material, the product **9** (5.9 g) was obtained followed by recovered starting material (2.6 g). The crystalline **9** was rinsed with 1:1 Et_2O–hexane to leave 5.4 g (62% based on recovered **4o**) of **9**, mp 275–277.5 °C.

***N,N*-Diethyl-2-formyl-3-oxo-4-methyl-4-aza-5α-androstane-17β-carboxamide (13).** A solution 0.5 N *i*-Pr_2NLi in hexane–pentane[44] (9.8 mL, 4.9 mequiv) was added dropwise (room temperature, N_2) to a stirred solution of **4p** (1.0 g, 2.58 mmol) in 35 mL of sieve-dried toluene. After 20 min, 1.0 mL of ethyl formate was added dropwise (sl. exotherm) to the heterogeneous mixture and stirring was continued for 30 min. The reaction mixture was neutralized by addition of glacial acetic acid and then was diluted with ethyl acetate. The organic solution was washed successively with 2.5 N HCl, water, saturated $NaHCO_3$, water, and saturated NaCl solution. Drying (Drierite) and evaporation left 1.2 g of a crystalline residue. Recrystallization from ether gave **13**, first crop, 661 mg, mp 153–156 °C; second crop, 187 mg, mp 147–152 °C (79%).

***N,N*-Diethyl-2,3-dioxo-4-methyl-4-aza-5α-androstane-17β-carboxamide (14).** Ozone was bubbled into a stirred solution of the 2-formyl compound **13** (500 mg, 1.20 mmol) in 8 mL of CH_2Cl_2 cooled at −78 °C until a definite blue color persisted for 4 min. The cold solution was purged with N_2 until colorless and then 0.5 mL of dimethyl sulfide was added. The nitrogen purge was continued as the mixture was allowed to come to 0 °C. The solution was evaporated at low (ca. 0 °C) temperature to leave a semicrystalline residue. Recrystallization from ethyl acetate gave 382 mg of **14** as prisms, mp 192–199 °C. An analytical sample had mp 190–195 °C.

***N,N*-Diethyl-2-oxo-3-methyl-3-aza-*A*-nor-5α-androstane-17β-carboxamide (15).** A solution of the 2-oxo lactam **14** (300 mg, 0.75 mmol) and 85% *m*-chloroperbenzoic acid (300 mg, 1.5 mmol) in ethylene dichloride (6 mL) was heated 1.0 h at reflux. The mixture was cooled and concentrated to ca. 2.0 mL. The residue was diluted with EtOAc and was washed successively with 10% $NaHSO_3$, water, saturated $NaHCO_3$, water, and saturated NaCl solution. Drying and concentration left a gum (270 mg) which crystallized on trituration with ether. Recrystallization from ether gave 160 mg of **15**, mp 153–164 °C. The mother liquor was chromatographed (HPLC, EtOAc, 4 ft × $^3/_8$ in. Porasil column) to give 55 mg additional of **15**, mp 158–165 °C (total yield 77%).

17β-Acetoxy-5-cyano-3,4-secoandrostane-3,4-dioic Acid (18). A mixture prepared from a solution of 4,5-epoxytestosterone acetate (**16**; 950 mg, 2.75 mmol) in 50 mL of EtOH and 1.20 g of NaCN in 5 mL of water was heated at reflux for 7 h. The solvent was evaporated and the residue dissolved in 2% NaOH solution. The aqueous solution was washed with Et_2O–EtOAc (1:2) and then acidified with 20% HCl (aqueous). The separated product was worked up in EtOAc (water, saturated NaCl wash, dried, and concentrated) to leave 1.0 g of crystalline **4,5-dicyano-3-androstene-3,17β-diol (17a)**, mp 217 °C dec. The **diacetate 17b** was prepared by reaction with acetic anhydride–pyridine (1:1, 10 mL) for 25 min. Separation from heptane–EtOAc gave **17b** (829 mg), mp 180–190 °C.

A suspension of RuO_3 (53%, 200 mg) in 70 mL of acetone was treated at room temperature with $NaIO_4$ (800 mg, saturated aqueous solution). To this suspension was added dropwise a solution of the diacetate **17b** (1.00 g, 2.36 mmol) in 70 mL of acetone. Periodically in the next 6 h a solution prepared from 7 g of $NaIO_4$ in 60 mL of 1:1 water–acetone was added to assure the presence of excess oxidant in the mixture. *i*-PrOH (20 mL) was added after stirring at room temperature for 16 h. The mixture was filtered through Supercel and the filtrate concentrated to 25 mL. The residue was acidified and extracted with EtOAc. After a water wash, the organic layer was extracted with 5% aqueous $NaHCO_3$ solution. After rinsing with EtOAc the basic extract was acidified with aqueous HCl solution. The product acid was worked up in EtOAc (H_2O, saturated NaCl solution wash, dried, and concentrated) to leave 450 mg of solid. Recrystallization from *i*-PrOH by addition of heptane gave 294 mg of **18**, mp 215–225 °C dec.

17β-Acetoxy-4-nitrilo-5α-androstan-3-oic Acid (19). The diacid **18** (300 mg, 0.74 mmol) was heated at 210–220 °C in a sublimator at 0.1 mmHg. After 20 min, decomposition–sublimation appeared complete and the sublimate was collected and separated from *i*-PrOH to give 95 mg of **19**, mp 237–239 °C. The filtrate was evaporated and the residue separated from EtOAc by addition of hexane to give 130 mg, mp 140–155 °C. In spite of the two different melting points, the two isolates had the same R_f values on TLC (silica gel 0.5% HCO_2H in Et_2O) and identical IR ($CHCl_3$) spectra.

17β-Hydroxy-3-azaandrostan-4-one (21). To a refluxing mixture of 64 mg (0.18 mmol) of the acid **19**, 39 mg of red HgO, and 1.0 mL of CCl_4 was added 0.20 mL of a Br_2 solution in CCl_4 (160 mg/mL) over a period of 30 min. After 1 h of reflux, 20 mg of HgO was added with 0.1 mL of Br_2 solution. After 2 h of reflux, 10 mg of HgO was added with 0.05 mL of Br_2 solution and reflux was continued for 1 h. After cooling, the mixture was diluted with $CHCl_3$ and worked up (washed with 5% aqueous HCl, water, and saturated NaCl solution, dried, and concentrated) to leave **17β-acetoxy-2-bromo-2,3-seco-*A*-norandrostane-3-nitrile (20)** as crystalline residue. This material, mp 120–150 °C was used without further purification in the next step.

A solution of the bromo nitrile **20** (63 mg, 0.16 mmol) and 0.5 mL of concentrated NH_4OH solution in 1.0 mL of EtOH was heated in a sealed tube at 155 °C for 17 h. The cooled solution was evaporated to a brown mass which was eluted on TLC (1 × 1000 μm × 20 cm × 20 cm, silica gel) with 10% MeOH–$CHCl_3$. The major band was isolated and crystallized from ether to give 24 mg of **21**, mp 214–214.5 °C.

4-Methyl-4-aza-5α-androstane-3,17-dione (22). To a suspension of **4b** (700 mg, 2.41 mmol) in 36 mL of acetone was added with stirring at room temperature 1.85 mL (14.8 mequiv) of 8 N chromic acid.[45] After 10 min, the mixture was treated with excess *i*-PrOH and then concentrated to dryness under reduced pressure. The residue was treated successively with 10% NaOH solution and $CHCl_3$. The organic layer was worked up (washed with 10% NaOH, water, saturated NaCl solution, dried, and evaporated) to give 650 mg of **22**, mp 277–279 °C. Anal. ($C_{18}H_{27}NO_2 \cdot {}^1/_2H_2O$).

In a similar fashion 20-hydroxy-4-methyl-4-aza-5α-pregnan-3-one (**4e**) and 20-hydroxy-4-aza-5α-pregnan-3-one were converted into **4-methyl-4-aza-5α-pregnane-3,20-dione (4d)**, mp 218–220 °C, and **4-aza-5α-pregnane-3,20-dione (4c)**, mp 272–275 °C, respectively.

Ethyl 4-Methyl-3-oxo-4-aza-5α-pregn-17(20)-en-21-oate (23a, R = C_2H_5). To a mixture of the ketone **22** (800 mg, 2.64 mmol) and methyl diethyl phosphonacetate (1.67 g, 7.92 mmol) was added at room temperature a solution prepared from 190 mg of sodium and 3.3 mL of EtOH. The mixture was heated at reflux for 4 h. The dark solution was concentrated and diluted with dilute HOAc solution. The product was worked up in Et_2O (washed with H_2O, $NaHCO_3$ solution, H_2O, and saturated NaCl solution, dried, and evaporated) to leave a crystalline residue. Recrystallization from Et_2O gave 461 mg of **23a**, mp 150–152 °C.

A solution of the ester **23a** (265 mg, 0.71 mmol) and 200 mg of K_2CO_3 in 10 mL of 10:1 MeOH–water was refluxed for 16 h.

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The mixture was concentrated and diluted with water. The aqueous layer was rinsed with EtOAc and then acidified. The product acid was isolated by filtration and dried to give 206 mg of **4-methyl-3-oxo-4-aza-5α-pregn-17(20)-en-21-oic acid (23b, R = H)**, mp 285–288 °C. The **sodium salt 23c** (R = Na) was obtained by treating a suspension of the acid **23b** in water with an equivalent amount of aqueous sodium hydroxide, allowing the mixture to stir for 30 min and then isolating the salt by lyophilization.

Other esters were converted in a similar manner to the corresponding acids (and sodium salts) as follows: **4-methyl-3-oxo-4-aza-5α-pregnane-20α-carboxylic acid (4u)**, mp 307–309 °C; **4-methyl-3-oxo-4-aza-5α-androstane-17β-carboxylic acid (4t)**, mp >300 °C; **4-methyl-3-oxo-4-aza-5α-cholan-24-oic acid (4v)**, mp 256–258 °C; **4-methyl-3-oxo-4-aza-5α-pregnan-21-oic acid (25b)**, mp 239–241 °C.

Ethyl 4-Methyl-3-oxo-4-aza-5α-pregnan-21-oate (25a). A solution of the olefinic steroid **23a** (150 mg, 0.40 mmol) in 7 mL of EtOH was hydrogenated in a Paar shaker (50 psi) at room temperature in the presence of 30 mg of 30% Pd/C catalyst for 5.5 h. Filtration followed by evaporation of the filtrate afforded **25a** as a colorless oil which crystallized on prolonged exposure to reduce pressure (0.1 min). Crystalline **25a** had mp 55–57 °C.

***N,N*-Diethyl-4-methyl-3-oxo-4-aza-5α-pregn-17(20)(*E*)-en-21-amide (24).** A suspension of the acid **23b** (190 mg, 0.55 mmol) in 3.3 mL of toluene and 0.185 mL of oxalyl chloride was stirred at room temperature for 15 min. The resulting solution was evaporated (<1 mmHg) and the residue was dissolved in anhydrous THF (2 mL). A solution of 0.30 mL of diethylamine in 1.2 mL of anhydrous THF was added and the mixture was stirred at room temperature for 1 h. The mixture was mixed well with ice water and extracted with CH_2Cl_2. After washing with water and saturated NaCl solution, the CH_2Cl_2 layer was dried and evaporated to leave 253 mg of crude, crystalline material. This material was purified by preparative TLC (3 × 1000 μm × 20 cm × 20 cm, eluted with 1:1 EtOAc–acetone) and crystallization from ether to give **24**, 121 mg, mp 164–171 °C.

A similar amidation procedure was used to prepare the following amides from the corresponding carboxylic acid precursors: ***N,N*-diethyl-4-methyl-3-oxo-4-aza-5α-pregnane-20α-carboxamide (4cc)**, mp 216–218 °C; ***N,N*-diethyl-4-methyl-3-oxo-4-aza-5α-androstane-17β-carboxamide (4p)**, mp 172–174 °C; ***N,N*-diethyl-4-methyl-3-oxo-4-aza-5α-cholan-24-amide (4dd)**, mp 165–167 °C; ***N,N*-Diethyl-4-methyl-3-oxo-4-aza-5α-pregnan-21-amide (26)**, mp 159–162 °C.

17β-Acetoxy-4a-aza-*A*-homo-5α-androstan-4-one (31). 17β-Hydroxy-5α-androstan-4-one[17] was prepared from 4-androsten-17β-ol tetrahydropyranyl ether by hydroboration, two oxidative steps, and hydrolysis. This material was acetylated in pyridine–acetic anhydride to give the acetate **45a** (X = O), mp 160–163 °C.

A solution of the acetate **45a** (2.0 g, 6 mmol) and $NH_2OH·HCl$ (420 mg, 6 mmol) in EtOH–pyridine (4:1, 150 mL) was allowed to stand at room temperature for 16 h. The solution was concentrated to a small volume at 30–40 °C under reduced pressure and diluted with water. The separated solid was removed, washed with water, and dried. Crystallization from Et_2O afforded the **oxime 45b** (X = NOH), mp 222–224 °C.

The oxime **45b** (500 mg, 1.44 mmol) was dissolved at −78 °C in 3.3 mL of redistilled thionyl chloride. After stirring for 2 min, this solution was added carefully to 50 mL of 4 N KOH solution at 20 °C. The solid that formed was separated and washed with water and a small amount of Et_2O. Crystallization from EtOAc gave 210 mg of the A-homo azasteroid **31**, mp 232–235 °C.

3-Aza-5α-androstan-17β-ol (30a, R = H). A mixture of the acetoxy lactam **28a** (x = 1)[18] (900 mg, 2.7 mmol) and 3.9 g of $LiAlH_4$ in 500 mL of THF was heated at reflux for 48 h. The mixture was cooled (0 °C) and treated with stirring with saturated aqueous NH_4Cl solution until the separated solid was granular enough for filtration. The filtered residue was washed with THF, and the combined filtrates were concentrated to a foam. This material crystallized from acetonitrile to leave 497 mg of **30a** (R = H), mp 88–90 °C, followed by vigorous bubbling at 114–116 °C.

The **3-acetyl-3-aza-5α-androstan-17β-yl acetate (30b)** (R = Ac) prepared in acetic anhydride–pyridine had mp 138–140 °C.

Reaction of the 2,2-Bis(phenylsulfenyl) Steroid 32 with Aqueous *N*-Bromosuccinimide. A solution of the bissulfenylated steroid **32** (400 mg, 0.66 mmol) in acetonitrile (1.0 mL) was added (20 °C) dropwise to a stirred suspension of NBS (600 mg, 3.37 mmol) in 2 mL of 10:1 acetonitrile–water. A 1:1 mixture of hexane–CH_2Cl_2 was added to the mixture 10 min after addition was complete. The organic layer was washed successively with saturated $NaHSO_3$, water, saturated Na_2CO_3, and water. After drying and concentration, a gummy residue was obtained which was eluted on three 20 cm × 20 cm × 1000 μm silica gel TLC plates with EtOAc. Two major bands were isolated: the faster, 120 mg and the slower, 223 mg. The faster material, which was recrystallized from toluene by addition of hexane, has mp 164–167 °C; NMR and M^+ (494), which corresponds to *N,N*-diethyl-2-(phenylsulfenyl)-3-oxo-4-methyl-4-aza-5α-androst-1-ene-17β-carboxamide (**33**).

The slower material, which was recrystallized from EtOAc, has mp 234–237 °C and IR, NMR, M^+ (480, 482), and C, H, N, Br which corresponds to *N,N*-diethyl-1α-bromo-2,3-dioxo-4-methyl-4-aza-5α-androstane-17β-carboxamide (**34**).

***N,N*-Diethyl-2-hydroxy-3-oxo-4-methyl-4-aza-5α-androstane-17β-carboxamide (35).** A mixture of the 1-bromo-2-oxoazasteroid **34** (35 mg, 0.07 mmol) and 150 mg of zinc powder was stirred in 1.0 mL of HOAc at room temperature (N_2) for 16 h. The mixture was diluted with EtOAc and filtered. The filtrate was concentrated to a gummy residue, redissolved in EtOAc, and successively washed with saturated $NaHCO_3$, water, and saturated NaCl solution. Evaporation of the dried solution left a noncrystalline residue which by TLC (EtOAc) was made up of a major (slower) and a minor (faster) component. The slower component (19 mg, 67%) was isolated by TLC (20 cm × 30 cm × 250 μm, EtOAc) and crystallized from Et_2O to give **35** as prisms, mp 163–166 °C, M^+ (404; high resolution, found, 404.3024; calcd, 404.3039). The minor component was not investigated further.

***N,N*-Diethyl-2β,4-dimethyl-3-oxo-4-aza-5α-androstane-17β-carboxamide (36).** To a solution of the steroid **4p** (190 mg, 0.49 mmol) in THF (1.0 mL) was added (N_2, −78 °C, stirring) a solution of 0.53 N *i*-Pr_2NLi in hexane–pentane[44] (0.92 mL, 0.49 mmol). The mixture was allowed to come to 0 °C and then added dropwise to a solution of CH_3I (140 mg, 1.0 mmol) in THF (2 mL). After standing for 1 h at room temperature, the mixture was diluted with water and extracted with EtOAc. The organic layer was washed successively with water, 1.0 N HCl, water, and saturated NaCl solution, then dried, and concentrated. The residue crystallized from EtOAc to give 70 mg of **36** as prisms, mp 138–140.5 °C. The material in the filtrate was chromatographed by HPLC (4 ft × $^3/_8$ in., Porasil, EtOAc) and the 2-methyl steroid eluted as a single peak with only the leading edge, indicating (NMR) the presence of a mixture. The remaining portion of the peak was collected and concentrated and the residue separated from heptane to give 67 mg (total yield 70%) of **36**, mp 138–140 °C.

A solution of this material (30 mg) and CH_3ONa (300 mg) in 3 mL of MeOH was refluxed (N_2) for 16 h. The solvent was removed and the residue treated with water and EtOAc. The organic layer was worked up and the crude product eluted on TLC (20 cm × 20 cm × 500 μm, EtOAc). The major band was isolated and analyzed by 300-MHz NMR. The major compound of the band was the same as that obtained above. A second component (ca. 25% of the mixture) shows a change of the 19-CH_3 shift from the 0.89 ppm of the starting material to 0.77 ppm and a movement of the 2-CHCH_3 doublet (J = 6 Hz) from 1.20 to 1.15 ppm.

Methyl 3-Oxo-5α-androst-1-ene-17β-carboxylate (38). To a solution of methyl 3-oxo-5α-androstane-17β-carboxylate, **37** (3.4 g, 10.3 mmol), and 2 drops of 48% aqueous HBr in 74 mL of HOAc was added a HOAc solution (20.4 mL, 10.2 mmol) which was 0.5 N in both Br_2 and NaOAc. When the color was discharged, ice water was added to precipitate the product. The crude 2-bromo derivative was filtered, washed with water, and dried in vacuo.

To a hot (130 °C) mixture of 4 g of LiBr and 8 g of Li_2CO_3 in anhydrous DMF was added with stirring the above bromo steroid. After 1.5 h at 130 °C, the solvent was removed under reduced pressure. The residue was worked up in EtOAc and after concentration was eluted through 100 g of silica gel with benzene. Crystallization of the major fraction gave 2.05 g of **38**, mp 186–188 °C.

Methyl 2-Oxa-3-oxo-5α-androstane-17β-carboxylate (40). A solution of the Δ^1-steroid **38** (1.0 g, 3.0 mmol) in a 2:1 mixture of $MeCl_2$–EtOAc (15 mL) was ozonized at −78 °C until blue color persisted for 2 min. The mixture was purged with N_2 as the temperature was allowed to rise to room temperature. The solution was evaporated and the residue treated with a solution prepared from 1.0 mL of 30% H_2O_2 in 10 mL of HOAc. After standing 3 h, the mixture was concentrated to a thick oil. The material was dissolved in Et_2O, washed with water, and extracted into 2.5 N NaOH solution. The aqueous layer was acidified and extracted with Et_2O. The organic layer was washed with water, dried, and concentrated to leave 958 mg of crude **17β-carbomethoxy-1-oxo-1,2-seco-*A*-nor-5α-androstan-2-oic acid (39).**

To a solution of the above aldehyde **39** (225 mg, 0.64 mmol) in a mixture of MeOH (17 mL) and water (5.6 mL) was added at room temperature a solution of $NaBH_4$ (100 mg, 2.6 mmol) in 9 mL of water. After 3 h, 2.5 N aqueous HCl solution was added and the solution concentrated one-half its volume. Water was added and the crude product separated. This material was chromatographed (1:1 EtOAc–C_6H_6) by TLC on 1000-μm silica gel plates. The major band was isolated and crystallized from Et_2O to give the 85 mg of the oxasteroid **40**, mp 202–204 °C.

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Registry No. 1a, 58-22-0; 1c, 57-83-0; 1f, 40736-33-2; 1g, 15959-00-9; 1h, 6693-98-7; 1k, 20817-72-5; 1l, 63079-23-2; 1m, 1865-62-9; 1n, 92472-21-4; 1o, 73671-97-3; 1t, 302-97-6; 1w, 2681-55-2; 1x, 1452-33-1; 1y, 92472-22-5; 1z, 74352-90-2; 1aa, 92472-20-3; 1bb, 74352-89-9; 1ee, 434-22-0; 2a, 1759-35-9; 2c, 3510-20-1; 2f, 92472-25-8; 2g, 92472-26-9; 2h, 92472-27-0; 2k, 92472-28-1; 2l, 92472-29-2; 2m, 92472-30-5; 2n, 92472-31-6; 2o, 73697-29-7; 2u, 92472-32-7; 2w, 92472-33-8; 2x, 16870-58-9; 2y, 92472-34-9; 2z, 92472-35-0; 2aa, 92472-23-6; 2bb, 92472-24-7; 2ee, 3762-52-5; 3a, 82093-09-2; 3b, 92472-37-2; 3c, 20283-95-8; 3d, 2102-23-0; 3f, 92472-40-7; 3g, 92472-41-8; 3h, 92472-42-9; 3i, 92472-43-0; 3j, 92472-44-1; 3k, 92472-45-2; 3l, 92472-46-3; 3m, 92472-47-4; 3n, 92489-87-7; 3o, 76763-13-8; 3p, 73671-98-4; 3q, 92472-48-5; 3r, 92472-49-6; 3s, 92472-50-9; 3u, 92472-51-0; 3u (methyl ester), 92524-41-9; 3w, 92472-52-1; 3x, 92472-53-2; 3y, 92472-54-3; 3z, 92472-55-4; 3aa, 92472-36-1; 3bb, 92472-38-3; 3ee, 92472-39-4; 4a, 76318-68-8; 4b, 86284-02-8; 4c, 73711-89-4; 4d, 73671-90-6; 4e, 7750-89-2; 4e (4-*H* deriv.), 76318-67-7; 4f, 92542-38-6; 4g, 86283-91-2; 4h, 73671-88-2; 4i, 73671-89-3; 4j, 86283-89-8; 4k, 53874-94-5; 4l, 92472-57-6; 4m, 86307-05-3; 4n, 92472-58-7; 4o, 73671-87-1; 4p, 73671-86-0; 4q, 92472-59-8; 4r, 92472-60-1; 4s, 86283-86-5; 4t, 76763-16-1; 4u, 92472-61-2; 4v, 86283-83-2; 4w, 86283-81-0; 4x, 86283-85-4; 4y, 76763-19-4; 4z, 73671-91-7; 4aa, 86283-79-6; 4bb, 89631-78-7; 4cc, 92618-96-7; 4dd, 86283-82-1; 4ee, 92472-56-5; 5, 92472-63-4; 6a, 92472-64-5; 6b, 92472-65-6; 6c, 92472-66-7; 6d, 92472-67-8; 6e, 92472-68-9; 7aα, 76763-12-7; 7aβ, 76776-74-4; (2α(*R*)-7b, 92473-05-7; (2α(*S*))-7b, 92473-04-6; (2β(*R*))-7b, 92473-03-5; (2β(*S*))-7b, 92472-69-0; 8, 76763-21-8; 9, 92472-70-3; 10, 92472-71-4; 11, 92472-72-5; 12(X = 0), 92472-73-6; 12(X = 1), 92472-74-7; 13, 92472-75-8; 14, 92472-76-9; 15, 92472-77-0; 16, 2944-75-4; 17a, 92472-78-1; 17b, 92472-79-2; 18, 92472-80-5; 19, 92472-81-6; 20, 92472-82-7; 21, 92472-83-8; 22, 86284-03-9; 23a, 92472-84-9; 23b, 92472-85-0; 23c, 92472-86-1; 24, 92472-87-2; 25a, 86283-88-7; 25b, 92472-88-3; 26, 86283-87-6; 27, 92472-89-4; 28a, 92472-90-7; 28b, 21522-08-7; 29a, 92472-91-8; 29b, 21522-14-5; 30a, 92472-92-9; 30b, 92472-93-0; 31, 73671-93-9; 32, 92472-94-1; 33, 92472-95-2; 34, 92472-96-3; 35, 92472-97-4; 36, 92472-98-5; 37, 4139-88-2; 38, 92472-99-6; 39, 92473-00-2; 40, 92473-01-3; 41, 92473-02-4; 42, 21813-68-3; 43, 25709-34-6; 44, 25744-31-4; 45a, 7417-26-7; 45b, 73672-01-2; CH_3NH_2, 74-89-5; NH_3, 7664-41-7; $C_2H_5NH_2$, 75-04-7; $C_6H_5NH_2$, 62-53-3; $HO(CH_2)_2NH_2$, 141-43-5; CH_3NHNH_2, 60-34-4; $(C_2H_5O)_2P(O)CO_2CH_3$, 1067-74-9; pregnenolone, 145-13-1; pregnenolone 21-pyridinium iodide, 73672-02-3; 17β-hydroxy-5α-androstan-4-one, 571-08-4; 5α-reductase, 9036-43-5.

Supplementary Material Available: A table listing additional analytical and spectral data for compounds described in this paper (22 pages). Ordering information is given on any current masthead page.

C(2)-Methylation Abolishes DA_1 Dopamine Agonist Activity of 2-Amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (6,7-ADTN): Steric Intolerance by the Receptor

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The synthesis of 2-amino-2-methyl-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene is reported. This compound did not produce vasodilation in the dog renal artery and was inactive as a DA_1-type dopamine agonist. This is in contrast to the 2-nonmethylated homologue 6,7-ADTN, which is a potent DA_1 agonist. High-field ^1H NMR studies of the *O,O*-dimethyl ethers for both compounds as their free bases in chloroform-*d* revealed that the 2-methyl homologue probably exists as a rapidly equilibrating mixture of conformers; it seems likely that it can adopt the active conformation proposed to be required by the dopamine receptor. The lack of activity is therefore attributed to the steric effect of the 2-methyl group, consistent with explanations offered by others that the dopamine receptor cannot tolerate alkylation at the α side-chain carbon.

As part of our continued interest in structure–activity relationships of dopamine agonists, we have been studying the differences in the structural requirements of agonists at the two subtypes of the peripheral dopamine receptors. Of interest in this regard was the apparent lack of dopamine agonist activity for α-methyl-substituted dopamine derivatives. α-Methyldopamine (1) lacks agonist activity at the renal dopamine receptor[1] and its *N*-methyl, *N,N*-dimethyl, and other N-alkylated derivatives lack dopamine

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