

of H<sub>2</sub> 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<sub>6</sub>H<sub>13</sub>NO<sub>3</sub>S, 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-(cyclohexylmethyl)-1-piperidinyl]-1-methylethylbenzophenone, 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 5 $\alpha$ -Reductase

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A series of A-ring heterocyclic steroids has been prepared and tested for inhibition of rat prostatic steroid 5 $\alpha$ -reductase in vitro. Strikingly high inhibitory activity was found with a group of 17 $\beta$ -substituted 4-methyl-4-aza-5 $\alpha$ -androstan-3-ones. These compounds were prepared from 3-keto- $\Delta^4$ -precursors by oxidative (O<sub>3</sub> or NaIO<sub>4</sub>-KMnO<sub>4</sub>) 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-5 $\alpha$ -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  $\Delta^1$ -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 5 $\alpha$ -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, 5 $\alpha$ -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,<sup>1</sup> acne, certain forms of hirsutism, and male pattern baldness.<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup>

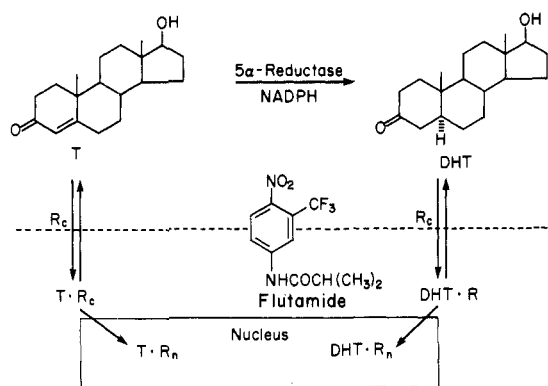
Selective blockage of the conversion of T into DHT would allow T to accumulate in the androgen-sensitive cell and attenuate only those responses attributable to DHT and its metabolites. Direct action of T via the receptor as well as its metabolism to estrogen or other metabolites could proceed, thus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

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(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.



**Figure 1.** Intracellular events of testosterone action.

and conversions of T in the absence of its 5 $\alpha$ -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- $\Delta^4$ -steroids.

The enzyme tolerated a wide variety of side chains at the 17 $\beta$ -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- $\Delta^4$  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 5 $\alpha$ - or 5 $\beta$ -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 5 $\alpha$ -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*.<sup>5</sup> Described below are the results of a structure-activity study of these compounds with respect to their *in vitro* inhibition of rat prostate 5 $\alpha$ -reductase.

## Results and Discussion

**Bioassay.** The *in vitro* inhibition of rat 5 $\alpha$ -reductase by various steroids is listed in Tables I and II. The enzyme assay was carried out as previously described,<sup>5</sup> 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  $\mu$ M. 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 [<sup>3</sup>H]T to [<sup>3</sup>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<sub>50</sub> in a subsequent paper.

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

**Table I.** *In Vitro* Inhibition of Rat Prostatic 5 $\alpha$ -Reductase by 4-Azasteroids

The chemical structure shows a steroid nucleus with a 4-aza-3-oxo group. The substituents R<sub>1</sub> and R<sub>2</sub> are indicated at the 1 and 2 positions, respectively.

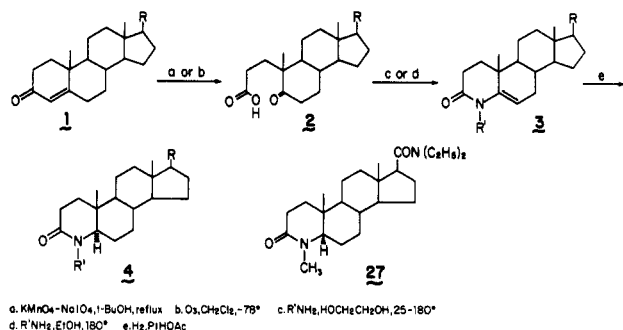
no.	R <sub>1</sub>	R <sub>2</sub>	% inhibtn (150 ng/tube)
4a	H	$\beta$ -OH	57
4b	CH <sub>3</sub>	$\beta$ -OH	72
4c	H	$\beta$ -COCH <sub>3</sub>	100
4d	CH <sub>3</sub>	$\beta$ -COCH <sub>3</sub>	100
4e	CH <sub>3</sub>	$\beta$ -CHOHCH <sub>3</sub>	100
4f	CH <sub>3</sub>	$\beta$ -CH(CH <sub>3</sub> )CH <sub>2</sub> OH	100
4g	CH <sub>3</sub>	$\alpha$ -OH, $\beta$ -CHOHCH <sub>3</sub>	100
4h	H	$\alpha$ -CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> O- $\beta$	68
4i	CH <sub>3</sub>	$\alpha$ -CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> O- $\beta$	81
4j	C <sub>2</sub> H <sub>5</sub>	$\alpha$ -CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> O- $\beta$	27
4k	CH <sub>3</sub>	$\beta$ -C <sub>10</sub> H <sub>21</sub>	7
4l	CH <sub>3</sub>	$\beta$ -CH <sub>2</sub> NH <sub>2</sub>	80
4m	CH <sub>3</sub>	$\beta$ -NHCOCH <sub>3</sub>	76
4n	CH <sub>3</sub>	$\alpha$ -NHCOCH <sub>3</sub>	87
4o	H	$\beta$ -CON(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	95
4p	CH <sub>3</sub>	$\beta$ -CON(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	99
4q	C <sub>6</sub> H <sub>5</sub>	$\beta$ -CON(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	5
4r	CH <sub>2</sub> CH <sub>2</sub> OH	$\beta$ -CON(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	0
4s	CH <sub>3</sub> NH	$\beta$ -CON(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	24
4t	CH <sub>3</sub>	$\beta$ -CO <sub>2</sub> Na	90
4u	CH <sub>3</sub>	$\beta$ -CH(CH <sub>3</sub> )CO <sub>2</sub> Na	96
4v	CH <sub>3</sub>	$\beta$ -CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> Na	88
4w	CH <sub>3</sub>	$\beta$ -CO <sub>2</sub> CH <sub>3</sub>	96
4x	CH <sub>3</sub>	$\beta$ -CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> CH <sub>3</sub>	84
4y	CH <sub>3</sub>	$\beta$ -CONH <sub>2</sub>	91
4z	CH <sub>3</sub>	$\beta$ -CONHC <sub>2</sub> H <sub>5</sub>	83
4aa	CH <sub>3</sub>	$\beta$ -CONH(CH <sub>2</sub> ) <sub>7</sub> CH <sub>3</sub>	100
4bb	CH <sub>3</sub>	$\beta$ -CON(i-C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub>	100
4cc	CH <sub>3</sub>	$\beta$ -CH(CH <sub>3</sub> )CON(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	83
4dd	CH <sub>3</sub>	$\beta$ -CH(CH <sub>3</sub> )(CH <sub>2</sub> ) <sub>2</sub> CON(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	100
23c	CH <sub>3</sub>	=CHCO <sub>2</sub> Na	92
24	CH <sub>3</sub>	=CHCON(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	100
25	CH <sub>3</sub>	$\beta$ -CH <sub>2</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	88
26	CH <sub>3</sub>	$\beta$ -CH <sub>2</sub> CON(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	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),  $\Delta^1$  (8), 2 $\alpha$ -OH, 2 = CHOH (35, 13), 3-thione, 3 = NCH<sub>3</sub> (6c, 6a), 3-deoxo (6e), 4-C<sub>2</sub>H<sub>5</sub> (4j), 3 = NH, 4-methylamino (6b, 4s), 1 $\alpha$ ,2 $\alpha$ -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  $\Delta^1$ -azasteroids (8 vs. 9). Other modifications of the A ring that result in compounds with retained enzyme inhibition include the 2 $\beta$ -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 5 $\alpha$ -H for optimal activity. A substantial loss of activity is found with

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

## Scheme I

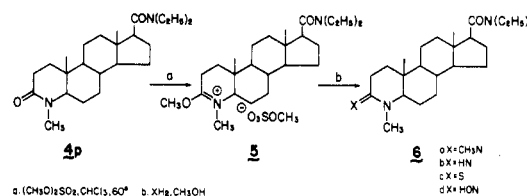


the  $\Delta^5$ -analogue **3b** and almost a complete loss is observed with the  $5\beta$ -compound **27**.

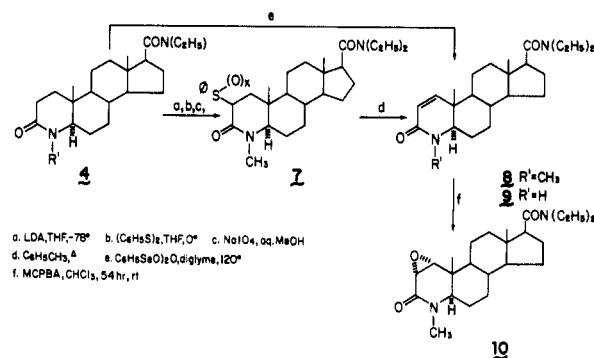
However, a great range of modifications of the side chain at C-17 is compatible with high  $5\alpha$ -reductase inhibition. As has been seen in the all-carbocyclic steroids,<sup>6</sup> the closest analogues to the natural substrate, i.e., the  $17\beta$ -hydroxy-androstanes **4a** and **4b**, are not 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 etiocholanolic (**4t**, **4w**, **4p**), 21-pregnanoic (**25**, **26**), bisnor-cholanolic (**4u**, **4cc**), and cholanolic 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 aza-pregnenamide **24**. The presence of a  $17\alpha$ -hydroxy group (**4g**) does not interfere with inhibitory activity, while the  $17\alpha$ -alkyl substitution observed by others<sup>8a,7,8</sup> to lower activity may explain the reduced activity found with the spiro-tetrahydrofurans **4h** and **4i**. Substitution of acet-amido 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- $\Delta^4$ -precursors (**1**) by the standard method of oxidative ring cleavage<sup>9</sup> followed by condensation with the appropriate amine (Scheme I; see Table III for R and R').<sup>10</sup> Hydrogenation of the resulting  $\Delta^5$ -enlactam **3** over a platinum catalyst afforded the desired  $5\alpha$ -4-azasteroids **4** in high stereochemical purity.<sup>11</sup> Only very minor quantities of byproducts, such as the deoxo

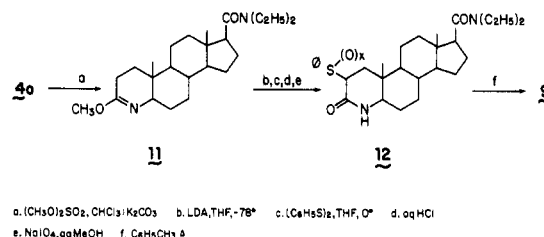
## Scheme II



## Scheme III



## Scheme IV



compound **6e** or the  $5\beta$ -isomer **27**, have been found. The oxidative ring cleavage with ozone worked well on a small scale ( $<10\text{ mmol}$ ) but was of little use on a large scale. The  $\text{KMnO}_4\text{--NaIO}_4$  reagent was preferred for large-scale preparations and was selective for the cleavage of the  $\alpha,\beta$ -unsaturated ketone system such as is found in stig-masta-4,22-diene-3-one (**1k**). Under appropriate conditions ozone selectivity cleaves the  $\Delta^{22}$ -double bond of the same material.<sup>12</sup>

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**).

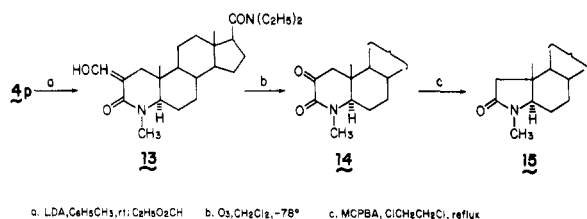
Changes made at the 1- and 2-positions of the 4-aza-steroid were generally initiated by formation of the anion at the 2-position by lithium diisopropylamide (Scheme III). Reaction of the anion with diphenyl disulfide afforded the 2-phenylthio derivative **7a** with some of the corresponding 2,2-disubstituted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

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- (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.
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- (11) Shoppee, C. W.; Killick, R. W.; Kruger, G. *J. Chem. Soc.* **1962**, 2275.

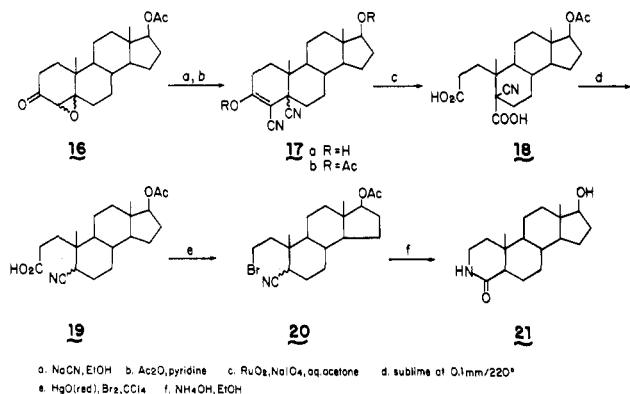
(12) Slomp, G.; Johnson, J. L. *J. Am. Chem. Soc.* **1958**, *80*, 915.

(13) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.

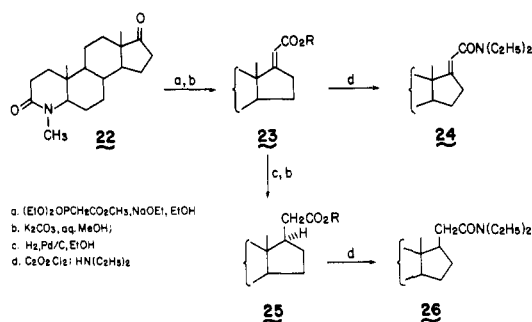
## Scheme V



## Scheme VI



## Scheme VII



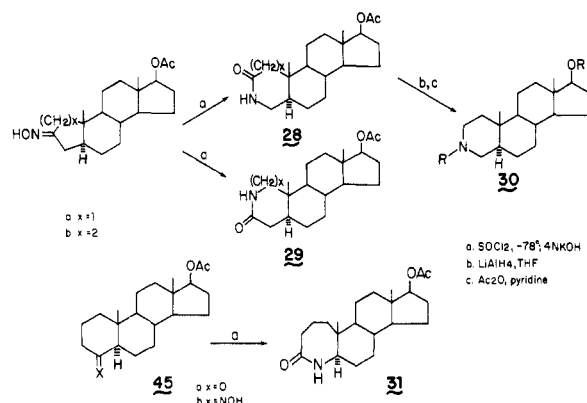
action under forcing conditions with *m*-chloroperbenzoic acid partially converted the unsaturated amide 8 into the 1 $\alpha$ ,2 $\alpha$ -epoxy derivative 10.

Introduction of a  $\Delta^1$ -double bond into the 4-unsubstituted azasteroid 4o could be accomplished by reaction with phenylseleninic anhydride,<sup>14</sup> but this reaction was not satisfactory for the preparation of  $\Delta^1$ -4-alkylated azasteroids.

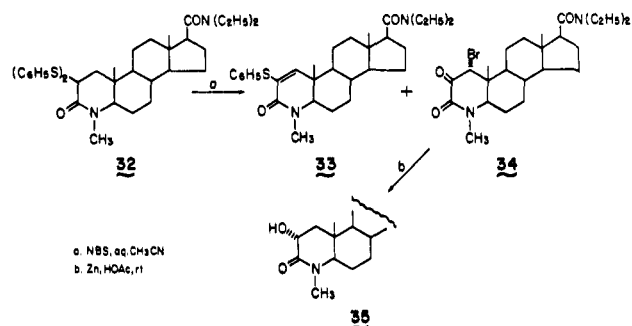
An alternate route to prepare the  $\Delta^1$ -4-unsubstituted azasteroid 9 involved the phenylsulfenylation<sup>15</sup> of the lactim methyl ether 11 followed by sequential hydrolysis, oxidation, and pyrolysis (Scheme IV).

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<sup>16a</sup> 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.<sup>16b</sup>

The A-homosteroid 31 was prepared from 4-oxo-5 $\alpha$ -androst-17 $\beta$ -yl acetate (45a)<sup>17</sup> by Beckmann rearrangement (Scheme VIII). Similarly, Beckmann rearrangements of the oximes of 5 $\alpha$ -dihydrotestosterone acetate and A-nor-2-oxo-5 $\alpha$ -androst-17 $\beta$ -yl acetate gave the known pairs of 5 $\alpha$ -steroidal A-ring lactams 28a, 29a; 28b and 29b, respectively.<sup>18</sup> 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 tetroxide 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 5 $\alpha$  (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 5 $\alpha$ -stereochemistry and the C-19 methyl is in the same positional orientation to the lactam moiety. As a rule, in 5 $\beta$  (A-B cis) steroids with polar functionalities in the A ring, the C-19 methyl proton resonances occur at shifts >1.0 ppm.<sup>19</sup>

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  $\Delta^5$ - and  $\Delta^{5(10)}$ -4-aza compounds, hydrogenation of which could lead to three (5 $\alpha$ ,10 $\beta$ ; 5 $\alpha$ ,10 $\alpha$ ; and 5 $\beta$ ,10 $\beta$ ) 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.<sup>28</sup>

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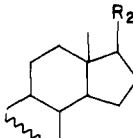
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Table II. In Vitro Inhibition of Rat Prostatic 5 $\alpha$ -Reductase by A-Ring-Modified Heterosteroids


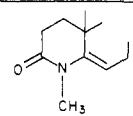
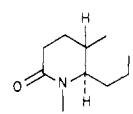
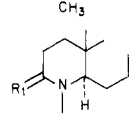
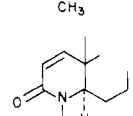
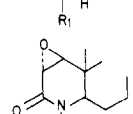
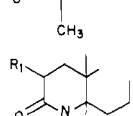
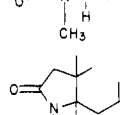
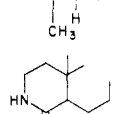
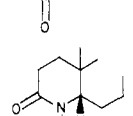
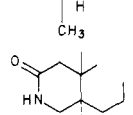
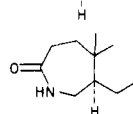
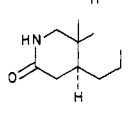
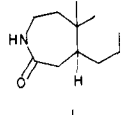
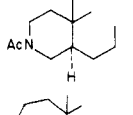
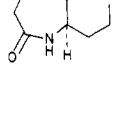

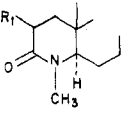
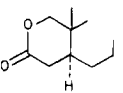
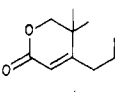
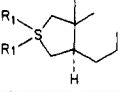
structure	no.	R <sub>1</sub>	R <sub>2</sub>	% inhibtn (150 ng/tube)
	3b		$\beta$ -OH	36
	4ee		$\beta$ -OH	81
	6a	$=NCH_3$	$\beta$ -CON(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	49
	6b	$=NH$	$\beta$ -CON(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	22
	6c	$=S$	$\beta$ -CON(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	50
	6d	$=NOH$	$\beta$ -CON(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	77
	6e	$=H_2$	$\beta$ -CON(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	44
	8	CH <sub>3</sub>	$\beta$ -CON(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	63
	9	H	$\beta$ -CON(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	74
	10		$\beta$ -CON(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	19
	13	$=CHOH$	$\beta$ -CON(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	48
	14	$=O$	$\beta$ -CON(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	78
	15		$\beta$ -CON(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	7
	21		$\beta$ -OH	0
	27		$\beta$ -CON(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	7
	28a		$\beta$ -OAc	0
	28b		$\beta$ -OAc	0
	29a		$\beta$ -OAc	35
	29b		$\beta$ -OAc	0
	30b		$\beta$ -OAc	33
	31		$\beta$ -OAc	94

Table II (Continued)

structure	no.	R <sub>1</sub>	R <sub>2</sub>	% inhibtn (150 ng/tube)
	35	$\alpha$ -OH	$\beta$ -CON(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	46
	36	$\beta$ -CH <sub>3</sub>	$\beta$ -CON(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	99
	40		$\beta$ -CO <sub>2</sub> CH <sub>3</sub>	0
	41		$\beta$ -OH, $\alpha$ -CH <sub>3</sub>	8
	42-44	O(O-2)	$\beta$ -OAc	0-13

The compounds containing a C17(20) double bond (23, 24) were prepared via reaction of the 17-ketone 22 with the anion of triethyl phosphonoacetate. This reaction gives exclusively  $\alpha,\beta$ -unsaturated esters of *E* geometry (Scheme VII).<sup>20</sup> Hydrogenation of 23 in the presence of palladium gave selectively the 17 $\beta$ -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<sub>3</sub> and 2-CHCH<sub>3</sub> displaced upfield from those of 36. Such effects would be expected for an axial ( $\beta$ ) to equatorial ( $\alpha$ ) isomerization.<sup>21</sup> On this basis, the stereochemistry of the initially isolated 2-methyl compound has been tentatively assigned the  $\beta$ -configuration.

Bromination-dehydrobromination of methyl 3-oxo-5 $\alpha$ -androstane-17-carboxylate afforded the corresponding  $\Delta^1$ -steroid 38. Ozonization of 38 followed by peracid workup and NaBH<sub>4</sub> reduction gave the 2-oxa analogue 40.

The known oxasteroid 41<sup>22</sup> and thiasteroids 42-44<sup>23</sup> were prepared, respectively, from 1,17 $\beta$ -dihydroxy-17 $\alpha$ -methyl-2-oxa-1-androsten-3-one and 5 $\alpha$ -androst-2-en-17 $\beta$ -yl acetate.

### Summary and Conclusions

Potent in vitro steroid 5 $\alpha$ -reductase inhibitory activity of A-ring heterosubstituted steroids resides uniquely with 3-oxo-4-aza-5 $\alpha$ -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 5 $\alpha$ -reduced steroid prior to ketonization and debinding from the enzyme.<sup>24</sup> 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<sup>5,24,25</sup> and has been found to be effective in reducing the size of the enlarged dog prostate.<sup>26</sup>

It is of interest that the structural requirements of the 5 $\alpha$ -reductase enzyme and the androgen receptor differ markedly.<sup>25a</sup> A subsequent paper will explore these differences and will present a more extensive study of structural features necessary for optimum 5 $\alpha$ -reductase activity.

### Experimental Section

**General Methods.** Melting points are uncorrected. <sup>1</sup>H NMR spectra, obtained with Varian T-60 and SC-300 spectrometers, were run in CDCl<sub>3</sub> solution and are reported as ppm values downfield from Me<sub>4</sub>Si. 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  $\times$  30 cm  $\mu$ Porasil column, a Series 400 refractometer, and a Series 440 ultraviolet absorbance detector. Preparative high-pressure LC separations were made on a Waters Associates Prep 500 chromatograph equipped with one or two PrepPaks (325 g of silica gel each). Thin-layer chromatography (TLC) was run on Analtech<sup>27</sup> silica gel coated plates in thicknesses of 250 (analytical), 1000, and 2000  $\mu$ m. 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<sub>1</sub> diffractometer by Jordan Hirshfield of the Department of Biophysics.<sup>28</sup> Optical rotations were measured in chloroform solution on a Perkin-Elmer Model 241 polarimeter using a 1-cm microcell.

**Methyl 3 $\beta$ -Hydroxy-5-androstene-17 $\beta$ -carboxylate.** Iodine (2.6 kg, 10.23 mol) was added portionwise over 15-30 min to an initially warm (90  $^{\circ}$ 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  $>100$   $^{\circ}$ 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<sub>2</sub>O. Air-drying gave 5.1 kg of crude pregnenolone 21-pyridinium iodide as a yellow-tan powder, mp 228-230  $^{\circ}$ C dec (lit.<sup>29</sup> mp 248-250  $^{\circ}$ C).

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 (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<sup>29</sup> 174–177 °C).

**Methyl 3-Oxo-4-androstene-17 $\beta$ -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  $Al(i\text{-}PrO)_3$  (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  $\times$  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  $\times$  500 mL) with cold hexane gave 1.975 kg of **1w**, mp 128–130 °C (lit.<sup>30</sup> 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-17 $\beta$ -carboxylic acid (1t)**: mp 245–248 °C;  $[\alpha]_D^{25} +143^\circ$  (1%, MeOH) (lit.<sup>31</sup> mp 247–249 °C;  $[\alpha]_D +156^\circ$ ).

***N,N*-Diethyl-3-oxo-4-androstene-17 $\beta$ -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-17 $\beta$ -carboxylic acid:

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

**17 $\beta$ -(Diethylcarbamoyl)-5-oxo-A-nor-3,5-secoandrostane-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  $\times$  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.

**17 $\beta$ -(Diethylcarbamoyl)-5-oxo-A-nor-3,5-secoandrostane-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-17 $\beta$ -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-17 $\beta$ -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- $\Delta^4$ -steroids that have been converted to the corresponding 4-aza- $\Delta^5$ -steroids **3**.

***N,N*-Diethyl-3-oxo-4-methyl-4-aza-5 $\alpha$ -androstane-17 $\beta$ -carboxamide (4p).** A solution of the  $\Delta^5$ -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  $\times$  500 mL of 1 N  $H_2SO_4$ , 1  $\times$  500 mL of saturated NaCl, 2  $\times$  500 mL of saturated  $NaHCO_3$ , and 1  $\times$  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,  $[\alpha]_D^{25} 16.1^\circ$ . 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  $\Delta^5$ -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 5 $\beta$ -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,  $[\alpha]_D^{25} 93.9^\circ$ .

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Table III. Conversion of 3-Keto- $\Delta^4$  Steroids into 4-Azasteroids

starting ketone	ring cleavage		ring closure		product (mp, °C)	hydrogenation product (mp, °C)	substituents <sup>b</sup>	
	method	product (mp, °C)	method	amine			R	R <sup>1</sup>
testosterone (1a)	A and B	2a (189-191)	I and II	NH <sub>3</sub>	3a (289-291) <sup>40</sup> 3b (194-196) 3c (290-292) <sup>40</sup> 3d (256-259) <sup>41</sup>	4a (257-259) <sup>42</sup> 4b (192-195)  4c (208-210) <sup>43</sup> 4f (194-197)	$\beta$ -OH $\beta$ -OH $\beta$ -COCH <sub>3</sub> $\beta$ -COCH <sub>3</sub> $\beta$ -CHOHCH <sub>3</sub> $\beta$ -CH(CH <sub>3</sub> )CH <sub>2</sub> OH	H CH <sub>3</sub> H CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>
20 $\alpha$ -(hydroxymethyl)-4-pregnen-3-one (1f) <sup>33</sup>	B	2f <sup>a</sup>	II	CH <sub>3</sub> NH <sub>2</sub>	3f (181-183)	4g (210-216)	$\alpha$ -OH, $\beta$ -CHOHCH <sub>3</sub>	CH <sub>3</sub>
17 $\alpha$ ,20-dihydroxy-4-pregnen-3-one (1g) <sup>34</sup>	B	2g <sup>a</sup>	II	CH <sub>3</sub> NH <sub>3</sub>	3g <sup>a</sup>	4h (283-285) 4i (138-140) 4j (glass) 4k (132-133) 4u (307-309)	$\alpha$ -CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> O- $\beta$ $\alpha$ -CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> O- $\beta$ $\alpha$ -CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> O- $\beta$ $\beta$ -C <sub>10</sub> H <sub>19</sub> $\beta$ -C <sub>10</sub> H <sub>21</sub> $\beta$ -CH(CH <sub>3</sub> )CO <sub>2</sub> H $\beta$ -CN	H CH <sub>3</sub> C <sub>2</sub> H <sub>5</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>
2',3'- $\alpha$ -tetrahydrofuran-2'-spiro-17-(4-androsten-3-one) (1h) <sup>35</sup>	A and B	2h (158-160)	I and II I and II II	NH <sub>3</sub> CH <sub>3</sub> NH <sub>2</sub> C <sub>2</sub> H <sub>5</sub> NH <sub>2</sub> CH <sub>3</sub> NH <sub>2</sub>	3h (239-241) 3i (174-176) 3j (137-139) 3k (158-160)	4l (154-156) 4m (284-287)	$\beta$ -CH <sub>2</sub> NH <sub>2</sub> $\beta$ -NHCOCH <sub>3</sub>	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>
4,22-stigmastadien-3-one (1k)	A	2k <sup>a</sup>	I	CH <sub>3</sub> NH <sub>2</sub>	3u (268-270) 3l (222-224)	4n (165-168)	$\alpha$ -NHCOCH <sub>3</sub>	CH <sub>3</sub>
17 $\beta$ -cyano-4-androsten-3-one (1l) <sup>36</sup>	B	2u <sup>c</sup>	I	CH <sub>3</sub> NH <sub>2</sub>	3m (242-244)	4o (263-265) 4p (172-174) 4q (220-222) 4r (148-150) 4s (227-229) 4w (133-135)	$\beta$ -CH <sub>2</sub> NH <sub>2</sub> $\beta$ -NHCOCH <sub>3</sub>	H CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub> HOCH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> NH CH <sub>3</sub>
17 $\beta$ -acetamido-4-androsten-3-one (1m) <sup>37</sup>	A	2m <sup>a</sup>	II	CH <sub>3</sub> NH <sub>2</sub>	3n (178-180)	4x (95-97) 4y (246-248) 4z (249-251) 4aa (109-111) 4bb (181-183) 4ee (225-228)	$\beta$ -CH(CH <sub>3</sub> )CH <sub>2</sub> CO <sub>2</sub> CH <sub>3</sub> $\beta$ -CONH <sub>2</sub> $\beta$ -CONHC <sub>2</sub> H <sub>5</sub> $\beta$ -CONH(CH <sub>2</sub> ) <sub>7</sub> CH <sub>3</sub> $\beta$ -CON( <i>i</i> -C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub> $\beta$ -OH (19-nor)	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> (19-nor)
17 $\alpha$ -acetamido-4-androsten-3-one (1n) <sup>37</sup>	A	2n <sup>a</sup>	II	CH <sub>3</sub> NH <sub>2</sub>	3o (250-253) 3p (121-123) 3q (189-192) 3r (144-146) 3s (130-132) 3w (159-161)	4x (95-97) 4y (246-248) 4z (249-251) 4aa (109-111) 4bb (181-183) 4ee (225-228)	$\beta$ -CON(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> $\beta$ -CON(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> $\beta$ -CON(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> $\beta$ -CON(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> $\beta$ -CON(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> $\beta$ -CO <sub>2</sub> CH <sub>3</sub>	H CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub> HOCH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> NH CH <sub>3</sub>
N,N-diethyl-3-oxo-4-androstene-17 $\beta$ -carboxamide (1o)	A and B	2o (205-207)	I and II I and II II II II I and II	NH <sub>3</sub> CH <sub>3</sub> NH <sub>2</sub> C <sub>2</sub> H <sub>5</sub> NH <sub>2</sub> HOCH <sub>2</sub> CH <sub>2</sub> NH <sub>2</sub> CH <sub>3</sub> NHNH <sub>2</sub> CH <sub>3</sub> NH <sub>2</sub>	3o (250-253) 3p (121-123) 3q (189-192) 3r (144-146) 3s (130-132) 3w (159-161)	4x (95-97) 4y (246-248) 4z (249-251) 4aa (109-111) 4bb (181-183) 4ee (225-228)	$\beta$ -CH(CH <sub>3</sub> )CH <sub>2</sub> CO <sub>2</sub> CH <sub>3</sub> $\beta$ -CONH <sub>2</sub> $\beta$ -CONHC <sub>2</sub> H <sub>5</sub> $\beta$ -CONH(CH <sub>2</sub> ) <sub>7</sub> CH <sub>3</sub> $\beta$ -CON( <i>i</i> -C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub> $\beta$ -OH (19-nor)	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>
methyl 3-oxo-4-androstene-17 $\beta$ -carboxylate (1w) <sup>30</sup>	A	2w (158-161)	I and II	CH <sub>3</sub> NH <sub>2</sub>	3x (103-105) 3y (248-250) 3z (242-246) 3aa (oil) 3bb (115-117) 3ee (215-217)	4x (95-97) 4y (246-248) 4z (249-251) 4aa (109-111) 4bb (181-183) 4ee (225-228)	$\beta$ -CH(CH <sub>3</sub> )CH <sub>2</sub> CO <sub>2</sub> CH <sub>3</sub> $\beta$ -CONH <sub>2</sub> $\beta$ -CONHC <sub>2</sub> H <sub>5</sub> $\beta$ -CONH(CH <sub>2</sub> ) <sub>7</sub> CH <sub>3</sub> $\beta$ -CON( <i>i</i> -C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub> $\beta$ -OH (19-nor)	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>
methyl 3-oxo-4-cholen-24-oate (1x) <sup>38</sup>	B	2x	II	CH <sub>3</sub> NH <sub>2</sub>	3x (103-105) 3y (248-250) 3z (242-246) 3aa (oil) 3bb (115-117) 3ee (215-217)	4x (95-97) 4y (246-248) 4z (249-251) 4aa (109-111) 4bb (181-183) 4ee (225-228)	$\beta$ -CH(CH <sub>3</sub> )CH <sub>2</sub> CO <sub>2</sub> CH <sub>3</sub> $\beta$ -CONH <sub>2</sub> $\beta$ -CONHC <sub>2</sub> H <sub>5</sub> $\beta$ -CONH(CH <sub>2</sub> ) <sub>7</sub> CH <sub>3</sub> $\beta$ -CON( <i>i</i> -C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub> $\beta$ -OH (19-nor)	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>
3-oxo-4-androstene-17 $\beta$ -carboxamide (1y) <sup>39</sup>	A	2y <sup>a</sup>	II	CH <sub>3</sub> NH <sub>2</sub>	3x (103-105) 3y (248-250) 3z (242-246) 3aa (oil) 3bb (115-117) 3ee (215-217)	4x (95-97) 4y (246-248) 4z (249-251) 4aa (109-111) 4bb (181-183) 4ee (225-228)	$\beta$ -CH(CH <sub>3</sub> )CH <sub>2</sub> CO <sub>2</sub> CH <sub>3</sub> $\beta$ -CONH <sub>2</sub> $\beta$ -CONHC <sub>2</sub> H <sub>5</sub> $\beta$ -CONH(CH <sub>2</sub> ) <sub>7</sub> CH <sub>3</sub> $\beta$ -CON( <i>i</i> -C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub> $\beta$ -OH (19-nor)	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>
N-ethyl-3-oxo-4-androstene-17 $\beta$ -carboxamide (1z)	B	2z	II	CH <sub>3</sub> NH <sub>2</sub>	3x (103-105) 3y (248-250) 3z (242-246) 3aa (oil) 3bb (115-117) 3ee (215-217)	4x (95-97) 4y (246-248) 4z (249-251) 4aa (109-111) 4bb (181-183) 4ee (225-228)	$\beta$ -CH(CH <sub>3</sub> )CH <sub>2</sub> CO <sub>2</sub> CH <sub>3</sub> $\beta$ -CONH <sub>2</sub> $\beta$ -CONHC <sub>2</sub> H <sub>5</sub> $\beta$ -CONH(CH <sub>2</sub> ) <sub>7</sub> CH <sub>3</sub> $\beta$ -CON( <i>i</i> -C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub> $\beta$ -OH (19-nor)	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>
N-octyl-3-oxo-4-androstene-17 $\beta$ -carboxamide (1aa)	A	2aa <sup>a</sup>	II	CH <sub>3</sub> NH <sub>2</sub>	3x (103-105) 3y (248-250) 3z (242-246) 3aa (oil) 3bb (115-117) 3ee (215-217)	4x (95-97) 4y (246-248) 4z (249-251) 4aa (109-111) 4bb (181-183) 4ee (225-228)	$\beta$ -CH(CH <sub>3</sub> )CH <sub>2</sub> CO <sub>2</sub> CH <sub>3</sub> $\beta$ -CONH <sub>2</sub> $\beta$ -CONHC <sub>2</sub> H <sub>5</sub> $\beta$ -CONH(CH <sub>2</sub> ) <sub>7</sub> CH <sub>3</sub> $\beta$ -CON( <i>i</i> -C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub> $\beta$ -OH (19-nor)	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>
N,N-diisopropyl-3-oxo-4-androstene-17 $\beta$ -carboxamide (1bb)	A	2bb (236-238)	I and II	CH <sub>3</sub> NH <sub>2</sub>	3x (103-105) 3y (248-250) 3z (242-246) 3aa (oil) 3bb (115-117) 3ee (215-217)	4x (95-97) 4y (246-248) 4z (249-251) 4aa (109-111) 4bb (181-183) 4ee (225-228)	$\beta$ -CH(CH <sub>3</sub> )CH <sub>2</sub> CO <sub>2</sub> CH <sub>3</sub> $\beta$ -CONH <sub>2</sub> $\beta$ -CONHC <sub>2</sub> H <sub>5</sub> $\beta$ -CONH(CH <sub>2</sub> ) <sub>7</sub> CH <sub>3</sub> $\beta$ -CON( <i>i</i> -C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub> $\beta$ -OH (19-nor)	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>
19-nortestosterone (1ee)	A and B	2ee (125-127)	I and II	CH <sub>3</sub> NH <sub>2</sub>	3x (103-105) 3y (248-250) 3z (242-246) 3aa (oil) 3bb (115-117) 3ee (215-217)	4x (95-97) 4y (246-248) 4z (249-251) 4aa (109-111) 4bb (181-183) 4ee (225-228)	$\beta$ -CH(CH <sub>3</sub> )CH <sub>2</sub> CO <sub>2</sub> CH <sub>3</sub> $\beta$ -CONH <sub>2</sub> $\beta$ -CONHC <sub>2</sub> H <sub>5</sub> $\beta$ -CONH(CH <sub>2</sub> ) <sub>7</sub> CH <sub>3</sub> $\beta$ -CON( <i>i</i> -C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub> $\beta$ -OH (19-nor)	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>

<sup>a</sup> Structure verified by <sup>1</sup>H NMR. <sup>b</sup> Other substituent at C-17 is hydrogen unless otherwise specified. <sup>c</sup> Structure verified by mass spectrum.



**17 $\beta$ -(Diethylcarbamoyl)-3-methoxy-4-methyl-4-azonia-5 $\alpha$ -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  $\text{CHCl}_3$  was refluxed ( $\text{N}_2$ ) for 64 h. Evaporation left a tacky residue which was triturated with 1:1 EtOAc-toluene (15 mL). The resulting solid was filtered under  $\text{N}_2$  and washed with 1:1 Et<sub>2</sub>O-EtOAc to leave 875 mg of **5**, mp 120–125 °C. A portion recrystallized twice from EtOAc- $\text{CH}_2\text{Cl}_2$  had mp 133–134 °C.

***N,N*-Diethyl-3-(methylimino)-4-methyl-4-aza-5 $\alpha$ -androstane-17 $\beta$ -carboxamide (6a) (X =  $\text{CH}_3\text{N}$ ).** Dry, gaseous  $\text{CH}_3\text{NH}_2$  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  $\text{CH}_3\text{OSO}_3\text{CH}_3$ ). Excess  $\text{CH}_3\text{NH}_2$  was removed by codistillation with methanol and the mixture was concentrated to a tacky residue. EtOAc-Et<sub>2</sub>O (1:1, 6 mL) trituration resulted in separation of a solid which was removed and rinsed with Et<sub>2</sub>O and then washed with H<sub>2</sub>O (2  $\times$  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-5 $\alpha$ -androstane-17 $\beta$ -carboxamide (6b, X = HN)** (102 mg, mp 178–184 °C).

***N,N*-Diethyl-3-thioxo-4-methyl-4-aza-5 $\alpha$ -androstane-17 $\beta$ -carboxamide (6c, X = S).** A solution of the steroidal salt **5** (50 mg, 0.095 mmol) and  $\text{NaSH}\cdot x\text{H}_2\text{O}$  (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  $\text{CH}_2\text{Cl}_2$ . The crude product was chromatographed by TLC (20 cm  $\times$  20 cm  $\times$  1000  $\mu\text{m}$ , 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-5 $\alpha$ -androstane-17 $\beta$ -carboxamide (6d, X = HON).** A solution of the steroid salt **5** (100 mg, 0.19 mmol),  $\text{HONH}_2\text{HCl}$  (69 mg, 1.0 mmol), and 0.1 mL of pyridine in anhydrous methanol (1.0 mL) was heated at reflux ( $\text{N}_2$ ) for 18 h. The solvent was largely removed at room temperature under a stream of nitrogen and the residue was dissolved in  $\text{CHCl}_3$ . 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-5 $\alpha$ -androstane-17 $\beta$ -carboxamide.** A solution of *i*-Pr<sub>2</sub>NLi in hexane-pentane<sup>44</sup> (6.0 mL, 3 mequiv) was added ( $\text{N}_2$ , –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 ( $\text{N}_2$ , 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  $\times$  20 cm  $\times$  20 cm  $\times$  2000  $\mu\text{m}$ , 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  $\mu$ Porasil) indicated it was a mixture of isomers. Recrystallization from ethyl acetate gave pure  $\alpha$ -isomer, mp 169–170 °C. The  $\beta$ -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  $\alpha$ -isomer as analyzed by HPLC.

***N,N*-Diethyl-3-oxo-4-methyl-4-aza-5 $\alpha$ -androst-1-ene-17 $\beta$ -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  $\text{NaIO}_4$  (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-1 $\alpha$ ,2 $\alpha$ -epoxy-3-oxo-4-methyl-4-aza-5 $\alpha$ -androstane-17 $\beta$ -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  $\text{NaHCO}_3$ , 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-5 $\alpha$ -androst-1-ene-17 $\beta$ -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  $\text{CHCl}_3$  and 1.5 mL of redistilled dimethyl sulfate was refluxed for 5 h and then in a 100 °C bath while the  $\text{CHCl}_3$  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  $\text{K}_2\text{CO}_3$  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-5 $\alpha$ -androst-3-ene-17 $\beta$ -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).<sup>44</sup> 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  $\text{N}_2$ . 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  $\times$  20 cm  $\times$  20 cm  $\times$  1000  $\mu\text{m}$  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-5 $\alpha$ -androstane-**

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**17 $\beta$ -carboxamide (12, x = 0).** Crystallization from EtOAc (0.5 mL) gave 38 mg, mp 194–198 $^{\circ}$ .

This crude phenylthio compound (12, 66 mg) was oxidized in 1.0 mL of MeOH with 48 mg of NaIO<sub>4</sub> 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  $\times$  20 cm  $\times$  1000  $\mu$ m silica gel plate eluting with 10% MeOH in EtOAc. The product (*R*<sub>f</sub> 0.5) was isolated and recrystallized from EtOAc to give 16 mg of 9, mp 276–278 $^{\circ}$ C.

***N,N*-Diethyl-3-oxo-4-aza-5 $\alpha$ -androst-1-ene-17 $\beta$ -carboxamide (9).** Seleninic Anhydride Oxidation.<sup>14</sup> 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 $^{\circ}$ C for 19 h. The solvent was removed under reduced pressure and the residue was worked up in CH<sub>2</sub>Cl<sub>2</sub> (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<sub>2</sub>Cl<sub>2</sub>-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<sub>2</sub>O-hexane to leave 5.4 g (62% based on recovered 4o) of 9, mp 275–277.5 $^{\circ}$ C.

***N,N*-Diethyl-2-formyl-3-oxo-4-methyl-4-aza-5 $\alpha$ -androstane-17 $\beta$ -carboxamide (13).** A solution 0.5 N *i*-Pr<sub>2</sub>NLi in hexane-pentane<sup>44</sup> (9.8 mL, 4.9 mequiv) was added dropwise (room temperature, N<sub>2</sub>) 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<sub>3</sub>, 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 $^{\circ}$ C; second crop, 187 mg, mp 147–152 $^{\circ}$ C (79%).

***N,N*-Diethyl-2,3-dioxo-4-methyl-4-aza-5 $\alpha$ -androstane-17 $\beta$ -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<sub>2</sub>Cl<sub>2</sub> cooled at –78 $^{\circ}$ C until a definite blue color persisted for 4 min. The cold solution was purged with N<sub>2</sub> 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 $^{\circ}$ C. The solution was evaporated at low (ca. 0 $^{\circ}$ C) temperature to leave a semicrystalline residue. Recrystallization from ethyl acetate gave 382 mg of 14 as prisms, mp 192–199 $^{\circ}$ C. An analytical sample had mp 190–195 $^{\circ}$ C.

***N,N*-Diethyl-2-oxo-3-methyl-3-aza-*A*-nor-5 $\alpha$ -androstane-17 $\beta$ -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<sub>3</sub>, water, saturated NaHCO<sub>3</sub>, 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 $^{\circ}$ C. The mother liquor was chromatographed (HPLC, EtOAc, 4 ft  $\times$  3/8 in. Porasil column) to give 55 mg additional of 15, mp 158–165 $^{\circ}$ C (total yield 77%).

**17 $\beta$ -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<sub>2</sub>O-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-3,17 $\beta$ -diol (17a), mp 217 $^{\circ}$ 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 $^{\circ}$ C.

A suspension of RuO<sub>3</sub> (53%, 200 mg) in 70 mL of acetone was treated at room temperature with NaIO<sub>4</sub> (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<sub>4</sub> 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<sub>3</sub> solution. After rinsing with EtOAc the basic extract was acidified with aqueous HCl solution. The product acid was worked up in EtOAc (H<sub>2</sub>O, 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 $^{\circ}$ C dec.

**17 $\beta$ -Acetoxy-4-nitrilo-5 $\alpha$ -androstane-3-oic Acid (19).** The diacid 18 (300 mg, 0.74 mmol) was heated at 210–220 $^{\circ}$ 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 $^{\circ}$ C. The filtrate was evaporated and the residue separated from EtOAc by addition of hexane to give 130 mg, mp 140–155 $^{\circ}$ C. In spite of the two different melting points, the two isolates had the same *R*<sub>f</sub> values on TLC (silica gel 0.5% HCO<sub>2</sub>H in Et<sub>2</sub>O) and identical IR (CHCl<sub>3</sub>) spectra.

**17 $\beta$ -Hydroxy-3-azaandrostane-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<sub>4</sub> was added 0.20 mL of a Br<sub>2</sub> solution in CCl<sub>4</sub> (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<sub>2</sub> solution. After 2 h of reflux, 10 mg of HgO was added with 0.05 mL of Br<sub>2</sub> solution and reflux was continued for 1 h. After cooling, the mixture was diluted with CHCl<sub>3</sub> and worked up (washed with 5% aqueous HCl, water, and saturated NaCl solution, dried, and concentrated) to leave 17 $\beta$ -acetoxy-2-bromo-2,3-seco-*A*-norandrostane-3-nitrile (20) as crystalline residue. This material, mp 120–150 $^{\circ}$ 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<sub>4</sub>OH solution in 1.0 mL of EtOH was heated in a sealed tube at 155 $^{\circ}$ C for 17 h. The cooled solution was evaporated to a brown mass which was eluted on TLC (1  $\times$  1000  $\mu$ m  $\times$  20 cm  $\times$  20 cm, silica gel) with 10% MeOH-CHCl<sub>3</sub>. The major band was isolated and crystallized from ether to give 24 mg of 21, mp 214–214.5 $^{\circ}$ C.

**4-Methyl-4-aza-5 $\alpha$ -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.<sup>45</sup> 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<sub>3</sub>. 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 $^{\circ}$ C. Anal. (C<sub>18</sub>H<sub>27</sub>NO<sub>2</sub> $\cdot$ 1/2 H<sub>2</sub>O).

In a similar fashion 20-hydroxy-4-methyl-4-aza-5 $\alpha$ -pregnan-3-one (4e) and 20-hydroxy-4-aza-5 $\alpha$ -pregnan-3-one were converted into 4-methyl-4-aza-5 $\alpha$ -pregnane-3,20-dione (4d), mp 218–220 $^{\circ}$ C, and 4-aza-5 $\alpha$ -pregnane-3,20-dione (4c), mp 272–275 $^{\circ}$ C, respectively.

**Ethyl 4-Methyl-3-oxo-4-aza-5 $\alpha$ -pregn-17(20)-en-21-oate (23a, R = C<sub>2</sub>H<sub>5</sub>).** 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<sub>2</sub>O (washed with H<sub>2</sub>O, NaHCO<sub>3</sub> solution, H<sub>2</sub>O, and saturated NaCl solution, dried, and evaporated) to leave a crystalline residue. Recrystallization from Et<sub>2</sub>O gave 461 mg of 23a, mp 150–152 $^{\circ}$ C.

A solution of the ester 23a (265 mg, 0.71 mmol) and 200 mg of K<sub>2</sub>CO<sub>3</sub> 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-5 $\alpha$ -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-5 $\alpha$ -pregnane-20 $\alpha$ -carboxylic acid (**4u**), mp 307–309 °C; 4-methyl-3-oxo-4-aza-5 $\alpha$ -androstane-17 $\beta$ -carboxylic acid (**4t**), mp >300 °C; 4-methyl-3-oxo-4-aza-5 $\alpha$ -cholan-24-oic acid (**4v**), mp 256–258 °C; 4-methyl-3-oxo-4-aza-5 $\alpha$ -pregnan-21-oic acid (**25b**), mp 239–241 °C.

**Ethyl 4-Methyl-3-oxo-4-aza-5 $\alpha$ -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-5 $\alpha$ -pregn-17(20)-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<sub>2</sub>Cl<sub>2</sub>. After washing with water and saturated NaCl solution, the CH<sub>2</sub>Cl<sub>2</sub> layer was dried and evaporated to leave 253 mg of crude, crystalline material. This material was purified by preparative TLC (3  $\times$  1000  $\mu$ m  $\times$  20 cm  $\times$  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-5 $\alpha$ -pregnane-20 $\alpha$ -carboxamide (**4cc**), mp 216–218 °C; *N,N*-diethyl-4-methyl-3-oxo-4-aza-5 $\alpha$ -androstane-17 $\beta$ -carboxamide (**4p**), mp 172–174 °C; *N,N*-diethyl-4-methyl-3-oxo-4-aza-5 $\alpha$ -cholan-24-amide (**4dd**), mp 165–167 °C; *N,N*-Diethyl-4-methyl-3-oxo-4-aza-5 $\alpha$ -pregnan-21-amide (**26**), mp 159–162 °C.

**17 $\beta$ -Acetoxy-4a-aza-A-homo-5 $\alpha$ -androstan-4-one (31).** 17 $\beta$ -Hydroxy-5 $\alpha$ -androstan-4-one<sup>17</sup> was prepared from 4-androsten-17 $\beta$ -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<sub>2</sub>OH·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<sub>2</sub>O 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<sub>2</sub>O. Crystallization from EtOAc gave 210 mg of the A-homo azasteroid **31**, mp 232–235 °C.

**3-Aza-5 $\alpha$ -androstan-17 $\beta$ -ol (30a, **R** = H).** A mixture of the acetoxy lactam **28a** ( $x = 1$ )<sup>18</sup> (900 mg, 2.7 mmol) and 3.9 g of LiAlH<sub>4</sub> 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<sub>4</sub>Cl 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-5 $\alpha$ -androstan-17 $\beta$ -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 bis-sulfenylated 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<sub>2</sub>Cl<sub>2</sub> was added to the mixture 10 min after addition was complete. The organic layer was washed successively with saturated NaHSO<sub>3</sub>, water, saturated Na<sub>2</sub>CO<sub>3</sub>, and water. After drying and concentration, a gummy residue was obtained which was eluted on three 20 cm  $\times$  20 cm  $\times$  1000  $\mu$ m 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<sup>+</sup> (494), which corresponds to *N,N*-diethyl-2-(phenylsulfenyl)-3-oxo-4-methyl-4-aza-5 $\alpha$ -androst-1-ene-17 $\beta$ -carboxamide (**33**).

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

***N,N*-Diethyl-2-hydroxy-3-oxo-4-methyl-4-aza-5 $\alpha$ -androstane-17 $\beta$ -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<sub>2</sub>) 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<sub>3</sub>, 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  $\times$  30 cm  $\times$  250  $\mu$ m, EtOAc) and crystallized from Et<sub>2</sub>O to give **35** as prisms, mp 163–166 °C, M<sup>+</sup> (404; high resolution, found, 404.3024; calcd, 404.3039). The minor component was not investigated further.

***N,N*-Diethyl-2 $\beta$ ,4-dimethyl-3-oxo-4-aza-5 $\alpha$ -androstane-17 $\beta$ -carboxamide (36).** To a solution of the steroid **4p** (190 mg, 0.49 mmol) in THF (1.0 mL) was added (N<sub>2</sub>, –78 °C, stirring) a solution of 0.53 N *i*-Pr<sub>2</sub>NLi in hexane–pentane<sup>44</sup> (0.92 mL, 0.49 mmol). The mixture was allowed to come to 0 °C and then added dropwise to a solution of CH<sub>3</sub>I (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  $\times$  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<sub>3</sub>ONa (300 mg) in 3 mL of MeOH was refluxed (N<sub>2</sub>) 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  $\times$  20 cm  $\times$  500  $\mu$ m, 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<sub>3</sub> shift from the 0.89 ppm of the starting material to 0.77 ppm and a movement of the 2-CHCH<sub>3</sub> doublet ( $J$  = 6 Hz) from 1.20 to 1.15 ppm.

**Methyl 3-Oxo-5 $\alpha$ -androst-1-ene-17 $\beta$ -carboxylate (38).** To a solution of methyl 3-oxo-5 $\alpha$ -androstane-17 $\beta$ -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<sub>2</sub> 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<sub>2</sub>CO<sub>3</sub> 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-5 $\alpha$ -androstane-17 $\beta$ -carboxylate (40).** A solution of the  $\Delta^1$ -steroid **38** (1.0 g, 3.0 mmol) in a 2:1 mixture of MeCl<sub>2</sub>-EtOAc (15 mL) was ozonized at -78 °C until blue color persisted for 2 min. The mixture was purged with N<sub>2</sub> 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<sub>2</sub>O<sub>2</sub> in 10 mL of HOAc. After standing 3 h, the mixture was concentrated to a thick oil. The material was dissolved in Et<sub>2</sub>O, washed with water, and extracted into 2.5 N NaOH solution. The aqueous layer was acidified and extracted with Et<sub>2</sub>O. The organic layer was washed with water, dried, and concentrated to leave 958 mg of crude 17 $\beta$ -carboxymethoxy-1-oxo-1,2-seco-**A-nor-5 $\alpha$ -androstane-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<sub>4</sub> (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<sub>6</sub>H<sub>6</sub>) by TLC on 1000- $\mu$ m silica gel plates. The major band was isolated and crystallized from Et<sub>2</sub>O 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; **7a $\alpha$** , 76763-12-7; **7a $\beta$** , 76776-74-4; (**2 $\alpha$ (*R*))-7b**, 92473-05-7; (**2 $\alpha$ (*S*))-7b**, 92473-04-6; (**2 $\beta$ (*R*))-7b**, 92473-03-5; (**2 $\beta$ (*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<sub>3</sub>NH<sub>2</sub>, 74-89-5; NH<sub>3</sub>, 7664-41-7; C<sub>2</sub>H<sub>5</sub>NH<sub>2</sub>, 75-04-7; C<sub>6</sub>H<sub>5</sub>NH<sub>2</sub>, 62-53-3; HO(CH<sub>2</sub>)<sub>2</sub>NH<sub>2</sub>, 141-43-5; CH<sub>3</sub>NHNH<sub>2</sub>, 60-34-4; (C<sub>2</sub>H<sub>5</sub>O)<sub>2</sub>P(O)CO<sub>2</sub>CH<sub>3</sub>, 1067-74-9; pregnenolone, 145-13-1; pregnenolone 21-pyridinium iodide, 73672-02-3; 17 $\beta$ -hydroxy-5 $\alpha$ -androstane-4-one, 571-08-4; 5 $\alpha$ -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<sub>1</sub> 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<sub>1</sub>-type dopamine agonist. This is in contrast to the 2-nonmethylated homologue 6,7-ADTN, which is a potent DA<sub>1</sub> agonist. High-field <sup>1</sup>H 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  $\alpha$  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  $\alpha$ -methyl-substituted dopamine derivatives.  $\alpha$ -Methyldopamine (**1**) lacks agonist activity

at the renal dopamine receptor<sup>1</sup> and its *N*-methyl, *N,N*-dimethyl, and other *N*-alkylated derivatives lack dopamine

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(1) Borne, R. F.; Forrester, M. L.; Waters, I. W. *J. Med. Chem.* 1977, 20, 771.