J. Med. Chem. 1990, 33, 937-942

Steroidal A Ring Aryl Carboxylic Acids: A New Class of Steroid 5α-Reductase Inhibitors

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Received August 3, 1989

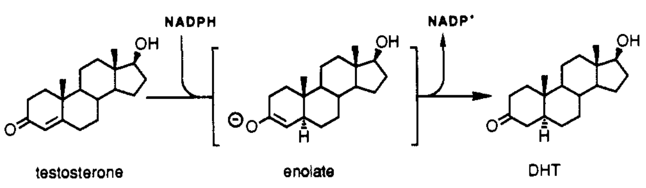
A series of 17β-carbamoyl-1,3,5(10)-estratriene-3-carboxylic acids has been prepared and evaluated in vitro as inhibitors of human and rat prostatic steroid 5α-reductase (EC 1.3.1.30). Potent inhibition of the human enzyme, in particular, was observed and preliminary studies using rat enzyme suggest that the inhibition results from the formation of an enzyme–NADP$^+$–inhibitor complex. The compounds were synthesized from estrone, generally employing a differentiated bis-triflate carbonylation strategy.

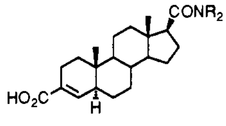
Recognition that prostatic growth is supported by dihydrotestosterone (DHT)[1] and that DHT is likely a causative factor in the disease benign prostatic hypertrophy (BPH)[2] has led to a search for potent inhibitors of steroid 5α-reductase (EC 1.3.1.30), the enzyme responsible for the production of DHT from testosterone (T).[3] On the basis of studies of males genetically deficient in this enzyme,[4] selective blockade of DHT biosynthesis is expected to provide potential treatment for BPH (as well as androgen-related skin disorders such as acne and male pattern baldness[5]) while classic testosterone-supported masculinity traits and normal male sexual functions are maintained.

Toward this end, preclinical studies with steroid 5α-reductase inhibitors have demonstrated selective retardation of prostatic growth in rats[6] and regression of prostatic size in dogs,[7] coinciding with suppression of prostatic DHT concentrations. One of these inhibitors, MK-906, a 4-aza-3-oxo steroid, is in clinical trials and is reported to lower serum DHT[8] and reduce prostatic volume in a significant percentage of patients.[9]

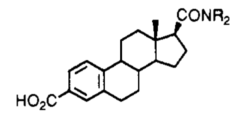
Chart I

Steroid 5α-Reductase:



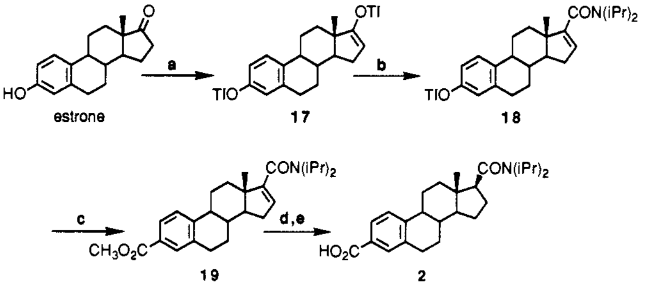


1 (steroidat acrylate)



2 R=iPr
3 R=H,tBu

Scheme I[a]



[a] (a) Tf_2O, base; (b) $Pd(OAc)_2(PPh_3)_2$, CO, i-Pr_2NH; (c) $Pd(OAc)_2(dppp)$, CO, MeOH; (d) H_2, PtO_2; (e) K_2CO_3, H_2O, MeOH.

Recently we described a new class of 3-androstene-3-carboxylic acids, "steroidal acrylates", which exhibit potent (nanomolar), uncompetitive (vs T) inhibition of human steroid 5α-reductase via a novel association with an enyzme–NAPD$^+$ complex.[10,11]

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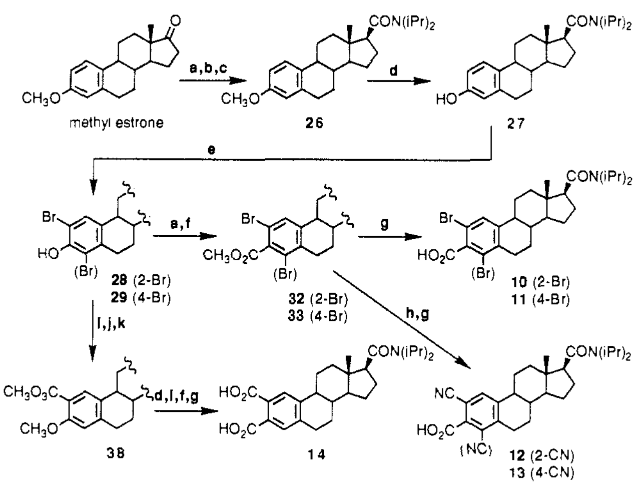
Scheme II[a]

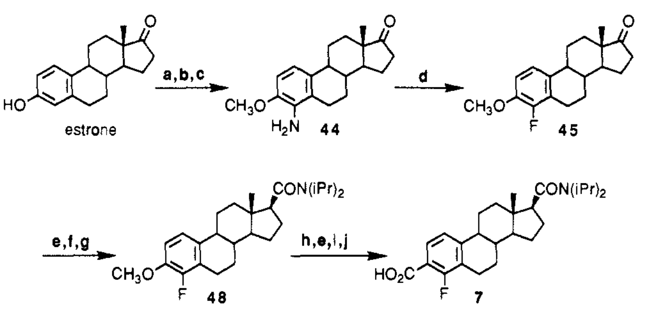


[a] (a) Tf$_2$O, base; (b) Pd(OAc)$_2$(PPh$_3$)$_2$, CO, i-Pr$_2$NH; (c) H$_2$, PtO$_2$; (d) BBr$_3$; (e) Br$_2$, HOAc; (f) Pd(OAc)$_2$(dppp), CO, MeOH; (g) K$_2$CO$_3$, H$_2$O, MeOH; (h) CuCN; (i) Me$_2$SO$_4$; (j) n-BuLi; CO$_2$; (k) CH$_2$N$_2$, NaH, Tf$_2$NPh.

These compounds (e.g. 1) were designed as mimics of the putative enzyme-bound enolate intermediate (Chart I) by incorporating sp^2-hybridized centers at C-3 and C-4, and most critically, an anionic carboxylic acid at C-3 as a charged replacement for the enolate oxyanion.[12] Due presumably to favorable electrostatic interactions between the carboxylate and the positively charged oxidized cofactor, the acrylates preferentially bind in a ternary complex with enzyme and NADP$^+$, which leads to the observed uncompetitive kinetics.[13]

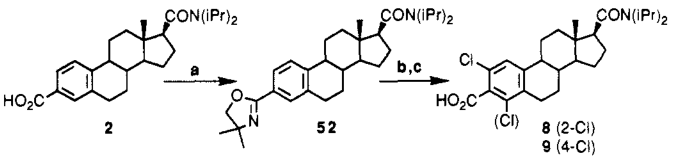
Prompted by structural novelty, potential metabolic dissimilarity to the steroidal acrylates, and nuclear relationship to estrone, a reported weak inhibitor of human 5α-reductase,[14] we have prepared a series of estratriene-3-carboxylates. Despite lacking the 19-methyl group, an element demonstrated to enhance binding in the acrylate[11] and 4-aza series[15] by 3–5-fold, the aryl acids **2** and **3** are potent inhibitors of human 5α-reductase, exhibiting apparent inhibition constants equal to or lower than those of the analogous acrylates **1**. Unlike the steroidal acrylates, however, these aryl acids exhibit greatly reduced affinity for the rat enzyme. In this paper we describe the syntheses and in vitro activities of this series of A ring aromatic steroidal carboxylic acids (**4–16**) with structural variations in the C-2 and C-4 substituents, in the degrees of unsaturation in the B and D rings, and in the C-17 carboxamide alkyl groups.

Scheme III[a]



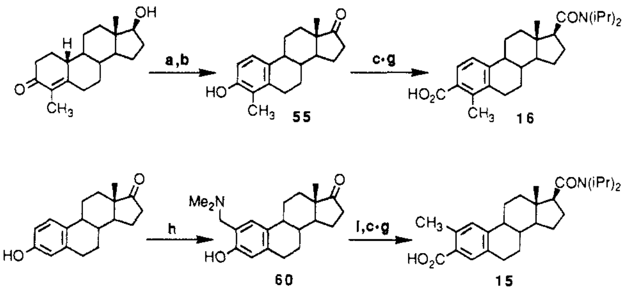
[a] (a) HNO$_3$, HOAc; (b) Me$_2$SO$_4$; (c) H$_2$, Raney Ni; (d) NaNO$_2$, HCl, HBF$_4$; xylene, Δ; (e) Tf$_2$O, base; (f) Pd(OAc)$_2$(PPh$_3$)$_2$, CO, i-Pr$_2$NH; (g) H$_2$, PtO$_2$; (h) BBr$_3$; (i) Pd(OAc)$_2$(dppp), CO, MeOH; (j) K$_2$CO$_3$, H$_2$O, MeOH.

Scheme IV[a]



[a] (a) SOCl$_2$; (b) n-BuLi; C$_2$Cl$_6$; (c) HCl.

Scheme V[a]



[a] (a) PCC; (b) Pd/C, p-cymene, Δ; (c) Tf$_2$O, base; (d) Pd(OAc)$_2$(PPh$_3$)$_2$, CO, i-Pr$_2$NH; (e) Pd(OAc)$_2$(dppp), CO, MeOH; (f) H$_2$, PtO$_2$; (g) K$_2$CO$_3$, H$_2$O, MeOH; (h) (CH$_2$O)$_x$, (CH$_3$)$_2$NCH$_2$N(CH$_3$)$_2$; (i) Raney Ni, Δ.

Chemistry

The 17β-carbamoylestratriene-3-carboxylates were derived from estrone through sequential introduction of differentiated carboxylate derivatives at C-3 and C-17 using palladium(0) catalyzed carbonyl insertion methodology. Treatment of estrone with trifluoromethanesulfonic anhydride and a hindered pyridine base[16] afforded bis-triflate **17** (Scheme I). The greater propensity for Pd insertion into the vinyl triflate over the aryl triflate allowed for the chemoselective introduction of the D ring carboxamide (in **18**) using bis(triphenylphosphine)palladium(II) acetate as catalyst.[17] Subsequent A ring carbomethoxylation (to afford **19**) was accomplished at slightly higher temperature by employing the more reactive [1,3-bis(diphenylphosphino)propane]palladium(II) acetate catalyst.[18] Catalytic hydrogenation of the D ring olefin yielded exclusively the 17β stereochemistry. Mild hydrolysis then provided the desired 3-carboxylic acid **2**.

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The differentiated double carbonylation strategy was also employed for the preparation of 2- or 4-substituted analogues, in some cases delaying one or both carbonylation steps until after the incorporation of the aryl substituent. Introduction of the 17β-carboxamide into O-methyl estrone (Scheme II, **26**) was followed by regiorandom monobromination[19] of the phenol. Bromophenols **28** and **29** were then separately homologated to bromo acids **10** and **11**. Copper cyanide displacement of bromine yielded cyano acids **12** and **13**. O-Methylation of **28** followed by metal–halogen exchange and carboxylation afforded 2-carbomethoxy derivative **38**, which was carried on to diacid **14**.

Fluorine was incorporated into the 4-position of estrone through the intermediacy of the diazonium salt derived from the monoaminophenol **44** (Scheme III).[20] Double carbonylation of **45** ultimately gave rise to fluoro acid **7**.

Introduction of chlorine at C-2 and C-4 was accomplished subsequent to both C-3 and C-17 carbonylation steps (Scheme IV). Ortho lithiation of the oxazoline derivative of 3-carboxylic acid **52** followed by hexachloroethane quenching provided 2- and 4-chlorinated oxazolines, which were hydrolyzed to give chloro acids **8** and **9**.

Finally, methyl substitution at C-2 and C-4 was accomplished by using classical methods (Scheme V). Aminomethylation of estrone[21] proceeded regiospecifically at C-2 and led to 2-methyl carboxylic acid **15**, while 4-methyl-19-nor-testosterone[22] was converted to 4-methyl carboxylic acid **16**.

In Vitro Activities

Earlier studies have demonstrated altered binding of 17-modified steroids to steroid 5α-reductases from various sources with the greatest positive effects on binding to the human enzyme being exerted by 17β-carboxamides.[23] Therefore, we elected to examine only two carboxamide side chain variations in this series: the diisopropyl and the mono-*tert*-butyl. Similarly to the general trend observed in the acrylate family,[11] the *tert*-butyl amide analogues (e.g. **3**) possessed approximately double the affinity for the rat prostatic enzyme as did diisopropyl analogue **2** but had approximately $^1/_2$ the affinity for the human prostatic enzyme.

Additional unsaturation in the B or D ring had minimal effects on activity.

Halogen (pseudohalogen) aryl substitution was expected to alter the electronic properties of the A ring, decreasing electron density and slightly lowering the pK_a, and in the case of fluorine and cyano, this was expected to provide potential sites for hydrogen bonding.[24,25] However, no significantly improved inhibition of human 5α-reductase was observed with any of these congeners (**7–13**); only an apparent steric intolerance in the C-4 region, which is supported by decreased activity of 4-methyl analogue **16**, was observed.

All compounds examined in this series have exhibited significantly reduced activity with the rodent enzyme relative to the human enzyme, emphasizing the reported[26] species differences in steroid 5α-reductases.

With the more readily available rat liver steroid 5α-reductase for dead-end inhibition studies,[27] compounds **2** and **3** each exhibited uncompetitive kinetic patterns versus T or NADPH. These data (not shown) suggest that the A ring aromatic acids, in analogy to the steroidal acrylates,[10,28] inhibit rat liver steroid 5α-reductase (and presumably the kinetically similar human enzyme[29]) by binding preferentially to an enzyme–NADP$^+$ complex.[32]

Experimental Section

General Methods. Melting points are uncorrected. ^{1}H NMR spectra were obtained in $CDCl_3$ solutions with Bruker AM-250 or Varian EM390 spectrometers and are reported (in part) as ppm downfield from Me_4Si with multiplicity, coupling constants (hertz), and assignments indicated parenthetically (also see the supplementary material). Mass spectra were obtained with a Finnigan-MAT quadrupole instrument generally with desorptive chemical ionization. Mass spectral data is reported as the $(M + H)^+$ parent followed by unassigned fragments (supplementary material). Chromatography refers to flash chromatography using Kieselgel 60, (230–400 mesh) silica gel.

3,17-Bis[[(trifluoromethyl)sulfonyl]oxy]estra-1,3,5(10),16-tetraene (17). To a cooled (0 °C) solution of estrone (16.2 g, 60 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (27 g, 130 mmol) in CH_2Cl_2 (500 mL) was slowly added trifluoromethanesulfonic anhydride (45.3 g, 160 mmol). The resulting solution was stirred at 0 °C for 2 h and then at ambient temperature for 4 h. The reaction mixture was then washed with 10% aqueous HCl, 10% aqueous $NaHCO_3$, and brine, dried over K_2CO_3, and concentrated. The residue was chromatographed (5% EtOAc in hexanes) to afford **17** as a white foam (25.3 g, 79%): NMR 1.01 (s, 3 H), 5.63 (m), 6.99 (s), 7.03 (d, 8.5), 7.31 (d, 8.5).

The following triflates were prepared in a similar fashion: trifluoromethyl 3-methoxyestra-1,3,5(10),16-tetraene-17-sulfonate (**24**), *N*,*N*-diisopropyl-3-[[(trifluoromethyl)sulfonyl]oxy]-2-bromoestra-1,3,5(10)-triene-17β-carboxamide **30**, *N*,*N*-diisopropyl-3-[[(trifluoromethyl)sulfonyl]oxy]-4-bromoestra-1,3,5(10)-triene-17β-carboxamide (**31**), trifluoromethyl 3-methoxy-4-fluoroestra-1,3,5(10),16-tetraene-17-sulfonate (**46**), *N*,*N*-diisopropyl-3-[[(trifluoromethyl)sulfonyl]oxy]-4-fluoroestra-1,3,5(10)-triene-17β-carboxamide (**50**), 3,17-bis[[(trifluoromethyl)-

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(27) Cleland, W. W. *Methods Enzymol.* **1979**, *63*, 103–138.

(28) Levy, M. A.; Brandt, M.; Holt, D. A.; Metcalf, B. W. *J. Steroid Biochem.*, in press.

(29) We and others have shown steroid 5α-reductase from human prostate,[31] rat prostate,[29] and rat liver[32] to follow sequential ordered kinetic mechanisms with cofactor binding preceding testosterone binding and following DHT release.

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(31) Levy, M. A.; Brandt, M.; Greway, A. T. *Biochemistry*, in press.

(32) The full details of the enzyme mechanistic studies will be published elsewhere.

sulfonyl]oxy]-4-methylestra-1,3,5(10),16-tetraene (**56**), 3,17-bis[[(trifluoromethyl)sulfonyl]oxy]-2-methylestra-1,3,5(10),16-tetraene (**62**), 3,17-bis[[(trifluoromethyl)sulfonyl]oxy]estra-1,3,5(10),6,8,16-hexaene (**66**), and *N*,*N*-diisopropyl-3-[[(trifluoromethyl)sulfonyl]oxy]estra-1,3,5(10),6-tetraene-17β-carboxamide (**73**).

***N*,*N*-Diisopropyl-3-[[(trifluoromethyl)sulfonyl]oxy]estra-1,3,5(10),16-tetraene-17-carboxamide (18).** A mixture of **17** (14 g, 26 mmol), palladium(II) acetate (500 mg, 2.23 mmol), triphenylphosphine (1.1 g, 4.19 mmol), diisopropylamine (50 mL), and DMF (100 mL) was heated at 60 °C under a carbon monoxide atmosphere (balloon) for 5 h. The reaction mixture was then concentrated, diluted with water, and thoroughly extracted with CH_2Cl_2. The organic extract was then washed with 10% aqueous HCl, 10% aqueous $NaHCO_3$, and brine and concentrated to a dark oil. Chromatography (15% EtOAc in hexanes) afforded **18** as a white powder (8.0 g, 59%): NMR 1.10 (s, 3 H), 5.68 (dd, 1.5, 2), 6.98 (s), 7.02 (d, 8.5), 7.32 (d, 8.5).

Other 16,17-unsaturated 17-carboxamides were prepared in an identical fashion: *N*-*tert*-butyl-3-[[(trifluoromethyl)sulfonyl]oxy]estra-1,3,5(10),16-tetraene-17-carboxamide (**21**) (replacing *tert*-butylamine for diisopropylamine), *N*,*N*-diisopropyl-3-methoxyestra-1,3,5(10),16-tetraene-17-carboxamide (**25**), *N*,*N*-diisopropyl-3-methoxy-4-fluoroestra-1,3,5(10),16-tetraene-17-carboxamide (**47**), *N*,*N*-diisopropyl-3-[[(trifluoromethyl)sulfonyl]oxy]-4-methylestra-1,3,5(10),16-tetraene-17-carboxamide (**57**), *N*,*N*-diisopropyl-3-[[(trifluoromethyl)sulfonyl]oxy]-2-methylestra-1,3,5(10),16-tetraene-17-carboxamide (**63**), and *N*,*N*-diisopropyl-3-[[(trifluoromethyl)sulfonyl]oxy]estra-1,3,5(10),6,8,16-hexaene-17-carboxamide (**67**) (reaction carried out at ambient temperature overnight).

Methyl 17-(*N*,*N*-Diisopropylcarbamoyl)estra-1,3,5(10),16-tetraene-3-carboxylate (19). A mixture of **18** (8.3 g, 16 mmol), palladium(II) acetate (224 mg, 1 mmol), 1,3-bis(diphenylphosphino)propane (dppp, 410 mg, 1 mmol), triethylamine (4.5 mL), methanol (32 mL), 1,2-dichloroethane (17 mL), and DMSO (50 mL) was heated at 70 °C under an atmosphere of CO for 5 h. The cooled reaction mixture was then diluted with $CHCl_3$, washed with H_2O, 10% aqueous HCl, 10% aqueous $NaHCO_3$, and brine, and concentrated. Chromatography (20% EtOAc in hexanes) yielded **19** (5.0 g, 73%): NMR 1.01 (s, 3 H), 3.90 (s, 3 H), 5.68 (m), 7.34 (d, 8), 7.77 (s), 7.78 (d, 8).

The following C-3 carbomethoxylated compounds were prepared analogously: methyl 17-(*N*-*tert*-butylcarbamoyl)estra-1,3,5(10),16-tetraene-3-carboxylate (**22**), methyl 17β-(*N*,*N*-diisopropylcarbamoyl)-2-bromoestra-1,3,5(10)-triene-3-carboxylate (**32**), methyl 17β-(*N*,*N*-diisopropylcarbamoyl)-4-bromoestra-1,3,5(10)-triene-3-carboxylate (**33**), dimethyl 17β-(*N*,*N*-diisopropylcarbamoyl)estra-1,3,5(10)-triene-2,3-dicarboxylate (**41**), methyl 17β-(*N*,*N*-diisopropylcarbamoyl)-4-fluoroestra-1,3,5(10)-triene-3-carboxylate (**51**), methyl 17-(*N*,*N*-diisopropylcarbamoyl)-4-methylestra-1,3,5(10),16-tetraene-3-carboxylate (**58**), methyl 17-(*N*,*N*-diisopropylcarbamoyl)-2-methylestra-1,3,5(10),16-tetraene-3-carboxylate (**64**), methyl 17-(*N*,*N*-diisopropylcarbamoyl)estra-1,3,5(10),6,8,16-hexaene-3-carboxylate (**68**), and methyl 17β-(*N*,*N*-diisopropylcarbamoyl)estra-1,3,5(10),6-tetraene-3-carboxylate (**74**).

Methyl 17β-(*N*,*N*-Diisopropylcarbamoyl)estra-1,3,5(10)-triene-3-carboxylate (20). A solution of **19** (7.4 g, 17.5 mmol) in EtOAc (125 mL) and EtOH (45 mL) was rapidly stirred over PtO_2 (800 mg) under an atmosphere of hydrogen (balloon) for 3 h. The catalyst was removed by filtration and the filtrate concentrated to yield **20** as a white solid (6.0 g, 81%): NMR 0.80 (s), 3.89 (s, 3 H), 7.34 (d, 8), 7.76 (s), 7.78 (d, 8).

Similar hydrogenations were carried out to produce the following compounds: methyl 17β-(*N*-*tert*-butylcarbamoyl)estra-1,3,5(10)-triene-3-carboxylate (**23**), *N*,*N*-diisopropyl-3-methoxyestra-1,3,5(10)-triene-17β-carboxamide) (**26**), *N*,*N*-diisopropyl-3-methoxy-4-fluoroestra-1,3,5(10)-triene-17β-carboxamide) (**48**), methyl 17β-(*N*,*N*-diisopropylcarbamoyl)-4-methylestra-1,3,5(10)-triene-3-carboxylate (**59**), methyl 17β-(*N*,*N*-diisopropylcarbamoyl)-2-methylestra-1,3,5(10)-triene-3-carboxylate (**65**), and methyl 17β-(*N*,*N*-diisopropylcarbamoyl)estra-1,3,5(10),6,8-pentaene-3-carboxylate (**69**).

17β-(*N*,*N*-Diisopropylcarbamoyl)estra-1,3,5(10)-triene-3-carboxylic Acid (2). A mixture of **20** (93 mg, 0.2 mmol) and K_2CO_3 (100 mg) in 3 mL of 10:1 $MeOH–H_2O$ was heated at reflux for 18 h. The mixture was then acidified with 10% aqueous HCl, diluted with H_2O, and thoroughly extracted with $CHCl_3$. Concentration of the organic extract followed by recrystallization from acetone yielded acid **2** as a white solid (81 mg, 90%): mp 233–234 °C; NMR 0.80 (s, 3 H), 7.38 (d, 8), 7.73 (s), 7.75 (d, 8). Anal. ($C_{26}H_{37}NO_3$) C, H, N.

Other esters were hydrolyzed by using a similar protocol to afford the following acids: 17β-(*N*-*tert*-butylcarbamoyl)estra-1,3,5(10)-triene-3-carboxylic acid (**3**) [Mp 235–240 °C. Anal. ($C_{24}H_{33}NO_3$) C, H, N.], 17β-(*N*,*N*-diisopropylcarbamoyl)estra-1,3,5(10),6-tetraene-3-carboxylic acid (**4**) [Mp 209–210 °C. Anal. ($C_{26}H_{35}NO_3\cdot{}^1/_4H_2O$) C, H, N.], 17β-(*N*,*N*-diisopropylcarbamoyl)estra-1,3,5(10),6,8-pentaene-3-carboxylic acid (**5**) [Mp 257–260 °C. Anal. ($C_{26}H_{33}NO_3$) C, H, N.], 17-(*N*-*tert*-butylcarbamoyl)estra-1,3,5(10),16-tetraene-3-carboxylic acid (**6**) [Mp 212–215 °C. Anal. ($C_{24}H_{31}NO_3$) C (calcd 75.56, found 76.36), H, N.], 17β-(*N*,*N*-diisopropylcarbamoyl)-4-fluoroestra-1,3,5(10)-triene-3-carboxylic acid (**7**) [Mp 245–248 °C (dec). Anal. ($C_{26}H_{36}FNO_3$) C, H, N.], 17β-(*N*,*N*-diisopropylcarbamoyl)-2-bromoestra-1,3,5(10)-triene-3-carboxylic acid (**10**) [Mp 294–300 °C. Anal. ($C_{26}H_{36}BrNO_3$) C (calcd 63.67, found 65.61), H, N.], 17β-(*N*,*N*-diisopropylcarbamoyl)-4-bromoestra-1,3,5(10)-triene-3-carboxylic acid (**11**) [Mp 276–280 °C dec. Anal. ($C_{26}H_{36}BrNO_3$) C, H, N.], 17β-(*N*,*N*-diisopropylcarbamoyl)-2-cyanoestra-1,3,5(10)-triene-3-carboxylic acid (**12**) [MP 270–273 °C dec. Anal. ($C_{27}H_{36}N_2O_3\cdot{}^1/_2H_2O$) C, H, N.], 17β-(*N*,*N*-diisopropylcarbamoyl)-4-cyanoestra-1,3,5(10)-triene-3-carboxylic acid (**13**) [Mp 240–242 °C dec. Anal. ($C_{27}H_{36}N_2O_3$) C, H, N.], 17β-(*N*,*N*-diisopropylcarbamoyl)estra-1,3,5(10)-triene-2,3-dicarboxylic acid (**14**) [Mp 180–187 °C. Anal. ($C_{27}H_{37}NO_5$) C, H, N.], 17β-(*N*,*N*-diisopropylcarbamoyl)-2-methylestra-1,3,5(10)-triene-3-carboxylic acid (**15**) [Mp 272–273 °C. Anal. ($C_{27}H_{39}NO_3$) C, H, N.], and 17β-(*N*,*N*-diisopropylcarbamoyl)-4-methylestra-1,3,5(10)-triene-3-carboxylic acid (**16**) [Mp 271–273 °C. Anal. ($C_{27}H_{39}NO_3$) C (calcd 76.20, found 75.48), H, N.].

17β-(*N*,*N*-Diisopropylcarbamoyl)estra-1,3,5(10)-trien-3-ol (27). To a 0 °C solution of **26** (4.8 g, 12 mmol) in dichloromethane (150 mL) was added a CH_2Cl_2 solution of boron tribromide (45 mL, 1 M, 45 mmol). The resulting solution was stirred at 0 °C for 2 h and then at 25 °C for 30 min. After cooling to 0 °C, methanol (50 mL) was added carefully, and the volatiles were then removed in vacuo. The residue was redissolved in CH_2Cl_2 and washed with H_2O, dried, treated with silica gel and charcoal, filtered, and concentrated. Trituration of the residue with acetone afforded 4.7 g (98%) of **27** as a white solid: NMR 0.77 (s, 3 H), 6.56 (d, 2.5), 6.62 (dd, 2.5, 8.5),, 7.08 (d, 8.5).

17β-(*N*,*N*-Diisopropylcarbamoyl)-2-bromoestra-1,3,5(10)-trien-3-ol (28) and 17β-(*N*,*N*-Diisopropylcarbamoyl)-4-bromoestra-1,3,5(10)-trien-3-ol (29). A solution of **27** (1.85 g, 4.82 mmol) in 185 mL of warm acetic acid was cooled to 20 °C and 4.48 mL (4.82 mmol) of a 1.08 M solution of bromine in acetic acid was added slowly. After stirring at ambient temperature for 5 min, the reaction mixture was poured into ice water and extracted twice with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed twice with H_2O, dried over anhydrous $MgSO_4$, and concentrated. Chromatography (2% followed by 5% ether in CH_2Cl_2) afforded 0.39 g (17%) of **28** and 0.75 g (34%) of **29**: NMR (**28**) 0.79 (s, 3 H), 6.74 (s), 7.32 (s); (**29**) 0.78 (s, 3 H), 6.86 (d, 8.5), 7.16 (d, 8.5).

Methyl 17β-(*N*,*N*-Diisopropylcarbamoyl)-2-cyanoestra-1,3,5(10)-triene-3-carboxylate (34). A mixture of **32** (33.2 mg, 0.0658 mmol), copper(I) cyanide (10.6 mg, 0.118 mmol), and *N*-methylpyrrolidinone (1.0 mL) was heated in an oil bath at 180 °C under an argon atmosphere for 1 h. The reaction mixture was cooled to room temperature and treated with an aqueous solution of ethylene diamine, and then extracted twice with EtOAc. The EtOAc extracts were washed once with a 10% aqueous solution of NaCN and twice with H_2O. Concentration yielded 25.7 mg (87%) of **34**: NMR 0.80 (s, 3 H), 3.98 (s, 3 H), 7.69 (s), 7.84 (s).

Methyl 17β-(*N*,*N*-diisopropylcarbamoyl)-4-cyanoestra-1,3,5(10)-triene-3-carboxylate (35) was prepared from **33** according to the procedure described for the preparation of **34**: NMR 0.80 (s, 3 H), 7.56 (d, 8), 7.88 (d, 8).

***N*,*N*-Diisopropyl-3-methoxy-2-bromoestra-1,3,5(10)-triene-17β-carboxamide (36).** A mixture of **28** (188 mg, 0.407

mmol), dimethyl sulfate (76.9 mL, 0.814 mmol), powdered anhydrous K_2CO_3 (112 mg, 0.814 mmol), and acetone (10 mL) was heated at reflux under an argon atmosphere for 1.25 h. The cooled reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The extract was washed with H_2O, dried, and concentrated to 162 mg (84%) of **36**: NMR 0.79 (s, 3 H), 3.85 (s, 3 H), 6.61 (s), 7.41 (s).

17β-(*N*,*N*-Diisopropylcarbamoyl)-3-methoxyestra-1,3,5(10)-triene-2-carboxylic Acid (37). A solution of **36** (151 mg, 0.317 mmol) in THF (5 mL) was added dropwise to a −78 °C solution of *n*-BuLi (0.285 mL, 2.5 M in hexane, 0.713 mmol) in THF (5 mL). Upon completion of the addition, the reaction was stirred at −78 °C for 5 min, and then powdered dry ice (CO_2) was added. After allowing the reaction mixture to slowly warm to room temperature, the mixture was poured into H_2O, acidified with dilute HCl, and extracted twice with CH_2Cl_2. The CH_2Cl_2 extracts were washed with H_2O, dried, and concentrated to give 125 mg (89%) of **37**: NMR 0.79 (s, 3 H), 4.03 (s, 3 H), 6.74 (s), 8.08 (s).

Methyl 17β-(*N*,*N*-Diisopropylcarbamoyl)-3-methoxyestra-1,3,5(10)-triene-2-carboxylate (38). The title compound was prepared by treatment of a solution of **37** in CH_2Cl_2 with ethereal diazomethane and used in the next step without purification or spectral characterization.

Methyl 17β-(*N*,*N*-Diisopropylcarbamoyl)-3-hydroxyestra-1,3,5(10)-triene-2-carboxylate (39). Compound **39** was prepared from **38** by using the procedure previously described for the preparation of **27**: NMR 0.79 (s, 3 H), 3.91 (s, 3 H), 6.67 (s), 7.71 (s).

Methyl 3-[[(Trifluoromethyl)sulfonyl]oxy]-17β-(*N*,*N*-diisopropylcarbamoyl)estra-1,3,5(10)-triene-2-carboxylate (40). A solution of **39** (24.3 mg, 0.055 mmol) in THF (2 mL) was added to a cold mixture of excess sodium hydride in THF (2 mL) and the resultant mixture stirred at room temperature 0.5 h. A solution of *N*-phenyltrifluoromethanesulfonimide (31.6 mg, 0.0885 mmol) in THF (2 mL) was added and the mixture was heated in an oil bath at 40 °C for 4 h. The mixture was diluted with CH_2Cl_2, washed twice with 5% aqueous $NaHCO_3$, dried, and concentrated to 26.1 mg (83%) of **40**: NMR 0.79 (s, 3 H), 3.93 (s, 3 H), 6.97 (s), 7.98 (s).

3-Hydroxy-4-nitroestra-1,3,5(10)-trien-17-one (42). Estrone was nitrated as described in ref 21 to afford the known compound **42**.

3-Methoxy-4-nitroestra-1,3,5(10)-trien-17-one (43). According to the method described in ref 21, **42** was methylated to yield **43**.

3-Methoxy-4-aminoestra-1,3,5(10)-trien-17-one (44). Compound **43** was reduced to **44** as described in ref 21.

3-Methoxy-4-fluoroestra-1,3,5(10)-trien-17-one (45). Compound **44** was converted to compound **45** as described in ref 21.

***N*,*N*-Diisopropyl-3-hydroxy-4-fluoroestra-1,3,5(10)-triene-17β-carboxamide (49).** Compound **48** was demethylated to provide **49** by using the procedure described for the preparation of **27**.

17β-(*N*,*N*-Diisopropylcarbamoyl)-3-(4,4-dimethyl-2-oxazolinyl)estra-1,3,5(10)-triene (52). A solution of **2** (2.07 g, 5.04 mmol), thionyl chloride (0.73 mL, 10.0 mmol), and CH_2Cl_2 (104 mL) was stirred at room temperature for 2 h. The CH_2Cl_2 solution then was concentrated at 50 °C on a rotary evaporator and the resultant acid chloride was dissolved in 30 mL of CH_2Cl_2. The acid chloride solution, cooled to 0 °C, was added slowly to a solution of 2-amino-2-methyl-1-propanol (0.897 g, 10.1 mmol) in 20 mL of CH_2Cl_2. The mixture was stirred at room temperature for several hours then washed twice with H_2O, dried, and concentrated to 2.26 g of a benzamide. Thionyl chloride (5.0 mL, 69 mmol) slowly was added to the benzamide and the resultant yellow solution was stirred at ambient temperature for 10 min and then diluted with 100 mL of petroleum ether. The solvent was decanted from the gummy precipitate and the precipitate was washed with additional petroleum ether. The precipitate was suspended in H_2O which was made basic with 10% NaOH and extracted with CH_2Cl_2. The extract was washed with H_2O, dried, and concentrated to 1.85 g (79%) of **52** as a tan foam: NMR 0.80 (s, 3 H), 1.37 (s, 6 H), 4.08 (s, 2 H), 7.3 (d, 8), 7.67 (d, 8), 7.68 (s).

17β-(*N*,*N*-Diisopropylcarbamoyl)-2-chloro-3-(4,4-dimethyl-2-oxazolinyl)estra-1,3,5(10)-triene (53) and 17β-(*N*,*N*-Diisopropylcarbamoyl)-4-chloro-3-(4,4-dimethyl-2-oxazolinyl)estra-1,3,5(10)-triene (54). A solution of **52** (1.18 g, 2.54 mmol) in dry THF (59 mL) was cooled in an ice bath under an argon atmosphere and treated successively with *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (0.84 mL, 5.6 mmol) and 2.5 M *n*-BuLi in hexane (2.23 mL, 5.59 mmol). The reddish-brown solution was stirred in the cold for 5 min, and then a solution of hexachloroethane (1.32 g, 5.55 mmol) in 24 mL of THF was added rapidly. After stirring for 5 min, the cooling bath was removed and stirring was continued for 30 min. The mixture then was diluted with H_2O and extracted twice with ethyl ether. The combined ether extracts were washed three times with H_2O, dried, and concentrated to 1.95 g of crude product. Chromatography (25% EtOAc in hexane) yielded 1.16 g of a mixture of **52** (ca. 49%), **53** (ca. 31%), and **54** (ca. 15%) which was used in the next step without further purification.

17β-(*N*,*N*-Diisopropylcarbamoyl)-2-chloroestra-1,3,5(10)-triene-3-carboxylic Acid (8) and 17β-(*N*,*N*-Diisopropylcarbamoyl)-4-chloroestra-1,3,5(10)-triene-3-carboxylic Acid (9). A solution of 0.58 g of the above mixture of **52** (ca. 49%), **53** (ca. 31%), and **54** (ca. 15%) in 227 mL of THF and 227 mL of 10% HCl was heated at reflux for 4 h and then concentrated to remove most of the THF. An additional 76 mL of 10% HCl was added and the reflux was continued overnight. The resultant dark mixture was cooled and extracted twice with CH_2Cl_2. The combined extracts were washed with H_2O, dried, and concentrated to 1.03 g of dark gummy oil. Preparative HPLC (silica gel, 12.5% EtOAc, 0.5% formic acid in hexane) provided 60.6 mg of **8** (mp 301–305 °C dec) and 29 mg of **9** (mp 262–265 °C dec): NMR (**8**) 0.79 (s, 3 H), 7.37 (s), 7.73 (s); (**9**) 0.76 (s, 3 H), 7.37 (d, 8), 7.73 (d, 8). Anal. ($C_{26}H_{36}ClNO_3$) (**8**) C, H, N; (**9**) C (calcd 70.01 found 71.04), H, N.

3-Hydroxy-4-methylestra-1,3,5(10)-trien-17-one (55). A solution of 4-methyl-4-estrene-3-one-17β-ol (4-methyl-19-nortestosterone prepared according to the procedure described by Atwater;[23] 12 g, 43.8 mmol) in 400 mL of CH_2Cl_2 was added to a stirred solution of pyridinium chlorochromate (14.2 g, 66 mmol) in 400 mL of CH_2Cl_2. After 2 h the mixture was filtered and the filtrate was treated with silica gel and charcoal, filtered, and concentrated. Trituration of the residue with cold acetone afforded 6.5 g (54%) of 4-methyl-4-estrene-3,17-dione.

A mixture of 4-methyl-4-estrene-3,17-dione (2 g, 7 mmol) and 2 g of 10% palladium on carbon in 100 mL of *p*-cymene was heated at reflux for 4 h. The hot mixture then was filtered and the filtrate was concentrated to yield 900 mg of the crude **55**, which was used in the next step without further purification: NMR 0.9 (s, 3 H), 2.1 (s, 3 H), 6.8 (d, 9), 7.0 (d, 9).

3-Hydroxy-2-[(dimethylamino)methyl]estra-1,3,5(10)-trien-17-one (60). Compound **60** was prepared as described in ref 22.

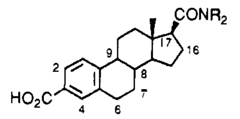
3-Hydroxy-2-methylestra-1,3,5(10)-trien-17-one (61). Compound **60** was reduced as described in ref 22 to provide **61**.

3-Acetoxy-*N*,*N*-diisopropylestra-1,3,5(10)-triene-17β-carboxamide (70). A solution of **27** (4.7 g, 12.3 mmol) in 100 mL of pyridine was treated with 70 mL of acetic anhydride for 18 h. The reaction mixture was poured into ice water and extracted with EtOAc. The organic extract was washed with 10% aqueous HCl, water, brine, and concentrated to afford 5.2 g (100%) of **70**.

17β-(*N*,*N*-Diisopropylcarbamoyl)-3-acetoxyestra-1,3,5(10)-trien-6-one (71). To a solution of **70** (5 g, 12 mmol) in 17 mL of glacial acetic acid was added a solution of chromium trioxide (3.5 g) in 23 mL of acetic acid and 4 mL of H_2O. After stirring for 18 h, ethanol (20 mL) was added and the resulting mixture was extracted with ethyl ether. The ethereal extract was washed with H_2O and saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. Chromatography (25% EtOAc in hexane) afforded 400 mg (8%) of *N*,*N*-diisopropyl **71**: mp 223–224 °C (recrystallized from methanol); NMR 0.84 (s, 3 H), 2.3 (s, 3 H), 7.3 (dd, 3, 9), 7.48 (d, 9), 7.8 (d, 3).

3-Hydroxy-*N*,*N*-diisopropylestra-1,3,5(10),6-tetraene-17β-carboxamide (72). A suspension of **71** (400 mg, 0.9 mmol) in 40 mL of methanol at 15 °C was treated with 800 mg of $NaBH_4$ for 1 h. HCl (3.5 mL) and H_2O (3.5 mL) was added and the resulting mixture was heated at reflux for 1 h. The mixture was cooled, diluted with H_2O, and extracted with EtOAc. The organic

Table I. Steroid 5α-Reductase in Vitro Inhibitory Activities



no.	unsaturn	substitn	*R*	$K_{i,app}$, nM human	$K_{i,app}$, nM rat
2			*i*-Pr	20	356
3			*t*-Bu,H	43	150
4	6–7		*i*-Pr	30	450
5	6-7,8-9		*i*-Pr	36	350
6	16–17		*t*-Bu,H	60	200
7		4-F	*i*-Pr	10	500
8		2-Cl	*i*-Pr	35	200
9		4-Cl	*i*-Pr	120	900
10		2-Br	*i*-Pr	76	260
11		4-Br	*i*-Pr	212	1900
12		2-CN	*i*-Pr	65	950
13		4-CN	*i*-Pr	200	>10000
14		2-COOH	*i*-Pr	5000	>10000
15		2-CH$_3$	*i*-Pr	60	340
16		4-CH$_3$	*i*-Pr	260	7000

extract was washed with H_2O and brine, dried, and concentrated to a solid. Chromatography (5% EtOAc in CH_2Cl_2) afforded 200 mg (58%) of **72**: mp 276–279 °C; NMR 0.8 (s, 3 H), 6.0 (d, 9), 6.4 (d, 9), 6.6–7.15 (m, 3 H).

Inhibitor Evaluation. Assays for steroid 5α-reductase were performed with microsomal-associated enzyme activity from surgically derived benign hyperplastic human prostatic tissue and whole rat ventral prostates. Prostatic microsomes were prepared as previously described for the rat[33] and human[34] tissues. Enzyme activity was determined by measuring the conversion of T to total 5α-reduced metabolites, represented by the sum of DHT and 5α-androstanediol (ADIOL).[33] Briefly, [^{14}C]T (55 mCi/mmol, Amersham) and inhibitors in ethanol were deposited in test tubes and the solvent was removed to dryness. Following addition of incubation buffer to the tubes, the solutions were equilibrated to 37 °C. A 20-μL aliquot of freshly prepared 10 mM NADPH solution was added to each tube immediately before initiation of the reaction with enzyme. The final concentration of cofactor in the 0.5-mL incubation was 400 μM. The rat enzyme incubation buffer consisted of 20 mM sodium phosphate, pH 6.6; that for human microsomes was 50 mM sodium citrate, pH 5.0. Following 20–30-min incubations, the reactions were quenched with 4 mL of ethyl acetate containing 0.15 μmol each of T, DHT, androstenedione, and ADIOL. The mixture was vortexed and centrifuged to separate the solvent layers, and the organic layer was removed. Upon evaporation of solvent in vacuo the residue was dissolved in 40 μL of 1:1 methanol–chloroform. Substrate and products were separated by TLC on silica gel plates (Baker, Si250F-PA) by developing twice with 1:9 acetone–chloroform and were evaluated with a Bioscan imaging scanner (Washington, DC). The relative amounts of radiolabel in substrate and products were used to calculate enzyme activity. Assays were conducted such that no more than 20% of initial T concentration was consumed in the reaction. Typically, the Michaelis constants for T with the rate and human prostatic enzymes were determined to be 0.9 and 4.5 μM, respectively.

Experiments to determine the potency of potential inhibitors were conducted at 400 μM NADPH, 1.2 μM T and 0–10 μM of test compound. Apparent inhibition constants ($K_{i,app}$) were determined for compounds that followed a linear response by Dixon analysis.[35] Standard errors associated with individual determinations of the apparent inhibition potencies ($K_{i,app}$) were consistently less than 20% of the values reported in Table I. Compounds were tested as inhibitors of the rat and human enzymes over several years with different preparations of microsomes; over this period of time, variability of inhibition potency was observed with some compounds. Consequently, a potency range of inhibition is presented for those compounds that were examined with more than one enzyme preparation. As convention, an inhibition potency of >10 000 has been used for compounds demonstrating less than 50% inhibition at the highest concentration tested. For comparison, $K_{i,app}$ values were determined for 17β-(*N-tert*-butylcarbamoyl)-3-oxo-4-aza-5α-androst-1-ene (MK-906) to be 6 nM and 8–30 nM for rat and human enzyme preparations, respectively, and are consistent with the reported[26] values of 5.8 and 26 nM.

Acknowledgment. Mass spectral and elemental analyses were performed by members of the Analytical Chemistry and the Physical and Structural Chemistry Departments of Smith Kline & French Laboratories. We thank Dr. M. Soloway, University of Tennessee Dept. of Urology, and Drs. V. Cabanas and Y. Costandi, Providence Hospital, Cincinnati, OH for supplies of human prostatic tissue.

Registry No. **2**, 124650-99-3; **2** acid chloride derivative, 124651-00-9; **3**, 124651-01-0; 4, 124651-02-1; **5**, 124651-03-2; **6**, 124651-04-3; **7**, 124651-05-4; **8**, 124651-06-5; **9**, 124651-07-6; **10**, 124651-08-7; 11, 124651-09-8; **12**, 124651-10-1; **13**, 124651-11-2; **14**, 124651-12-3; **15**, 124651-13-4; **16**, 124651-14-5; **17**, 124651-15-6; 18, 124651-16-7; **19**, 124651-17-8; **20**, 124779-78-8; **21**, 124651-18-9; **22**, 124651-19-0; **23**, 124651-20-3; **24**, 95667-45-1; **25**, 119190-26-0; **26**, 119169-91-4; **27**, 124651-21-4; **28**, 124651-22-5; **29**, 124651-23-6; **30**, 124651-24-7; **31**, 124651-25-8; **32**, 124651-26-9; **33**, 124651-27-0; **34**, 124685-49-0; **35**, 124651-28-1; **36**, 124651-29-2; **37**, 124651-30-5; **38**, 124651-31-6; **39**, 124651-32-7; **40**, 124651-33-8; 41, 124651-34-9; **42**, 5976-74-9; 43, 14846-62-9; **44**, 13010-21-4; **45**, 16205-29-1; **46**, 124651-35-0; **47**, 124651-36-1; 48, 124651-37-2; **49**, 124651-38-3; **50**, 124651-39-4; **51**, 124651-40-7; **52**, 124651-41-8; **53**, 124651-42-9; **54**, 124651-43-0; **55**, 68969-90-4; **56**, 124651-44-1; **57**, 124651-45-2; **58**, 124651-46-3; **59**, 124651-47-4; **60**, 96111-26-1; **61**, 2626-12-2; **62**, 124685-84-3; **63**, 124651-48-5; **64**, 124651-49-6; **65**, 124651-50-9; **66**, 124685-85-4; **67**, 124651-51-0; **68**, 124651-52-1; **69**, 124651-53-2; **70**, 124651-54-3; **71**, 124651-55-4; **72**, 124651-56-5; **73**, 124651-57-6; **74**, 124651-58-7; *i*-Pr$_2$NH, 108-18-9; Tf$_2$NPh, 37595-74-7; estrone, 53-16-7; trifluoromethanesulfonic anhydride, 358-23-6; methylestrone, 1624-62-0; 2-amino-2-methyl-1-propanol, 124-68-5; 4-methyl-4-estren-3-on-17β-ol, 6959-54-2; 4-methyl-4-estrene-3,17-dione, 124651-59-8; steroid 5α-reductase, 72412-84-1.

Supplementary Material Available: Selected physical and analytical data (C, H, N, partial NMR, and MS) for compounds described in this paper (15 pages). Ordering information is given on any current masthead page.

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