98483-18-2; 41, 98483-19-3; 42, 98483-20-6; 3,3-dimethyl-2-pentanone, 20669-04-9; 3,3-dimethyl-2-nonanone, 62399-67-1; 4,4-dimethyl-2-decanone, 98483-21-7; 3-cyclobutyl-2-propanone, 13027-76-4; cyanoacetamide, 107-91-5; ethyl formate, 109-94-4; sodium 3-oxo-5,5-dimethylhexanal, 98483-22-8; ethyl cyanoacetate, 105-56-6; 1,2-dihydro-2-oxo-6-(2-methylpropyl)-3-pyridinecarbonitrile, 80065-99-2; 1,2-dihydro-2-oxo-6-(2,2-dimethylpropyl)-3-pyridinecarbonitrile, 75587-95-0; 1,2-dihydro-2-oxo-6-(1,1-dimethylethyl)-3-pyridinecarbonitrile, 4138-19-6.

Supplementary Material Available: The mass, infrared, and ^1H NMR spectral data of all new numbered compounds (4 pages). Ordering information is given on any current masthead page.

Antiandrogenic Activity of a Series of Des-A-Steroid Derivatives

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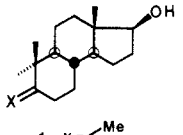
In the search for new antiandrogens, a number of des-A-steroids were prepared by condensation of Grignard reagents with lactone **3**. From the resulting key intermediates **5**, various structural modifications were performed such as the introduction of an additional unsaturation to afford dienones **8** and aromatic derivatives **10** or the introduction of an alkyl substituent mostly in position 10 (**11–13**) but also in some cases in position 16 (**22**). In addition, 13-ethyl analogues were also prepared from lactone **4**. The relative binding affinities (RBAs) for the androgen receptor of these compounds were determined under various conditions. Some compounds exhibit a capacity to interact with the receptor comparable to that of testosterone. One of the most potent compounds is 17β-hydroxy-des-A-androsta-9,11-dien-5-one (**8b**), RBA value 73% of that of testosterone. More interestingly, several compounds were found to have an antiandrogenic profile in vitro and in vivo. One of the most effective compounds is 10-ethyl-17β-hydroxy-des-A-estra-9-en-5-one (**5c**), which exhibits a strong local antiandrogenic activity in hamsters, without any significant systemic antiandrogenic effects. The corresponding 17β-acetyl derivative (RU 38882) has been selected for extended pharmacological studies.

Although some nonsteroidal compounds are known to interact with the androgen receptor and to have antiandrogenic activities,[1-3] most of the known androgens and/or antiandrogens of therapeutic interest belong to the steroid series.

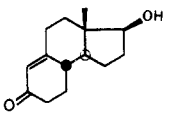
However, it was reported a few years ago that several derivatives not having the usual tetracyclic system of the steroids such as 16,17-secosteroids or compounds lacking either the D or the A ring of the steroid nucleus[5-7] exhibited some weak androgenic and/or antiandrogenic activity in animals. Of particular interest is the result of Wolff and Zanati, which showed weak androgenic activity for the tricyclic derivative **1** while no hormonal activity was found for the closely related compounds **2**[7] and **5a** (racemate).[8]



1 X = Me, H

2 X = CH_2

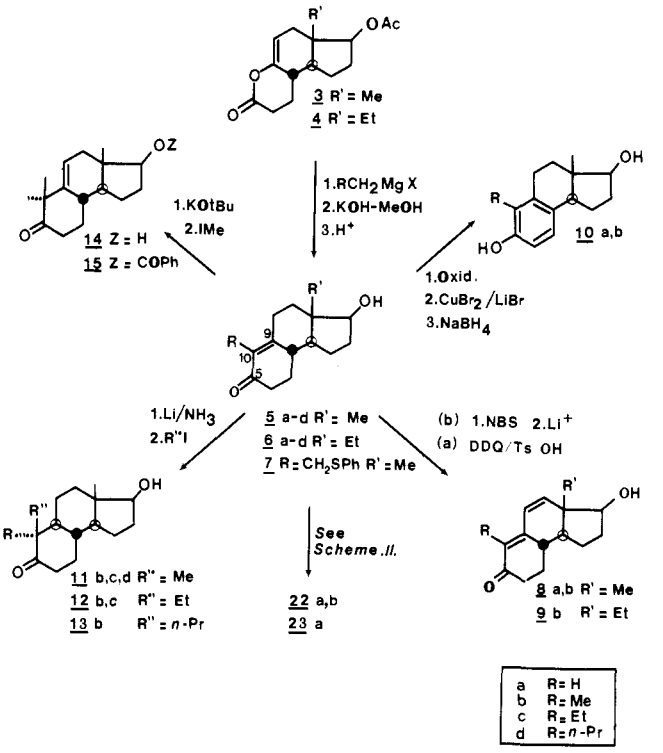
11b X = O



5a

As part of our steroid antihormone program, compounds **1** and **2** were prepared again and were found to be practically devoid of hormonal activities as measured by their ability to interact with the hormonal receptors. But interestingly, some intermediates of their synthesis such as the closely related ketone **11b** exhibited a relatively good affinity for the androgen receptor. This unexpected result led us to prepare a certain number of des-A-steroids starting from enones of general formulas **5** and **6**. The synthetic modifications were principally concentrated on obtaining derivatives mono- or dialkylated in position 10 with various degrees of unsaturation in the steroid nucleus

Scheme I



(Scheme I). In addition, some substrates were further alkylated in position 16 (Scheme II) since in steroid series

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(1) Neri, R.; Florance, K.; Koziol, P.; Van Cleave, S. *Endocrinology* **1972**, *91*, 427.

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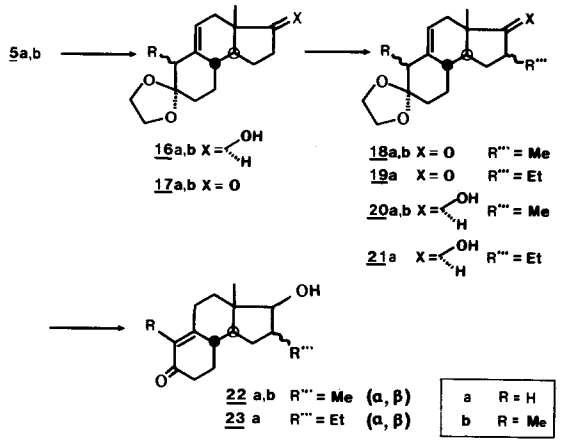
Scheme II

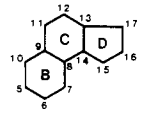


this modification is known to induce some interesting antiandrogenic activity.[9,10]

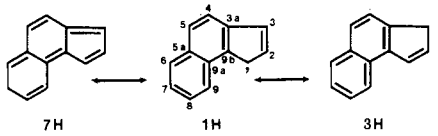
The androgenic and/or antiandrogenic activity of these compounds was evaluated by measuring their ability to interact with the androgen receptor under conditions that enable us to discriminate potent androgenic derivatives from weak agonists with potential antiandrogenic activity. On the basis of these results, some representative compounds of the series were tested in vivo for confirmation of their antiandrogenic activity.

Nomenclature. In the interest of conformity we have assimilated the tricyclic compounds with des-A-steroids in this paper with respect to the steroid numerotation. However, in the Experimental Section the nomenclature adopted is derived from the benz[e]indene as recommended by IUPAC.

steroid numerotation



benz[e]indene numerotation



tautomeric forms of the formula

Chemistry

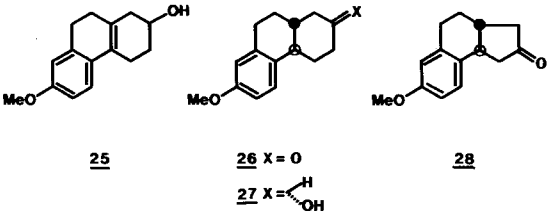
Δ^9-Des-A-Steroids Monoalkylated in Position 10. Our first approach, which involved the monoalkylation with methyl iodide of the readily available and optically active enone **5a** benzoate[11] via its imine or enamine derivatives (Stork's method[12]), resulted in very poor yields of the desired methyl enone **5b** (15%). Alternatively, the benzoate of the latter compound **5b** was easily prepared by a less common sequence[13] involving the reaction of **5a** benzoate with formaldehyde and thiophenol in triethanolamine followed by desulfurization of the intermediate sulfide **7**. However, it turned out that the more general and more convenient method for the preparation of the 10-alkyl enones **5** and **6** was, in spite of low yields, the Fujimoto–Belleau reaction[14] performed on lactones **3** and **4**.[15,16] Both enantiomers of lactone **3**, obtained as intermediates in the total synthesis of steroids, were used to prepare **5c** and its enantiomer. Physical properties of enones **5** and **6** are summarized in Table I.

Table I. Physical Properties of Enones 5 and 6

compd	R	R′	mp, °C	recryst solvent[a]	$[\alpha]^{25}_D$, deg (1%, MeOH)	formula[b]
5a[16]	H	Me	109	IPE	−32.5	
5b[c]	Me	Me	170	A	−30	
5c[d,e]	Et	Me	113	IPE	−36	$C_{16}H_{24}O_2$
5d[d,f]	*n*-Pr	Me	Oil		−35	
6a[16]	H	Et	153	EA	−59	
6b	Me	Et	181	A/H	−54	$C_{16}H_{24}O_2$
6c	Et	Et	131.5	A/H	−58	$C_{17}H_{26}O_2$
6d	*n*-Pr	Et	127	A	−55	$C_{18}H_{28}O_2$

[a] Key: A = acetone; EA = ethyl acetate; H = hexane; IPE = diisopropyl ether. [b] Analyzed for C and H; see the Experimental Section. [c] Literature[34] mp 169.5–170 °C. [d] Literature[15] in this reference **5c** and **5d** are described as not being crystallized. [e] The enantiomer has also been prepared from the enantiomeric lactone **3** *ent*. [f] Not analyzed.

Chart I



Polyunsaturated Des-A-Steroids. Two types of modifications were performed on the enones **5** and **6**. The first one was the introduction of an additional double bond in position 11, achieved either by treatment of **5a** benzoate with DDQ and 1 equiv of TsOH[17] or in three steps from **5b** or **6b** acetates by treatment with AC_2O–TSOH followed by bromination with NBS and then dehydrobromination with LiBr–Li_2CO_3 in DMF. The second modification consisted in the preparation of some aromatic B-ring derivatives. The preparation of **10a** has been previously described.[18] The methylated phenol **10b** was prepared in three steps: oxidation of **5b**, treatment of the resulting diketone with $CuBr_2$–LiBr in refluxing acetonitrile,[19] and then reduction of the 17-keto function. This sequence gives better results than the direct aromatization of **5b**. For biochemical testing some related compounds shown

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Table II. Physical Properties of *gem*-Dialkyl Derivatives 11–13

compd	R	R″	yield, %	mp, °C	recryst solvent[a]	$[\alpha]^{25}_D$, deg (1%, $CHCl_3$)	formula[b]
11b[c]	Me	Me	40	98, 108	A/H	+52	$C_{16}H_{26}O_2 \cdot C_3H_6O$
11c	Et	Me	60	118	EA/H	+40	$C_{17}H_{28}O_2$
11d	*n*-Pr	Me	46	100	EA/H	+39	$C_{18}H_{30}O_2$
12b	Me	Et	33	101	EA/H	+72	$C_{17}H_{28}O_2$
12c	Et	Et	70	122.5	EA/H	+61	$C_{18}H_{30}O_2$
13b[d]	Me	*n*-Pr	34	121	E	+73	$C_{18}H_{30}O_2$

[a] See footnote *a*, Table I; E = ether. [b] Analyzed for C and H; see the Experimental Section. [c] Solvated with 1 mol of acetone; lit.[33] mp 99–100 °C. [d] Literature[33] mp 117–118.5 °C.

Table III. Physical Properties of 16-Alkyl Derivatives 18, 19, 22, and 23

compd	R	R‴	mp, °C	recryst solvent[a]	$[\alpha]^{25}_D$, deg (1%, $CHCl_3$)	δ(angular Me)[b]	formula[c]
18a	H	α-Me	110	E/H	+102	0.90	
18a	H	β-Me	120	A/H	+116	0.82	
19a	H	α-Et	oil		+65	0.90	
19a	H	β-Et	75	EA/H	+142	0.78	
18b	Me	α-Me	136	E/H	+110	0.87	
18b	Me	β-Me	oil			0.80	
22a	H	α-Me	resin		−52	0.94	
22a	H	β-Me	87	H	−38	0.90	$C_{15}H_{22}O_2$
23a	H	α-Et	86.5	EA/H	−77	0.95	$C_{16}H_{24}O_2$
23a	H	β-Et	144	EA/H	−27	0.90	$C_{16}H_{24}O_2$
22b	Me	α-Me	139	M/W	−51	0.90	$C_{16}H_{24}O_2$
22b	Me	β-Me	81	E/H	−32	0.86	$C_{16}H_{24}O_2$

[a] See footnote *a*, Tables I and II; M = methanol; W = water. [b] ^1H NMR δ ($SiMe_4$) at 90 MHz in $CDCl_3$. [c] Only final products **22** and **23** have been analyzed with the exception of the amorphous enone **22a** (R‴ = α-Me).

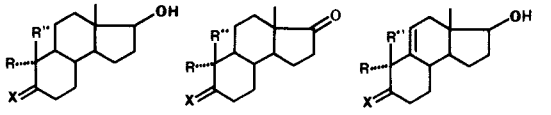
in Chart I were prepared as racemates following procedures previously described by Daum et al.[20] (compounds **25–27**) and Johns and Salamon[21] (compound **28**).

Des-A-Steroids Dialkylated in Position 10. The thermodynamic dimethylation of the enone **5a** benzoate afforded the expected unsaturated ketone **14**, which could only be hydrogenated to **11b** with difficulty. However, this latter ketone was obtained in good yields by reduction of enone **5b** with lithium in ammonia followed by trapping the resulting enolate with methyl iodide under conditions described by Stork et al.[22] Other *gem*-disubstituted ketone (**11–13**) were similarly prepared in fair to good yields, starting from enones **5b–d** and appropriate alkyl iodides R″I.

When R″ is different from R, only one epimer was isolated, accompanied in some cases by the saturated ketone as a byproduct. The stereochemistry of isomers **11–13** was assigned assuming the entry of alkyl group R″ to be from the β face as has been reported in analogous cases.[23] Physical properties are summarized in Table II.

Des-A-Steroids Alkylated in Position 16. Ketones **22** and **23** were obtained from enones **5a** and **5b** from the sequence illustrated in Scheme II. Intermediate ketones **17a** and **17b** were easily obtained in two steps by conventional procedures, namely protection of the 5-ketone as an ethylene ketal and oxidation of the 17β-hydroxyl group of **16a** and **16b**. The direct alkylation of these ketones afforded 16α-alkyl derivatives **18** and **19** with a high stereoselectivity, accompanied by very small amounts of 16β-epimers and 16,16-dialkyl derivatives as was mentioned previously.[10] Subsequent equilibration of 16α-alkyl ketones **18** and **19** afforded mixtures of 16-epimers from which the most stable 16β-isomer could easily be separated by chromatography. Reduction of 17-ketone and deprotection of the ketal led to the expected products **22** and **23**. Their physical properties are summarized in Table III.

Table IV. Relative Binding Affinities (RBAs) for the Androgen Receptor



1, **2**, **11–13**, **29**, **30** **31** **14**, **24**

compd	R	R″	X	30 min	24 h
testosterone				100	100
dihydrotestosterone				120	180
cyproterone acetate				40	8
1	Me	Me		0.8	0.4
2	Me	Me	$=CH_2$	3	0.2
11b	Me	Me	=O	17	2
11c	Et	Me	=O	22	10
11d	*n*-Pr	Me	=O	9	3
12b	Me	Et	=O	0.8	0.4
12c	Et	Et	=O	1	0.6
13b	Me	*n*-Pr	=O	0.02	0
29	H	H	=O	0.7	0
30[a]	Me	H	=O	7	1
31	Me	Me	=O	0.1	0
14	Me	Me	=O	12	6
24	Me	Me		0.2	0.01

[a] This compound has been isolated as a byproduct in the preparation of 13b; mp 95 °C (lit.[34] mp 94–95 °C).

Androgenic and Antiandrogenic Activity

Relative Binding Affinities (RBAs) for the Androgen Receptor. The compounds shown in Tables IV–VII were tested in vitro for their ability to interact with hormonal receptors. The discussion will be focused on the data obtained with the androgen receptor since in most cases no significant interaction was observed with estrogen, progesterone, or corticoid receptors.

It has previously been suggested that the measurements of RBA at different incubation times could reflect the

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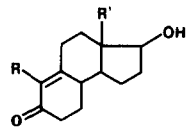
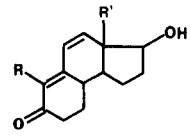
Table V. Relative Binding Affinities for the Androgen Receptor



5, 6



8, 9

compd	R	R'	30 min	24 h
5a	H	Me	0.5	1
5b	Me	Me	46	4
5c	Et	Me	7.2	1
5c *ent*	Et	Me	0.2	0.02
5d	*n*-Pr	Me	0.4	0.3
6a	H	Et	1	0.1
6b	Me	Et	11	5
6c	Et	Et	10	1.2
6d	*n*-Pr	Et	2	0.3
8a	H	Me	1.6	1.2
8b	Me	Me	73	8
9b	Me	Et	41	29

Table VI. Relative Binding Affinities for the Androgen Receptor: 16-Alkyl Derivatives **22** and **23** (Scheme II)

compd	R	R'''	30 min	24 h
22a	H	α-Me	0.5	0.1
22a	H	β-Me	0.4	0.1
22b	Me	α-Me	7	1
22b	Me	β-Me	17	2
23a	H	α-Et	0.5	0.1
23a	H	β-Et	1	1

Table VII. Relative Binding Affinities for the Androgen Receptor: Aromatic Compounds (Scheme I and Chart I)

compd	30 min	24 h
10a	11	2
10b	0.2	0.1
25 (±)	0.3	0.1
26 (±)	1	0.1
27 (±)	0.3	0.1
28 (±)	0	0

kinetics of the interaction of the substrate with the receptor.[24] Potential agonists could be predicted when RBA increases with time, while on the contrary weak agonists or even antagonists could be expected when RBA decreases with increasing time of incubation.[25,26] Thus, the RBAs of compounds for the androgen receptor were measured by their ability to inhibit the specific binding of [^{3}H]testosterone with the androgen receptor of castrated rat prostate under two sets of incubation conditions: 30 min and 24 h, at 0 °C as described in the Experimental Section.

In general, all the tested compounds have lower affinities than testosterone itself (RBA ≤ 100), although surprisingly some of them exhibit a capacity to interact with the androgen receptor comparable to that of testosterone. For example, the RBA of the dienone **8b** after a short incubation time equals 73% that of testosterone. But, all have RBA values that decrease when time of incubation increases, thus suggesting that these compounds even if they are able to interact with the androgen receptor form complexes that dissociate more rapidly than the testosterone–androgen receptor complex itself.

A more thorough examination of the RBA data at short time of incubation reveals some structural features favorable to an interaction with the androgen receptor.

1. In the saturated series (Table IV) the presence of an equatorial methyl substituent in position 10 appears to be necessary in order to have some affinity for the androgen receptor (compounds **29** and **30**). The introduction of an additional methyl in position 10β, corresponding to the 19-methyl of the steroids, enhances the interaction with the receptor (**11b**), but the replacement of this substituent by an ethyl (**12b**) or a propyl (**13b**) drastically reduces the activity. On the contrary the same modifications carried out in the 10α equatorial position allow the affinity to be retained (**11c** and **11d**). Replacing the 5-ketone by a methylene group (**2**) or a methyl (**1**) greatly decreases the interaction.

2. The introduction of a double bond in position 9(10) has a favorable effect when a methyl or an ethyl group is present at C-10 (**5b** and **5c**, Table V). The same is true for the 13-ethyl series (**6b, 6c**). Lengthening the side chain decreases the affinity (**5d, 6d**), whereas an additional double bond has a favorable influence (**8b** and **9b** in comparison to **5b** and **5c**). The other modifications carried out in these series such as the introduction of a 16α- or 16β-alkyl (Table VI) or aromatization of the B ring (**10a** and **10b**, Table VII) have a detrimental effect on the affinity for the androgen receptor.

3. As expected, compounds belonging to the antipodal series such as **5c** *ent* (Table V) are devoid of affinity for the androgen receptor.

Discussion. In the steroid series it is well established that the presence of both a 3-keto and 17β-OH group is essential for interaction with the androgen receptor, a step that in most cases is a determinant for biological activity. One of the most astonishing results of this study is the noticeable affinity for the androgen receptor found with some of the tricyclic derivatives, although the distances separating the two oxygen functions (17β-OH and 3-keto groups) are much shorter than in the steroid series (10.9 Å for testosterone and 8.9 Å for the tricyclic derivative **5c** as determined by conformational analysis by means of the SCRIPT program[27]). Moreover, it appeared that a methyl in position 10 in the plane of the molecule in the unsaturated series or in 10α equatorial configuration in the saturated series is essential for significant interaction with the receptor, suggesting that this substituent which mimicks the 1-methylene group of the natural hormone plays an important role in the binding to the receptor. A substituent more bulky than an ethyl, in the same position, has an adverse effect.

A second point is the favorable effect due to the introduction of conjugated double bonds through rings B and C, which parallels the enhancement of affinity observed for certain estra-4,9-diene and 4,9,11-triene derivatives in comparison to 19-nortestosterone.[28,29] Thus, flexibility and flatness of the tricyclic molecules especially around the virtual A ring is crucial for the activity.

These results suggest that similar types of interaction are involved between the androgen receptor and either the steroids or these tricyclic compounds. However, all these compounds have RBA values that decrease with increasing time of incubation, suggesting that, even if these compounds are able to interact to a certain extent with the

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Table VIII. Systematic (Subcutaneous) Antiandrogenic Activities

compd (5 mg/day)	% inhibn of wt inc, mg	
	prostate	seminal vesicles
cyproterone acetate[a]	90	73
5b	27	54
5c	59	73
5c acetate	50	50
6b	10[b]	50
8b	25	45
11b	49	63

[a] 1 mg/day. [b] Not significant.

androgen receptor, they form complexes much more labile than the testosterone–receptor complex.[24] This could certainly be related to the shortening of the steroid skeleton, leading to a weaker interaction with the binding sites that normally bind to the A ring of testosterone.

In Vivo Studies. It has previously been shown that compounds that form labile complexes with the androgen receptor (RBA values decreasing with increasing time of incubation) are potential antiandrogens.[26] Some des-A-steroids were therefore selected first on the basis of their ability to interact with the androgen receptor and second according to the degree of modification of their RBA values. The antiandrogenic activity of these compounds has been evaluated after subcutaneous (sc) administration to the rat and after topical application on the hamster flank organ, a well-known androgen-dependent sebaceous tissue.[30,31]

When administered subcutaneously to immature castrated rats, these compounds prevent to varying extent the increase in prostate and seminal vesicles weight triggered by simultaneous sc administration of testosterone propionate. Under these conditions, all these compounds are weak antiandrogens as compared to cyproterone acetate. The least effective compound is **6b**, the most active being **5c** (Table VIII).

Similar results were obtained when these compounds were applied locally on one hamster flank organ (Table IX). The most active compound is **5c** acetate, which at a daily dose of 1 mg/hamster prevents up to 80% of the increase in the weight of the treated flank organ triggered by sc administration of testosterone propionate. Under these conditions, **5c** acetate appears slightly more active than cyproterone acetate (Table X). Moreover, it does not significantly prevent either the increase in the untreated flank organ weight nor the increase in the prostate weight. This suggests that when applied topically, **5c** acetate exhibits a strong local antiandrogenic activity, without presenting any significant systemic antiandrogenic effect. In addition, **5c** acetate has been shown to have a marked local antiandrogenic activity on the rat sebaceous gland (to be published) and is now under clinical trials for the topical treatment of androgen-dependent skin disorders such as hyperseborrhea, acne, hirsutism, and androgenic alopecia.

Experimental Section

The structures of all compounds are supported by IR spectra (Perkin-Elmer 297) and ^{1}H NMR spectra (Perkin-Elmer R 32 and, in certain cases, Varian FT 80); chemical shifts are reported in part per million downfield from an internal $Si(CH_3)_4$ standard. Melting points were either taken on a Kofler hot-stage apparatus or recorded on a Perkin-Elmer DSC 2 microcalorimeter with simultaneous control of the purity. Specific rotations were measured with a Perkin-Elmer 241 micropolarimeter.

The silica gel used for column chromatography was silica gel 60 (Merck, 230–400 mesh) and for the TLC plates, silica gel 60 F 254 (Merck).

The elemental analyses were performed by the Service Central d'Analyse of the CNRS and are within ±0.4% of the calculated value when specified by symbols.

[3*S*(3α,3aα,5aβ,7α,9aα,9bβ)]-3a,6,6,7-Tetramethyldodecahydro-1*H*-benz[*e*]inden-3-ol (1). A stirred mixture of 1,4-dibromo-1,4-seco-2,3-bisnor-5α-androstan-17β-ol acetate[32] (0.115 g, 0.255 mmol), 98% hydrazine hydrate (1 mL), 5% Pd/C catalyst (0.05 g), and ethanol (3 mL) was refluxed for 2 h. After filtration of the catalyst, the solution was poured into H_2O, extracted with Et_2O, dried (Na_2So_4), and evaporated to dryness. The crude product (0.08 g) was recrystallized from hexane to give the pure compound 1: 0.04 g (60%); mp 119 °C (lit.[7] mp 115–117 °C).

[3*S*(3α,3aα,9aα,9bβ)]-7-Methylene-3a,6,6-trimethyldodecahydro-1*H*-benz[*e*]inden-3-ol (2). A suspension of methyltriphenylphosphonium bromide (4.28 g, 12 mmol), *t*-BuOK (1.35 g, 12 mmol), and dioxane (60 mL) was stirred at room temperature for 20 min. Compound **11b**[33] (1 g, 4 mmol) was added, and the agitation was continued for an additional 1 h. The mixture was poured into H_2O extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and concentrated to dryness, and the residue was chromatographed on a column of silica gel (70 g). Elution with cyclohexane/EtOAc (7:3) gave **2**, 0.835 g (84%). The product was recrystallized from diisopropyl ether: mp 135 °C (lit.[7] mp 112–114 °C); $[\alpha]^{25}_D$ +50.5° (1%, $CHCl_3$); NMR δ 0.78 (3a-Me), 1.02, 1.1 (6,6-Me_2), ~4.62 (methylene H). Anal. ($C_{17}H_{28}O$) C, H.

[3*S*(3α,3aα,9aα,9bβ)]-3a,6-Dimethyl-3-hydroxy-1,2,3,3a,4,5,8,9,9a,9b-decahydro-7*H*-benz[*e*]inden-7-one (5b) Benzoate. A solution of enone **5a** benzoate[11] (0.5 g, 1.54 mmol), thiophenol (0.18 g, 1.635 mmol), and 40% aqueous formaldehyde (0.6 mL, 8 mmol) in triethanolamine (4 mL) was refluxed for 16 h. After cooling, the mixture was diluted with H_2O and extracted with Et_2O. The extract was washed with 5% aqueous HCl, dried, and evaporated. Column chromatography of the crude product on silica gel (eluent acetone/hexane (3:17)) afforded the sulfide **7**, 0.43 g (oil). A solution of this material in acetone was refluxed for 5 h with commercial Raney nickel (Prolabo). After filtration of the catalyst, evaporation of the filtrate gave the benzoate of **5b**: 0.26 g (50%); mp 107 °C (lit.[34] mp 107–108 °C).

General Method for the Preparation of Enones 5 and 6 (Fujimoto–Belleau Reaction, Table I). To a solution of the enol lactone **3** or **4** (1 mmol) (prepared as described in ref 15 and 16a) in anhydrous THF (3 mL) was added at −60 °C during 30 min the appropriate Grignard reagent (1.5 mmol) in ethereal solution. After stirring at −60 °C for 1 h, the reaction mixture was poured into saturated NH_4Cl solution and the reaction product was extracted with Et_2O. The organic extract was washed and dried (Na_2SO_4). After removal of the solvent the residue was dissolved in 2 N methanolic KOH solution (4 mL) and the resultant mixture refluxed for 1 h. The cooled mixture was neutralized with AcOH and evaporated under reduced pressure. The residue was then diluted with H_2O and extracted with Et_2O or CH_2Cl_2. Chromatography of the crude product on silica gel (eluent EtOAc/hexane (3:7)) afforded pure enones (20–50% yield).

[3*S*(3α,3aα,9aα,9bβ)]-6-Ethyl-3a-methyl-1,2,3,3a,4,5,8,9,-9a,9b-decahydro-7*H*-benz[*e*]inden-7-one (5c) Acetate. A solution of **5c** (6 g, 24.12 mmol) in acetic anhydride (12 mL) and pyridine (24 mL) was kept overnight at room temperature. After dilution with H_2O the acetyl derivative was filtered off, washed with H_2O, dried (6.8 g, mp 86 °C) and recrystallized from hexane to give the pure material: 6.5 g; mp 90 °C; $[\alpha]^{25}_D$ −34.5° (1%, EtOH). Anal. ($C_{18}H_{26}O_3$) C, H.

[3*S*(3α,3aα,9aα,9bβ)]-3-Hydroxy-3a-methyl-1,2,3,3a,8,9,-9a,9b-octahydro-7*H*-benz[*e*]inden-7-one (8a). A mixture of **5a** benzoate (0.102 g, 0.315 mmol), DDQ (0.072 g, 0.315 mmol), and $TsOH·H_2O$ (0.06 g, 0.315 mmol) in benzene (10 mL) was

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Table IX. Local (Topical) Antiandrogenic Activities in the Hamster

compd	dose	organ wt, mg ± SEM: flank organ, treated	flank organ, untreated	prostate
control		11.4 ± 0.8		68 ± 5
TP (sc)[c]	125 μg	37.6 ± 2.1		165 13
TP (sc) + 5b	1 mg	36.8 ± 5.7	37.3 ± 3.9	144 ± 25
TP (sc) + 5c	1 mg	27.8 ± 2.5[a]	34.8 ± 2.8	134 ± 12
TP (sc) + 5c acetate	200 μg	22.8 ± 1.2[a]	31.7 ± 1.9	145 ± 13
TP (sc) + 5c acetate	1 mg	16,8 ± 1.4[a]	33.0 ± 1.5	143 ± 8
TP (sc) + 6b	1 mg	31.9 ± 4.2	35.2 ± 3.7	137 ± 7
TP (sc) + 11b	1 mg	28.4 ± 2.7[b]	36.7 ± 2.2	135 ± 5

[a] Statistically different from TP-treated hamster at $p \leq 0.01$. [b] Statistically different from TP-treated hamster at $p \leq 0.05$. [c] TP = testosterone propionate.

Table X. Topical Antiandrogenic Activities of 5c acetate and Cyproterone Acetate in the Hamster

compd	dose	organ wt, mg ± SEM: flank organ, treated	flank organ, untreated	prostate
control		13.9 ± 0.6	15.3 ± 1.7	31 ± 3
TP (sc)[c]	125 μg	48.5 ± 5.2	49.4 ± 7	171 ± 35
TP (sc) + 5c acetate	40 μg	38.9 ± 0.7	46.2 ± 6.5	125 ± 12
TP (sc) + 5c acetate	200 μg	31.1 ± 7.3[b]	42.9 ± 7.6	108 ± 44
TP (sc) + 5c acetate	1 mg	24.8 ± 4.0[a]	46.8 ± 2	111 ± 25
TP (sc) + CA[d]	40 μg	40.8 ± 1.4	53.6 ± 3.8	133 ± 19
TP (sc) + CA	200 μg	35.3 ± 7.9[b]	40.1 ± 5.4	110 ± 19
TP (sc) + CA	1 mg	32.1 ± 2.5[a]	35.8 ± 7.6	106 ± 33

[a-c] See footnotes, Table IX. [d] CA = cyproterone acetate.

heated to reflux for 2 min. The crystals formed by rapid cooling of the reaction mixture at room temperature were separated by suction filtration. The filtrate was directly chromatographed through a short column of Al_2O_3 to give 0.069 g (70%) of **8a** benzoate. This benzoate was refluxed (1 h) in 2 N alcoholic NaOH solution (1.5 mL). The reaction was poured into H_2O and extracted with Et_2O. Drying and evaporation gave the crystalline compound **8a**, 0.035 g (50%). Analytical sample was recrystallized from Et_2O: mp 126.5 °C; $[\alpha]^{25}_D$ −199° (0.2%, $CHCl_3$). Anal. ($C_{14}H_{18}O_2$) C, H.

[3*S*(3α,3aα,9aα,9bβ)]-3a-Ethyl-3-hydroxy-6-methyl-1,2,3,3a,8,9,9a,9b-octahydro-7*H*-benz[*e*]inden-7-one (9b). A solution of **6b** (0.18 g, 0.725 mmol) in acetic anhydride (1 mL) and pyridine (1 mL) was kept at room temperature for 16 h and then poured into 10% aqueous H_2SO_4. The precipitate was filtered off, washed with H_2O, dried (0.21 g, mp 99 °C), and used directly in the next step.

A solution of this acetate (0.21 g, 0.724 mmol) in acetic anhydride (0.8 mL) containing $TsOH·H_2O$ (0.01 g) was left at room temperature for 16 h. H_2O (0.4 mL) and AcOH (0.3 mL) were then added. After an additional 2 h, the reaction mixture was cooled at 5 °C and stirred for 2 h with 0.13 g (0.73 mmol) of NBS. Addition of H_2O (0.8 mL) precipitated the crystalline brominated product, which was collected by filtration: 0.19 g (74%); mp 120 °C. Under a nitrogen atmosphere, a suspension of this material (0.19 g, 0.53 mmol), LiBr (0.095 g, 1.09 mmol), and Li_2CO_3 (0.045 g) in DMF (4.5 mL) was cautiously heated in order to distill off the majority of the solvent. To the cooled residue were added H_2O (5 mL) and AcOH (0.1 mL), and the reaction mixture was extracted with CH_2Cl_2. Evaporation of the solvent afforded the acetate of **9b**, 0.142 g (90%). Saponification of this crude material by refluxing (45 min) with 1 N NaOH (3 mL) and ethanol (2 mL) followed by chromatography on silica gel of the crude product (elution with hexane/acetone (17:3)) and recrystallization in acetone/hexane gave pure **9b** solvated with acetone: mp 155 °C; $[\alpha]^{25}_D$ −207° (1%, $CHCl_3$). Anal. ($C_{16}H_{22}O_2·0.5C_3H_6O$) C, H.

[3*S*(3α,3aα,9aα,9bβ)]-3a,6-Dimethyl-3-hydroxy-1,2,3,3a,8,9,9a,9b-octahydro-7*H*-benz[*e*]inden-7-one (8b). This compound was prepared in four steps from **5b** by the procedure described for **9b**.

The acetylation of **5b** with Ac_2O/TsOH followed by bromination with NBS afforded the crude brominated derivative (74%). The analytical sample of [3*S*(3α,3aα,9aα,9bβ)]-5-bromo-3a,6-dimethyl-3-hydroxy-1,2,3,3a,4,5,8,9,9a,9b-decahydro-7*H*-benz[*e*]inden-7-one 3-acetate was obtained after recrystallization from methylene chloride/diisopropyl ether: mp 140 °C; $[\alpha]^{25}_D$ +226° (1%, $CHCl_3$). Anal. ($C_{17}H_{23}O_3Br$) C, H.

The dehydrobromination of this crude intermediate with $LiBr/Li_2CO_3$ in DMF gave the acetate of **8b**, which was purified by chromatography on silica gel and crystallized from petroleum ether: yield 75%; mp 75 °C; $[\alpha]^{25}_D$ −143° (1%, $CHCl_3$). Anal. ($C_{17}H_{22}O_3$) C, H.

Saponification and recrystallization from diisopropyl ether yielded the pure alcohol **8b**: 88%; mp 156 °C; $[\alpha]^{25}_D$ −188° (1%, $CHCl_3$). Anal. ($C_{15}H_{20}O_2$) C, H.

[3*S*(3α,3aα,9bβ)]-3a,6-Dimethyl-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indene-3,7-diol (10b). A stirred suspension of diketone **33**[35] (0.3 g, 1.29 mmol), $CuBr_2$ (0.58 g, 2.6 mmol), and LiBr (0.115 g, 1.32 mmol) in CH_3CN (5 mL) was refluxed for 20 h under nitrogen. The mixture was cooled, diluted with H_2O, and extracted with Et_2O. The organic phase was washed with 1 N HCl, dried, and evaporated under reduced pressure. The residue was filtered through a silica gel column with a mixture of hexane/EtOAc (4:1) as an eluent to give 0.2 g (65%) of pure [3a*S*(3aα,9bβ)]-3a,6-dimethyl-7-hydroxy-1,2,3a,4,5,9b-hexahydro-3*H*-benz[*e*]inden-3-one: mp 200 °C; $[\alpha]^{25}_D$ +95° (1%, MeOH). To a solution of the above compound (0.09 g, 0.39 mmol) in MeOH (2.5 mL) was added $NaBH_4$ (0.06 g, 1.58 mmol). The reaction mixture was stirred at room temperature for 4 h and then poured into ice/5% aqueous HCl, and the precipitated solid was filtered off, washed with H_2O, and dried. Recrystallization in acetone/hexane gave 0.037 g (40%) of pure hydroxyphenol **10b**: mp 198 °C; $[\alpha]^{25}_D$ +17.4° (1%, MeOH); NMR δ 0.6 (3a-Me), 2.1 (6-Me), 6.64 (aromatic H). Anal. ($C_{15}H_{20}O_2$) C, H.

General Method for the Preparation of *gem*-Dialkylated Ketones 11–13. To a solution of Li metal (0.24 g, 34.5 mmol) in liquid NH_3 (150 mL) was added the enone **5** or **6** (2 mmol) in Et_2O (7 mL) and THF (23 mL). After the mixture was stirred for 20 min, the alkyl iodide (50 mmol) in Et_2O (20 mL) was added and stirring was continued for an additional 2 h 30 min. After evaporation of NH_3 the residue was poured into H_2O and extracted with Et_2O. The organic extract was washed with H_2O, dried (Na_2SO_4), and evaporated under reduced pressure. The crude product was chromatographed through a column of silica gel (eluent acetone/hexane (3:17)) and recrystallized from an appropriate solvent. Physical constants, yields, and other characteristics are listed in Table II.

[3*S*(3α,3aα,9aα,9bβ)]-3-Hydroxy-3a,6,6-trimethyl-1,2,3,3a,4,6,8,9,9a,9b-decahydro-7*H*-benz[*e*]inden-7-one Benzoate (15). To a stirred solution of *t*-BuOK prepared from K (1.8 g, 46 mmol) and *t*-BuOH (50 mL) was added **5a** benzoate (5 g, 15.4 mmol) in anhydrous benzene (50 mL). To the resulting suspension was added dropwise 5 mL (80 mmol) of IMe. The mixture was allowed to stand at room temperature for 20 h, poured into 5% aqueous HCl, and extracted with Et_2O. Column chromatography of the crude product (5.6 g) on silica gel, using acetone/hexane (3:17) as an eluent, followed by recrystallization from MeOH/H_2O afforded pure material: 1.75 g (32%); mp 120

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°C; $[\alpha]^{25}_D$ +38.5° (1%, EtOH). Anal. ($C_{23}H_{28}O_3$) C, H.

[3*S*(3α,3aα,9aα,9bβ)]-3-Hydroxy-3a,6,6-trimethyl-1,2,3,3a,4,6,8,9,9a,9b-decahydro-7*H*-benz[*e*]inden-7-one (14). A solution of **15** (1.8 g, 5.1 mmol) in 10 N aqueous NaOH (2 mL), H_2O (3 mL), and MeOH (15 mL) was refluxed for 1 h. After dilution with water, the precipitate was filtered off, dried (1.05 g (85%)), and recrystallized from MeOH/H_2O to give the pure alcohol **14**: mp 117 °C (lit.[33,36] mp 119–120 °C); $[\alpha]^{25}_D$ +39° (1%, EtOH); $[\alpha]^{25}_{365}$ −40° (1%, EtOH). Anal. ($C_{16}H_{24}O_2$) C, H.

[3a*S*(3aα,9aα,9bβ]-3a-Methyl-1,2,4,6,8,9,9a,9b-octahydrospiro[7*H*-benz[*e*]indene-7,2′-[1,3]dioxolan]-3(3a*H*)-one (17a). A mixture of enone **5a**[16] (2 g, 9.09 mmol), ethylene glycol (4 mL), benzene (60 mL), and TsOH·H_2O (0.05 g) was refluxed for 4 h with simultaneous removal of water by a Dean–Stark separator. The reaction mixture was cooled, washed with 1 M $NaHCO_3$ and H_2O, dried, and evaporated. The residue was recrystallized from MeOH/H_2O containing a drop of pyridine to afford 2.08 g (87%) of **16a**: mp 109 °C; NMR δ 0.75 (3a-Me). This compound (2.0 g, 7.57 mmol) was oxidized by pyridinium dichromate (7.12 g, 18.9 mmol) in a mixture of CH_2Cl_2 (6 mL) and DMF (15 mL) at room temperature for 2 h. The reaction mixture was poured into H_2O and extracted with Et_2O. The crude product was recrystallized from aqueous MeOH containing a drop of pyridine to afford 1.2 g (60%) of pure ketone **17a**: mp 122 °C; $[\alpha]^{25}_D$ +126° (1%, $CHCl_3$); NMR δ 0.88 (3a-Me). Anal. ($C_{16}H_{22}O_3$) C, H.

[3a*S*(3aα,9aα,9bβ)]-3a,6-Dimethyl-1,2,4,6,8,9,9a,9b-octahydrospiro[7*H*-benz[*e*]indene-7,2′[1,3]-dioxolan]-3(3a*H*)-one (17b). A mixture of enone **5b** (5.5 g, 23.5 mmol), ethylene glycol (5.5 mL), ethyl orthoformate (9 mL, 55 mmol), and TsOH·H_2O (0.2 g) in benzene (200 mL) was heated at reflux for 3 h under nitrogen. After addition of Na_2CO_3 (2 g), the reaction mixture was filtered and the filtrate evaporated in vacuo. The crude residual oil was chromatographed on 200 g of silica gel. Elution with hexane/acetone (9:1) gave 3.22 g (50%) of **16b** (oil, mixture of epimers in position 6).

Oxidation of **16b** (1.9 g, 6.82 mmol) was performed by pyridinium dichromate as for **16a**. Recrystallization of the crude product from hexane gave 1.235 g (65%) of **17b** (epimeric mixture at C-6): mp 95 °C; NMR δ 0.85 (3a-Me).

General Method for the Preparation of 16-Alkyl Derivatives 22 and 23. A 1.6 M solution of *n*-BuLi in hexane (1.5 mL, 2.4 mmol) was added to a solution of diisopropylamine (0.34 mL, 2.4 mmol) in THF (4 mL) at 0 °C under nitrogen. After stirring for 10 min at 0 °C, a solution of ketone **17** (2 mmol) in THF (26 mL) was added dropwise. After 20 min at room temperature, alkyl iodide (10 mmol) was introduced and the reaction allowed to stand for 30 min, poured into H_2O, and extracted with Et_2O. The crude 16α-alkylated ketones **18** and **19** were purified by column chromatography (silica gel, eluent ether/hexane (2:3) or EtOAc/hexane (1:9)).

The 16β-epimers **18** and **19** were obtained in the following way: a solution of 16α-alkylated ketone (1 mmol) in 2 N methanolic KOH (4 mL) was refluxed for 1.5 h. After the usual workup, the crude mixture of both epimers (16α/16β (1:3)) was separated on silica gel (eluent EtOAc/hexane (1:9)), the 16α-epimer being eluted first. Physical properties for the above compounds are listed in Table III.

Reduction of the carbonyl group was then performed by $LiAlH_4$ in ether (reflux 1 h) to give pure 17β-hydroxy compounds **20** and **21** (quantitative yields).

A solution of the above compounds (100 mg) and TsOH·H_2O (~5 mg) in acetone (2 mL) and H_2O (0.5 mL) was refluxed for 1 h. After the usual workup, the crude product was filtered through a short column of silica gel (eluent acetone/hexane (1:4)) to give pure ketones **22** and **23** (60–70% yield). Physical properties are listed in Table III.

[3*S*(3α,3aα,9aα,9bβ)]-3a,6,6,7-Tetramethyl-2,3,3a,4,6,7,8,-9,9a,9b-decahydro-1*H*-benz[*e*]indene-3,7-diol (24). To a solution of ketone **15** (0.5 g, 1.42 mmol) in THF (5 mL) and Et_2O (5 mL) was added under nitrogen 1.6 M MeLi in Et_2O (10 mL), and the mixture was heated with reflux for 2 h. The cooled reaction mixture was poured into H_2O and extracted with Et_2O. The organic extract, dried (Na_2SO_4) and evaporated, afforded the crude material, 0.4 g. Recrystallization from MeOH gave **24** solvated with MeOH; 0.175 g (42%). An analytical sample was obtained by sublimation: mp 215 °C; $[\alpha]^{25}_D$ +22° (1%, EtOH). Anal. ($C_{17}H_{28}O_2$) C, H.

[3*S*(3α,3aα,5aβ,9aα,9bβ)]-3-Hydroxydodecahydro-7*H*-benz[*e*]inden-7-one (29). A solution of **5a** (0.6 g, 2.72 mmol) in THF (3 mL) and *tert*-butyl alcohol (0.5 mL) was added dropwise to a stirred solution of Li metal (75 mg, 10.8 mmol) in liquid NH_3 (25 mL). After 5 min *tert*-butyl alcohol (1 mL) was added and the stirring was continued until decoloration of the reaction mixture. After evaporation of the ammonia, the residue was diluted with H_2O and extracted with methylene chloride. The extract was washed with H_2O, dried, and evaporated. Column chromatography of the crude product on silica gel [90 g, Et_2O/EtOAc (19:1)] gave 0.4 g (66%) of ketone **29**. The analytical sample was recrystallized from aqueous MeOH and then from Et_2O/hexane: mp 96 °C; $[\alpha]^{25}_D$ −39° (1%, $CHCl_3$). Anal. ($C_{14}H_{26}O_2$) C, H.

[3a*S*(3aα,5aβ,9aα,9bβ)]-3a,6,6-Trimethyloctahydro-1*H*-benz[*e*]indene-3,7(2*H*,3a*H*)-dione (31). A solution of hydroxy ketone **11b** (0.065 g, 0.26 mmol) in acetone (1 mL) was stirred at room temperature for 10 min with 0.12 mL of Jones chromic reagent.[37] The reaction mixture was poured into H_2O and was extracted with Et_2O. After removal of the solvent, the residual diketone (0.064 g, 100%) was recyrstallized from Et_2O hexane; mp 80 °C. Anal. ($C_{16}H_{24}O_2$) C, H.

Measurement of the Relative Binding Affinities for the Androgen Receptor of Castrated Rat Prostate. Adult male rats (Sprague–Dawley, 200 g) were castrated 1 day before sacrifice. Prostates were immediately removed and homogenized in 5 vol (w/v) of Tris buffer (Tris 10 mM, HCl pH 7.4). Cytosol was obtained by centrifugation of the homogenates at 105000*g* for 45 min.

Aliquots of 125 μL of cytosol were incubated for 30 min or 24 h at 0–4 °C in the presence of 5 mM [^{3}H]testosterone (sp act. 54 Ci/mmol) in the absence or presence of various concentrations (1–2500 nM) of the test compounds. (All the compounds were added to 10 μL of Tris buffer containing 10% of pure ethanol.) After incubation, 100-μL aliquots were stirred for 10 min at 4 °C with 100 μL of a Dextran-coated charcoal suspension (charcoal norit A 1.25%, Dextran 70000, 0.625%) in a microter plate and centrifuged at 2500 rev/mn for 10 min in a Christ-Heraeus Minifuge (4 °C). The radioactivity of 100-μL supernatant aliquots, containing the labeled hormone bound to the receptor (B), was measured. The ratio B/B_0, where B_0 represents the concentration of bound labeled testosterone in the absence of competitor (B_0 = 5500 cpm), was plotted against the concentration of unlabeled competitor added. The concentration of competitor required for a 50% displacement (IC_{50}) of [^{3}H]testosterone from its specific binding sites (after substraction of nonspecific binding) was determined graphically. The ratio (×100) of the IC_{50}s for testosterone and competitor gives the relative binding affinities (RBAs) of the competitor.

Antiandrogenic Activity in the Rat, by Subcutaneous Route. Groups of five immature male rats (70 g), castrated 24 h beforehand, received for 4 days daily subcutaneous injections of 50 μg of testosterone propionate either alone or in combination with 5 mg of test compounds. Controls received solvent only (sesame oil containing 5% benzyl alcohol). The animals were sacrificed 24 h after the last injection. Their prostates and seminal vesicles were excised and weighed.

Local Antiandrogenic Activity in the Hamster. Groups of four male hamsters (100–110 g), castrated 7 days beforehand, received for 8 days daily subcutaneous injections of 125 μg/hamster of testosterone propionate in 0.1 mL of saline containing 0.2% of tween. The test compounds (at the indicated doses) were applied topically in 20 μL of pure ethanol on the right flank organ once a day for 8 days, while the contralateral flank organ received ethanol only. Animals were sacrificed 24 h after the last treatment. The flank organs and prostates were excised and weighed.

Registry No. 1, 38555-03-2; **2**, 40401-20-5; **3**, 4968-04-1; **4**, 4222-93-9; **5a**, 25547-76-6; **5a** benzoate, 23477-71-6; **5b**, 14030-26-3;

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5-Br-**5b** acetate, 83646-99-5; **5b** benzoate, 19614-35-8; **5c**, 98483-27-3; **5c** acetate, 98574-25-5; **5d**, 98483-28-4; **6a**, 23613-75-4; **6b**, 98574-26-6; **6b** acetate, 98574-27-7; 5-Br-**6b** acetate, 83647-01-2; **6c**, 98483-29-5; **6d**, 98483-30-8; **7**, 98483-52-4; **8a**, 98483-31-9; **8a** benzoate, 98483-32-0; **8b**, 98483-33-1; **8b** acetate, 98483-34-2; **9b**, 98483-35-3; **9b** acetate, 98483-36-4; **10a**, 4019-92-5; **10b**, 98574-28-8; **10b** ketone, 98574-36-8; **11b**, 76225-57-5; **11c**, 98483-37-5; **11d**, 98483-38-6; **12b**, 98483-39-7; **12c**, 98483-40-0; **13b**, 76225-13-3; **14**, 76225-64-4; **15**, 56116-09-7; **16a**, 98483-41-1; α-**16b**, 98574-29-9; β-**16b**, 98574-30-2; **17a**, 98483-42-2; α-**17b**, 98574-31-3; β-**17b**, 98574-32-4; α-**18a**, 98483-43-3; β-**18a**, 98574-33-5; (2α,6α)-**18b**, 98574-34-6; (2β,6α)-**18b**, 98632-56-5; (2α,β)-**18b**, 98574-37-9; (2β,6β)-**18b**, 98574-38-0; α-**19a**, 98483-44-4; β-**19a**, 98574-35-7; α-**22a**, 98509-00-3; β-**22a**, 98483-45-5; α-**22b**, 98483-46-6; β-**22b**, 98483-47-7; α-**23a**, 98483-48-8; β-**23a**, 98483-49-9; **24**, 98483-50-2; **25**, 10232-46-9; **26**, 10232-57-2; **27**, 10232-54-9; **28**, 68875-97-8; **29**, 35130-89-3; **30**, 15247-10-6; **31**, 98483-51-3; **33**, 10072-75-0; MeBr, 74-83-9; EtBr, 74-96-4; PrBr, 106-94-5; BuBr, 109-65-9; MeI, 74-88-4; EtI, 75-03-6; PrI, 107-08-4; 1,4-dibromo-1,4-*seco*-2,3-bisnor-5α-androst-17β-ol acetate, 23015-70-5.

Dopamine Receptor Agonist Activity of Some 5-(2-Aminoethyl)carbostyril† Derivatives

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The potency of β-adrenoreceptor agonists, e.g., isoproterenol, is strikingly increased by substitution of the meta catecholic hydroxyl group with the NH group of a carbostyril system. To explore the possibility that comparable potency enhancement might occur upon similar modification of the catechol ring of dopamine, a series of 5-(2-aminoethyl)carbostyril derivatives was prepared and examined for D-1 and D-2 dopamine receptor-stimulating activity. Only the parent compound, 5-(2-aminoethyl)-8-hydroxycarbostyril (**2**), produced measurable activation of dopamine-sensitive adenylate cyclase (29% at a concentration of 10 μM). Some of the compounds, however, did produce significant activity in tests, namely displacement of [^{3}H]spiroperidol binding from bovine pituitary homogenate and an isolated perfused rabbit ear artery preparation, that measure interaction with D-2 receptors. Potency of the carbostyrils was enhanced by 8-hydroxylation and by appropriate substitution of the amino group of the ethylamine side chain. The most potent member of the series was 8-hydroxy-5-[2-[[2-(4-hydroxyphenyl)ethyl]-*n*-propylamino]ethyl]carbostyril (**16b**). This compound was about 3 times more effective than dopamine in the D-2 receptor tests. Clearly, the results of this study indicate that potency of dopamine receptor agonists is not increased by carbostyril replacement of the *m*-hydroxyl as is noted with the β-adrenergic receptor agonists.

Structure–activity relationship (SAR) studies among dopamine (DA) receptor agonists are ambiguous regarding the significance of the catechol system for binding to, and activation of, DA receptors. Both hydroxyl groups apparently are important for stimulation of the D-1[1] or DA_1[2-4] subpopulations of DA receptors that are involved in activation of DA-sensitive adenylate cyclase and initiation of smooth muscle relaxation, respectively. There are notable exceptions to this generalization, however. Thus, some 2-aminotetralins that bear only a single hydroxyl group in a position meta to the embedded ethylamine side chain, depending to a large extent on the nature of substitution on the basic nitrogen, retain a marked degree of D-1 agonist activity. Although selective noncatecholic DA_1 receptor agonists have not been identified, stimulation of this receptor subtype is also dependent upon the pattern of substitution of the nitrogen.[6] Clearly, the catecholic system is not required for activation of the D-2 (not associated, or negatively linked with cyclic-AMP)[1] and the DA_2 (located on sympathetic nerve endings and subserving inhibition of norepinephrine release) receptors.[2-4] Thus, the monohydroxylated tyramine derivatives RU 24213 [*N*-*n*-propyl-*N*-(2-phenylethyl)tyramine] and RU 24926 [*N*-*n*-propyl-*N*-[2-(4-hydroxyphenyl)ethyl]tyramine] are selective D-2 receptor agonists.[7,8] Among the many other noncatecholic DA relatives that are capable of stimulating D-2 or DA_2 receptors,[9] the octahydropyrazolo[3,4-*g*]-quinoline LY 141865,[10-12] piribedil [1-[3,4-(methylenedioxy)benzyl]-4-(2-pyrimidyl)piperazine] and related compounds,[15] 4-[2-(dipropylamino)ethyl]indole,[16] and various

† *Chemical Abstracts* nomenclature is 5-(2-aminoethyl)-2-(1*H*)-quinolone; however, in this paper the more common carbostyril naming is employed.

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