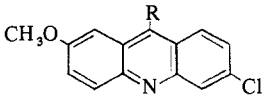
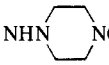
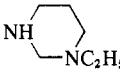
Table II. Chemical Data



Serial no.	R	Reaction temp, °C	Yield, %	Crystn solvent	Mp, °C[a]	Formula	Analyses
1	$NHCH(CH_3)-C(H)=C(H)CH_2N(C_2H_5)_2\cdot 2HCl$	120	16.0	EtOH	240–241 dec	$C_{23}H_{28}ClN_3O\cdot 2HCl$	C, H, N
2	$NHCH(CH_3)-C(H)=C(H)CH_2N(C_2H_5)_2\cdot 2HCl$	120	70.0	MeOH–EtOH	249–250 dec	$C_{23}H_{28}ClN_3O\cdot 2HCl$	C, H, N
3	$NHCH(CH_3)C\equiv CCH_2N(C_2H_5)_2\cdot 2HCl$	140–150	50.0	EtOH–*i*-PrOH	225–226 dec	$C_{23}H_{26}ClN_3O\cdot 2HCl$	C, H,[b] N
4	$NHNHCH(CH_3)CH_2N(CH_3)_2$	90–100	30.0	Cyclohexane	104–105.5	$C_{19}H_{23}ClN_4O$	C, H, N
5	$NHNHCH(CH_3)CH_2CH_2N(CH_3)_2\cdot 2HCl$	90–100	17.0	*i*-PrOH	233.5–235 dec	$C_{20}H_{25}ClN_4O\cdot 2HCl$	C, H, N[c]
6	$NHNHCH(C_2H_5)CH_2N(CH_3)_2\cdot 2HCl$	90–100	18.0	*i*-PrOH	238–240 dec	$C_{20}H_{25}ClN_4O\cdot 2HCl$	C,[d] H, N
7		110–115	64.0	EtOH–petroleum ether	123 (previous shrinkage)	$C_{19}H_{21}ClN_4O$	C, H, N
8		120–130	22.0	EtOH	285–288 dec	$C_{21}H_{24}ClN_3O\cdot 2HCl\ 0.5H_2O$	C, H, N

[a] All melting points are uncorrected. [b] H: calcd, 6.01; found, 6.43. [c] N: calcd, 12.56; found, 12.15. [d] C: calcd, 53.64; found, 54.17.

solution; the product was extracted with ether or CH_2Cl_2 several times, the combined extracts were dried (K_2CO_3) and filtered, and solvent was removed under reduced pressure. The product was purified by column chromatography on basic alumina, activity 1, using ether as en eluting solvent and then crystallized either as a free base or as hydrochloride salt.

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Communications to the Editor

Synthesis of an Androgenic–Anabolic Nonsteroid

Sir:

We describe the synthesis of tricyclic compounds corresponding to steroids lacking ring A which have significant androgenic activity. This finding is of importance in connection with the question of whether the intact steroid nucleus is a *sine qua non* for the production of various kinds of hormonal effects. Numerous synthetic estrogens lacking the steroid nucleus have been synthesized[1] and have found utility as drugs for contraceptive, antineoplastic, and obstetrical purposes, but attempts to find similar agents in the androgens have produced only inactive compounds[2] or compounds having only 1–2% of the activity of testosterone.[3] Our recent studies on the structural requirements in the A ring of steroids for androgenic action[4] indicated that only the steric, and not the electronic, characteristics of ring A are important in eliciting this biological response. Therefore, it appeared feasible to prepare a nonsteroidal androgen lacking an A ring but in which hydrogen atoms of methyl groups at C-10 and C-5 would replace the carbon atoms at C-2 and C-3. In such a compound, the conformation of the carbon atoms of the C-5 and C-10 methyl groups is fixed because of the relatively inflexible nature of the condensed tricyclic ring system and although the hydrogen atoms may assume a variety of conformations, the most stable is a staggered chair-like structure placing hydrogen atoms in the approximate vicinity of C-2 and C-3 in ring A (Figure 1). Thus, this molecule could assume the conformation of an androstane derivative flattened at C-2 and/or C-3 which we have shown to be important for hormonal activity.[4]

Reduction of 1,4-dibromo-1,4-*seco*-2,3-bisnor-5α-androstan-17β-ol acetate[5] with lithium aluminum hydride gave **1**, mp 115–117°, which on acetylation (Ac_2O) furnished **2**, mp 82–83°. Similarly, reduction of 1,4-dibromo-7α-methyl-1,4-*seco*-2,3-bisnor-5α-androstan-17β-ol[6] yielded **4**, mp 117–118°. Oxidation of **1** with 8 *N* chromium trioxide in acetone solution followed by treatment with methylmagnesium bromide in ether solution gave **3**, mp 132–134°. Dehydrohalogenation of 1,4-dibromo-1,4-*seco*-2,3-bisnor-5α-estran-

Table I. Androgenic-Myotrophic Assay

Compd (total dose, mg)	Wt, mg[a] (assay)			Body wt, g	
	Ventral prostate	Seminal vesicle	Levator ani	Initial	Final
Castrate[b] control	16.2 ± 1.97	12.9 ± 0.12	23.2 ± 1.36	55	90
Testosterone[b] (0.3)	37.6 ± 2.54 (<0.001)	17.5 ± 0.72 (<0.01)	27.6 ± 2.55 (NS)[c]	55	91
Testosterone[b] (1.5)	76.8 ± 6.86 (<0.001)	46.4 ± 4.46 (<0.001)	44.8 ± 3.35 (<0.001)	56	93
Testosterone[b] (3.0)	127.9 ± 11.55 (<0.001)	77.8 ± 4.92 (<0.001)	64.7 ± 3.69 (<0.001)	56	93
1 (3.0)	36.7 ± 6.27 (<0.01)	17.9 ± 1.36 (<0.01)	42.9 ± 3.78 (<0.001)	56	87
2 (3.0)	25.1 ± 3.72 (<0.05)	14.7 ± 0.27 (<0.01)	40.5 ± 2.24 (0.001)	56	90
3 (3.0)	34.1 ± 6.79 (<0.05)	22.8 ± 0.87 (<0.001)	45.5 ± 0.62 (<0.001)	56	90
4 (3.0)	38.0 ± 4.22 (<0.001)	19.5 ± 1.12 (<0.001)	48.2 ± 2.20 (<0.001)	55	93
5 (3.0)	18.6 ± 2.60 (NS)	11.4 ± 0.20 (NS)	23.3 ± 3.30 (NS)	56	91
6 (3.0)	16.7 ± 0.21 (NS)	13.7 ± 1.15 (NS)	26.5 ± 3.06 (NS)	56	87

[a]Mean ± standard error. [b]Composite values from 15 to 25 rats. [c]Not significant at 0.05 level.

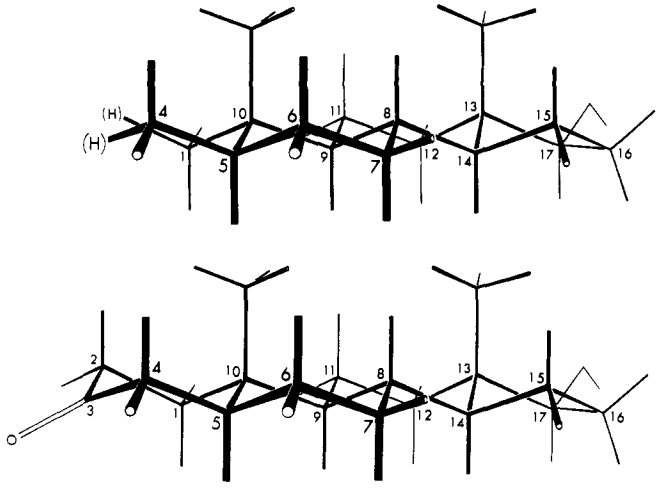
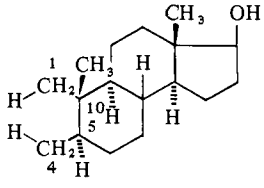
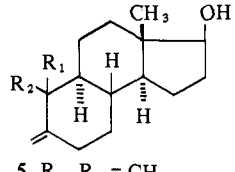


Figure 1. Models of 1 and 5α-dihydrotestosterone showing correspondence of hydrogen atoms with C-2 and C-3.

17β-ol acetate[6] with potassium *tert*-butoxide in dimethyl sulfoxide solution afforded **5**. The action of sodium methoxide on 1,4-dibromo-1,4-*seco*-2,3-bisnor-5α-androstan-17β-ol acetate[5] gave **7**, mp 100–102°, which was reduced with lithium aluminum hydride in tetrahydrofuran to give **6**, mp 112–114°. Satisfactory combustion analyses for carbon and hydrogen were obtained for all compounds for which melting points are reported. Confirmatory high-resolution mass spectrometric measurement of the molecular ion was obtained for compounds **1–5**.



1
2, 17β-OAc
3, 17α-Me
4, 7α-Me



5, $R_1, R_2 = CH_2$
6, $R_1 = R_2 = Me$
7, $R_1 = Me$; $R_2 = CH_2Br$

Biological examination[7] was carried out by injecting the compounds as suspensions in carboxymethyl cellulose solution to castrate rats for 7 consecutive days with autopsy on the day after the last treatment day. Testing was done at Endocrine Laboratories, Madison, Wis. The organ weights obtained are shown in Table I. Our data show that compound **1** has anabolic (levator ani) activity in the range of clinically useful compounds[8] with low androgenic (ventral prostate and seminal vesicle) activity. Similarly, the 17-acetate **2** and the 17α-methyl **3** derivatives exhibit corresponding activity, while enhancement of potency is obtained by introduction of the 7α-methyl **4** group analogous to the case in testosterone.[9] If the activity of **1** is, in fact, due to the spatial relationship of two hydrogens approximating the position of C-2 and C-3, one would expect that derivatives **5** and **6** having methylene groups in place of methyl groups would lack activity and this was confirmed by the results.

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