A-Nor-5α-androstane Derivatives. IV. New Structures with Potential Antiimplantation Activity

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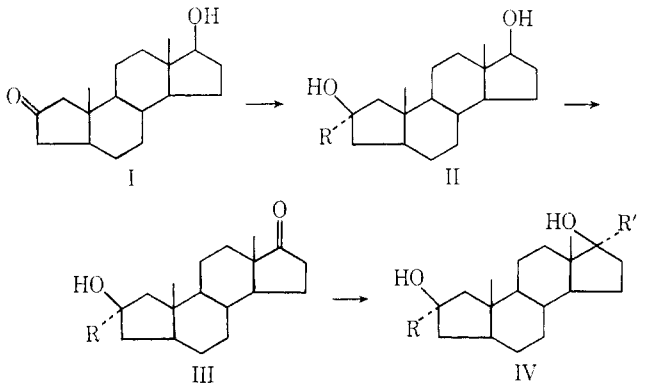
Received November 22, 1968

The preparation of a number of A-nor-5α-androstanes is described. The majority of the new structures are 2,17-disubstituted diols; their stereochemistry is established by nmr spectroscopy and correlated with structures from previous papers. A number of compounds are of interest as implantation inhibitors and a brief biological summary drawn from published work is included.

The preparation of a number of A-nor-5α-androstanes and their stereochemical correlations has been reported in the first three papers of this series.[1-3] The discovery that these substances have antihormonal properties[4] and especially their potential use as antiimplantation agents has prompted the present more detailed study of the structure-activity relationship within this class of compounds.

A. 2,17-Disubstituted A-Nor-5α-androstanes.—The sequence I → IV (Scheme I) was selected for the preparation of compounds listed in Table I for several reasons. Since the majority of the desired new structures (IV) differ only in the nature of the substituent R′, they could be prepared from a common precursor III (R = C≡CH) with well-established stereochemistry at C-2.[1] For most of the other compounds it was preferable to first introduce the substituents R at C-2, by reaction of the known ketol I[1] with an appropriate nucleophile, followed by oxidation of the diol(s) II to the ketol(s) III. Separation of C-2 isomers was best achieved with these intermediates, which were also found to be suitable for establishing their stereochemistry at C-2 based on nmr evidence (see Tables II–IV). This sequence also allowed testing of some of the ketols II, which were of potential biological interest.

SCHEME I



In all these compounds the stereochemistry at C-17 can safely be assumed to be as shown in IV, if one accepts the general rule of preponderant α-side attack by nucleophiles on the C-17 carbonyl of the steroids.

Compounds IVa–j could all have been prepared from III by reaction with the appropriate nucleophiles. In practice, however, difficulties arose in a number of cases, essentially because of solubility problems. These difficulties were overcome by masking the tertiary OH group in III, as the tetrahydropyranyl ether, prior to the Grignard-type reactions. Following these reactions, the protecting group was readily removed by acid treatment. This was the preferred method for IVe–i.

To eliminate repetition, only representative examples for these procedures have been included in the Experimental Section.

A remaining structural problem that had to be solved with a number of compounds of Table I was the determination of the stereochemistry at C-2. It is well established that the introduction of a substituent or functional group into the steroidal skeleton produces a well-defined incremental shift in the position of absorption of the C-18 and C-19 methyl protons, which is substantially independent of other substituents in the molecule.

Table II shows the increments produced by the introduction of different substituents as previously determined by us,[2] and Table III those obtained in the course of the present work, along with the data from which they were calculated. Table IV presents a comparison of the experimentally observed chemical shifts for the remaining compounds of Table I and their isomers, whenever the latter could be isolated and appropriately purified, along with the shifts calculated by utilizing the data from Tables II and III. The excellent correlation bears out the stereochemical assignments for the compounds in question, and further supports the utility of the method in assigning stereochemistry to various substituents, even when applied to two substituents on the same carbon.

Turning now to specific cases, IVa was best prepared by ethynylation of ketol VIa, previously described by Rull and Ourisson.[5] We have prepared VIa by reaction of MeMgBr with A-nor-5α-androstane-2,17-dione 2-ethylene ketal (V), followed by hydrolysis. The same ketal V, upon ethynylation yielded the ketol VIb, which was hydrogenated to give the ketol VIc.

(1) M. Minssen and J. Jacques, *Bull. Soc. Chim. France*, 71 (1965).

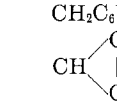
(2) J. Jacques, M. Minssen, D. Varech, and J. Basselier, *Bull. Soc. Chim. France*, 77 (1965).

(3) M. Minssen, M. J. Brienne, and J. Jacques, *ibid.*, 814 (1965).

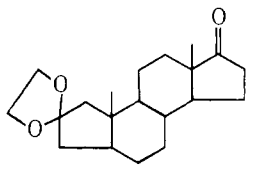
(4) (a) J. Jacques and G. Pincus, "Hormonal Steroids, Biochemistry, Pharmacology and Therapeutics," Vol. I, L. Martini and A. Pecile, Ed., Academic Press, London and New York, 1962, p 3; (b) G. Pincus and B. Bialy, *Recent Progr. Hormone Res.*, **19**, 201 (1963); (c) U. K. Banik and G. Pincus, *Proc. Soc. Exp. Biol.*, **111**, 596 (1962).

(5) T. Rull and G. Ourisson, *Bull. Soc. Chim. France*, 1573 (1958).

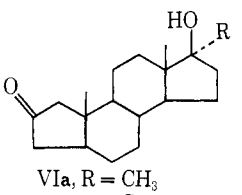
TABLE I

IV	R	R′	Mp, °C	[α]D, deg	Formula[e]
a	C≡CH	CH_3	170		$C_{21}H_{32}O_2$
b	C≡CH	C_2H_5	154	+9	$C_{22}H_{34}O_2$[b,d]
c	C≡CH	$CH{=}CH_2$	122–124	+9.6[a]	$C_{22}H_{32}O_2$[c,d]
d	C≡CH	C≡CCl	180–181	−4.9[a]	$C_{22}H_{29}O_2Cl\cdot 0.5H_2O$
e	C≡CH	$C{\equiv}CCH_3$	195–196	−24.6[a]	$C_{23}H_{32}O_2$
f	C≡CH	$CH_2C{\equiv}CH$	80–82	−6.7	$C_{23}H_{32}O_2$
g	C≡CH	$CF{=}CF_2$	143–144	+16.2[a]	$C_{22}H_{29}O_2F_3$
h	C≡CH	$CH_2C(CH_3){=}CH_2$	144–145	+13.1[a]	$C_{24}H_{36}O_2$
i	C≡CH	$CH_2C_6H_5$	165–167	−16.2[a]	$C_{27}H_{36}O_2$
j	C≡CH		135–137	+130	$C_{24}H_{34}O_2$
k	H	C≡CH	201–203	−43.0[a]	$C_{20}H_{30}O_2$
l	CH_3	H	160–161	+14.9	$C_{19}H_{32}O_2$
m	β-CH_3	H	219	+11.8	$C_{19}H_{32}O_2$
n	CH_3	C≡CH	197–198	−42.8	$C_{21}H_{32}O_2$
o	β-CH_3	C≡CH	169–170	−42.2	$C_{21}H_{32}O_2$
p	CH_3	CH_3	212–213	−4.0[a]	$C_{20}H_{34}O_2$
q	$CH{=}CH_2$	C≡CH	74–75	−42.9[a]	$C_{22}H_{32}O_2\cdot H_2O$
r	$CH_2C{\equiv}CH$	C≡CH	64–65	−25.8[a]	$C_{23}H_{32}O_2\cdot 0.5H_2O$

[a] Measured in $CHCl_3$. [b] C: calcd, 79.95; found, 79.53. [c] C: calcd, 80.44; found, 79.97. [d] Due to difficulties in desolvating these compounds, no better results could be obtained. [e] All compounds were analyzed for C, H.



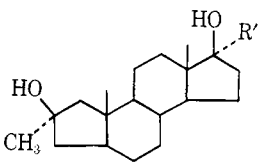
V



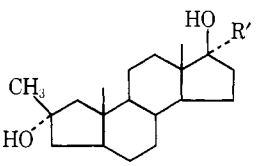
VIa, R = CH_3
b, R = C≡CH
c, R = C_2H_5

The latter gave IVb after ethynylation at C-2.

Compound IVk was the major isomer obtained upon $NaBH_4$ reduction of ketol VIb. Compound IVl was prepared as shown above, from I, and the two isomeric diols IVl and m separated at this point. Stereochemical assignments follow from the data shown in Tables II and III. Since oxidation and subsequent C-17 ethynylation were performed separately on both IVl and m, structures IVn and o are unambiguously established and nicely confirmed by the nmr data.



IVl, R′ = H
n, R′ = C≡CH



IVm, R′ = H
o, R′ = C≡CH

Compound IVp was obtained directly from A-nor-5α-androstane-2,17-dione[6] with the isomer shown being formed almost exclusively. To avoid any ambiguities, IVq was prepared by first partially hydrogenating II (R = C≡CH)[1] to the corresponding vinyl analog II (R = CH=CH)[2] and then proceeding according to II → III → IV. A modified Reformatzky reaction on ketol I gave a mixture of isomeric carbinols II (R = $CH_2C{\equiv}CH$). On chromatography the major component was conclusively identified as the 2β-hydroxy isomer from its nmr data.

(6) F. L. Weisenborn and H. E. Applegate, *J. Am. Chem. Soc.*, **81**, 1960 (1959).

TABLE II

NMR INCREMENTS OF SUBSTITUTED A-NOR-5α-ANDROSTANES[a]

Substituent	Increment, Hz C_{19}	Increment, Hz C_{18}
2β-OH	+15.5	+0.5
2α-OH	+1.5	0
17β-OH	+1	+3.5
2-=O	+11.5	+1.5
17-=O	+1.5	+10.5
2α-C≡CH	−0.5	−1.5
2β-C≡CH	+10.5	0
2α-C_2H_5[1]	+3.5	+0.5

[a] Increments were previously established.[2] In the parent, A-nor-5α-androstane, C_{19} = 39 Hz and C_{18} = 41.5 Hz.

TABLE III

NMR INCREMENTS OBTAINED ON SUBSTITUTED A-NOR-5α-ANDROSTANES IN THE PRESENT WORK[a]

Substituents	C_{19}, Hz Obsd	C_{19}, Hz Increment	C_{18}, Hz Obsd	C_{18}, Hz Increment
2β,17β-(OH)$_2$-2α-C≡CH-*17α-CH_3* (IVa)	56	+1	51	+7
2β,17β-(OH)$_2$-*2α-CH_3* (IVl)	56	+0.5	44	−1.5
2α,17β-(OH)$_2$-*2β-CH_3* (IVm)	43	+1.5	43	−2
2-Keto-17β-OH-*17α-C≡CH* (VIb)	51.5	0	51.5	+5
17-Keto-2β-OH-*2α-propargyl* (III, R = propargyl)	59	+3	52.5	0
2β,17β-(OH)$_2$-*2α-CH=CH_2* (II, R = vinyl)	59.5	+4	45.5	0

[a] New substituents are italicized.

The last step in this, as well as in the previous sequence, failed to yield appreciable amounts of C-17 ethynylcarbinols under the usual Stavely conditions[7] used in the previous papers. After some experimentation it was found that good yields of IVq and r could be obtained with an "inverse addition" technique that also proved to be the method of choice for obtaining compound IVn.

B. Miscellaneous A-Nor Steroids.—Although A-nortestosterone and A-norpregnanedione have been prepared before,[6] it was of interest to examine the in-

(7) H. E. Stavely, *ibid.*, **62**, 489 (1940).

TABLE IV

NMR SIGNALS OF C-18 AND C-19 METHYLS IN VARIOUS SUBSTITUTED A-NOR-5α-ANDROSTANES

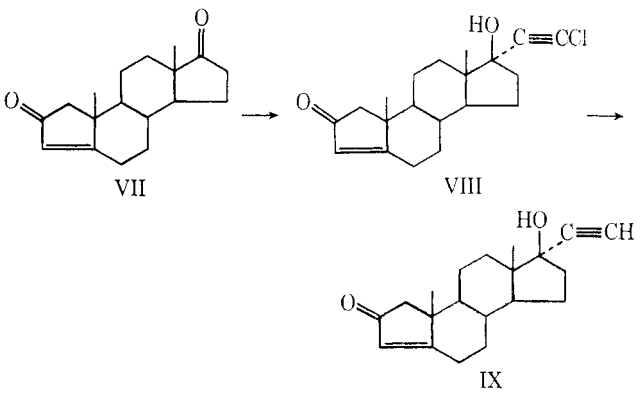
Substituents	C19, Hz Obsd	C19, Hz Calcd	C18, Hz Obsd	C18, Hz Calcd
2β,17β-(OH)2-2α-CH3-17α-C≡CH (IVn)[a]	55	56	49	48.5
2α,17β-(OH)2-2β-CH3-17α-C≡CH (IVo)[a]	44	43	48.5	46.5
2β,17β-(OH)2-2α,17α-(CH3)2 (IVp)[a]	55	57	50	50.5
2β,17β-(OH)2-2α-CH=CH2-17α-C≡CH (IVq)[a]	60	59.5	51.0	50.5
2β,17β-(OH)2-2α-propargyl-17α-C≡CH (IVr)[a]	57	58.5	50	50.5
2β,17β-(OH)2-2α-C2H5 (II, R = C2H5)[a]	57.5	59	44.5	46
2β,17β-(OH)2-2α-propynyl (II, R = propynyl)[b]	54	55	43.5	44
2-Keto-17β-OH-17α-C2H5 (VIe)[c]	51.5	52.5	53.5	53.5

[a] Using the values from Tables II and III. [b] Assuming Δ 2α-CH3C≡C = Δ 2α-CH≡C. [c] Assuming Δ 17α-C2H5 = Δ 17α-CH3.

fluence of an ethynyl group on the biological activities of these molecules.

In view of the previously observed[8] selectivity in a low-temperature chloroethynylation[9] it seemed promising to attempt the same reaction on the readily available[6] A-norandrostenedione VII. Not only was good selectivity observed, but, since it was also found[10] that a haloethynyl halogen could be hydrogenolized smoothly with Zn in AcOH, the desired 17α-ethynyl-A-nortestosterone (IX) was obtained in a two-step sequence as shown in Scheme II.

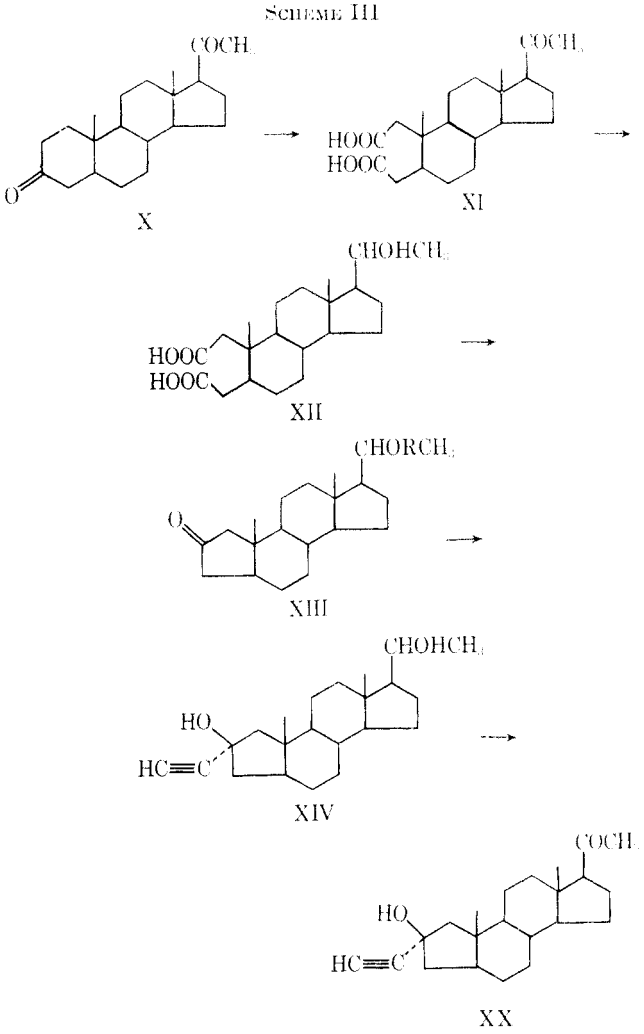
SCHEME II



It is interesting to note, that after completion of this work the preparation of IX from VII has been published,[11] *via* a six-step synthesis.

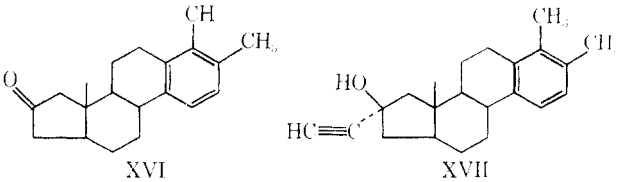
The sequence X → XV shown in Scheme III outlines the preparation of 2α-ethynyl-5α-pregnan-2β-ol-20-one (XV) using several conventional steps. 2,3-Seco-5α-pregnan-20-one-2,3-dioic acid (XI)[5,12] was treated with excess $NaBH_4$ and yielded a crystalline mixture of the C-20 epimeric alcohols XII. Cyclization and hydrolysis of the crude acetate (XIII, R = CH_3CO) gave the corresponding ketol (XIII, R = H), whose structure was verified by oxidation to the known[5] A-nor-5α-pregnane-2,20-dione. Ethynylation of XIII followed

SCHEME III



by oxidation led to one major product which was assigned the desired structure XV.

In order to establish whether the surprising estrogenic activity of 2α,17α-diethynyl-A-nor-5α-androstane-2,17-diol[13] might be due to a metabolic pathway leading to structures related to estrone or a gonane (or their antipodes), we have prepared the D-homo aromatic derivative XVII, which could be prepared from a C-17 ethynylcarbinol. It had been shown previously[14] that formic acid treatment of steroidal 17-ethynylcarbinols produces ring enlargement with aromatization in ring D. Starting with the ethynyl ketol VIb the rearranged ketone XVI was in fact easily obtained. The latter, upon ethynylation yielded the desired compound (XVII).



Following an observation of Dorfman[15] who had

(8) T. B. Windholz, J. H. Fried, H. Schwam, and A. A. Patchett, *J. Am. Chem. Soc.*, **85**, 1707 (1963).

(9) H. G. Viehe, *Chem. Ber.*, **92**, 1270 (1959).

(10) (a) T. B. Windholz, A. A. Patchett, and J. H. Fried, U. S. Patent 3,374,255 (1968); (b) T. B. Windholz, R. Rettenmaier, and R. D. Brown, to be published.

(11) S. D. Levine, *Steroids*, **1**, 477 (1966).

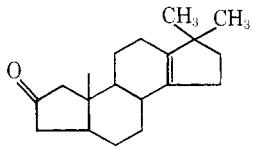
(12) R. E. Marker, O. Kamm, and D. M. Jones, *J. Am. Chem. Soc.*, **59**, 1595 (1937).

(13) S. L. Steelman and D. J. Patanelli, Proceedings of the 2nd International Congress of Hormonal Steroids, Milan, 1966, L. Martini, F. Fraschini, and M. Motta, Ed., Excerpta Medica Foundation, Amsterdam & New York, 1967, p 559.

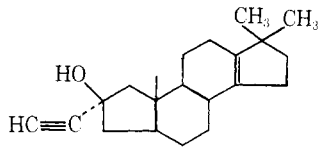
(14) M. Dvolaitzky, A. M. Giroud, and J. Jacques, *Bull. Soc. Chim. France*, 62 (1963).

(15) R. I. Dorfman, *Steroids*, **2**, 185 (1963).

shown that some ψ-androstenes show antihormonal activities, we have also prepared structure XIX. The intermediate ketone XVIII was obtained by acid treatment of ketol VIa.



XVIII



XIX

Biological Activities.—The estrogenic and implantation-inhibiting activities of most of the compounds listed in Table I have been described by Steelman and Patanelli.[13] It can be stated in general that at least one ethynyl group is needed for good activity, but the 2α-ethynyl derivatives allow a greater variation of substituents at C-17. In fact, substituents other than ethynyl at C-2 show a marked decrease in estrogenicity which is paralleled by a decrease in antiimplantation activity. A more favorable ratio of these activities is shown by IVi and IVj. A general decrease in activity is noted when R′ is other than ethynyl with the exception of trifluorovinyl (IVg) which is a potent inhibitor of implantation. This latter compound is also a good estrogen.

The compounds described in section B do not possess activities that would make them of interest for fertility control.

Experimental Section

Unless otherwise noted, melting points were taken on a Kofler block and are corrected, optical rotations, unless otherwise indicated, were measured in dioxane at the concentration indicated in parentheses, nmr spectra were run at 60 MHz in $CDCl_3$ with TMS as an internal standard, and Analtech 250-μ silica plates were used for tlc. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values. We thank Dr. N. R. Trenner and his associates (Rahway) and Mrs. L. Lacombe (Paris) for the instrumental analyses, Mr. R. N. Boos and his associates (Rahway) and the Service Central de Microanalyse du C.N.R.S. (Paris) for the elemental analyses.

Tetrahydropyranyl Ether of 2α-Ethynyl-A-nor-5α-androstan-2β-ol-17-one (III, R = C≡CH; 2-THP).—A 6-g sample of 2α-ethynyl-A-nor-5α-androstan-2β-ol-17-one was suspended in 30 ml of dihydropyran, freshly distilled from NaH. After adding 0.3 g of TsCl, the mixture was stirred overnight at room temperature under N_2. The clear solution obtained was poured into ice water containing sufficient Na_2CO_3 to keep the pH at 9.5. After repeated extractions with Et_2O, the combined organic phase was washed (H_2O), dried ($MgSO_4$), and concentrated *in vacuo*. The oily residue obtained (8.52 g) showed no OH group in the ir and no starting material on tlc. The excess weight represents some polymerized dihydropyran derivative that did not interfere with further reactions.

2α-Ethynyl-17α-trifluorovinyl-A-nor-5α-androstane-2,17β-diol (IVg).—A 2.84-g sample of the above tetrahydropyranyl ether was dissolved in 37 ml of dry THF and added during 30 min at −25° to a Grignard reagent which was prepared as follows. An ice-cold solution of 17 g of bromotrifluoroethylene in 30 ml of THF was slowly added to a flask containing 2.95 g of Mg turnings and a few crystals of I_2. After the reaction was started, addition was continued but the reaction flask was kept at −25°. When all of the bromide was added, the mixture was stirred for another 2–2.5 hr at −25° at which point the Mg had practically all disappeared. After addition of the steroid solution, the reaction mixture was stirred for another 2 hr at −25° and then allowed to come to room temperature overnight. It was worked up with ice water containing NH_4Cl, repeatedly extracted (Et_2O), washed (saturated NH_4Cl), dried ($MgSO_4$), and concentrated *in vacuo* to 3 g of a brown foam.

A 2.5-g sample of this crude product was chromatographed on 80 g of neutral alumina. From the fractions eluted with C_6H_6 containing 30% of Et_2O, there was obtained 458 mg of the desired product, and from the other fractions, 941 mg of product with the tetrahydropyranyl group partially hydrolyzed.

These two crops were combined and the protecting group was hydrolyzed by stirring for 4 hr at room temperature in 85 ml of MeOH, containing 2 ml of concentrated HCl. After conventional work-up, the product (927 mg) was chromatographed on 32 g of acid-washed alumina. Elution with 10–25% C_6H_6 gave 574 mg of crude product; crystallization from ether–petroleum ether gave 452 mg of IVg, mp 140–143°. The analytical sample had mp 143–144°. *Anal.* ($C_{22}H_{29}F_3O_2$) C, H.

2α-Ethynyl-17α-cyclopropyl-A-nor-5α-androstane-2,17β-diol (IVj).—A solution of cyclopropyllithium was prepared by adding 9 g of bromocyclopropane in 20 ml of dry ether to a suspension of 1 g of Li (cut into small pieces) in 27 ml of ether. The reaction was first allowed to proceed at room temperature; after addition was complete, the mixture was refluxed for 2 hr under N_2. This solution was added dropwise to 1 g of 2α-ethynyl-A-nor-5α-androstan-2β-ol-17-one dissolved in 100 ml of dry C_6H_6. After the addition was completed (30 min) the mixture was refluxed for 16 hr. Work-up consisted of quenching with ice water containing $NaHCO_3$, repeated extraction (Et_2O), washing (H_2O), drying, and concentrating *in vacuo* to an orange oil, 1.47 g. This crude product still showed the presence of starting material by tlc and ir.

Half of the total crude was chromatographed on 25 g of acid-washed alumina and the fractions eluted with C_6H_6 and 35–60% ether were combined to yield 270 mg of product that was homogeneous by tlc and did not show any residual carbonyl. Crystallization from ether–petroleum ether gave 178 mg of IVj, mp 136–137°. *Anal.* ($C_{23}H_{34}O_2$) C, H.

17α-Ethynyl-A-nor-5α-androstane-2β,17β-diol (IVk).—After dissolving 400 mg of 17α-ethynyl-A-nor-5α-androstan-2-one in 12 ml of dry THF, a solution of 400 mg of $NaBH_4$ in 4 ml of ice water was added dropwise with stirring and ice cooling. The mixture was then allowed to come to room temperature, stirred for another hour, ice-cooled again, and brought to pH 6.5 with saturated NaH_2PO_4. The resultant precipitate showed no ir C=O absorption. Chromatography on 34 g of Al_2O_3 gave material homogeneous by tlc from the early C_6H_6 fractions containing 10% ether and amounted to 475 mg after crystallization from petroleum ether (bp 30–60°). No other product was obtained pure. The analytical sample had mp 201–203° and $[\alpha]D$ −43.0° ($CHCl_3$). The 19-CH_3 protons were found at 55.9 Hz in the nmr spectrum *Anal.* ($C_{20}H_{30}O_2$) C, H.

2α-Methyl-A-nor-5α-androstane-2,17β-diol (IVl).—To a solution of MeLi, prepared by reaction of 75 ml (1.2 moles) of MeI in Et_2O (400 ml) with 14 g (2 g-atoms) of Li in 400 ml of Et_2O, was added a solution of 55 g (0.2 mole) of A-nor-5α-androstanolone in 400 ml of dry THF. After heating under reflux for 4 hr, the mixture was cooled, poured onto ice, and extracted (Et_2O). The extracts, after washing (H_2O), drying ($MgSO_4$), and evaporation, afforded 70 g of crude product; crystallization from 160 ml of *i*-Pr_2O gave a first crop of 40 g of pure product, mp 160–161°, $[\alpha]D$ +14.9°, $[\alpha]_{364}$ +48.5° (*c* 0.5). *Anal.* ($C_{19}H_{32}O_2$) C, H.

2β-Methyl-A-nor-5α-androstane-2,17β-diol (IVm).—On another occasion, reaction of 66 g of A-nor-5α-androstanolone in the above fashion had given directly 58.7 g of IVl. Treatment of the mother liquors with Girard's T reagent gave 2.3 g of starting ketone. Chromatography of the nonketonic mother liquors on silica gave, upon elution with 35% hexane in EtOAc, 1.2 g of IVm which was recrystallized from acetone–pentane; mp 219°, $[\alpha]D$ +11.8°, $[\alpha]_{364}$ +33.4° (*c* 0.7). *Anal.* ($C_{19}H_{32}O_2$) C, H.

2α-Methyl-A-nor-5α-androstan-2β-ol-17-one (III, R = CH_3).—A solution of 26 g of IVl in 700 ml of C_6H_6 was treated dropwise, with stirring, with 80 ml of a solution of 16 g of $Na_2Cr_2O_7$ in 68 ml of H_2O and 12 ml of concentrated H_2SO_4, added over 0.5 hr. After standing overnight, the organic phase was decanted, washed ($Na_2S_2O_3$, H_2O), and dried, and the resultant clear yellow solution evaporated. The residue was crystallized from 220 ml of MeOH and 50 ml of H_2O, giving 23.1 g of ketone, mp 194°, $[\alpha]D$ 87.2° (*c* 0.4). *Anal.* ($C_{19}H_{30}O_2$) C, H.

2β-Methyl-A-nor-5α-androstan-2α-ol-17-one.—By the above procedure, IVm was oxidized to 2β-methyl-A-nor-5α-androstan-2α-ol-17-one and recrystallized from *i*-Pr_2O, mp 202°, $[\alpha]D$ +84.9 (*c* 1.0). *Anal.* ($C_{19}H_{30}O_2$) C, H.

2α-Methyl-17α-ethynyl-A-nor-5α-androstane-2,17β-diol (IVn) (Inverse Ethynylation).—Dry acetylene was bubbled into a solution of 1 g of 2α-methyl-A-nor-5α-androstan-2β-ol-17-one

in 40 ml of dry C_6H_6 and 200 ml of dry Et_2O for 30 min. To this mixture was added dropwise within 45 min at room temperature, a freshly prepared solution of 2 g of K in 40 ml of *t*-AmOH, and the acetylene stream was maintained during this period and for another 16 hr. The reaction was worked up as usual[1] yielding 1.08 g of product that contained only a small amount of unchanged ketone. Chromatography, followed by two recrystallizations (Et_2O), yielded a first crop of 600 mg of IVn, mp 197–198°, $[\alpha]D$ −42.8° (*c* 1.0). *Anal.* ($C_{21}H_{32}O_2$) C, H.

2β-Methyl-17α-ethynyl-A-nor-5α-androstane-2α,17β-diol (IVo).—Conversion of 2β-methyl-A-nor-5α-androstan-2α-ol-17-one to IVo was carried out as above with the 2α-methyl isomer, followed by recrystallization from aqueous MeOH; mp 169–170°, $[\alpha]D$ 42.2° (*c* 1.0). *Anal.* ($C_{21}H_{32}O_2$) C, H.

2α-Propargyl-A-nor-5α-androstan-2β-ol-17-one (III, R = $CH_2CH{=}CH$).—A solution of 3 g of A-norandrostanolone (I) in 60 ml of dioxane was added to 6.1 g of Zn dust, freshly activated in the usual manner with 8 ml of 2.5 *N* HCl, then washing and drying. Half of the dioxane was removed by distillation and 84 ml of propargyl bromide was added dropwise to the remaining reaction mixture while it was kept at reflux. When the addition was completed (30 min), the mixture was cooled, poured into ice-cold dilute HCl, and extracted several times with C_6H_6. After the usual work-up, 4.68 g of a dark residue was obtained. It was dissolved in pyridine (46 ml), cooled, and added to a cold suspension of 4.6 g of CrO_3 in 46 ml of pyridine. After stirring at room temperature overnight, the usual work-up yielded 3.2 g of a dark ketonic material. Careful column chromatography on 80 g of acid-washed alumina yielded 205 mg of crystalline material from the C_6H_6–10% Et_2O fractions, that was not homogeneous, representing a mixture of isomers that could not be separated. The combined C_6H_6–15% ether fractions yielded 1.2 g of crystalline material from ether–petroleum ether representing pure 2α-propargyl-A-nor-5α-androstan-2β-ol-17-one, mp 189–190°. The analytical sample had mp 192–193°. *Anal.* ($C_{21}H_{30}O_2$) C, H.

17α-Chloroethynyl-A-nor-5α-testosterone (VIII).—To $NaNH_2$ from 314 mg of Na in 14 ml of liquid NH_3 [$Fe(NO_3)_3$] at −70°, a solution of 0.443 ml of *cis*-dichloroethylene in 1.4 ml of dry Et_2O was added in 10 min with stirring. Cooling was discontinued, the mixture was refluxed under an acetone–Dry Ice condenser for 30 min, and a solution of 920 mg of A-norandrostenedione[7] in 7 ml of THF was added within 3 min, followed by 2 hr of stirring under reflux. Careful work-up, involving addition of NH_4Cl, evaporation of NH_3, venting with N_2, and Et_2O extraction in the usual manner, yielded 985 mg of crude product. It was chromatographed on 40 g of acid-washed alumina, and the fractions eluted with C_6H_6 containing 10–30% Et_2O were combined and crystallized with petroleum ether yielding 762 mg of VIII, mp 99–103°, uv max (C_2H_5OH) 233 mμ (ε 14,000). The analytical sample had mp 102–104°, $[\alpha]D$ = −97.7° ($CHCl_3$). *Anal.* ($C_{20}H_{25}ClO_2$) C, H.

17α-Ethynyl-A-nortestosterone (IX).—A 445-mg sample of VI was dissolved in 18 ml of AcOH and treated in portions with 445 mg of Zn dust. Stirring was continued for 4 hr at room temperature; the mixture was filtered, the cake was washed (Et_2O), the filtrate was poured into ice water and extracted (Et_2O), and the extract was washed to neutrality, dried ($MgSO_4$), and concentrated. The residue was crystallized (Et_2O), yielding 370 mg of IX, mp 190–191°, uv max (C_2H_5OH) 234 mμ (ε 14,700). The analytical sample (from Et_2O) had mp 196–198°, $[\alpha]D$ −91.4° ($CHCl_3$). *Anal.* ($C_{20}H_{26}O_2$) C, H.

A-Nor-5α-pregnan-20-ol-2-one (XIII, R = H).—A 2.76-g sample of 2,3-seco-5α-pregnan-20-one-2,3-dioic acid (VII)[11,12] was dissolved in 50 ml of dioxane and 80 ml of MeOH. It was treated under ice cooling with 3 g of $NaBH_4$, and the mixture was allowed to warm to room temperature and stirred overnight under N_2. It was cooled again and treated with 110 ml of saturated NaH_2PO_4. The resultant crystalline product was filtered, dissolved in H_2O, and acidified with HCl to pH 2. The diacid (2.14 g) had mp 250–256° and was characterized by ir (absence of C=O at 5.82 μ), tlc (single spot, R_F 0.55 in $CHCl_3$ containing 10% AcOH), and by a negative dinitrophenylhydrazine test.

Cyclization of 2.14 g of the diacid was performed[16] by refluxing for 3 hr with 21 ml of Ac_2O, cooling, adding 1.37 g of anhydrous NaOAc, and refluxing for an additional 2 hr with good stirring. After cooling and filtration of the reaction mixture, the filtrate was concentrated to dryness *in vacuo* to give 2.12 g of practically homogeneous (tlc) powder, best purified as the 20-ol. This was prepared by dissolving the acetate in 20 ml of EtOH, 586 mg of NaOH, and 1.6 ml of water, and refluxing for 3 hr under N_2. After cooling the mixture, H_2O was added and the steroid was extracted (Et_2O); the extract was then dried and concentrated. Crystallization (Et_2O) yielded 1.4 g of A-nor-5α-pregnan-20-ol-2-one (XIII, R = H). The ir spectrum showed absorptions at 2.78 (OH) and 5.72 (C=O) μ; the sample was homogeneous on tlc (R_F 0.3 in C_6H_6 containing 30% Et_2O), but the broad melting range indicated a mixture of isomers at C-20.

For further characterization, a sample was oxidized with CrO_3–pyridine, to the known[5] A-norpregnane-2,20-dione. The dione had mp 176–177° (lit.[5] mp 177–179°). The ir spectrum showed C=O at 5.72 and 5.85 μ, but no OH; $[\alpha]D$ +249.2° ($CHCl_3$) (lit.[5] +255°).

2α-Ethynyl-A-nor-5α-pregnan-2β-ol-20-one (XV).—A 600-mg sample of XIII (R = H) was azeodried in 17 ml of C_6H_6, 17 ml of THF was added, and this solution was added dropwise over 1 hr to a mixture of 515 mg of K, 15 ml of *t*-AmOH, and 40 ml of THF which was saturated with acetylene, as described before. After addition of the steroid, the acetylene was kept slowly bubbling through the mixture overnight. The usual work-up gave 600 mg of product consisting mainly of the desired XIV, contaminated with unreacted starting material. This total crude product was oxidized in a pyridine solution (6 ml) with 600 mg of CrO_3 and 6 ml of cold pyridine in the usual manner. Upon work-up 525 mg of a crude ketone was obtained and immediately chromatographed on 12.5 g of acid-washed alumina. The fractions eluted with C_6H_6 proved to be homogeneous on tlc; they were combined and crystallized from ether–petroleum ether, yielding 233 mg of XV, mp 216–220°, $[\alpha]D$ +96°. The stereochemistry at C-2 was assigned as α-ethynyl, based on the chemical shift on the C-19 protons (55.2 Hz) and in analogy without previous findings. The analytical sample had mp 219–221°. *Anal.* ($C_{22}H_{32}O_2$) C, H.

17α-Ethynyl-A-nor-5α-androstan-17α-ol-2-one (VIb).—A solution of 5.6 g of K in 85 ml of *t*-AmOH was added to 400 ml of Et_2O along with a solution of 7 g of 2,2-ethylenedioxy-A-nor-5α-androstan-17-one (V)[8] in 20 ml of C_6H_6. The mixture was saturated with acetylene in the fashion of the Stavely ethynylation conditions. After the usual work-up, 7.0 g of crude product was obtained. A solution of 0.77 g of this material in 10 ml of HOAc and 5 ml of H_2O was heated under reflux for 30 min to give 0.55 g of pure product. Recrystallization from aqueous HOAc gave an analytical sample: mp 260°, $[\alpha]^{22}_{578}$ +100.3°, $[\alpha]^{22}_{364}$ +81.3° (*c* 1.15). *Anal.* ($C_{20}H_{28}O_2$) C, H.

17,17a-Dimethyl-18-nor-D-homo-A-nor-5α-androsta-13,15,17-(17a)-trien-2-one (XVI).—A solution of 1 g of VIb in 14 ml of HCO_2H with a crystal of *p*-toluenesulfonic acid was heated under reflux for 1 hr, cooled, and treated with 3 ml of H_2O. The crystalline product was isolated by filtration and washed with aqueous HCO_2H, and 650 mg of yellow product was obtained, mp 150–165°, recrystallized from EtOH, giving a pure product, mp 177–178°, $[\alpha]D$ +84° (*c* 0.62). *Anal.* ($C_{20}H_{26}O$) C, H.

2α-Ethynyl-17,17a-dimethyl-18-nor-D-homo-A-nor-5α-androsta-13,15,17(17a)-trien-2β-ol (XVII).—A solution of 0.9 g of XVI in 15 ml of dry THF was added dropwise, with stirring, to a solution of 2.5 g of lithium acetylide–ethylene diamine complex in 25 ml of DMSO under N_2. After addition, stirring was maintained for another 2 hr, the mixture then was treated carefully with saturated NH_4Cl, extracted (Et_2O), dried, and evaporated to give 854 mg of crude product. Chromatography on 40 g of alumina with 30% Et_2O in C_6H_6 gave, after elution of a small amount of XVI, 460 mg of ethynylated product. Pure XVII was obtained upon recrystallization from aqueous dimethoxyethane; mp 148°, $[\alpha]D$ −41° (*c* 0.92). *Anal.* ($C_{22}H_{28}O$) C, H.

17α-Ethyl-A-nor-5α-androstan-17β-ol-2-one (VIc).—A mixture of 1.5 g of ketol VIb and 300 mg of 5% Pd–C in 30 ml of EtOH was hydrogenated at atmospheric pressure; the theoretical amount of H_2 was absorbed in 30 min. After filtration, the filtrate was heated to boiling and treated with H_2O; 1.03 g of a heavily solvated crystalline product was obtained, mp 147–149°, $[\alpha]D$ +136.5° (*c* 1.0). *Anal.* ($C_{20}H_{32}O_2$) C, H.

2α-Ethynyl-17α-ethyl-A-nor-5α-androstane-2β,17β-diol (IIb).—A solution of 0.8 g of VIc in 8 ml of dry THF was added dropwise to a homogeneous solution of 6 g of lithium acetylide–ethylenediamine complex in 30 ml of dry DMSO under N_2. Stirring was maintained for 2 hr after addition was complete, and the mixture was then carefully treated with saturated aqueous NH_4Cl and extracted (Et_2O). A resinous product was

(16) Method of Dr. George Gal, Merck and Co., Inc., Rahway, N. J. (personal communication).

obtained which solidified. A $CHCl_3$ solution, upon standing for a few hours, afforded 300 mg of a crystalline product, mp 151–154°. Chromatography of the mother liquors (400 mg) on 12 g of alumina with eluents ranging from 30% Et_2O in C_6H_6 to pure Et_2O furnished an additional 230 mg of the same material, heavily solvated with $CHCl_3$; yield 60%, mp 154°, $[\alpha]D^{24}$ +9° (*c* 1.5). *Anal.* ($C_{22}H_{34}O_2$) C, H.

17,17-Dimethyl-18-nor-A-nor-5α-androst-13-en-2-one (XVIII).—A solution of 5 g of VIa[5] in 50 ml of HCO_2H was allowed to stand overnight at room temperature. After addition of a little H_2O, the solution was heated for 15 min on the steam bath. Addition of more H_2O precipitated 3.43 g of product which was recrystallized from hexane, giving a first crop of 1.4 g, mp 115°. The mother liquors were filtered through a short alumina column and the crystalline material obtained was recrystallized from hexane; mp 115°, $[\alpha]^{22}_{578}$ +127.6°, $[\alpha]^{22}_{364}$ +955° (*c* 1.03). *Anal.* ($C_{19}H_{28}O$) C, H.

2α-Ethynyl-17,17-dimethyl-18-nor-A-norandrost-13-en-2β-ol (XIX).—To a solution of 1.4 g of lithium acetylide–ethylenediamine complex in 10 ml of dry DMSO was added dropwise a solution of 0.8 g of 17,17-dimethyl-18-nor-A-nor-5α-androst-13-en-2-one in 20 ml of dry THF, with stirring under N_2. Stirring was maintained for 3.5 hr after addition was complete, and the reaction was then worked up in the usual manner (*vide supra*) to give 0.86 g of resin which still possessed ketone. Treatment with Girard's T reagent removed the starting material and gave 400 mg of ethynylcarbinol which was recrystallized twice from aqueous MeOH to give 290 mg of XIX. Drying under reduced pressure removed solvent of crystallization to give an analytical sample, mp 85°, $[\alpha]^{22}D$ +1.4°, $[\alpha]^{22}_{364}$ +17° (*c* 0.72). *Anal.* ($C_{21}H_{30}O$) C, H.

Acknowledgment.—The authors wish to express their appreciation to Dr. A. A. Patchett (Rahway) for his continued interest and many helpful discussions.

Antiandrogenic and Progestational Activity of Some 17-Oxygenated 15-Dehydro Steroids

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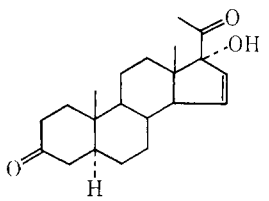
Received October 10, 1968

The synthesis of a group of steroids related to 17α-hydroxy-15-dehydroprogesterone is described. Several of these compounds exhibited moderate antiandrogenic activity by subcutaneous administration in castrate rats. A few 17α-acetoxy-15-dehydroprogesterones showed slight progestational activity when injected intramuscularly in rabbits.

Although the great interest in enhancement of progestational activity has led to numerous modifications of the steroid molecule,[2] relatively little is known about the effect of such structural modifications on the antiandrogenic activity. Introduction of a methyl or chloro substituent and/or unsaturation at C-6,[3] as well as a 1,2α-cyclomethylene moiety[4] in the 17-oxygenated progesterone molecule have been among the major structural changes leading to compounds with increased antiandrogenic activity.

The preparation of 16-unsubstituted 17α-hydroxy-15-pregnen-20-ones from the corresponding 16-pregnen-20-ones was recently reported from these laboratories.[5] Biological evaluation of several of the 17α-hydroxy-15-pregnen-20-ones revealed antiandrogenic activity in castrate rats treated with testosterone. The two most active compounds among the 16-unsubstituted 15-dehydropregnanes were found to be **1** and **2a**. In an attempt



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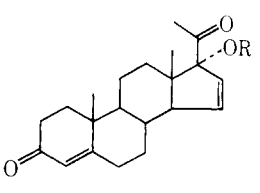
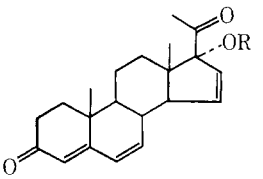


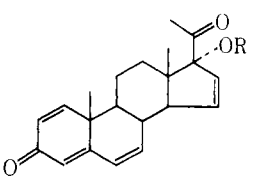
2a, R = H
b, R = $COCH_3$

to prepare 15-dehydro steroids with increased antiandrogenic activity, we set out to synthesize dehydrogenated derivatives of **2** as well as simple modified structures related to the 5α,15-dehydro steroid **1**.

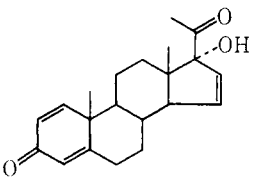
Dehydrogenation of **2a** with chloranil gave **3a**, which



3a, R = H
b, R = $COCH_3$



4a, R = H
b, R = $COCH_3$



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was then converted with 2,3-dichloro-4,5-dicyanobenzoquinone (DDQ) into **4a**. When **2** was treated with DDQ directly, the 1,4,15-triene **5** was obtained. Similarly the 17-acetate **2b** was converted into **3b**, which then afforded **4b**. When **4a** was allowed to react with a large excess of diazomethane, the pyrazoline **6** was isolated in low yield. The conversion of the 1α,2α-(4′,3′,1′-pyrazolino)-4,6-dien-3-one system to the corresponding 1,2α-cyclomethylene-4,6-dien-3-one has been effected by pyrolysis[6] or by treatment with acid.[7] When **6** was subjected to either of these procedures none of the desired **7** was obtained. Treatment of **4a** with dimethylsulfoxonium

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