

## Steroids. CCV.<sup>1</sup> Ring A Modified Hormone Analogs. Part I. Some Ring A Olefins

A. BOWERS, A. D. CROSS, J. A. EDWARDS, H. CARPIO, M. C. CALZADA, AND E. DENOT

*Research Laboratories, Syntex, S.A., Apartado 2679, Mexico, D.F., Mexico*

*Received July 30, 1962*

A number of general requirements necessary for steroid hormones to exhibit biological activity are discussed. The importance of steroid-protein interactions is noted and it is proposed that the biological activity of "non-classical" androstanes is reflected in their electron density pattern in ring A. The preparation and androgenic-myotrophic activities of some  $\Delta^1$ ,  $\Delta^2$ ,  $\Delta^3$  and  $\Delta^4$  C-3-deoxy androstanes is described and the importance of  $sp^2$  hybridization at C-2 and C-3 is discussed.

During the last decade the major efforts of steroid chemists have been concerned with modifying the structures of the naturally occurring hormones testosterone, progesterone and hydrocortisone. The rationale behind these tremendous efforts lay in the idea that it should be possible to increase selectively certain parameters of biological activity of the parent hormone and reduce or leave unchanged the less desirable types of activity. It was never clear, however, whether or not a clean separation of the various biological activities of a given hormone was theoretically feasible. Nevertheless a considerable measure of success has been realized in the fields of modified androgens, progestational agents and cortical hormones by following this strictly empirical approach.

Until very recently, all of the successful work along these lines was concerned with the introduction of new functional groups into the naturally occurring hormones. In particular, notable successes were realized by the introduction of methyl and hydroxyl groups, halogen atoms or new centers of unsaturation in key positions throughout the molecule.<sup>2</sup> In 1959, however, it was found that a basic structural feature common to all steroid hormones, namely, an oxygen atom at C-3, was not necessary for biological activity.<sup>3,4</sup> Shortly afterwards other biologically active androstanes lacking a C-3 oxygen atom were reported.<sup>5-7</sup>

These results which showed that "non-classical" structures were biologically active led us to consider what information was available or could be deduced with respect to the requirements for biological activity, and prior to defining the objectives of the program outlined in this and the following five papers, an attempt will be made to put into perspective the present state of our knowledge concerning the general requirements for biological activity of steroid hormones.

**General Requirements for Biological Activity.**—Although little is known about the mechanism of action of steroid hormones at the cellular level, one may rati-

alize that the structure of an active hormone must meet certain basic requirements such as:

(1) Its structure should be compatible with the requirements for efficient transport to the target organ. This is very probably directly related to its ability to bind to plasma proteins.<sup>8</sup>

(2) It should have a reasonable half-life so that its metabolic breakdown by oxidative or reductive processes is not so rapid that it is prevented from exercising its hormonal action at the target organ. The deactivation of structurally sensitive hormones is very probably directly related to their degree of binding with plasma proteins.<sup>8</sup>

(3) Having reached the target organ the steroid hormone has to exert chemical control over one or more metabolic reactions either by its effect on enzyme processes,<sup>10</sup> or by altering the permeability of the cell membrane or the membrane around the mitochondria or some other sub-cellular structures.

The requisites may very well have different structural requirements and it is probable that biological activity is only observed in compounds where these structural features overlap.

With this background and the tenet that some form of interaction of steroid hormones with a biological structure involving proteins is a necessary prerequisite for a compound to be an active hormone, a program was initiated to explore the biological activity of a variety of  $17\beta$ -hydroxy androstanes which lacked a C-3 oxygen atom but which retained a center of unsaturation in Ring A.

Our basic concept was to vary the electron density pattern in and around Ring A, since in conjunction with steric properties the electron density pattern should be related to the ability to bond to protein-like struc-

(8) The true significance of the binding of steroid hormones to plasma proteins is not yet clear. For many years it has been considered that the transport of steroids in blood involved prior association with plasma proteins. However, it has been pointed out<sup>9</sup> that although this concept is probably valid for constituents which are insoluble in blood unless they are bound to plasma proteins such a limitation does not apply to steroid hormones at physiological concentrations. It is not unlikely that the relative strength of binding of steroid hormones to plasma proteins may have a regulating influence on the availability of the hormones to target tissues. Thus the equilibrium between bound and unbound hormones may be part of the control mechanism of hormone activity and it may well be that the unbound portion of the steroid hormone represents the active fraction available to the cellular membrane.<sup>9</sup>

(9) For authoritative discussions of the biological significance of steroid-protein binding cf. U. Westphal, "Mechanism of Action of Steroid Hormones," edited by C. A. Villee and L. L. Engel, Pergamon Press, 1961, pp. 33-89, and H. N. Antoniades "Hormones in Human Plasma," Little Brown and Co., Boston, Mass., 1960, pp. 456-477.

(10) For detailed speculation as to how steroid hormones can affect enzyme processes at a target organ cf. "Mechanism of Action of Steroid Hormones" edited by C. A. Villee and L. L. Engel, Pergamon Press, 1961, particularly the articles by L. L. Engel, C. A. Villee and R. I. Dorfman.

(1) Steroids CCIV. P. Crabbé, *Tetrahedron*, in press.

(2) For recent summaries cf., (a) L. F. Fieser and M. Fieser "Steroids," Reinhold Publishing Corp., New York, N. Y. 1959, chapters 17, 18 and 19; (b) H. J. Ringold and A. Bowers, "Comprehensive Biochemistry," Vol. 2, edited by E. H. Stotz, Elsevier Publishing Co., Houston, Texas, in press, 1962.

(3) M. S. de Winter, C. M. Siegmann and S. A. Szpilfogel, *Chem. Ind. (London)*, 905 (1959).

(4) N. E. Borglin, *Acta Endocrinologica*, Supplementum LVIII (1960).

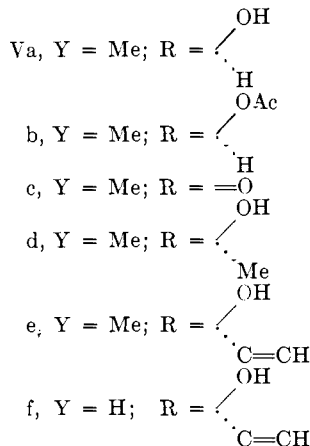
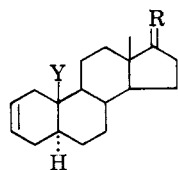
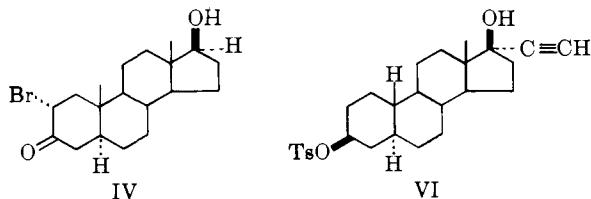
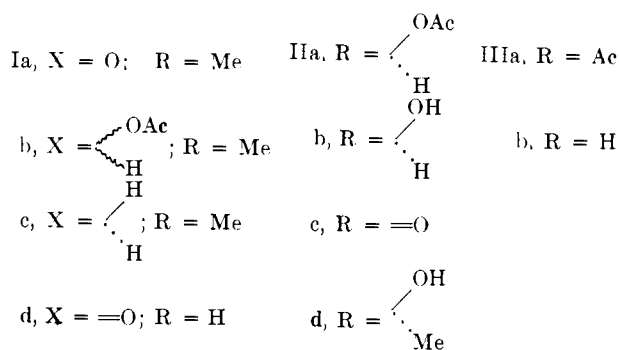
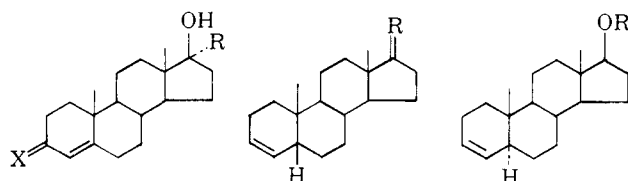
(5) R. O. Clinton, A. J. Manson, F. W. Stonner, A. L. Beyler, G. O. Potts and A. J. Arnold, *J. Am. Chem. Soc.*, **81**, 1513 (1959); R. O. Clinton, *et al.*, *ibid.*, **83**, 1478 (1961).

(6) J. A. Zderic, O. Halpern, H. Carpio, A. Ruiz, D. C. Limón, L. Magaña, H. Jinnémez, A. Bowers and H. J. Ringold, *Chem. Ind. (London)*, 1625 (1960).

(7) R. O. Clinton, A. J. Manson, F. W. Stonner, A. L. Beyler, R. G. Christiansen, G. O. Potts and A. Arnold, *J. Org. Chem.*, **26**, 279 (1961).

tures, for example, to charged subsites of enzymatic active centers.<sup>11</sup> This paper describes the preparation of some  $\Delta^1$ ,  $\Delta^2$ ,  $\Delta^3$  and  $\Delta^4$  C-3 deoxyandrostanes<sup>12</sup> and the importance of  $sp^2$  hybridization at C-2 and C-3 for myotrophic activity.

The progestational activity noted<sup>4</sup> for some  $17\alpha$ -alkyl and alkynyl-19-nor- $\Delta^4$ -androstene- $17\beta$ -ols prompted us to prepare the 3-deoxy analog of  $17\alpha$ -methyltestosterone to determine whether the results observed in the 19-nor series could be extended to other hormonal types. Clearly, it was also important to evaluate the biological activity of other ring A olefins.



Reduction of  $17\alpha$ -methyltestosterone (Ia) with lithium aluminum hydride and acetylation with acetic anhydride and pyridine gave a mixture ( $3\alpha$  and  $3\beta$ ) of allylic acetates (Ib) which was treated according to Hallsworth, Henbest and Wrigley's procedure<sup>13</sup> with lithium in ethylamine to afford  $17\alpha$ -methyl- $\Delta^4$ -androstene- $17\beta$ -ol (Ic).

A plausible approach to  $\Delta^3$ -androstene- $17\beta$ -ol (IIIb) appeared to be *via* the Wolff-Kishner reduction of testosterone (Id) since Jeger<sup>14</sup> showed that  $\Delta^4$ -cholestene-3-one underwent Wolff-Kishner reduction to afford a complex mixture of products including  $\Delta^3$ -cholestene in 25% yield. Djerassi and Fishman<sup>15</sup> also reported that a similar reduction of  $\Delta^4$ -22a-spirostene-3-one led to a mixture of six products from which it was possible to isolate both the corresponding  $5\alpha$ - and  $5\beta$ - $\Delta^3$ -olefins.

Wolff-Kishner reduction of testosterone (Id) produced an inseparable mixture of products. Acetylation of this mixture followed by alumina chromatography readily furnished pure  $\Delta^3$ - $5\beta$ -androstene- $17\beta$ -ol acetate (IIa).<sup>16</sup> Mild alkaline hydrolysis of this acetate gave the  $17\beta$ -alcohol (IIb) which then was oxidized to the ketone (IIc). Treatment of the latter with methylmagnesium bromide furnished  $17\alpha$ -methyl- $\Delta^3$ - $5\beta$ -androstene- $17\beta$ -ol (IIc).

After the completion of this work a brief publication by Crastes de Paulet and Bascoul<sup>17</sup> recorded the Wolff-Kishner reduction of testosterone, by the more vigorous conditions developed by Barton and co-workers,<sup>18</sup> to afford a separable mixture (after acetylation) of  $\Delta^2$ - $5\alpha$ - and  $\Delta^3$ - $5\beta$ -androstene- $17\beta$ -ol acetates.

In our hands the most convenient approach to  $\Delta^3$ - $5\alpha$ -androstene- $17\beta$ -ol acetate (IIIa) involved the treatment of testosterone with a very large excess of zinc in acetic acid as described by McKenna, Norymberski and Stubbs.<sup>19</sup> Reductive cleavage of the acetate by lithium aluminum hydride led to the corresponding alcohol (IIIb).

Borohydride reduction of  $2\alpha$ -bromodihydrotestosterone<sup>20</sup> (IV), then subjection of the crude reaction product to the action of zinc and acetic acid, and alkaline methanol, furnished  $\Delta^2$ -androstene- $17\beta$ -ol (Va). Acetylation then led to the  $17\beta$ -acetate (Vb), while oxidation<sup>21</sup> gave the corresponding  $17$ -ketone (Vc).<sup>22</sup> With methyl- and ethynylmagnesium bromides and this ketone there resulted  $17\alpha$ -methyl- $\Delta^2$ -androstene- $17\beta$ -ol (Vd) and  $17\alpha$ -ethynyl- $\Delta^2$ -androstene- $17\beta$ -ol (Ve), respectively. The 19-nor analog (Vf) of the latter product was arrived at from  $17\alpha$ -ethynyl-19-norandro-

(13) A. S. Hallsworth, H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 1969 (1957).

(14) O. Jeger, *Helv. Chim. Acta*, **32**, 1825 (1949).

(15) C. Djerassi and J. Fishman, *J. Am. Chem. Soc.*, **77**, 4291 (1955).

(16) Extensive rechromatography of impure fractions yielded considerable quantities of non-crystalline material but it was not possible to isolate any pure  $\Delta^3$ - $5\alpha$ -androstene- $17\beta$ -ol acetate (IIIa).

(17) A. Crastes de Paulet and J. Bascoul, *Bull. Soc. Chim.*, 442 (1961).

(18) D. H. R. Barton, D. A. J. Ives and B. R. Thomas, *J. Chem. Soc.*, 2056 (1955).

(19) J. McKenna, J. K. Norymberski and R. D. Stubbs, *ibid.*, 2502 (1959).

(20) C. Djerassi, *J. Org. Chem.*, **12**, 823 (1947).

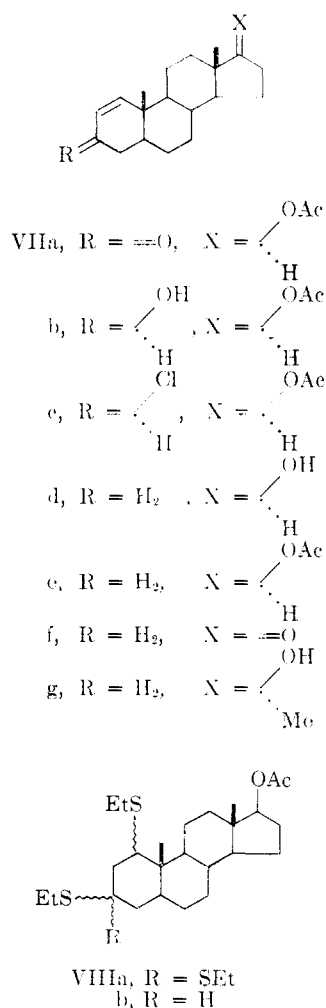
(21) K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(22) J. Iriarte, G. Rosenkranz and F. Sondheimer, *J. Org. Chem.*, **20**, 542 (1955), described the preparation of this compound by an alternate procedure which does not preclude the possibility that the product is admixed with small amounts of the corresponding  $\Delta^3$ -isomer. In this connection cf. I. Malunowicz, J. Fajkos and F. Sorm, *Coll. Czech. Comm.*, **25**, 1359 (1960).

(11) For a theoretical treatment of the bonding of unsaturated molecules to proteins, cf. K. Ohki, *Z. Vitamin-Hormon-u., Fermentforsch.*, **8**, 111 (1956).

(12) For a preliminary communication describing a part of this work, cf. J. A. Edwards and A. Bowers, *Chem. Ind.* (London), 1962 (1961).

stane-3 $\beta$ ,17 $\beta$ -diol<sup>23</sup> by a sodium acetate in acetic anhydride elimination reaction upon the intermediate 3 $\beta$ -tosylate (VI).<sup>24</sup>



For the preparation of  $\Delta^1$ -androstenes,  $\Delta^1$ -5 $\alpha$ -androstene-3-one-17 $\beta$ -ol acetate (VIIa)<sup>25</sup> was reduced by lithium tri-*t*-butoxy aluminum hydride<sup>26</sup> to  $\Delta^1$ -5 $\alpha$ -androstene-3 $\beta$ -17 $\beta$ -diol-17-acetate (VIIb),<sup>27</sup> which with thionyl chloride in benzene solution yielded a mixture of the desired 3 $\beta$ -chloro- $\Delta^1$ -5 $\alpha$ -androstene-17 $\beta$ -ol acetate (VIIc) and a small amount of a halogen-free compound. Separation of the  $\Delta^1$ -3 $\beta$ -chloro derivative (VIIc) was not attempted; instead the mixture was subjected to reductive dehalogenation by lithium aluminum hydride in ether.<sup>28</sup> Chromatography then allowed the separation of pure  $\Delta^1$ -androstene-17 $\beta$ -ol (VIId) from the unwanted inert by-product.<sup>29,30</sup> Acetylation and oxidation,<sup>21</sup> respectively, of  $\Delta^1$ -androstene-17 $\beta$ -ol led to the 17 $\beta$ -acetate (VIIe) and 17-ketone (VIIf). From treatment of the latter with

methylmagnesium bromide there was obtained 17 $\alpha$ -methyl- $\Delta^1$ -5 $\alpha$ -androstene-17 $\beta$ -ol (VIIg).

In an earlier, abortive attempt to acquire the  $\Delta^1$ -5 $\alpha$ -androstenes ethanethiol was condensed with  $\Delta^1$ -5 $\alpha$ -androstene-3-one-17 $\beta$ -ol acetate<sup>25</sup> (VIIa) in the presence of boron trifluoride and the crystalline product was treated with partly deactivated Raney nickel to effect desulfurization without concomitant sequestration of the  $\Delta^1$ -double bond.<sup>31</sup> However, the final product still contained a high percentage of sulfur. Nuclear magnetic resonance (n.m.r.) spectra revealed the structures of the compounds, before and after the Raney nickel treatment, as (VIIIa) and (VIIIb), respectively.<sup>32</sup>

The appearance of a triplet (*J*, 7.3 c. s.) at 8.65, 8.78, and 8.89  $\tau$  equivalent to nine protons indicated the presence in the ethanethiol condensate (VIIa) of three equivalent methyl groups in the environment  $\text{CH}_3\text{CH}_2\text{---S---}$ . A characteristic quartet centered at 7.54  $\tau$  with a little more underlying absorption, totalling approximately seven protons, agreed with three methylenes as in  $\text{CH}_3\text{CH}_2\text{S}$  plus an extra proton on carbon bearing sulfur. Thus it appears that a 1,4 addition of ethane thiol to the  $\Delta^1$ -3-ketone (VIIa) precedes condensation of two further molecules of the thiol at C-3. Ample precedent for this reaction has been established.<sup>33</sup> The absence of olefinic proton resonances from the n.m.r. spectrum of VIIa supports this conclusion. After partial desulfurization only six methyl protons corresponding to  $\text{CH}_3\text{CH}_2\text{S}$  remain in the product. Six protons in the environment  $\text{H---C---S}$  also appear in the n.m.r. spectrum, the major part of this resonance again being in the form of a quartet typical of an ethyl methylene group.<sup>35</sup> That six and not four protons remain attached to carbon bearing sulfur militates for the proposed structure (VIIIb) rather than the isomeric 3 $\alpha$ ,3 $\beta$ -diethylthio compound.

In Table I are collected optical rotation and infrared absorption data of some  $\Delta^1$ ,  $\Delta^2$ ,  $\Delta^3$  and  $\Delta^4$  androstenes. These data may be compared with those of the analogous cholestenes.<sup>36</sup> Alone they do not permit a differentiation of double bond position, whereas the n.m.r. spectra are completely diagnostic.<sup>37</sup>

(29) Thionyl chloride-benzene has been employed previously to substitute the hydroxyl of  $\Delta^1$ -cholestene-3 $\beta$ -ol by chlorine, but no second product corresponding to ours is mentioned in the literature.<sup>28</sup> ( cursory examination of this unknown product revealed the absence of hydroxyl groups, and of strong ultraviolet absorption, and a resistance to attack by aluminum hydride ion.)

(30) Ultraviolet spectral examination of the crude reduction product revealed no trace of diene contaminants formed through an elimination reaction, as is recorded for the analogous reaction in the preparation of  $\Delta^1$ -cholestene.<sup>28</sup>

(31) G. B. Spero, A. V. McIntosh and R. H. Levin, *J. Am. Chem. Soc.*, **70**, 1907 (1948).

(32) N.m.r. spectra were obtained for purified chloroform solutions at 60 Mc, using tetramethylsilane as an internal reference standard. Chemical shifts are quoted as  $\tau$  values.<sup>32</sup> A. D. C. thanks the Universidad Nacional Autónoma de México and Prof. A. Sandoval for time on the Varian A-60 spectrometer.

(33) G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

(34) P. Striebel and Ch. Trömm, *Helv. Chim. Acta*, **37**, 1094 (1954); Pl. A. Plattner, A. Fürst and H. Els, *ibid.*, **37**, 1399 (1954); J. Roubé, M. Rouéro, C. Dienassi and G. Rosenkranz, *J. Am. Chem. Soc.*, **73**, 1528 (1951).

(35)  $\tau$  values for these protons correspond closely to those quoted for the triethio structure (VIIIa). For characteristic proton resonance frequencies see L. M. Zuckerman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, chapter IV.

(36) Cf. L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp. 253 and 277.

(37) A discussion of the n.m.r. spectra of these ring A androstenes and of their long-range shielding effects will be presented elsewhere by A. D. Cross, forthcoming publication.

(23) A. Bowers, II, J. Ringold and E. Denot, *J. Am. Chem. Soc.*, **80**, 6115 (1958).

(24) This method of preparation<sup>22</sup> does not preclude that VI is contaminated with small amounts of the corresponding  $\Delta^2$ -isomer although it behaved in every way as a pure compound.

(25) A. Bittenandt and H. Dannenberg, *Ber.*, **73**, 206 (1940).

(26) H. C. Brown and R. F. McFarlin, *J. Am. Chem. Soc.*, **80**, 5372 (1958).

(27) The homogeneity of this allylic 3 $\beta$ -alcohol was established by gas chromatography. Reoxidation furnished the enone (VIIa). Earlier experiments demonstrated that sodium borohydride gives a mixture of 3 products (gas chromatogram) of which the  $\Delta^1$ -3 $\beta$ -alcohol (VIIb) constituted 90-92%.

(28) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 3289 (1956).

TABLE I  
ROTATIONS, AND =C—H DEFORMATION FREQUENCIES  
(FOR SOLID PHASE SPECTRA) OF SOME 5 $\alpha$ -ANDROSTENES

Double bond position	—17 $\beta$ -Hydroxy-androstenes—		—17 $\beta$ -Hydroxy-17 $\alpha$ -methyl-androstenes		=C—H Deformation frequency, cm. <sup>-1</sup>
	[ $\alpha$ ] <sub>D</sub> <sup>o</sup>	[M] <sub>D</sub> <sup>o</sup>	[ $\alpha$ ] <sub>D</sub> <sup>o</sup>	[M] <sub>D</sub> <sup>o</sup>	
$\Delta^1$	+25	+68	$\pm 0$	+0	663
$\Delta^2$	+55	+151	+47	+129	663
$\Delta^3$	+50	+137	..	..	668 <sup>38</sup>
$\Delta^4$	+59	+162	+59	+162	815

**Biological Activities.**—The compounds were assayed<sup>40</sup> in the immature castrate male rat (21–23 days of age) by daily injection for 7 days. For the oral assays the rats were gavaged once daily for 10 days. In both assays the animals were autopsied 24 hr. after the last treatment and androgenic and anabolic (myotrophic) activities of the steroids were calculated on the basis of the weights of the seminal vesicles, ventral prostates and levator ani muscles.<sup>40</sup> Testosterone and 17 $\alpha$ -methyl-testosterone were always used as the standards for the subcutaneous and oral routes of administration, respectively.

Table II summarizes our preliminary biological findings.<sup>41</sup> These should only be considered as approximations. A detailed study of the biological activities of some of the compounds reported in this and the following four papers, together with a statistical evaluation, will be reported at a later date by Dr. R. Dorfman and his colleagues.

It can be seen that the  $\Delta^1$ ,  $\Delta^2$  and  $\Delta^3$  olefins all exhibit reasonable anabolic activity, the anabolic androgenic ratio being more favorable in the latter two compounds. The  $\Delta^4$ -olefin exhibited only very weak activity, and  $\Delta^3$ -5 $\beta$ -androstene-17 $\beta$ -ol (IIb) was inactive at a daily dose level of 3.0 mg.

TABLE II  
RING A OLEFINS OF 5 $\alpha$ -ANDROSTANE-17 $\beta$ -OL  
BY SUBCUTANEOUS ADMINISTRATION  
(ACTIVITY OF TESTOSTERONE = 1.0)

Unsaturation in ring A	Androgenic	Anabolic
$\Delta^1$	0.35	1.0
$\Delta^2$	0.5	1.5
$\Delta^3$	0.4	0.8
$\Delta^4$	0.1	0.1

The influence of a 17 $\alpha$ -methyl group was particularly marked in the case of the  $\Delta^2$ -olefin. 17 $\alpha$ -Methyl- $\Delta^2$ -androstene-17 $\beta$ -ol in the oral assay had approximately 0.5 times the androgenic and 2.0 times the anabolic activity of methyltestosterone.

From the results outlined above, from those given in the succeeding four papers, and from those published elsewhere<sup>3–7</sup> it may be concluded that a high electron

density at C<sub>2</sub> and/or C<sub>3</sub> in 17 $\beta$ -hydroxyandrostane is a factor strongly promoting high myotrophic activity. Prior to the discovery of the biologically active C-3-desoxy-steroids<sup>3</sup> this structural requirement was always satisfied by a C-3-carbonyl or oxidizable C-3-hydroxyl group. The desired structural feature may now be defined more broadly to include all 17 $\beta$ -hydroxyandrostanes which have a high electron density in or near the C<sub>2</sub> and C<sub>3</sub> positions. This definition includes compounds such as C-3 alcohols which can undergo transformation to such a system by oxidation. In view of the activity of olefins as well as ketones it is pertinent to note that C-3-ketones may be active primarily as enols or enolate anions where a  $\Delta^2\pi$  bond is present.

Furthermore, introduction of more than one sp<sup>2</sup> hybridized carbon atom into ring A results in a pronounced flattening of the ring from a cyclohexane chair form to a more planar conformation in which the steroid may be better able to rest on a receptor surface with a concomitant increase in the degree of orbital overlap.

### Experimental<sup>42</sup>

**17 $\alpha$ -Methyl- $\Delta^4$ -androstene-17 $\beta$ -ol (Ic).**—Sodium borohydride (3.0 g.) in water (5 ml.) and tetrahydrofuran (30 ml.) was added dropwise to a solution of 17 $\alpha$ -methyltestosterone (Ia) (3.0 g., m.p. 163–164°) in tetrahydrofuran (300 ml.). After the addition was complete the solution was kept (1.5 hr.) and then diluted with 200 ml. of ice-water. The precipitate was collected, washed with water until neutral, and dried, to afford a product (2.79 g.), m.p. 155–160°. A solution of this product in 10 ml. of pyridine and 5 ml. of acetic anhydride, was kept 0.75 hr. at room temperature before being poured into water. Ethyl acetate extracts of the aqueous mixture were washed with dilute hydrochloric acid and with water, dried, and evaporated to leave a residue which was treated immediately with a solution of 1 g. of lithium in 25 ml. of ethylamine for 20 min. at 10°. This mixture then was poured into dilute hydrochloric acid and the precipitate filtered off and washed to furnish 1.56 g. of a solid, m.p. 158–184°, which by purification through chromatography over alumina (Grade III), and elution with benzene, afforded 410 mg. of 17 $\alpha$ -methyl- $\Delta^4$ -androstene-17 $\beta$ -ol (Ic), m.p. 114–117°, raised by several recrystallizations from methanol-water to 119–121°, [ $\alpha$ ]<sub>D</sub> +59°,  $\nu_{\max}$  3360 (s) and 815 cm.<sup>-1</sup> (m).

*Anal.* Calcd. for C<sub>20</sub>H<sub>32</sub>O: C, 83.27; H, 11.18; O, 5.55. Found: C, 82.92; H, 10.88; O, 5.76.

**Wolf-Kishner Reduction of Testosterone.**—A solution of 20 g. of testosterone in 1 l. of ethylene glycol and 20 ml. of hydrazine hydrate was heated under reflux (1 hr.), cooled to 70°, and a solution of 20 g. of sodium in 200 ml. of ethylene glycol then was added. The reaction mixture was distilled until a still-head temperature of 210° was obtained and then kept under reflux during 12 hr. After concentration to half volume the reaction solution was poured into 3 l. of water. Filtration furnished 18.9 g. of amorphous solid, m.p. 110–120°, demonstrably a mixture by chromatography on paper, but affording no pure component through alumina chromatography.

The crude product (18.8 g.) was treated at room temperature with 50 ml. of pyridine and 10 ml. of acetic anhydride during 24 hr. Dilution with 1.5 l. of ice-cold 10% hydrochloric acid precipitated a solid which was collected, washed and dried (18.55 g.) prior to chromatography over 2.5 kg. of alumina (Grade III). Hexane-benzene (5:1) elution removed from the alumina 4.5 g. of  $\Delta^3$ -5 $\beta$ -androstene-17 $\beta$ -ol acetate (IIa) as prisms from methylene chloride and ethyl acetate, m.p. 144–145°,

(38) For characteristic infrared absorption frequencies of substituted olefins see A. D. Cross, "An Introduction to Practical Infrared Spectroscopy," Butterworths, London, 1960, p. 58.

(39) Reported,<sup>19</sup> [ $\alpha$ ]<sub>D</sub> +145°,  $\nu_{\max}$  669 cm.<sup>-1</sup>.

(40) L. G. Hershberger, E. G. Shipley and R. K. Meyer, *Proc. Soc. Exptl. Med.*, **83**, 175 (1953).

(41) The bio-assays were carried out by Dr. R. Dorfman at the Worcester Foundation, Shrewsbury, Mass., or by Dr. E. G. Shipley, Endocrine Laboratories, Madison, Wisconsin.

(42) All rotations are for chloroform solutions, ultraviolet spectra for ethanol solutions, and infrared spectra for KBr disks, except where stated otherwise. Microanalyses are by Midwest Micro Laboratories, Indianapolis 20, Indiana, or by Dr. A. Bernhardt, Mulheim (Ruhr), Germany. In this, and the following five papers, except where stated, alumina was neutralized before use by stirring with ethyl acetate and reactivated by heating at 120° for 72 hr. Grades of activity, where given, are those of H. Brockmann and H. Schodder [*Ber.*, **74**, 73 (1941)].

homogeneous to gas or paper chromatography,  $[\alpha]_D -3.5^\circ$ ,  $\nu_{\max}$  1735 (s), 1235 (s), 3010 (w), 1650 (w) and 684  $\text{cm}^{-1}$  (s).

*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{32}\text{O}$ : C, 79.70; H, 10.19; O, 10.11. Found: C, 79.81; H, 10.18; O, 10.07.

Further chromatography of impure fractions permitted the isolation of more pure product, but no other reaction product could be isolated in a pure state.

**$\Delta^3$ -5 $\beta$ -Androstene-17 $\beta$ -ol (IIb).**—The acetate IIa (0.5 g.) in methanol (50 ml.) containing potassium hydroxide (2.0 g.) was heated under reflux for 3 hr. Dilution with water, ethyl acetate extraction and washing in the normal manner yielded a solid, purified by crystallization from hexane-ethanol to afford 360 mg. of IIb, m.p. 132–133°  $[\alpha]_D +13^\circ$ ,  $\nu_{\max}$  3370 (m), 1654 (w), 678  $\text{cm}^{-1}$  (s).

*Anal.* Calcd. for  $\text{C}_{19}\text{H}_{30}\text{O}$ : C, 83.15; H, 11.02. Found: C, 83.03; H, 11.03.

**17 $\alpha$ -Methyl- $\Delta^3$ -5 $\beta$ -androstene-17 $\beta$ -ol (IIc).**—A solution of 500 mg. of  $\Delta^3$ -5 $\beta$ -androstene-17 $\beta$ -ol in 25 ml. of acetone was kept at 0° and Jones reagent<sup>21</sup> added dropwise with stirring until an excess was apparent. Isolation of the product in the normal manner led to crude  $\Delta^3$ -5 $\beta$ -androstene-17-one (IIc), m.p. 68–73°,  $\nu_{\max}$  1745 (s), 1655 (w) and 680 (s)  $\text{cm}^{-1}$ . No satisfactorily pure product could be obtained for analysis. A solution of 400 mg. of the ketone in 50 ml. of tetrahydrofuran was kept under reflux with 10 ml. of ethereal 4 N methylmagnesium bromide for 5 hr., and the whole was then poured into water. Extraction with ethyl acetate, chromatography of the 200 mg. of derived oil over alumina (Grade III), and elution with benzene and benzene-ether (5:1) gave 180 mg. of 17 $\alpha$ -methyl- $\Delta^3$ -5 $\beta$ -androstene-17 $\beta$ -ol (IIc) as prisms from methanol-water, m.p. 122–124°,  $[\alpha]_D +10^\circ$ ,  $\nu_{\max}$  3300 (s) and 680  $\text{cm}^{-1}$  (s).

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{32}\text{O}$ : C, 83.27; H, 11.18; O, 5.55. Found: C, 83.37; H, 11.33; O, 5.48.

**$\Delta^3$ -5 $\alpha$ - and  $\Delta^3$ -5 $\beta$ -Androstene-17 $\beta$ -ol-acetates (IIIa and IIIa').**—A solution of 4 g. of testosterone acetate in 550 ml. of acetic acid was treated in 6 portions with 150 g. of zinc at room temperature during 1.5 hr. with constant agitation. After filtration there were isolated, in the manner described by McKenna-Norymberski and Stubbs,<sup>19</sup>  $\Delta^3$ -5 $\alpha$ -androstene-17 $\beta$ -ol-acetate (IIIa), m.p. 119–120°,  $[\alpha]_D +33^\circ$  (lit.<sup>19</sup> m.p. 117–118°,  $[\alpha]_D +42^\circ$ ), and  $\Delta^3$ -5 $\beta$ -androstene-17 $\beta$ -ol-acetate (IIIa'), identical (w.p. and infrared) with a sample prepared by the alternate route described above.

A solution of 50 mg. of the 5 $\alpha$ -isomer (IIIa) in 5 ml. of tetrahydrofuran was treated with 100 mg. of lithium aluminum hydride in 5 ml. of the same solvent and kept under reflux (1 hr.). Work up in the normal manner afforded  $\Delta^3$ -5 $\alpha$ -androstene-17 $\beta$ -ol,  $[\alpha]_D +50^\circ$ , m.p. 152–153° (lit.<sup>19</sup> 147–150°),<sup>43</sup>  $\nu_{\max}$  3450 (s), 1650 (w) and 668  $\text{cm}^{-1}$  (s).

**$\Delta^2$ -Androstene-17 $\beta$ -ol (Va).**—Sodium borohydride (1.6 g.) was added to an ice-cold solution of 10 g. of 2 $\alpha$ -bromodihydrotestosterone,<sup>20</sup> in 350 ml. of dry ethanol. After 1 hr. water was added and the product was filtered off and dried. A mixture of the crude bromohydrin, 32 g. of zinc dust and 100 ml. of glacial acetic acid was heated under reflux with stirring for 1 hr. Removal of the zinc by filtration and precipitation with water afforded 7.2 g. of a mixture of Va and its corresponding acetate. This mixture then was combined with the products from two additional 10-g. reactions from 2 $\alpha$ -bromodihydrotestosterone and the total material (22 g.) was dissolved in 400 ml. of methanol. After the addition of 400 ml. of 10% aqueous methanolic sodium hydroxide solution (methanol-water 9:1) the resulting mixture was boiled (2 hr.). After the removal of ca. 400 ml. of methanol under reduced pressure, water was added and the precipitate was collected, washed with water and dried to yield 20 g. of crude Va. This material was dissolved in benzene-hexane (3:1) and chromatographed over 720 g. of alumina. The product eluted with benzene and with mixtures of benzene-ether (9:1 and 4:1) was crystallized from methanol-water to give 11 g. of Va, m.p. 167–168°. Further concentration of the mother liquors and cooling furnished an additional 1.8 g. of the same compound (Va) with m.p. 163–165°. After further recrystallization from methanol-water a pure sample showed m.p. 169–170°,  $[\alpha]_D +55^\circ$ ,  $\nu_{\max}$  1660 (m) and 665 (s)  $\text{cm}^{-1}$ ; reported m.p. 165°.<sup>44</sup>

**$\Delta^2$ -Androstene-17 $\beta$ -ol-17-acetate (Vb).**—Treatment of 2 g. of  $\Delta^2$ -androstene-17 $\beta$ -ol with 60 ml. of 1:2 acetic anhydride-pyridine at room temperature for 18 hr. followed by isolation of the product with ethyl acetate gave 2.3 g. of the acetate (Vb). Crystallization from methanol provided 1.7 g., m.p. 93–94°. A pure sample showed m.p. 94–95°,  $[\alpha]_D +49^\circ$ , reported m.p. 96°,<sup>44</sup>  $\nu_{\max}$  1740 (s), 1660 (w) 675  $\text{cm}^{-1}$  (s).

**$\Delta^2$ -Androstene-17-one (Vc).**—A stirred solution of 7.8 g. of  $\Delta^2$ -androstene-17 $\beta$ -ol in 640 ml. of acetone was cooled to 0–5° and treated dropwise with 12.2 ml. of 8 N chromium trioxide reagent.<sup>21</sup> After 3 min. the reaction was diluted with 5 l. of water. The precipitate was removed by filtration and dried to afford 7.5 g. of Vc,<sup>22</sup> m.p. 102–104°, raised by crystallizations from acetone-hexane to 106–108° (5.4 g.), unchanged upon further crystallization;  $[\alpha]_D +150^\circ$ ; reported m.p. 104–105°,  $[\alpha]_D +146^\circ$  (in EtOH)<sup>45</sup>;  $\nu_{\max}$  1750 (s), and 667  $\text{cm}^{-1}$  (s).

**17 $\alpha$ -Methyl- $\Delta^2$ -androstene-17 $\beta$ -ol (Vd).**—A solution of 9.5 g. of  $\Delta^2$ -androstene-17-one and 240 ml. of dry benzene was added with stirring to a refluxing solution containing 215 ml. of 4 N ethereal methylmagnesium bromide and 950 ml. of benzene. The reaction mixture was heated under reflux for an additional 20 hr. after the addition of the steroid was complete. After cooling an excess of 10% aqueous ammonium chloride solution was added. The organic layer then was washed well with water. Removal of the solvent gave 10 g. of a gelatinous product which was dissolved in 200 ml. of benzene-hexane (1:2) and chromatographed on 400 g. of alumina. Elution with mixtures of benzene-hexane (1:1, 2:1 and 4:1) and crystallization of the resulting product afforded 7.2 g. of 17 $\alpha$ -methyl- $\Delta^2$ -androstene-17 $\beta$ -ol, m.p. 155–157°. Two additional crystallizations did not raise the m.p.:  $[\alpha]_D +47^\circ$ ,  $\nu_{\max}$  1660 (w), 663  $\text{cm}^{-1}$  (s).

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{32}\text{O}$ : C, 83.27; H, 11.18; O, 5.54. Found: C, 83.02; H, 11.16; O, 6.00.

**17 $\alpha$ -Ethylnyl- $\Delta^2$ -androstene-17 $\beta$ -ol (Ve).**—A current of dry, purified acetylene was passed for 3 hr. through a solution of 25 ml. of 4 N ethereal methylmagnesium bromide and 100 ml. of dry tetrahydrofuran. The resulting solution of ethynylmagnesium bromide was heated under reflux and then 1 g. of  $\Delta^2$ -androstene-17-one dissolved in 50 ml. of tetrahydrofuran was added dropwise during 20 min. After heating for 7 hr. the reaction was cooled and treated with an excess of 10% aqueous ammonium chloride solution. Dilution with 1 l. of water and isolation with ethyl acetate afforded 1.4 g. of product which was dissolved in benzene-hexane (4:1) and absorbed onto 54 g. of alumina. Elution with benzene and benzene-ether (9:1) gave 0.7 g. of Ve, which was crystallized from acetone-hexane to yield 0.3 g.; m.p. 165–169°, raised by further recrystallization from the same solvents to m.p. 175–178°,  $[\alpha]_D -2^\circ$ ,  $\nu_{\max}$  3275 (m), 1655 (w), 670 (s)  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{30}\text{O}$ : C, 84.51; H, 10.13. Found: C, 84.40; H, 10.25.

**17 $\alpha$ -Ethylnyl-19-norandrostane-3 $\beta$ ,17 $\beta$ -diol-3-tosylate (VI).**—A mixture of 0.4 g. of 17 $\alpha$ -ethylnyl-19-norandrostane-3 $\beta$ ,17 $\beta$ -diol and 0.4 g. of *p*-toluenesulfonyl chloride in 10 ml. of pyridine was kept for 2 days at room temperature. The reaction mixture then was diluted with 100 ml. of water and extracted with methylene chloride (3  $\times$  100 ml.). The combined extracts were washed with 5% aqueous hydrochloric acid and 5% sodium bicarbonate solutions and finally with water to neutrality. Removal of the solvent *in vacuo* and crystallization from ether-hexane yielded 0.4 g. of the tosylate (VI), m.p. 147–152°, raised by further recrystallizations from ether-hexane to m.p. 157–159°,  $[\alpha]_D -28^\circ$ ,  $\lambda_{\max}$  226  $\mu$ ,  $\log \epsilon$  4.08,  $\nu_{\max}$  1640 (w) and 1600  $\text{cm}^{-1}$  (w).

*Anal.* Calcd. for  $\text{C}_{27}\text{H}_{38}\text{O}_4\text{S}$ : C, 71.02; H, 7.95; S, 7.02. Found: C, 70.62; H, 7.92; S, 6.66.

**17 $\alpha$ -Ethylnyl- $\Delta^2$ -19-norandrostene-17 $\beta$ -ol (Vf).**—A mixture of 3.1 g. of tosylate VI, 3.1 g. of sodium acetate, 27.5 ml. of acetic acid and 2.8 ml. of acetic anhydride was heated under reflux for 3 hr. Water (300 ml.) was added and the resulting solution was extracted with methylene chloride. The organic phase was washed well with 5% sodium carbonate solution and with water, dried over sodium sulfate and concentrated. The resulting oil (2.5 g.) dissolved in 52 ml. of methanol was treated with 52 ml. of 4% aqueous methanolic sodium hydroxide solution

(43) All the  $\Delta^3$ -compounds reported in this paper were found to be homogeneous by gas chromatography. Samples, apparently pure as judged by infrared and paper chromatography, but which melted slightly lower and over a broader range frequently appeared to be less than 95% pure when analyzed by gas chromatography.

(44) R. E. Marker, O. Kanam, D. M. Jones and L. W. Nixon, *J. Am. Chem. Soc.*, **59**, 1363 (1937).

(45) V. Prelog, L. Ružička, P. Meister and P. Wieland, *Helv. Chim. Acta.*, **28**, 618 (1945).

(methanol-water 19:1) and the mixture heated under reflux for 2 hr. Dilution with water and isolation of the product with methylene chloride provided 2.2 g. of an oil, which was adsorbed from benzene-hexane (1:1) onto alumina (86 g.). Elution with mixtures of benzene-hexane (3:2 and 4:1) and pure benzene afforded 0.9 g. of the  $\Delta^2$ -compound (Vf) which crystallized from ether-hexane to yield 0.7 g., m.p. 104–107°. The analytical sample prepared from the same solvent mixture exhibited m.p. 108–109°,  $[\alpha]_D +25.5^\circ$ ,  $\nu_{\max}^{CO^2}$  3200 (m), 660  $\text{cm}^{-1}$  (s).

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{28}\text{O}$ : C, 84.45; H, 9.92. Found: C, 84.12; H, 9.88.

**$\Delta^1$ -5 $\alpha$ -Androstene-3 $\beta$ ,17 $\beta$ -diol-17-acetate (VIIb).**—Lithium tri-*t*-butoxyaluminum hydride (14.7 g.) was added to a solution of 14.7 g. of  $\Delta^1$ -5 $\alpha$ -androstene-3-one-17 $\beta$ -ol acetate in 550 ml. of anhydrous tetrahydrofuran and heated under reflux for 1 hr. After removal of the solvent under vacuum, water was added and the product extracted with methylene dichloride, washed with water and isolated by evaporation of the dried solution. Recrystallization from methanol-water gave 12.7 g. of VIIb as prisms (86%), m.p. 143–144°,  $[\alpha]_D -43.5^\circ$ ,  $\nu_{\max}$  3480 (m), 1735 (s) and 1235  $\text{cm}^{-1}$  (s).

*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{32}\text{O}_3$ : C, 75.86; H, 9.70; O, 14.44. Found: C, 75.92; H, 9.75; O, 14.52.

Slow addition of Jones reagent<sup>21</sup> to a solution of VIIb in acetone, then work-up in the conventional manner, regenerated the enone (VIIa), identical by m.p. and infrared spectrum with an authentic sample.

**$\Delta^1$ -5 $\alpha$ -Androstene-17 $\beta$ -ol (VIIId).**—A solution of 10 g. of the allylic alcohol (VIIb) in 200 ml. of benzene was kept at 5–8° and treated with 10 ml. of purified thionyl chloride<sup>46</sup> for 1 hr. with stirring. Evaporation at room temperature *in vacuo* left a solid residue to which was added solid sodium bicarbonate, then a solution of sodium bicarbonate. Extraction with methylene dichloride gave a solution which, after several water washes was dried and evaporated to furnish a solid residue which was then dissolved in 1.5 l. of ether. Lithium aluminum hydride (7.0 g.) was added cautiously, and the whole maintained under reflux overnight. After destruction of the excess of the reagent by ethyl acetate, 250 ml. of saturated sodium potassium tartrate solution was added and the mixture extracted with ether (4  $\times$  250 ml.). Evaporation of the washed and dried ether extracts gave a solid which was chromatographed over 300 g. of alumina. Elution with 3:1 hexane-methylene dichloride furnished 4.3 g. of VIIId, m.p. raised by several recrystallizations from acetone-hexane to 157–158°,  $[\alpha]_D +24.7^\circ$ ,  $\nu_{\max}$  3240 (s), 3020 (w), and 668  $\text{cm}^{-1}$  (s).

*Anal.* Calcd. for  $\text{C}_{19}\text{H}_{26}\text{O}$ : C, 78.03; H, 11.03; O, 10.94. Found: C, 78.46; H, 10.60; O, 10.74. For a sublimed sample: *Anal.* Calcd. for  $\text{C}_{19}\text{H}_{26}\text{O}$ : C, 83.15; H, 11.02; O, 5.83. Found: C, 82.83; H, 10.83; O, 6.12.

Earlier fractions from the column gave the minor product, which after recrystallization from ether had m.p. 218–221°. The same compound was isolated in small quantity when attempts were made to obtain by crystallization from methanol a pure component of the mixture resulting from the action of thi-

onyl chloride upon the allylic alcohol (VIIb). Crystallization from ethanol-methylene dichloride yielded the pure compound, m.p. 225–227°  $[\alpha]_D \pm 0^\circ$ ,  $\nu_{\max}$  1235 (s) and 1735  $\text{cm}^{-1}$  (s).

*Anal.* Found: C, 70.23; H, 9.64; O, 20.76.

**$\Delta^1$ -5 $\alpha$ -Androstene-17 $\beta$ -ol Acetate (VIIe).**—A mixture of 2 ml. of pyridine, 0.8 ml. of acetic anhydride, and 350 mg. of the above alcohol (VIIId) was kept at room temperature overnight. The usual work up afforded 350 mg. of the acetate (VIIe), which after several recrystallizations from methanol had m.p. 127–128°,  $[\alpha]_D -15.4^\circ$ , and  $\nu_{\max}$  3010 (w), 1743 (s), 1230 (s), 1652 (w), 750 (m), 723 (m) and 703  $\text{cm}^{-1}$  (s).

*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{32}\text{O}_2$ : C, 79.70; H, 10.19; O, 10.11. Found: C, 79.39; H, 10.26; O, 10.20.

**$\Delta^1$ -5 $\alpha$ -Androstene-17-one (VIIf).**—Oxidation at 0° of 100 mg. of  $\Delta^1$ -5 $\alpha$ -androstene-17 $\beta$ -ol in 4 ml. of acetone with 0.2 ml. of Jones reagent,<sup>21</sup> isolation of the product and crystallization from aqueous methanol afforded 85 mg. of the ketone VIIf as prisms, m.p. 98–100°,  $[\alpha]_D +103^\circ$ ,  $\nu_{\max}$  3025 (w), 1740 (s), and 665  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{19}\text{H}_{26}\text{O}$ : C, 83.77; H, 10.36. Found: C, 83.76; H, 10.65.

**17 $\alpha$ -Methyl- $\Delta^1$ -5 $\alpha$ -androstene-17 $\beta$ -ol (VIIg).**—To a solution of 400 mg. of VIIf in 45 ml. of dry ether was added 9.5 ml. of 4 *N* methylmagnesium bromide in ether and the mixture kept 1.5 hr. at reflux, before pouring onto ice-water containing ammonium chloride. Extraction with ethyl acetate gave 420 mg. of crude VIIg, m.p. 120–122°. Recrystallization from aqueous methanol furnished the pure compound, m.p. 135–136°,  $[\alpha]_D \pm 0^\circ$ ;  $\nu_{\max}$  3380 (s), 3010 (w), 1650 (w), and 663  $\text{cm}^{-1}$  (s).

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{32}\text{O}$ : C, 83.27; H, 11.18; O, 5.55. Found: C, 83.55; H, 11.37; O, 5.25.

**Reaction of Ethanethiol with  $\Delta^1$ -5 $\alpha$ -Dihydrotestosterone Acetate.**— $\Delta^1$ -5 $\alpha$ -Dihydrotestosterone acetate (250 mg.) was treated with 1 ml. of ethanethiol and 0.1 ml. of boron trifluoride etherate at room temperature for 2 hr., and then poured into water. Extraction with ethyl acetate and repeated washing with 5% sodium hydroxide solution, then with water, yielded, on evaporation of the dried solution, a solid product. The latter was absorbed from hexane onto 10 g. of neutral alumina. Elution with hexane led to 170 mg. of 1,3,3-trithioethyl-5 $\alpha$ -androstane-17 $\beta$ -ol acetate (VIIIa), with m.p. 150–151°, raised by recrystallization from methanol to m.p. 152–153°,  $[\alpha]_D +52.4^\circ$ ,  $\nu_{\max}$  1735 (s) and 1240  $\text{cm}^{-1}$  (s).

*Anal.* Calcd. for  $\text{C}_{27}\text{H}_{46}\text{O}_2\text{S}_3$ : C, 65.64; H, 9.30; O, 6.42; S, 19.25. Found: C, 65.98; H, 9.60; O, 5.67; S, 19.05.

**Raney Nickel Desulfurization of 1,3,3-Trithioethyl-5 $\alpha$ -androstane-17 $\beta$ -ol Acetate.**—Raney nickel (8 g.) was kept under 800 ml. of boiling acetone for 1 hr. after which 800 mg. of the trithioethyl derivative (VIIIa) was added in 100 ml. of acetone, and the whole kept under reflux a further 4 hr. Filtration and evaporation yielded 700 mg. of oily product which after chromatography over 100 g. of neutral alumina afforded in the hexane eluates 200 mg. of 1,3-dithioethyl-5 $\alpha$ -androstane-17 $\beta$ -ol acetate (VIIIf), crystallizing from methanol as prisms, m.p. 136–137°,  $[\alpha]_D +125.3^\circ$ ,  $\nu_{\max}$  1741 (s), 1245  $\text{cm}^{-1}$  (s).

*Anal.* Calcd. for  $\text{C}_{25}\text{H}_{42}\text{O}_2\text{S}_2$ : C, 68.46; H, 9.65; O, 7.30; S, 14.59. Found: C, 69.14; H, 8.85; O, 7.13; S, 14.55.

(46) Cf. A. I. Vogel, "Practical Organic Chemistry," Longmans, London, 1948, p. 185.