[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX S. A., MEXICO, D. F., MEX.]

Steroids. CXLV.[1] 2-Methylandrostane Derivatives. Demonstration of Boat Form in the Bromination of 2α-Methyl-androstan-17β-ol-3-one

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Sodium borohydride reduction of 2α-methylandrostan-17β-ol-3-one (Ia) led to a mixture of the 3β,17β-diol II and the 3α,17β-diol III while lithium aluminum hydride reduction of I and of 2α,17α-dimethylandrostan-17β-ol-3-one (Ib) gave exclusively the 3β,17β-diols. The 1-dehydro derivatives IV of Ia and Ib were prepared by bromination–dehydrobromination and the 1,4-bis-dehydro derivative V of Ib was prepared by selenium dioxide dehydrogenation or by dibromination–dehydrobromination. Kinetically controlled bromination of Ia or of its enol acetate VI yielded 2α-bromo-2β-methylandrostan-17β-ol-3-one acetate (VIIb) in which ring A is in the *boat* conformation (XIII) while acid-catalyzed equilibration of VIIb afforded the thermodynamically more stable 2β-bromo-2α-methylandrostan-17β-ol-3-one acetate (VIII) and the rearrangement product 4α-bromo-2α-methylandrostan-17β-ol-3-one acetate (IX). These results demonstrate that in the 2-methyl series kinetic bromination of the ketone and enol acetate follow the same stereochemical course and indicate that the kinetic bromination proceeds in an equatorial manner followed by conformational inversion to a *boat* (XIII) while the thermodynamic product is the 2β-bromo axial compound.

The marked anti-tumor activity[2,3] of 2α-methylandrostan-17β-ol-3-one[4,5] (Ia) and of 2α,17α-dimethylandrostan-17β-ol-3-one[4,5] (Ib) promoted our interest in the synthesis of structural modifications of these molecules. In this paper we describe the preparation of the corresponding 3,17-diols of Ia and of Ib, the 2-methyl-Δ^1-3-keto compounds and the 2-methyl-$\Delta^{1,4}$-3-keto dienone derived from Ib,[6] these compounds being of interest for biological evaluation. In the course of bromination–dehydrobromination experiments carried out with 2α-methylandrostan-17β-ol-3-one certain anomalies were noted that invoked the necessity of assigning a boat conformation (XIII) to 2α-bromo-2β-methylandrostan-17β-ol-3-one acetate (VIIb). This result was in accord with that found in the 2α-methylcholestanone series which is discussed in the preceding paper[7] and a more intensive study of the bromination of I paralleled the study of the bromination of 2α-methylcholestanone. The pertinent bromination experiments are discussed in the latter portion of this paper while the mechanism of bromination is considered in detail in the third paper[8] of this series.

2α-Methylandrostane-3,17-diols.—Reduction of 2α-methylandrostan-17β-ol-3-one (Ia) with sodium borohydride in methanol gave about six parts of 2α-methylandrostane-3β,17β-diol (IIa) to one part of 2α-methylandrostane-3α,17β-diol (IIIa). Although neither compound formed a precipitate with alcoholic digitonin solution, nor was it possible after acetylation to differentiate by infrared means[9] the equatorial 3α-acetate from the axial 3β-acetate, comparison of molecular rotation data (Table I) definitely established, as anticipated, that the more prevalent isomer was the 3β-equatorial. In the case of androstane-3,17β-diol, acetylation of the 3β,17β-diol leads to a −50 ΦD shift while acetylation of the 3α,17β-diol leads to a +7 ΦD shift. In the case of 2α-methylcholestan-3β-ol[10] where the 3β-hydroxy configuration has been proved the 3-acetate exhibits a ΔΦD of −179 compared to the free compound. It is evident from Table I that IIa with an ΦD shift after acetylation of −164 is the 3β-isomer. When the reduction of Ia was carried out with lithium aluminum hydride instead of sodium borohydride only the 3β-equatorial isomer was obtained.[11] Similarly, 2α,17α-dimethylandrostan-17β-ol-3-one (Ib) was reduced with lithium aluminum hydride exclusively to 2α,17α-dimethylandrostan-3β,17β-diol (IIb).

TABLE I

MOLECULAR ROTATION DIFFERENCES

Compound	$[\phi]_D$[a]	$\Delta[\phi]_D$ (acetate-free)
Androstane-3β,17β-diol diacetate	+ 12[b]	
	− 38[b]	− 50
Androstane-3α,17β-diol diacetate	+ 38[b]	
	+ 45[b]	+ 7
2α-Methylcholestane-3β-ol	+ 32[10]	
acetate	−147[10]	−179
2α-Methylandrostane-3β,17β-diol	+ 31	
diacetate	−133	−164
2α-Methylandrostane-3α,17β-diol	+ 67	
diacetate	+148	+ 81

[a] $[\phi]$ = molecular rotation (see footnote 21 in ref. 8.) [b] Determined in these laboratories.

Δ^1-2-Methylandrosten-17β-ol-3-ones.—Bromination of 2α-methylandrostan-17β-ol-3-one (Ia) with one equivalent of bromine in acetic acid and in the presence of an equivalent amount of sodium acetate gave a bromo-ketone which, without purification, was dehydrobrominated with collidine yielding Δ^1-2-methylandrosten-17β-ol-3-one (IVa), λ_{max} 241 mμ, log ε 3.99. Compound IVa lacked the characteristic[10] infrared carbon–carbon stretch band of Δ^4-3-ketones found at about 1620 cm.$^{-1}$ and was

(1) Paper CXLIV, J. S. Mills, O. Candiani and C. Djerassi, *J. Org. Chem.*, **25**, 1056 (1960).

(2) C. Huggins and K. Mainzer, *J. Exptl. Med.*, **105**, 485 (1957).

(3) C. M. Blackburn and D. S. Childs, Jr., *Proc. Staff Meet., Mayo Clinic*, **34**, 113 (1959).

(4) H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **21**, 1333 (1956).

(5) H. J. Ringold, E. Batres, O. Halpern and E. Necoechea, THIS JOURNAL, **81**, 427 (1959).

(6) 2-Methyl-$\Delta^{1,4}$-androstadien-17β-ol-3-one has been previously described; J. Iriarte and H. J. Ringold, *Tetrahedron*, **3**, 28 (1958).

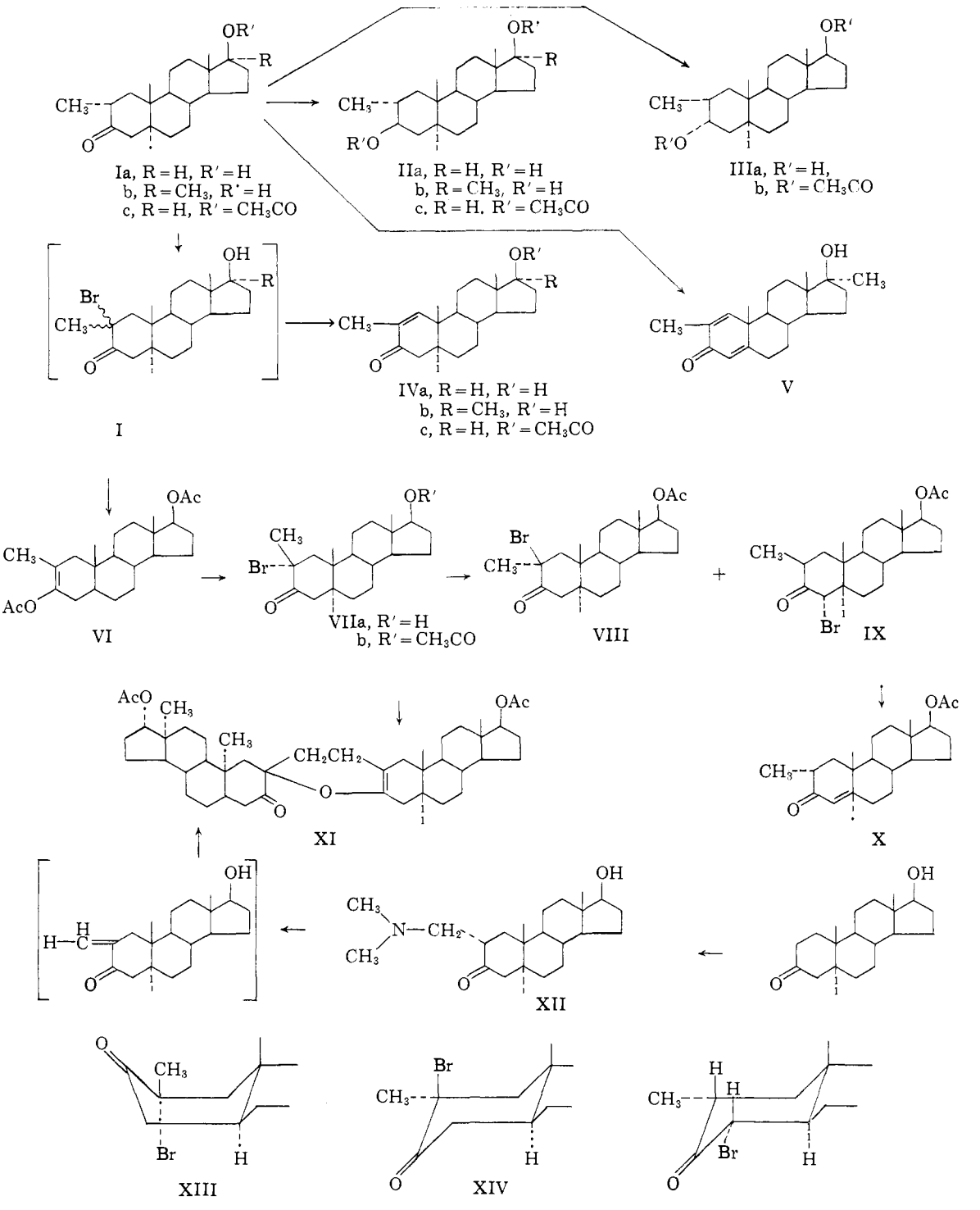
(7) C. Djerassi, N. Finch, R. C. Cookson and C. W. Bird, THIS JOURNAL, **82**, 5488 (1960).

(8) R. Villotti, H. J. Ringold and C. Djerassi, *ibid.*, **82**, Nov. 5 (1960).

(9) R. N. Jones, P. Humphries, F. Herling and K. Dobriner, *ibid.*, **73**, 3215 (1951).

(10) Y. Mazur and F. Sondheimer, *ibid.*, **80**, 5220 (1958).

(11) The course of hydride reduction was similar with 2α-methylcholestanone; see refs. 7 and 10.



shown by direct comparison to be different from the known[4,5] 2α-methyltestosterone. Similar bromination of 2α,17α-dimethylandrostan-17β-ol-3-one followed by calcium carbonate–dimethylacetamide dehydrobromination[12] yielded Δ^1-2,17α-dimethylandrosten-17β-ol-3-one (IVb). Treatment of Ib with two equivalents of bromine gave the intermediate 2,4-dibromo compound which was dehydrobrominated with calcium carbonate–dimethylformamide to $\Delta^{1,4}$-2,17α-dimethylandrostadien-17β-ol-3-one (V), λ_{max} 248 mμ, a product also obtained by dehydrogenation of Ib with selenium dioxide in boiling *t*-butyl alcohol.[13]

It was later found that Δ^1-2-methylandrosten-17β-ol-3-one could best be prepared, as the 17-acetate IVc, by conversion of Ia to its enol acetate

(12) Private communication from Glaxo Laboratories Ltd.

(13) Ch. Meystre, H. Frey, W. Voser and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956); S. A. Szpilfogel, T. A. P. Posthumus, M. S. De Winter and D. A. Van Dorp, *Rec. trav. chim.*, **75**, 475 (1956).

17-acetate VI, bromination in the presence of pyridine or of sodium acetate and dehydrobromination of the intermediate 2α-bromo-2β-methyl-3-ketone VIIb with boiling collidine.

Configuration of Bromo Ketones.—As stated above, kinetically controlled bromination of the enol acetate VI in the presence of pyridine[14] or of sodium acetate[7] gave a monobromo ketone VIIb, m.p. 112–115°, $[\alpha]D$ −6°, whose bromine atom location was established at C-2 by collidine dehydrobromination to Δ^1-2-methylandrosten-17β-ol-3-one acetate (IVc) or by dinitrophenylhydrazine elimination to the corresponding phenylhydrazone. Both the infrared[15] and ultraviolet[16] spectrum of IVc were characteristic of an axial halo ketone and in accord with the anticipated[17] 2β-bromo-2α-methyl configuration. However, the rotatory dispersion curve of VIIb exhibited a negative Cotton effect with trough at 337.5 mμ while according to the axial halo ketone rule[18] a 2β-bromo-3-keto-5α-steroid should exhibit a strongly positive Cotton effect. Thus, on the basis of these measurements and following the argument developed in the preceding paper[7] for the 2-bromocholestanone case, VIIb can only possess the 2α-bromo(axial)-2β-methyl ring A *boat* configuration (XIII) for which a negative Cotton effect would be predicted.[7,18] Since under identical non-equilibrating bromination conditions cholestanone enol acetate gave 2α-bromocholestanone[7] (bromine equatorial, ring A *chair*), and androstan-17β-ol-3-one enol acetate 17-acetate also gave 2α-bromoandrostan-17β-ol-3-one acetate[8] we believe that *the kinetically controlled product in the bromination of these enol acetates is the 2α-equatorial bromo compound* which remains as such in the absence of a 2β-methyl group but undergoes a "flip" to the ring A *boat* conformation in the presence of a 2β-methyl group. This did not establish, however, that bromination of a 3-ketone would follow the same stereochemical course as bromination of the corresponding enol acetate.

To establish this point, 2α-methylandrostan-17β-ol-3-one (Ia) and its 17-acetate Ic were brominated in acetic acid in the presence of one equivalent of sodium acetate. The sodium acetate was dissolved in the bromine solution which was added dropwise to the steroid dissolved in acetic acid after the bromination had been initiated by the addition of a trace of hydrogen bromide. Thus, it was usually possible by this procedure to brominate while keeping the concentration of hydrogen bromide at a minimum and to effect bromination of the 3-ketone under apparent nonequilibrating conditions providing that bromine addition was at just the proper rate. When the bromine solution was added too rapidly the excess sodium acetate which was concomitantly added quenched the reaction which could then be re-initiated only by the addition of excess hydrogen bromide leading in general to partial equilibration.

When 2α-methylandrostan-17β-ol-3-one (Ia) was brominated by this procedure (*i.e.*, without stoppage) and the reaction mixture immediately precipitated in water, a single bromo ketone (VIIa) was obtained. Compound VIIa exhibited a negative Cotton effect curve (trough at 335 mμ), its ultraviolet and infrared spectra were characteristic of an axial halo ketone and on dehydrobromination by collidine or by dinitrophenylhydrazine gave Δ^1-2-methylandrosten-17β-ol-3-one (IVa) and its dinitrophenylhydrazone, respectively. Acetylation of VIIa at room temperature with acetic anhydride–pyridine gave the 17-acetate identical with VIIb obtained by bromination of the enol acetate. Thus VIIa must be assigned the structure 2α-bromo-2β-methylandrostan-17β-ol-3-one (ring A *boat*) (XIII) and in this case *kinetically controlled bromination of the ketone follows the same stereochemical course as bromination of the enol acetate.*

Having established the product of kinetically controlled bromination it now became of interest to determine if the 2α-bromo compound VII was also the thermodynamically stable isomer. For this purpose, a preliminary experiment was carried out in which VIIb was allowed to stand at room temperature in a solution of acetic acid containing hydrogen bromide and aliquots were withdrawn at intervals of 5 minutes to 20 hours. The specific rotation, the ultraviolet maximum and the first rotatory dispersion extremum of each aliquot were determined (Table II).

TABLE II

HBr CATALYZED EQUILIBRATION OF 2α-BROMO-2β-METHYL-ANDROSTAN-17β-OL-3-ONE ACETATE (VIIb)

Equilibration time, min.	$[\alpha]D$	λ_{max}^{EtOH} (u.v.)	Rotatory dispersion Curve, mμ	Trough or peak
0	− 6°	309 (2.09)	338	(− 470°)
5	+ 5	308 (2.10)	338	(− 340)
20	+ 7	308 (1.98)	335	(− 198)
80	+24	303 (1.86)	327.5	(+ 712)
320	+38	302 (1.80)	327.5	(+ 900)
1200	+42	301 (1.81)	325	(+1045)

It may be seen from Table II that VIIb appeared to undergo isomerization under these conditions and that equilibrium was reached at a period between 4 hours and 20 hours with $[\alpha]D$, λ_{max} and rotatory dispersion curve peaks essentially constant. The intensity (+1045°) of the rotatory dispersion curve peak after 20 hours equilibration was indicative of the formation of another axial α-halo ketone. The drop in the ultraviolet maximum to 301 mμ and the drop in intensity to log ε 1.81 indicated the formation of some equatorial α-halo ketone, and further the position of the rotatory dispersion curve peak at 325 mμ was intermediate between an axial and an equatorial α-halo ketone.[19]

(14) E. R. H. Jones and D. J. Wluka, *J. Chem. Soc.*, 911 (1959).

(15) R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, THIS JOURNAL, **74**, 2828 (1952).

(16) R. C. Cookson, *J. Chem. Soc.*, 282 (1954).

(17) This structure would be predicted on the basis of the assumption that kinetically controlled bromination of a cyclohexanone affords the axially oriented bromo-ketone, E. J. Corey, THIS JOURNAL, **76**, 175 (1954). Furthermore the tacit assumption is made (see ref. 10) that the chair form of the enol is involved; for further discussion on this point see ref. 8.

(18) C. Djerassi, "Optical Rotatory Dispersion. Applications to Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, Chapter 9.

(19) C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, THIS JOURNAL, **80**, 1216 (1958).

TABLE III

CONSTANTS OF BROMO-2-METHYLANDROSTAN-17β-OL-3-ONE ACETATE ISOMERS

Compound, androstan-17β-ol-3-one acetate	M.p., °C.	$[\alpha]_D$	λ_{max}^{EtOH} (u.v)	λ_{max}^{KBr} (i.r)	Rotatory dispersion curve peak
2α-Bromo-2β-methyl- (VIIb)	112–115	− 6°	309 (2.09)	5.79, 5.86	337.5 (−494°)
2β-Bromo-2α-methyl- (VIII)	135–140	+100	307 (2.06)	5.81, 5.86	330 (+2480)[a]
4α-Bromo-2α-methyl- (IX)	147–150	− 28	None	5.80	302.5 (+222)

[a] The amplitude of the Cotton effect curve of the corresponding 19-nor-bromo ketone (ref. 8) is somewhat greater but such increase appears to be characteristic of 19-nor-3-keto steroids in general; C. Djerassi, O. Halpern, V. Halpern and B. Riniker, THIS JOURNAL, **80**, 4001 (1958).

A preparative 20-hour equilibration of VIIb was then run under the same conditions and the reaction product fractionally crystallized yielding two new bromo ketones VIII and IX, isomeric with the starting material. The former, m.p. 135–140°, $[\alpha]_D$ +100°, whose bromine atom was axial by ultraviolet and infrared spectra, exhibited a strongly positive Cotton effect rotatory dispersion curve (+2500° at 330 mμ) as would be anticipated[18] for a 2-axial bromo-3-keto-5α-hydrogen ring A *chair* steroid, and was dehydrobrominated by collidine or by the dinitrophenylhydrazine method to Δ¹-2-methylandrosten-17β-ol-3-one 17-acetate (IVc) and its dinitrophenylhydrazone. The bromo ketone VIII can thus be assigned the 2β-bromo-2α-methylandrostan-17β-ol-3-one acetate ring A *chair* structure XIV.

The third isomeric bromo ketone IX exhibited m.p. 147–150°, $[\alpha]_D$ −28°. Its infrared and ultraviolet absorption spectra were indicative of an equatorial bromo ketone while the rotatory dispersion curve exhibited a low intensity positive Cotton effect with a peak at 302.5 mμ, consistent[18,19] with an equatorial α-halo ketone. When IX was dehydrobrominated with collidine and with 2,4-dinitrophenylhydrazine yielding 2α-methyltestosterone acetate (X) and its dinitrophenylhydrazone, it became obvious that IX is 4α-bromo-2α-methylandrostan-17β-ol-3-one acetate ring A *chair* (XV), a product arising from acid-catalyzed bromine migration.

Further confirmation of the nature of the equilibriumpr oducts was obtained when a 23-hour isomerization experiment was worked up yielding a mixture of bromo compounds ($[\alpha]_D$ +36°) which was dehydrobrominated with lithium carbonate–lithium bromide[20] in boiling dimethylformamide. The dehydrobromination product was chromatographically separated yielding almost equal amounts of 2α-methyltestosterone acetate (X) and of 2-methyl-Δ¹-androsten-17β-ol-3-one acetate (IVc). These experiments establish conclusively that *kinetically controlled bromination of 2α-methylandrostan-17β-ol-3-one, its 17-acetate and its enol acetate 17-acetate, yield the 2α-bromo compound*[21] *VII while the thermodynamically more stable isomer is the 2β-bromo (axial) derivative VIII.*

Several anomalies transpired during various dehydrobromination experiments and require further discussion. When the pure 4α-bromo compound IX was dehydrobrominated by heating together a mixture of the compound and 2,4-dinitrophenylhydrazine in acetic acid the hydrazone derivative of 2α-methyltestosterone acetate was the sole reaction product. However, when 2,4-dinitrophenylhydrazine was added to a solution of IX in hot acetic acid a mixture of Δ¹- and Δ⁴-2-methyl dinitrophenylhydrazones was obtained. To determine the course of this rearrangement IX was heated for a few minutes in boiling acetic acid but in the absence of dinitrophenylhydrazine. Hydrogen bromide was liberated almost immediately and chromatographic separation of the mixture led to the isolation of both 2α-methyltestosterone acetate and 2-methyl-Δ¹-androsten-17β-ol-3-one acetate, the latter probably having been formed by some hydrogen bromide-catalyzed isomerization of the 4-bromo to the 2β-bromo compound VIII, both bromo compounds then undergoing thermal dehydrohalogenation.

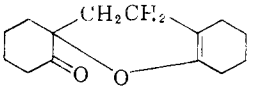
When pure 2α-bromo-2β-methyl compound VIIb was dehydrobrominated with lithium carbonate–lithium bromide–dimethylformamide, a by-product (XI) was isolated as well as the expected Δ¹-2-methyl compound IVc. Compound XI did not exhibit selective absorption in the ultraviolet and on the basis of elemental analysis and its high melting point we suspected that XI was the dimer derived from the exocyclic 2-methyleneandrostan-17β-ol-3-one acetate,[22] a possible dehydrobromination product. This was readily confirmed when we subjected 2-dimethylaminomethylandrostan-17β-ol-3-one (XII), prepared by the Mannich condensation of androstan-17β-ol-3-one with dimethylamine hydrochloride, to slow passage over an alkaline alumina column. Under these conditions we could not isolate the intermediate 2-methylene compound but only dimeric material which on acetylation was identical with XI.

Biological Activity.[23]—By the oral route IVb and V exhibited high myotrophic and low androgenic activity in the castrate male rat (7-day assay) when compared with 17α-methyltestosterone.

(20) R. Joly and J. Warnant, *Bull. soc. chim. France*, 367 (1958).

(21) In the succeeding paper (ref. 8) of this series arguments are developed which suggest strongly that this invokes kinetically controlled bottom side (equatorial) bromination with conformational change to the boat form (XIII) of ring A occurring after bromination.

(22) It has been shown, K. Dimroth, K. Resin and H. Zetzsch, *Ber.*, **73B**, 1399 (1940), that 2-methylenecyclohexanone rapidly forms a dimer to which the structure i has been assigned.



i

(23) Bioassays by Dr. R. I. Dorfman, The Worcester Foundation for Experimental Biology.

Experimental[24]

2α-Methylandrostan-17β-ol-3-one Acetate (Ic).—2α-Methylandrostan-17β-ol-3-one[4,5] (Ia) (280 mg.) was acetylated for 2 days at 0° with acetic anhydride (2 ml.) and pyridine (4 ml.). Removal of the solvent *in vacuo* and crystallization of the residue from methanol containing a few drops of water afforded 230 mg. of acetate Ic, m.p. 160–163°, $[\alpha]D + 29°$.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89; O, 13.85. Found: C, 76.02; H, 10.00; O, 13.89.

2α-Methylandrostane-3β,17β-diol (IIa) and 2α-Methylandrostane-3α,17β-diol (IIIa) by Sodium Borohydride Reduction of Ia.—Sodium borohydride (0.38 g.) was added in portions to a stirred solution of 0.91 g. of 2α-methylandrostan-17β-ol-3-one[4,5] (Ia) in 50 ml. of methanol. After standing for 3 hours at room temperature the solution was concentrated *in vacuo* to *ca.* 15 ml. and 30 ml. of 1% hydrochloric acid was added. The precipitate, 0.72 g., m.p. 165–215°, was collected and the mother liquors on extraction with chloroform yielded an additional 0.14 g. of crude reduction product, m.p. 160–212°. The combined precipitates were chromatographed on 27 g. of ethyl acetate-washed alumina. The benzene–chloroform eluates (19:1, 9:1 and 4:1) after crystallization from aqueous methanol yielded 0.30 g. of pure 2α-methylandrostane-3β,17β-diol (IIa), m.p. 175–177°, $[\alpha]D + 10°$, and a second fraction of 0.26 g., m.p. 170–174°.

Anal. Calcd. for $C_{20}H_{34}O_2 \cdot {}^1/_2H_2O$: C, 76.14; H, 11.18; O, 12.68. Found: C, 76.04; H, 11.24; O, 12.54.

2α-Methylandrostane-3β,17β-diol diacetate (IIc), prepared by pyridine–acetic anhydride treatment of IIa and crystallized from methanol, exhibited m.p. 148–153° with resolidification and m.p. 159–160°, $[\alpha]D -34°$.

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81; O, 16.39. Found: C, 73.66; H, 9.61; O, 16.97.

Elution of the alumina column with benzene–chloroform (1:1) and crystallization from methanol gave 0.09 g. of **2α-methylandrostane-3α,17β-diol** (IIIa), m.p. 246–248°, $[\alpha]D + 22°$.

Anal. Calcd. for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18; O, 10.44. Found: C, 78.28; H, 11.24; O, 10.59.

2α-Methylandrostane-3α,17β-diol diacetate (IIIb) prepared from acetic anhydride–pyridine acetylation and crystallized from methanol melted at 191–193°, $[\alpha]D + 38°$.

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81; O, 16.39. Found: C, 73.85; H, 9.35; O, 16.49.

Reduction of 2α-Methylandrostan-17β-ol-3-one (Ia) with Lithium Aluminum Hydride.—A solution of 0.11 g. of lithium aluminum hydride in 50 ml. of tetrahydrofuran was added dropwise over a 30-minute period to a stirred solution of 0.91 g. of Ia in 30 ml. of tetrahydrofuran. Stirring was continued for an additional 2 hours when 10 ml. of ethyl acetate followed by 100 ml. of 20% sulfuric acid were cautiously added (nitrogen atmosphere). The mixture was extracted several times with chloroform, the extract washed with water, dried and evaporated leaving a solid residue, m.p. 163–171°. Chromatography on alumina, as described above, gave 0.65 g. of 2α-methylandrostane-3β,17β-diol (IIa), identical with the sodium borohydride reduction product, but none of the 3α-isomer IIIa could be detected.

2α,17α-Dimethylandrostane-3β,17β-diol (IIb).—A mixture of 2α,17α-dimethylandrostan-17β-ol-3-one[4,5] (Ib) (2 g.), lithium aluminum hydride (1 g.) and tetrahydrofuran (200 ml.) was boiled for 4 hours under nitrogen and then cooled. Acetone (20 ml.) was cautiously added, then ice-cold dilute sulfuric acid and the reduction product was isolated by ethyl acetate extraction. Chromatography over 100 g. of alkaline alumina gave, in the benzene eluates, the 3β,17β-diol (1.7 g., m.p. 120–124°) which was recrystallized several times from acetone–hexane yielding 1.0 g. of pure IIb, m.p. 125–128°, $[\alpha]D - 26°$. No 3α-isomer could be detected.

Anal. Calcd. for $C_{21}H_{36}O_2 \cdot {}^1/_2C_3H_6O$: C, 77.31; H, 11.24; O, 11.44. Found: C, 77.22; H, 11.19; O, 11.40.

2,17α-Dimethyl-Δ¹-androsten-17β-ol-3-one (IVb).—A solution of 2.5 g. of anhydrous sodium acetate and 5.5 g. of bromine (1.1 equiv.) in 100 ml. of glacial acetic acid was prepared and then added dropwise over a 40-minute period to 10 g. of Ib in 100 ml. of acetic acid care being taken that the rate of bromine addition did not exceed the rate of uptake. The solution was poured with stirring into ice-water, the crude bromo compound filtered, washed, dried *in vacuo* and then dissolved in 100 ml. of dimethylacetamide. Finely divided calcium carbonate[12] (5 g.) was added and the stirred suspension boiled for 30 minutes, cooled, filtered and the solution concentrated *in vacuo* to a small volume. Water was added and the product isolated by ethyl acetate extraction as an oil. Chromatography on 300 g. of alkaline alumina gave in the hexane–benzene (1:4) fractions after acetone–hexane recrystallization, 2.3 g. of IVb, m.p. 146–151°, $[\alpha]D + 29°$, λ_{max} 241 mμ, log ε 4.00, infrared λ_{max}^{KBr} 5.99 μ.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.96; H, 10.19; O, 10.11. Found: C, 79.95; H, 10.11; O, 10.23.

2,17α-Dimethyl-Δ¹,⁴-androstadien-17β-ol-3-one (V). (a) **By Dibromination–Dehydrobromination.**—A solution of 1 g. of 2α,17α-dimethylandrostan-17β-ol-3-one (Ib) in 10 ml. of anhydrous dioxane was treated dropwise over a 30-minute period with a solution of 1.1 g. of bromine in 15 ml. of dioxane. The straw-colored solution was poured into water, the gummy precipitate filtered, washed with water and crystallized from aqueous methanol yielding 1.25 g. of intermediate 2,4-dibromo compound which without further purification was dehydrobrominated by boiling for 1 hour with 1 g. of finely divided calcium carbonate in 10 ml. of dimethylformamide. The hot mixture was filtered, the solution concentrated to dryness *in vacuo*, water added and the precipitate collected. Crystallization from acetone–ether gave 0.31 g. of V, m.p. 178–183°, λ_{max} 248 mμ, log ε 4.19. The analytical specimen from the same solvent pair melted at 187–191°, $[\alpha]D - 10°$, λ_{max} 248 mμ, log ε 4.21; infrared λ_{max}^{KBr} 5.98, 6.10 μ.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.17; H, 9.61. Found: C, 79.76; H, 9.44.

(b) **By Selenium Dioxide Dehydrogenation.**[13]—A mixture of 2α,17α-dimethylandrostan-17β-ol-3-one (0.5 g.), selenium dioxide (0.65 g.), pyridine (0.1 ml.) and *t*-butyl alcohol (30 ml.) was boiled, with stirring, for 96 hours under a nitrogen atmosphere. The cooled solution was filtered through Celite, evaporated to dryness and water was added. The crude product after crystallization from acetone (carbon) gave 0.18 g. of dienone V, m.p. 184–189°, λ_{max} 248 mμ, log ε 4.19, which gave no melting point depression with the product obtained in (a) and whose infrared spectrum was identical.

2-Methyl-Δ¹-androsten-17β-ol-3-one (IVa) without Isolation of the Bromo Intermediate.—A solution of 2.8 g. of 2α-methylandrostan-17β-ol-3-one (Ia) in 20 ml. of acetic acid was treated with a drop of hydrogen bromide–acetic acid and then a solution of 1.62 g. of bromine and 0.83 g. of sodium acetate in 30 ml. of acetic acid was added dropwise over a 30-minute period with stirring. Ice-water (200 ml.) was added, the crude 2-bromo compound filtered, washed and dried *in vacuo*, and the product was dehydrobrominated by heating in 40 ml. of boiling collidine for one hour. The cooled collidine mixture was filtered free of collidine hydrobromide and the filtrate concentrated *in vacuo* to *ca.* 10 ml. and poured into 250 ml. of cold dilute sulfuric acid solution. The gummy precipitate was filtered, dried and then chromatographed on 100 g. of alkaline alumina. The hexane–benzene (1:3) fractions were pooled and recrystallized from acetone–hexane yielding 0.475 g. of 2-methyl-Δ¹-androsten-17β-ol-3-one (IVa), m.p. 155–158°, $[\alpha]D + 52°$, λ_{max} 241 mμ, log ε 3.99, infrared λ_{max}^{KBr} 5.99 μ; mixture melting point 135–150° with 2α-methyltestosterone[4,5] of melting point 154–155°.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00; O, 10.58. Found: C, 79.06; H, 9.77; O, 11.00.

2-Methyl-Δ¹-androsten-17β-ol-3-one Acetate (IVc).—Acetylation of 1 g. of IVc by heating for one hour at 90° with

(24) Melting points are uncorrected. Rotations were determined in chloroform and ultraviolet absorption spectra in 95% ethanol solution. Infrared spectra were determined with a Perkin-Elmer model 21 spectrophotometer. We are grateful to Dr. J. Matthews for determination of rotations and spectral data.

10 ml. of acetic anhydride–pyridine (1:1) gave, after the usual work-up and crystallization from acetone–hexane 0.83 g. of IVc, m.p. 145–148°, $[\alpha]D$ + 32°, λ_{max} 241 mμ, log ε 4.03; infrared λ_{max}^{KBr} 5.78, 6.00 μ.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36; O, 13.93. Found: C, 76.69; H, 9.30; O, 13.68.

2-Methyl-Δ¹-androsten-17β-ol-3-one 2,4-Dinitrophenylhydrazone. Procedure for Dinitrophenylhydrazone Formation.[25]—2-Methyl-Δ¹-androsten-17β-ol-3-one (IVa) (300 mg.) and 2,4-dinitrophenylhydrazine (200 mg.) were added to 10 ml. of glacial acetic acid at room temperature. A current of nitrogen was passed over the surface of the solution while the mixture was rapidly brought to the boiling point by heating on a hot-plate. The acetic acid was allowed to evaporate in the nitrogen stream for about 5 minutes until incipient crystallization occurred. The cooled solution was filtered and the **dinitrophenylhydrazone** of IVa recrystallized from chloroform–ethanol, m.p. 266–268°; $\lambda_{max}^{CHCl_3}$ 386 mμ, log ε 4.47.

Anal. Calcd. for $C_{26}H_{34}N_4O_5$: C, 64.71; H, 7.10; N, 11.61; O, 16.58. Found: C, 64.90; H, 7.21; N, 11.77; O, 16.66.

2-Methyl-Δ¹-androsten-17β-ol-3-one acetate 2,4-dinitrophenylhydrazone was prepared from 2-methyl-Δ¹-androsten-17β-ol-3-one acetate (IVc) as described above and crystallized from methylene dichloride–ethanol, m.p. 263–265°, $\lambda_{max}^{CHCl_3}$ 385 mμ, log ε 4.42.

Anal. Calcd. for $C_{28}H_{36}N_4O_6$: C, 64.10; H, 6.92; N, 10.68; O, 18.30. Found: C, 64.02; H, 6.98; N, 10.58; O, 18.30.

2α-Methyltestosterone Acetate (X).—2α-Methyltestosterone[4,5] was acetylated in the usual manner and crystallized from acetone, yielding the 17-acetate X, m.p. 184–186°, $[\alpha]D$ + 101°, λ_{max} 240 mμ, log ε 4.22; infrared λ_{max}^{KBr} 5.80, 6.03, 6.19(m)μ.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36; O, 13.93. Found: C, 76.55; H, 9.19; O, 14.38.

2α-Methyltestosterone Acetate 2,4-Dinitrophenylhydrazone.—Treatment of X as described above gave the 2,4-dinitrophenylhydrazone, m.p. 272–275°, $\lambda_{max}^{CHCl_3}$ 385 mμ, log ε 4.44.

Anal. Calcd. for $C_{28}H_{36}N_4O_6$: C, 64.10; H, 6.92; N, 10.68; O, 18.30. Found: C, 64.16; H, 6.90; N, 10.72; O, 18.21.

2-Methyl-Δ²-androstene-3,17β-diol Diacetate (VI).—A solution of 5.0 g. of 2α-methylandrostan-17β-ol-3-one (Ia) and 0.5 ml. of concentrated sulfuric acid[26] in 400 ml. of freshly distilled isopropenyl acetate was boiled under reflux for 4 hours. Benzene (100 ml.) was added and 450 ml. of solvent was removed by distillation. The residue was diluted with 200 ml. of benzene, the solution washed three times with 50-ml. portions of water, dried over sodium sulfate and evaporated to dryness. The product was recrystallized twice from methanol yielding 4.15 g. of enol acetate VI, m.p. 171–173°, $[\alpha]D$ + 45°; infrared λ_{max}^{KBr} 5.75, 5.80 and 8.15–8.27 (broad) μ.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34; O, 16.47. Found: C, 74.19; H, 8.96; O, 16.97.

Bromination of 2-Methyl-Δ²-androstene-3,17β-diol Diacetate (VI). Preparation of 2α-Bromo-2β-methylandrostan-17β-ol-3-one 17-Acetate (VIIb). (a) Bromination in the Presence of Pyridine.—A solution of 1 g. of enol acetate VI in 45 ml. of acetic acid and 5 ml. of pyridine was treated with a solution of 0.53 g. of bromine in 5 ml. of acetic acid and allowed to stand overnight at room temperature before precipitating in 1 l. of ice-water. The precipitate of VIIb was filtered and *without purification* exhibited m.p. 110–112°, $[\alpha]D$ − 9°, λ_{max} 302–312 mμ, log ε 2.01; R.D. in methanol (*c*,0.0575): $[\alpha]_{400}$ +113°, $[\alpha]_{332.5}$ −473°, $[\alpha]_{290}$ +1468°. Recrystallization from hexane gave 0.51 g. (46%) of **2α-bromo-2β-methylandrostan-17β-ol-3-one acetate (VIIb)**, m.p. 112–115° dec., $[\alpha]D$ −6°. λ_{max} 309 mμ, log ε 2.07; infrared λ_{max}^{KBr} 5.79, 5.86 μ; negative Cotton effect (*c*,0.0575 in methanol) with trough at $[\alpha]_{337.5}$ −494° (for curve see ref. 18, p. 127).

Anal. Calcd. for $C_{22}H_{33}BrO_3$: C, 62.11; H, 7.82; Br, 18.78; O, 11.28. Found: C, 62.34; H, 7.52; Br, 19.03; O, 11.42.

(b) Bromination in the Presence of Sodium Acetate.[27]—The solvent[7] used in this experiment was prepared by mixing 160 ml. of glacial acetic acid, 40 ml. of carbon tetrachloride and 2.0 g. of anhydrous sodium acetate. 2-Methyl-Δ²-androstene-3,17β-diol diacetate (VI) (2.0 g.) was dissolved in 156 ml. of the above solvent and 18.8 ml. of bromine solution (0.75 ml. of bromine in 50 ml. of the solvent) was added dropwise with stirring over a 30-minute period. After an additional 20 minutes stirring the reaction mixture was diluted with water and the product extracted into hexane. The extract was washed to neutrality with bicarbonate and with water and then evaporated to dryness yielding a crystalline mass which recrystallized from methanol as colorless needles of VIIb, m.p. 113–115° (1.27 g.). This product was identical with VIIb obtained in part (a) above by ultraviolet, infrared, rotatory dispersion curve and mixture melting point determination.

Dehydrobromination of 2α-Bromo-2β-methylandrostan-17β-ol-3-one Acetate (VIIb). (a) With Collidine.—Bromo ketone VIIb (1.0 g.) was heated for 30 minutes in 10 ml. of boiling collidine. The cooled mixture was diluted with 50 ml. of ethyl acetate and washed with dilute sulfuric acid and then water. Evaporation of the dried (sodium sulfate) extract gave a semi-crystalline residue which was chromatographed on 50 g. of ethyl acetate-washed alumina. The hexane–benzene (19:1) fractions yielded, after recrystallization from acetone–hexane, 0.52 g. of 2-methyl-Δ¹-androsten-17β-ol-3-one acetate (IVc), m.p. 144–146°, λ_{max} 241 mμ, log ε 4.01.

(b) With Dinitrophenylhydrazine.—2α-Bromo-2β-methylandrostan-17β-ol-3-one acetate (VIIb) was heated with 2,4-dinitrophenylhydrazine in acetic acid and under nitrogen as described above. The product after crystallization from methylene dichloride–ethanol melted at 263–265°, $\lambda_{max}^{CHCl_3}$ 385 mμ, log ε 4.41, and was shown by mixture melting point determination and by infrared comparison to be identical with the 2,4-dinitrophenylhydrazone derived from 2-methyl-Δ¹-androsten-17β-ol-3-one acetate.

Bromination of 2α-Methylandrostan-17β-ol-3-one (Ia). Isolation of 2α-Bromo-2β-methylandrostan-17β-ol-3-one (VIIa).—A solution of 3.04 g. of 2α-methylandrostan-17β-ol-3-one in 50 ml. of glacial acetic acid was treated with one drop of hydrogen bromide-saturated acetic acid and then dropwise over a 45-minute period with a solution of 1.76 g. of bromine and 0.90 g. of anhydrous fused sodium acetate in 50 ml. of acetic acid. The addition rate was regulated so that it did not exceed the bromine uptake rate. Water (150 ml.) was added with stirring and the resulting gum scratched until solidification occurred and it could be filtered. The product was washed, dried *in vacuo*, and recrystallized twice from methanol yielding 2.17 g. (56%) of pure **2α-bromo-2β-methylandrostan-17β-ol-3-one (VIIa)**, m.p. 130–132° dec., $[\alpha]D$ −5°, λ_{max} 311 mμ, log ε 2.10, infrared λ_{max}^{KBr} 5.83 μ negative Cotton effect (*c*, 0.061 in dioxane) with trough at $[\alpha]_{335}$ −662°.

Anal. Calcd. for $C_{20}H_{31}BrO_2$: C, 62.64; H, 8.15; Br, 20.87; O, 8.35. Found: C, 62.65; H, 7.87; Br, 21.17; O 8.42.

Acetylation of 2α-Bromo-2β-methylandrostan-17β-ol-3-one.—A solution of 0.26 g. of VIIa in 1 ml. of pyridine and 1 ml. of acetic anhydride was allowed to stand for 16 hours at room temperature. The solvent was removed *in vacuo* without heating and the residue crystallized from methanol yielding 0.18 g. of **2α-bromo-2β-methylandrostan-17β-ol-3-one acetate (VIIb)**, m.p. 112–114°, $[\alpha]D$ −5°, identical with the sample prepared from the enol acetate VI.

Dehydrobromination of 2α-Bromo-2β-methylandrostan-17β-ol-3-one (VIIa). (a) With Collidine.—Compound VIIa (1.1 g.) was dehydrobrominated with 30 ml. of boiling collidine as described in the preparation of IVa above. The crude dehydrobromination product was purified by chromatography on 30 g. of alkaline alumina. The hexane–benzene (1:3) fractions yielded, after recrystallization from acetone–hexane, 0.4 g. of **Δ¹-2-methylandrosten-17β-ol-3-one (IVa)**, m.p. 155–157°, λ_{max} 241 mμ, log ε 4.00, identical with the sample reported above.

(25) *Cf.* V. R. Mattox and E. C. Kendall, THIS JOURNAL, **70**, 882 (1948); C. Djerassi, *ibid.*, **71**, 1003 (1949).

(26) Somewhat better yields are obtained by the substitution of *p*-toluenesulfonic acid for sulfuric acid. Private communication from Dr. J. C. Orr.

(27) Experiment carried out by Dr. J. C. Orr of these laboratories.

(b) **With 2,4-Dinitrophenylhydrazine.**—Treatment of VIIa with dinitrophenylhydrazine in boiling acetic acid for 5 minutes as described above gave the **2,4-dinitrophenylhydrazone** of **2-methyl-Δ^1-androsten-17β-ol-3-one**, m.p. 266–268°, identical with the product prepared from IVa.

Hydrogen Bromide-catalyzed Equilibration of **2α-Bromo-2β-methylandrostan-17β-ol-3-one Acetate (VIIb).** (a) **Kinetic Run.**—To VIIb, 1.2 g., dissolved in 30 ml. of glacial acetic acid, three drops of saturated hydrogen bromide–acetic acid solution was added with stirring. Stirring was discontinued and at given intervals aliquots of 5 ml. were withdrawn and added to 50 ml. of stirred ice-cold water. The precipitates were filtered after standing for 3 to 5 minutes, washed well with water and dried for 1 hour over potassium hydroxide in a vacuum desiccator and then dried for 1 hour in high vacuum. The constants, which were then determined, are recorded in Table II of the text.

(b) **Preparative Equilibration.** Isolation of **4α-Bromo-2α-methylandrostan-17β-ol-3-one Acetate (IX)** and **2β-Bromo-2α-methylandrostan-17β-ol-3-one Acetate (VIII).**—A solution of 1.0 g. of VIIb in 30 ml. of glacial acetic acid containing 3 drops of hydrogen bromide–acetic acid was allowed to stand for 20 hours at room temperature. The water-precipitated and washed product was dried overnight in a vacuum desiccator and then suspended in 40 ml. of ether. The mixture was boiled for a few minutes and the insoluble portion (mainly IX) filtered. This fraction, **4α-bromo-2α-methylandrostan-17β-ol-3-one acetate (IX)**, after three crystallizations from methylene dichloride–methanol melted constantly at 147–150° dec. (0.12 g.), $[\alpha]_D$ −28°, no ultraviolet maximum between 270–320 mμ, infrared λ_{max}^{KBr} 5.80 μ, positive Cotton effect (*c*, 0.108 in methanol) with peak at $[\alpha]_{302.5}$ + 222° (for curve see ref. 18, p. 127).

Anal. Calcd. for $C_{22}H_{33}BrO_3$: C, 62.11; H, 7.85; Br, 18.78; O, 11.28. Found: C, 62.24; H, 7.61; Br, 18.96; O, 11.52.

The ether solution was concentrated, depositing a mixture of IX and of VIII, and then was taken to dryness. Several recrystallizations of the residue from methylene dichloride–methanol gave 0.25 g. of pure **2β-bromo-2α-methylandrostan-17β-ol-3-one acetate (VIII)**, m.p. 135–140° dec., $[\alpha]_D$ + 100°, λ_{max} 307 mμ, log ϵ 2.06; infrared λ_{max}^{KBr} 5.86, 5.81 μ; positive Cotton effect (*c*, 0.090 in methanol) with peak at $[\alpha]_{330}$ +2480°.

Anal. Calcd. for $C_{22}H_{33}BrO_3$: C, 62.11; H, 7.85; Br, 18.78. Found: C, 62.03; H, 7.59; Br, 19.00.

(c) **Preparative Equilibration Followed by Dehydrobromination.**—2α-Bromo-2β-methylandrostan-17β-ol-3-one acetate (VIIb) (0.9 g.) was equilibrated with hydrogen bromide–acetic acid for 23 hours as described above. The crude product ($[\alpha]_D$ + 36°. Found: Br, 16.0) was dehydrobrominated by heating for 3.5 hours, in a nitrogen atmosphere, with 2.0 g. of lithium carbonate and 1.5 g. of lithium bromide in 70 ml. of boiling dimethylformamide. The cooled suspension was filtered and the filtrate concentrated to dryness *in vacuo*. The residue was chromatographed on 50 g. of silica gel whence the first group of benzene eluates (259 mg.) were combined and crystallized from acetone–hexane yielding 80 mg. of **Δ^1-2-methylandrosten-17β-ol-3-one acetate (IVc)**, m.p. 143–146°. Continued elution with benzene yielded 264 mg. of product which after acetone–hexane recrystallization yielded 75 mg. of **2α-methyltestosterone acetate (X)**, m.p. 170–174°. Rechromatography of the mother liquors furnished an additional 83 mg. of IVc, m.p. 145–148°, and 54 mg. of X, m.p. 175–180°. Identity of these fractions was established by ultraviolet spectrum, by conversion to their 2,4-dinitrophenylhydrazones, by mixture melting point determination and by infrared comparison with authentic samples.

Dehydrobromination of 2β-Bromo-2α-methylandrostan-17β-ol-3-one Acetate (VIII). (a) **With Collidine.**—Compound VIII, 1.42 g., was dehydrobrominated with 10 ml. of boiling collidine as described above for the preparation of IVa and the crude reaction product chromatographed on 50 g. of neutral alumina. The hexane eluates were crystallized from acetone–hexane yielding 0.53 g. of **2-methyl-Δ^1-androsten-17β-ol-3-one acetate (IVc)**, m.p. 143–145°, $[\alpha]_D$ + 31°, λ_{max} 241 mμ, log ϵ 4.01. The infrared spectrum was identical with an authentic specimen and the two samples gave no melting point depression on admixture.

(b) **With Dinitrophenylhydrazine.**—Dehydrobromination in hot acetic acid, effected as described above, gave the authentic **2,4-dinitrophenylhydrazone** of **2-methyl-Δ^1-androsten-17β-ol-3-one acetate**, m.p. 263–265°.

Dehydrobromination of 4α-Bromo-2α-methylandrostan-17β-ol-3-one Acetate (IX). (a) **With Collidine.**—Compound IX, 0.83 g., was dehydrobrominated with 10 ml. of boiling collidine as described for IVa. The residue was chromatographed on 15 g. of silica, hexane–benzene (1:1) eluting material melting between 160–175° which was combined and recrystallized from methanol yielding 0.29 g. of **2α-methyltestosterone acetate (X)**, m.p. 178–180°, λ_{max} 240 mμ, log ϵ 4.20 and 0.14 g. of X, m.p. 165–167°, λ_{max} 240 mμ, log ϵ 4.19. Neither sample gave a melting point depression with analytically pure X of m.p. 184–186° and the infrared spectra of the three samples were virtually superimposable.

(b) **With 2,4-Dinitrophenylhydrazine.**—Dehydrobromination of IX with dinitrophenylhydrazine in boiling acetic acid as described above gave **2α-methyltestosterone acetate 2,4-dinitrophenylhydrazone**, m.p. 271–273°, $\lambda_{max}^{CHCl_3}$ 385 mμ, log ϵ 4.43, identical with the product prepared from X.

Thermal Dehydrobromination of 4α-Bromo-2α-methylandrostan-17β-ol-3-one Acetate (IX).[27]—A solution of 4α-bromo-2α-methylandrostan-17β-ol-3-one (39 mg.) in acetic acid (1.0 ml.) was boiled on a hot-plate. Evolution of hydrogen bromide was rapid but had ceased after 3 minutes. After 6 minutes boiling, only about 0.2 ml. of solvent remained. Cooling and addition of methanol yielded 28 mg. of tan crystals which was chromatographed on 1.0 g. of ethyl acetate-washed alumina. The first product eluted from the column (16 mg.) was shown to be **2-methyl-Δ^1-androsten-17β-ol-3-one acetate (IVc)**. Recrystallization from methanol gave material of m.p. 139–141°, undepressed on admixture with authentic IVc. Identity was further established by infrared comparison and by conversion to the dinitrophenylhydrazone.

The second substance eluted from the column, **2α-methyltestosterone acetate (X)** (11 mg.) was recrystallized from methanol to m.p. 178–181° undepressed with authentic X and was converted to the 2,4-dinitrophenylhydrazone of X, m.p. 268–270°, whose infrared spectrum in chloroform confirmed the assigned structure.

2-Dimethylaminomethylandrostan-17β-ol-3-one (XII).—A mixture of androstan-17β-ol-3-one (6 g.), paraformaldehyde (2.5 g.), dimethylamine hydrochloride (5 g.) and 96% ethanol (75 ml.) was boiled for 3.5 hours and then concentrated to about half the original volume. Water (200 ml.) was added, then 5 ml. of concentrated hydrochloric acid and the insoluble residue filtered. The filtrate was basified with potassium carbonate solution and the Mannich base isolated by ether extraction. Crystallization from acetone gave 4.1 g. of 2-dimethylaminomethylandrostan-17β-ol-3-one, m.p. 167–170°. The analytical specimen from the same solvent melted at 170–171° dec.

Anal. Calcd. for $C_{22}H_{37}NO_2$: C, 76.00; H, 10.73; N, 4.05. Found: C, 76.09; H, 10.70; N, 4.26.

Dimer of 2-Methyleneandrostan-17β-ol-3-one Acetate (XI). (a) **From 2-Dimethylaminoandrostan-17β-ol-3-one (XII).**—A solution of 100 mg. of XII in 2 ml. of benzene was adsorbed onto a column of 3 g. of alkaline alumina and allowed to stand for 1.25 hours. The product, isolated by chloroform elution, was acetylated with 2 ml. of pyridine and 1.7 ml. of acetic anhydride at room temperature for 16 hours. Isolation in the usual manner gave a residue melting at 235–245°. Crystallization from acetone yielded the analytical specimen, m.p. 249–250°, $[\alpha]_D$ +47°, no selective absorption in the ultraviolet; infrared λ_{max}^{KBr} 5.81 μ.

Anal. Calcd. for $C_{44}H_{64}O_6$: C, 76.70; H, 9.36; O, 13.93. Found: C, 76.72; H, 8.86; O, 13.97.

(b) **From 2α-Bromo-2β-methylandrostan-17β-ol-3-one Acetate (VIIb).**—A mixture of VIIb (0.90 g.), lithium carbonate (2.0 g.) and lithium bromide (1.5 g.) was heated in boiling dimethylformamide for 3.5 hours under a nitrogen atmosphere. The cooled suspension was filtered and the filtrate evaporated to dryness, *in vacuo*. The residue was chromatographed on 50 g. of silica gel yielding in the benzene–chloroform fractions, 0.26 g. of 2-methyl-Δ^1-androsten-17β-ol-3-one acetate (IVc), m.p. 140–145°, while the chloroform eluate gave, after crystallization from methanol, 0.165 g. of dimer XI, m.p. 235–237°. Further recrystallization raised the melting point to 245–247°, undepressed on admixture with the product obtained in (a), and the infrared spectra of the two samples were identical.