charcoal, and evaporated again under reduced pressure; yield 300 mg., m.p. 182–184°, $[\alpha]^{20}D$ −31° (*c* 1 in water).

Anal. Calcd. for $C_{10}H_{19}O_6N$: C, 48.17; H, 7.70; N, 5.62. Found: C, 48.01; H, 7.61; N, 5.52.

[CONTRIBUTION FROM THE RESEARCH DIVISION OF THE SCHERING CORP.]

New Anabolic Agents: 9α,11β-Dihalogenoandrostane Derivatives

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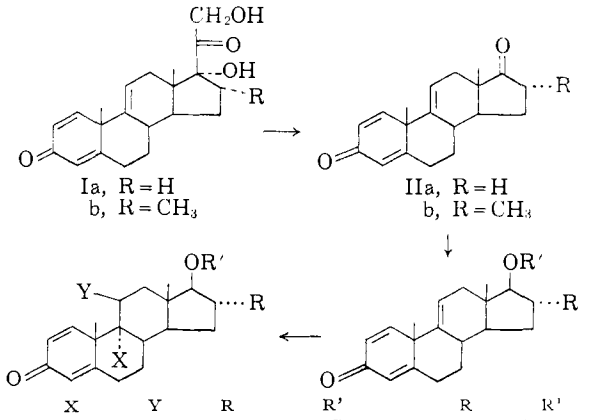
A number of 9α,11β-dihalogeno derivatives of testosterone, 1-dehydrotestosterone, methyltestosterone and 1-dehydromethyltestosterone have been synthesized. Some of these compounds possess favorable anabolic–androgenic ratios.

The synthesis of 19-nortestosterone[2] in 1950 (and the subsequently recognized fact[3] that this compound showed a favorable anabolic–androgenic ratio relative to testosterone) marked the beginning of an intensive search[4] for anabolic agents in both the androstane and estrane series.

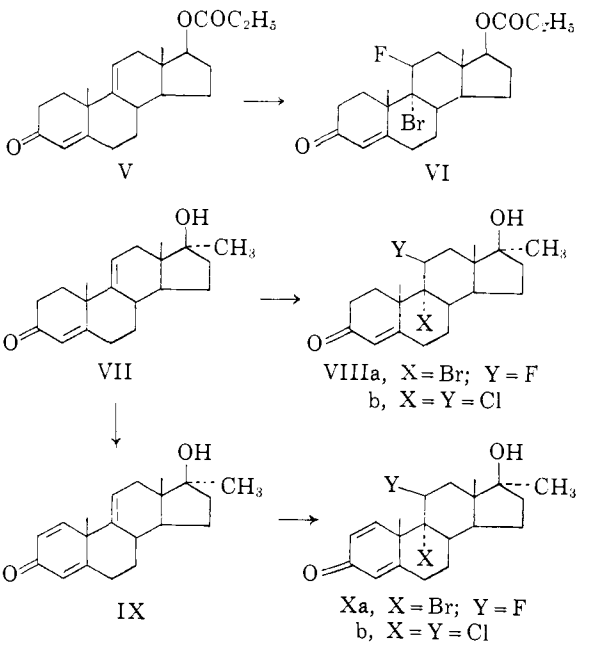
CHART I



	X	Y	R	R'		R	R'
IVa	Br	Cl	H	COC_2H_5	IIIa	H	H
b	Br	F	H	COC_2H_5	b	H	COC_2H_5
c	Cl	Cl	H	COC_2H_5	c	CH_3	H
d	Cl	F	H	COC_2H_5	d	CH_3	COC_2H_5
e	Cl	F	H	H			
f	Br	F	CH_3	COC_2H_5			
g	Cl	Cl	CH_3	COC_2H_5			
h	Br	$OCOCH_3$	H	COC_2H_5			
i	Br	$OSO_2C_6H_5$	H	COC_2H_5			

In view of the physiological activity manifested by 9,11-dihalogenocorticoids[5] and progestins,[6] the preparation and biological evaluation of the corresponding androstane analogs were undertaken in these laboratories. As will be shown in the sequel, this new class of hormone analogs provides yet another example of physiologically active 9α,11β-dihalogeno steroids.

CHART II



The androstatrienediones IIa and IIb served as starting materials for the key intermediates IIIb and IIId, which led to a series of 9,11-disubstituted derivatives of 1-dehydrotestosterone propionate.

Thus, enzymic reduction[7,8] at C-17 of 1,4,9(11)-androstatriene-3,17-dione[5,9] proceeded uneventfully in 55% yield, to give 1,4,9(11)-androstatrien-17β-ol-3-one (IIIa) which was converted to the 17β-propionate IIIb.

The preparation of 16α-methyl-1,4,9(11)-androstatriene-3,17-dione (IIb) from 16α-methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione-21-acetate[10] followed conventional procedures (*i.e.*, hydrolysis to the 21-alcohol followed by sodium bismuthate degradation), and reduction by yeast then afforded the desired 17β-ol IIIc and thence the 17β-propionate IIId.

(1) C. H. Robinson, L. E. Finckenor, R. Tiberi and Eugene P. Oliveto (Natural Products Research Dept.); M. Eisler, R. Neri, A. Watnick and P. L. Perlman (Biochemistry Dept.); P. Holroyd and W. Charney (Industrial Microbiology Dept.).

(2) A. J. Birch, *J. Chem. Soc.*, 367 (1950).

(3) (a) L. G. Hershberger, E. G. Shipley and R. K. Meyer, *Proc. Soc. Exper. Med.*, **83**, 175 (1953); (b) R. S. Stafford, B. J. Bowman and K. J. Olsen, *ibid.*, **86**, 322 (1954); (c) F. J. Saunders and V. A. Drill, *Endocrinol.*, **58**, 567 (1956).

(4) (a) For pertinent references see L. F. Fieser and M. Fieser, "Steroids," Reinhold Publ. Corp., New York, N. Y., 1959, p. 592 *et seq.* (b) See also R. O. Clinton, A. J. Manson, F. W. Stonner, A. L. Beyler, G. O. Potts and A. Arnold, THIS JOURNAL, **81**, 1513 (1959).

(5) C. H. Robinson, L. Finckenor, E. P. Oliveto and D. H. Gould, *ibid.*, **81**, 2191 (1959).

(6) H. Reimann, E. P. Oliveto, R. Neri, M. Eisler and P. Perlman, *ibid.*, **82**, 2308 (1960).

(7) L. Mamoli and A. Vercellone, *Ber.*, **70**, 470 (1937).

(8) H. L. Herzog, M. A. Jevnik, P. L. Perlman, A. Nobile and E. B. Hershberg, THIS JOURNAL, **75**, 266 (1953).

(9) B. J. Magerlein and J. A. Hogg, *ibid.*, **80**, 2220 (1958).

(10) E. P. Oliveto, R. Rausser, L. Weber, A. L. Nussbaum, W. Gebert, C. T. Coniglio, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman and M. M. Pechet, *ibid.*, **81**, 4431 (1959).

The 9α,11β-dihalogenated derivatives of IIIb and IIId were secured by procedures essentially the same as those previously used[5] in the cortical series, namely the use of N-haloamides in the presence of the appropriate anion. However, the addition of ClF to the 9(11)-double bond, while employing N-chlorosuccinimide and hydrogen fluoride (thus being analogous with the method of BrF addition developed in these laboratories) was performed in pyridine–carbon tetrachloride mixtures.[11]

The structures of compounds IVa–IVg are assigned on the bases of elemental analysis, spectroscopic evidence and analogy with the additions to the 9(11)-double bond reported earlier.[5]

The mildness of the N-chlorosuccinimide–hydrogen fluoride system described above is worthy of note. Addition of ClF can be carried out in the presence of an unprotected secondary hydroxyl, as exemplified by the conversion of 1,4,9(11)-androstatrien-17β-ol-3-one to the 9α-chloro-11β-fluoro-1,4-androstadien-17β-ol-3-one (IVe) in good yield. Propionylation of IVe in pyridine with propionic anhydride gave the 17β-propionate IVd, prepared also by addition of ClF to 1,4,9(11)-androstatrien-17β-ol-3-one 17β-propionate (IIIb).

A 1,2-dihydro analog of the above compounds was also prepared, by the addition of BrF to 4,9-(11)-androstadien-17β-ol-3-one 17β-propionate,[12] to give 9α-bromo-11β-fluoro-4-androsten-17β-ol-3-one 17β-propionate (VI).

Since the 9α-bromo-11β-fluoro- and 9α-bromo-11β-chloro-1-dehydrotestosterone derivatives (IVb and IVa, respectively) displayed similar activities, we were led to speculate whether the nature of the 11-substituent was critical. To test this hypothesis, we prepared 9α-bromo-11β-acetoxy-1-dehydrotestosterone propionate (IVh) by the N-haloamide procedure,[13] and attempted to prepare the 9α-bromo-11β-methoxy analog. Treatment of the 1,4,9(11)-triene IIIb with N-bromoacetamide in methanol[14] gave very poor yields of solid bromine-containing product. However, addition of 1.1 equivalents of *p*-toluenesulfonic acid to the reaction mixture resulted in the isolation of a crystalline product, IVi, in excellent yield.

Elemental analysis indicated that we have in hand a compound resulting from the addition of Br–$C_6H_5SO_3$ to IIIb. The infrared spectrum showed bands at 7.32 and 7.44 μ and a very strong band at 8.54 μ (the latter being a summation band due partly to the 17-propionate group) characteristic of *p*-toluenesulfonate esters.[15] The ultraviolet absorption maximum appeared at 230 mμ (24,300) and is consistent with the presence of the A ring chromophor and a *p*-toluenesulfonate ester. The ultraviolet absorption due to an isolated tosylate grouping appears at 224–226 mμ (ε ~ 10,000) in the case of saturated steroidal 12α-tosylates[16] and tosylated sugars.[17]

In steroids containing an α,β-unsaturated ketone grouping and a 12α-tosylate, the observed ultraviolet absorption maxima are now similar to the curves constructed by adding the absorptions of the two chromophors.[16,18] Specific examples are 12α-tosyloxy-17α-methylprogesterone (λ_{max} 229 mμ, ε 17,800) and 12α-tosyloxyprogesterone (λ_{max} 228 mμ, ε 25,000).

We therefore formulate IVi as 9α-bromo-1,4-androstadiene-11β,17β-diol-3-one 11β-tosylate 17β-propionate. The procedure described above thus offers a route to the previously inaccessible steroidal 9α-halo-11β-tosylates and, possibly, to cyclic and acyclic α-halo-arylsulfonyl esters by a one-step process from olefins.

We finally turned our attention to the 17α-methyltestosterone series, and the bromofluoro and dichloro analogs VIIIa and VIIIb of methyltestosterone were prepared from 17α-methyl-4,9(11)-androstadien-17β-ol-3-one (VII).[19]

Conversion of VII to the 1-dehydro compound IX was accomplished microbiologically, using *Bacillus sphaericus*.[20] The 9,11-dihalogenated derivatives Xa and Xb of 1-dehydromethyltestosterone were then secured by our standard procedures.

Finally it may be noted that the assumption that no inversion had occurred at C-16 in the preparation of 16α-methyl-1,4,9(11)-androstatriene-3,-17-dione (IIb) has been confirmed in the following way. Sodium bismuthate degradation of 16β-methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione[21] furnished a methylandrostatrienedione *differing* from IIb. This 17-ketone, which is thus the 16β-methyl analog of IIb, has been reduced to the corresponding 17β-alcohol, which differs from 16α-methyl-1,4,9(11)-androstatrien-17β-ol-3-one (IIc). The 16α-configuration for IIc is thereby confirmed.

A preliminary screening test for androgenic and myotrophic activity of the compounds was done using the immature male rat weighing 50–60 g. Androgenic activity was revealed by the increase in weight of the seminal vesicles and prostate over the controls. Myotrophic activity was determined by the increase in the levator ani muscle. If the compound was inactive as an androgen or in the myotrophic test no further tests were performed. If, however, the compound showed either androgenic or anabolic (myotrophic) activity, a 6-point bioassay was carried out to determine the dose response curve. The assay used was the response of the castrate rat seminal vesicle and growth of the levator ani, ac-

(11) Dr. M. Tanabe (Stanford Research Institute, Menlo Park, Calif.) has also independently observed the addition of chlorine fluoride to a $\Delta^{9(11)}$-steroid, using N-chlorosuccinimide and hydrogen fluoride in dimethylformamide. We wish to thank Dr. Tanabe for communicating his results to us, prior to publication.

(12) F. W. Heyl and M. E. Herr, THIS JOURNAL, **77**, 488 (1955).

(13) C. H. Robinson, L. Finckenor, M. Kirtley, D. Gould and E. P. Oliveto, *ibid.*, **81**, 2195 (1959).

(14) *Cf.* W. H. Puterbaugh and M. S. Newman, *ibid.*, **79**, 3469 (1957).

(15) *Cf.* L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 364.

(16) C. R. Engel, K. F. Jennings and C. Just, THIS JOURNAL, **78**, 6153 (1956).

(17) A. L. Bernoulli and H. Stauffer, *Helv. Chim. Acta*, **23**, 615 (1940).

(18) G. Just and C. R. Engel, *J. Org. Chem.*, **23**, 12 (1958).

(19) M. E. Herr, J. A. Hogg and R. H. Levin, THIS JOURNAL, **78**, 500 (1956).

(20) T. H. Stoudt, W. J. McAleer, J. M. Chemerda, M. A. Kozlowski, R. F. Hirschmann, V. Marlatt and R. Miller, *Arch. Biochem. and Biophys.*, **59**, 304 (1955).

(21) A detailed account of the preparation of these 16β-methyl compounds, and of some subsequent transformations, will be given shortly.

cording to the method of Hershberger, Shipley and Meyer.[3a]

Compounds IVc and IVe were found to have strong androgenic activity and no estimation was made of the myotrophic–androgenic activity ratio. Table I summarizes the myotrophic–androgenic activity of compounds IVa, IVb, IVd, VIIIa, Xa and Xb. Compound IVb has high myotrophic (anabolic) activity, and low androgenic activity. In comparing compounds IVa and IVd to compound IVb, interesting biological results are noted. The substitution of a chlorine atom for fluorine at C-11 reduces the myotrophic activity, while the substitution of a chlorine at C-9 instead of bromine further reduces the myotrophic–androgenic ratio when compared to the standard, testosterone propionate.

In compound VIIIa in which methyltestosterone has been modified by the insertion of a 9α-bromo-11β-fluoro grouping, the myotrophic ratio is increased. Dehydrogenation of compound VIIIa at C-1 and C-2, resulting in compound Xa, lowers the ratio appreciably. Compound Xb which is the 9α,11β-dichloro analog of compound Xa, shows an appreciable increase in the myotrophic–androgenic ratio (Table I).

TABLE I

SUMMARY OF ASSAYS OF MYOTROPHIC AND ANDROGENIC ACTIVITY[a]

Compound	Androgenic	Myotropic	M/A ratio[b]	Ref. cmpd.[c]
IVa	0.044 (0.029–0.054)	0.340 (0.220–0.570)	7.7	TP
IVb	0.06 (0.04–0.11)	0.77 (0.47–1.34)	12.8	TP
IVd	0.51 (0.40–0.64)	0.84 (0.54–1.86)	1.6	TP
VIIIa	0.04 (0.03–0.05)	0.17 (0.04–0.30)	4.2	MT
Xb	0.60 (0.45–0.80)	3.0 (1.7–7.8)	5.0	MT
Xa	0.12 (0.07–0.18)	0.23 (0.11–0.37)	1.9	MT

[a] Six point assay. [b] Myotrophic/androgenic = potency ratio. [c] TP = Testosterone propionate; MT = methyltestosterone; figures in parentheses indicate ranges.

Experimental[22]

16α-Methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione (Ib).—A solution of 16α-methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 21-acetate[10] (10 g.) in 0.27 *N* methanolic perchloric acid[23] (70 ml.) was allowed to stand at room temperature for 17 hours. The reaction mixture was poured into water (3.0 l.) and extracted with methylene chloride. The methylene chloride was washed with water, 10% aqueous sodium carbonate and water, dried ($MgSO_4$) and concentrated to dryness *in vacuo*. The crude product was crystallized from acetone–hexane and yielded, in two crops, Ib (5.4 g.). The analytical sample had m.p. 228–231°, $[\alpha]D$ + 8°, λ_{max}^{MeOH} 238 mμ (16,100); λ_{max}^{Nujol} 2.94, 5.80, 6.03, 6.24 μ.

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.39; H, 8.03.

(22) Melting points were obtained on the Kofler block. Rotations were measured at 25° in dioxane solution at about 1% concentration. We are indebted to the Physical Chemistry Department, Schering Corp., for measurement of ultraviolet and infrared spectra. Microanalyses were carried out by Mr. E. Conner (Microanalytical Laboratory, Schering Corp.), and by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(23) J. Fried and E. F. Sabo, THIS JOURNAL, **79**, 1130 (1957).

16α-Methyl-1,4,9(11)-androstatriene-3,17-dione (IIb).—To a solution of 16α-methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione (Ib, 5.0 g.) in 50% aqueous acetic acid (300 ml.) at 90–100° was added sodium bismuthate (25 g.) and the suspension was stirred at 90–100° for 0.5 hour. The reaction mixture was filtered and extracted with methylene chloride. The methylene chloride was washed successively with water, 10% aqueous sodium hydroxide and water, dried ($MgSO_4$) and evaporated *in vacuo* to yield oil (2.5 g.). The oil was filtered through Florisil (75 g.) in ether–hexane (1:1) giving solid which was crystallized from acetone–hexane to yield IIb, (1.5 g.), m.p. 138–139°, $[\alpha]D$ + 83°, λ_{max}^{MeOH} 238 mμ (15,500); λ_{max}^{Nujol} 5.78, 6.00, 6.15, 6.23 μ.

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.31; H, 8.13.

1,4,9(11)-Androstatrien-17β-ol-3-one (IIIa) by Enzymic Reduction of 1,4,9(11)-Androstatriene-3,17-dione.[5,9]—The inoculum consisted of a 24-hour culture of *Saccharomyces cerevisiae* (A.T.T.C. No. 4125) grown on a shaker at 28°. A 6% level was used for inoculum. For both the inoculum and the fermentor the following medium was used: Difco yeast extract (1%), KH_2PO_4 (0.45%), Na_2HPO_4 (0.47%), dextrose (6%), *p*H 6.8.

The fermentor was made up, the medium (10 liters) was poured in, and the entire assembly was autoclaved at 121° for 30 minutes. After inoculation the air-flow was adjusted to 1 volume of air per volume of medium per minute. After 25 hours growth, a solution of 1,4,9(11)-androstatriene-3,17-dione (1.0 g.) in ethanol (20 ml.) was added, and the air-rate was increased to 1.5 volumes of air per volume of medium per minute. Fermentation was continued until a chromatographic sample showed that all the starting material had been converted. (This usually took *ca.* 120 hours after addition of the steroid.) Fresh sterile medium was added daily to make up loss due to evaporation. The steroid was extracted from the broth by adsorption upon Bentonite, and was then eluted with methanol, the methanol eluates being evaporated to dryness *in vacuo*. Paper chromatography (toluene–propylene glycol system) confirmed conversion of the starting material to a more polar product. The crude residue was now exhaustively extracted with ether, and the ethereal extract was filtered through a column of Florisil. The solids thereby obtained were crystallized from acetone–hexane to give IIIa (550 mg.), m.p. 140–145°. The analytical sample, prepared by recrystallization from acetone–hexane had m.p. 145–148°, $[\alpha]D$ −28°, λ_{max}^{MeOH} 238 mμ (15,300); λ_{max}^{Nujol} 2.92, 6.02, 6.16, 6.24 μ.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 79.91; H, 8.90.

1,4,9(11)-Androstatriene-17β-ol-3-one 17β-Propionate (IIIb).—The foregoing compound (IIIa, 450 mg.) was treated with propionic anhydride (5 ml.) in pyridine (10 ml.) and the solution was left at room temperature for 17 hours. Water was then added, and the mixture, after 3 hours, was extracted with methylene chloride. The extract was washed successively with 2 *N* hydrochloric acid and water, evaporated *in vacuo*, and the crude residue was filtered through a short Florisil column in ether solution. Evaporation of the eluate and crystallization from acetone–hexane furnished pure IIIb, m.p. 137–138°, $[\alpha]D$ −12°, λ_{max}^{MeOH} 238 mμ (15,600); λ_{max}^{Nujol} 5.78, 6.02, 6.16, 6.24, 8.40 μ.

Anal. Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.94; H, 8.46.

16α-Methyl-1,4,9(11)-androstatrien-17β-ol-3-one (IIIc) by Enzymic Reduction of 16α-Methyl-1,4,9(11)-androstatriene-3,17-dione (IIb).—The 16α-methyl-1,4,9(11)-androstatriene-3,17-dione was reduced enzymically by exactly the same procedure described for the preparation of IIIa. The crude product was filtered through a column of Florisil, in ether, and the solids thereby obtained were crystallized from acetone–hexane to give pure IIIc, m.p. 172–174°, $[\alpha]D$ −46°, λ_{max}^{MeOH} 238 mμ (15,400); λ_{max}^{Nujol} 2.92, 6.03, 6.18, 6.24 μ.

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.71; H, 8.56.

16α-Methyl-1,4,9(11)-androstatrien-17β-ol-3-one 17β-Propionate (IIId).—To a stirred solution of 16α-methyl-1,4,9(11)-androstatrien-17β-ol-3-one (IIIc, 3.0 g.) in pyridine (30 ml.) was added propionic anhydride (3.0 ml.) and the solution was left at room temperature for 18 hours.

Water (3.0 ml.) was added and the mixture allowed to stand for 15 minutes before being poured into cold 5% aqueous sulfuric acid (300 ml.). The crude solid was filtered, dried and crystallized from acetone–hexane to yield IIId (1.6 g.), m.p. 140–143°, $[\alpha]D$ −27°, λ_{max}^{MeOH} 238 mμ (15,600); λ_{max}^{Nujol} 5.75, 5.98, 6.14, 6.22, 8.38 μ.

Anal. Calcd. for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 77.68; H, 8.80.

9α-Bromo-11β-chloro-1,4-androstadien-17β-ol-3-one 17β-Propionate (IVa).—To a stirred solution of 1,4,9(11)-androstatrien-17β-ol-3-one 17β-propionate (IIIb, 800 mg.) and lithium chloride (4.0 g.) in glacial acetic acid (30 ml.) was added N-bromoacetamide (367 mg.) followed immediately by an anhydrous solution of hydrogen chloride (92 mg.) in tetrahydrofuran (0.5 ml.). Stirring was continued for 3 hours, after which the reaction mixture was poured into cold water (300 ml.) and filtered. The crude product was dried *in vacuo* and crystallized from ether–pentane to yield pure IVa (530 mg.), m.p. 128–130° dec., $[\alpha]D$ + 116°, λ_{max}^{MeOH} 239 mμ (13,800); λ_{max}^{Nujol} 5.76, 5.96, 6.12, 6.18, 8.40 μ.

Anal. Calcd. for $C_{22}H_{28}O_3BrCl$: C, 57.96; H, 6.19; Br, 17.53; Cl, 7.78. Found: C, 58.01; H, 6.36; Br, 17.50; Cl, 7.95.

9α-Bromo-11β-fluoro-1,4-androstadien-17β-ol-3-one 17β-Propionate (IVb).—To a stirred solution of 1,4,9(11)-androstatrien-17β-ol-3-one 17β-propionate (IIIb, 600 mg.) in diethylacetic acid (25 ml.) was added N-bromoacetamide (267 mg.) followed immediately by a solution of hydrogen fluoride (570 mg.) in tetrahydrofuran (2 ml.). Stirring was continued at room temperature for 24 hours and the reaction mixture was then poured into cold 10% aqueous sodium carbonate solution (300 ml.) and extracted with methylene chloride. The extract was washed successively with 10% aqueous sodium carbonate solution, *N* sodium thiosulfate solution and water, dried ($MgSO_4$) and evaporated *in vacuo*. The crude residue was crystallized from ether–pentane twice to give IVb (240 mg.), m.p. 164–165°, $[\alpha]D$ + 64°, λ_{max}^{MeOH} 239 mμ (14,400); λ_{max}^{Nujol} 5.80, 6.02, 6.15, 6.22, 8.40 μ.

Anal. Calcd. for $C_{22}H_{28}O_3BrF$: C, 60.14; H, 6.42; Br, 18.19; F, 4.32. Found: C, 60.22; H, 6.55; Br, 18.43; F, 4.13.

1,4,9(11)-Androstatrien-17β-ol-3-one 17β-Propionate (IIIb) from 9α-Bromo-11β-fluoro-1,4-androstadien-17β-ol-3-one 17β-Propionate (IVb).—To a solution of IVb (300 mg.) in acetone (20 ml.) was added chromous chloride solution[24] (20 ml., 5-ml. portions every 5 minutes). The reaction mixture was poured into water, extracted with methylene chloride, dried ($MgSO_4$) and concentrated to dryness to yield a colorless oil (200 mg.). Crystallization from acetone–hexane (b.p. 65°) yielded IIIb (50 mg.), m.p. 133–135°, undepressed on admixture with authentic IVb, infrared spectrum (Nujol) identical with that of authentic IIIb.

9α,11β-Dichloro-1,4-androstadien-17β-ol-3-one 17β-Propionate (IVc). A.—To a stirred, cooled (−20 to −25°) solution of 1,4,9(11)-androstatrien-17β-ol-3-one 17β-propionate (IIIb, 800 mg.) in carbon tetrachloride (30 ml.) and pyridine (0.7 ml.) was added chlorine (183 mg.) in carbon tetrachloride (3.0 ml.). Stirring was continued for 15 minutes at −20 to −25°, and then at room temperature for 1 hour. The reaction mixture was then poured into water (300 ml.) and the carbon tetrachloride layer was separated, washed successively with *N*-aqueous sodium thiosulfate, 10% aqueous sulfuric acid, 10% aqueous sodium bicarbonate and water, dried ($MgSO_4$) and evaporated *in vacuo*. The crude residue was crystallized from ether–pentane, to furnish IVc (186 mg.), m.p. 170–173°, $[\alpha]D$ + 105°, λ_{max}^{MeOH} 237 mμ (14,600); λ_{max}^{Nujol} 5.82, 6.04, 6.14, 6.22, 8.40 μ.

Anal. Calcd. for $C_{22}H_{28}O_3Cl_2$: C, 64.23; H, 6.86; Cl, 17.24. Found: C, 64.24; H, 7.15; Cl, 17.04.

A second crop of IVc (195 mg.) was obtained from ether–pentane, m.p. 166–170°; this material was identical with the analytical sample as judged by infrared comparison.

B.—Compound IVc was also prepared from IIIb (800 mg.) by the procedure described earlier for IVa, substituting N-chlorosuccinimide (345 mg.) for N-bromoacetamide. The crude product was chromatographed on Florisil, elution with ether–hexane (4:1) yielding solid which was crystallized from ether–pentane to give IVc (188 mg.), m.p. 170–173°, λ_{max}^{MeOH} 237 mμ (14,600). The infrared spectrum (Nujol) was identical with the spectrum of IVc prepared as in (A) above.

9α-Chloro-11β-fluoro-1,4-androstadien-17β-ol-3-one 17β-Propionate (IVd).—To a stirred suspension of 1,4,9(11)-androstatrien-17β-ol-3-one 17β-propionate (IIIb, 1.0 g.) in carbon tetrachloride (30 ml.) and pyridine (4 ml.) was added hydrogen fluoride (588 mg.) in chloroform–tetrahydrofuran (3:1; 1.5 ml.) and freshly crystallized N-chlorosuccinimide (432 mg.). Stirring was continued for 20 hours, and the reaction mixture was poured into 5% aqueous sodium carbonate solution (300 ml.) and extracted with methylene chloride. The methylene chloride extract was washed successively with water, 5% aqueous sulfuric acid, *N* sodium thiosulfate and water, dried ($MgSO_4$) and evaporated *in vacuo*. Trituration with ether gave a solid, which was crystallized from acetone–hexane to yield IVd (330 mg.), m.p. 171–175°, $[\alpha]D$ + 63°, λ_{max}^{MeOH} 237 mμ (15,000); λ_{max}^{Nujol} 5.80, 6.02, 6.14, 6.22, 8.40 μ.

Anal. Calcd. for $C_{22}H_{28}O_3ClF$: C, 66.91; H, 7.15; Cl, 8.98; F, 4.81. Found: C, 66.55; H, 7.17; Cl, 9.15; F, 4.64.

9α-Chloro-11β-fluoro-1,4-androstadien-17β-ol-3-one 17β-Propionate (IVd) from 9α-Chloro-11β-fluoro-1,4-androstadien-17β-ol-3-one (IVe).—A solution of IVe (80 mg.) in pyridine (0.80 ml.) and propionic anhydride (0.16 ml.) was left at room temperature for 17 hours. Water (0.2 ml.) was added and the mixture was poured into cold 10% aqueous sulfuric acid (10 ml.). The precipitated solid was filtered, dried and crystallized from acetone–hexane to yield IVd (65 mg.), m.p. 170–173°, (m.p. undepressed on admixture with authentic IVd); infrared spectrum (Nujol) identical with that of authentic IVd.

9α-Chloro-11β-fluoro-1,4-androstadien-17β-ol-3-one (IVe).—To a stirred solution of 1,4,9(11)-androstatrien-17β-ol-3-one (IIIa, 1.0 g.) and N-chlorosuccinimide (900 mg.) in carbon tetrachloride (30 ml.) and pyridine (4 ml.) was added hydrogen fluoride (588 mg.) in chloroform–tetrahydrofuran (3:1, 1.5 ml.). Stirring was continued for 20 hours. The reaction mixture was poured into 10% aqueous sodium carbonate (300 ml.), extracted with methylene chloride, washed with 5% aqueous sulfuric acid and water, dried ($MgSO_4$) and concentrated to yield a yellow solid. Crystallization from acetone–hexane afforded IVe (650 mg.), m.p. 210–215° dec. Recrystallization from acetone–hexane afforded the analytical sample, m.p. 212–215° dec., $[\alpha]D$ +73°, λ_{max}^{MeOH} 237 mμ, (14,900); λ_{max}^{Nujol} 2.94, 3.02, 6.02, 6.14, 6.20 μ.

Anal. Calcd. for $C_{19}H_{24}O_2ClF$: C, 67.34; H, 7.14; Cl, 10.47; F, 5.61. Found: C, 67.76; H, 6.82; Cl, 10.78; F, 5.46.

9α-Bromo-11β-fluoro-16α-methyl-1,4-androstadien-17β-ol-3-one 17β-Propionate (IVf).—To a solution of 16α-methyl-1,4,9(11)-androstatrien-17β-ol-3-one 17β-propionate (IIId, 700 mg.) in diethylacetic acid (28 ml.) was added N-bromoacetamide (300 mg.) followed immediately by hydrogen fluoride (395 mg.) in a solution of chloroform–tetrahydrofuran (3:1, 1.5 ml.) and stirring was continued for 18 hours. (The reaction was carried out in a polyethylene bottle using magnetic stirring.) The reaction mixture was poured into 10% aqueous sodium carbonate (300 ml.), extracted with methylene chloride, and the extract was washed with 5% aqueous sodium hydroxide and water, dried ($MgSO_4$) and concentrated to dryness. The crude product was triturated with ether and the residual solid recrystallized from aqueous methanol to yield IVf (380 mg.), m.p. 163–165°, $[\alpha]D$ + 35° λ_{max}^{MeOH} 239 mμ (14,400); λ_{max}^{Nujol} 5.78, 6.00, 6.12, 6.18, 8.40 μ.

Anal. Calcd. for $C_{23}H_{30}O_3BrF$: C, 60.93; H, 6.67; Br, 17.63; F, 4.19. Found: C, 61.21; H, 6.79; Br, 17.01; F, 3.89.

9α,11β-Dichloro-16α-methyl-1,4-androstadien-17β-ol-3-one 17β-Propionate (IVg).—To a stirred solution of 16α-methyl-1,4,9(11)-androstatrien-17β-ol-3-one 17β-propionate (IIId, 700 mg.), lithium chloride (3 g.) and N-chlorosuccinimide (290 mg.) in acetic acid (30 ml.) was added aqueous *N* hydrochloric acid (2.23 ml.) and stirring was continued for 3 hours. The reaction mixture was poured into water

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(300 ml.), filtered and dried to yield 700 mg. of crude product. Crystallization from acetone–hexane afforded IVg (280 mg.), m.p. 188–192° dec., $[\alpha]D$ + 80°, λ_{max}^{MeOH} 237 mμ (15,000); λ_{max}^{Nujol} 5.80, 6.02, 6.14, 6.20, 8.40 μ.

Anal. Calcd. for $C_{23}H_{30}O_3Cl_2$: C, 64.94; H, 7.11; Cl, 16.67. Found: C, 65.02; H, 7.41; Cl, 16.81.

9α-Bromo-1,4-androstadiene-11β,17β-diol-3-one 11β-Acetate 17β-Propionate (IVh).—To a stirred solution of 1,4,9(11)-androstatrien-17β-ol-3-one 17β-propionate (IIIb, 750 mg.) and lithium acetate (3.0 g.) in glacial acetic acid (30 ml.) was added N-bromoacetamide (335 mg.). The mixture was stirred for 24 hours at room temperature and was then poured into water (300 ml.), and filtered. The dried residue was crystallized from ether–pentane to give IVh (526 mg.), m.p. 161–166° dec., $[\alpha]D$ + 99°, λ_{max}^{MeOH} 239 mμ (13,600); λ_{max}^{Nujol} 5.75, 5.78, 6.02, 6.14, 6.22, 8.15, 8.36 μ.

Anal. Calcd. for $C_{24}H_{31}O_5Br$: C, 60.12; H, 6.52; Br, 16.67. Found: C, 60.28; H, 6.44; Br, 16.94.

9α-Bromo-1,4-androstadiene-11β,17β-diol-3-one 11β-*p*-Toluenesulfonate 17β-Propionate (IVi).—To a stirred solution of 1,4,9(11)-androstatrien-17β-ol-3-one 17β-propionate (IIIb, 1.0 g.) and *p*-toluenesulfonic acid monohydrate (615 mg.) in methanol (40 ml.) was added N-bromoacetamide (455 mg.). The solution immediately turned yellow, but after 15 minutes had decolorized and a crystalline solid had been deposited. The reaction mixture was chilled in the refrigerator for 0.5 hour and then filtered to yield IVi (780 mg.), m.p. 125–127° dec., $[\alpha]D$ + 50°, λ_{max}^{MeOH} 230 mμ (24,300); λ_{max}^{Nujol} 5.78, 5.98, 6.12, 6.18, 6.24, 6.7, 7.32, 7.44, 8.54 μ.

Anal. Calcd. for $C_{29}H_{33}O_6BrS$: C, 58.88; H, 5.96; Br, 13.51; S, 5.42. Found: C, 59.00; H, 6.03; Br, 14.29; S, 5.40.

9α-Bromo-11β-fluoro-4-androsten-17β-ol-3-one 17β-Propionate (VI).—By the procedure used for IVb, 4,9(11)-androstadien-17β-ol-3-one 17β-propionate (V, 1.0 g.) was converted to the 9α-bromo-11β-fluoro derivative VI which after two crystallizations from ether–pentane (yield 255 mg.) had m.p. 170–175°, $[\alpha]D$ + 80°, λ_{max}^{MeOH} 239 mμ (16,200); λ_{max}^{Nujol} 5.78, 6.02, 6.18, 8.08 μ.

Anal. Calcd. for $C_{22}H_{30}O_3BrF$: C, 59.86; H, 6.85; Br, 18.11; F, 4.30. Found: C, 59.82; H, 6.68; Br, 18.16; F, 4.05.

9α-Bromo-11β-fluoro-17α-methyl-4-androsten-17β-ol-3-one (VIIIa).—To a stirred solution of 17α-methyl-4,9(11)-androstadien-17β-ol-3-one (VII, 2.0 g.) in diethylacetic acid (120 ml.) was added hydrogen fluoride (5.8 g.) in chloroform–tetrahydrofuran (20.8 ml.) followed immediately by N-bromoacetamide (1.42 g.). The reaction mixture was stirred at room temperature for 2 hours, poured into water (1.2 l.) containing sodium carbonate (120 g.) and extracted with methylene chloride. The methylene chloride was washed with 5% aqueous sodium hydroxide and water, dried ($MgSO_4$) and concentrated to dryness to yield a yellow oil. The oil was chromatographed on silica gel (60 g., Davison Chem. Co., 100–200 mesh) and the product eluted with ether–hexane (3:2). Crystallization from acetone–hexane gave VIIIa, (500 mg.), m.p. 190–195° dec., $[\alpha]D$ + 84°, λ_{max}^{MeOH} 240 mμ (15,400); λ_{max}^{Nujol} 2.92, 5.98, 6.14 μ.

Anal. Calcd. for $C_{20}H_{28}O_2BrF$: C, 60.15; H, 7.07; Br, 20.01; F, 4.76. Found: C, 61.00; H, 7.25; Br, 19.82; F, 4.41.

9α,11β-Dichloro-17α-methyl-4-androsten-17β-ol-3-one (VIIIb).—Chlorine gas was bubbled at a slow rate for 30 seconds into a solution of 17α-methyl-4,9(11)-androstadien-17β-ol-3-one (VII, 1.0 g.) in methylene chloride (40 ml.) and pyridine (20 ml.). The mixture was stirred at room temperature for 1 hour, diluted with methylene chloride (100 ml.), washed with cold 10% aqueous sulfuric acid, *N* sodium thiosulfate and water, dried ($MgSO_4$) and concentrated to dryness. The residue was triturated with ether and the solid residue was then crystallized from acetone–hexane to yield VIIIb, (285 mg.), m.p. 228–234° dec., $[\alpha]D$ + 152°, λ_{max}^{MeOH} 238 mμ (16,800); λ_{max}^{Nujol} 2.94, 6.01, 6.16 μ.

Anal. Calcd. for $C_{20}H_{28}O_2Cl_2$: C, 64.69; H, 7.60; Cl, 19.10. Found: C, 64.47; H, 7.52; Cl, 19.24.

17α-Methyl-1,4,9(11)-androstatrien-17β-ol-3-one (IX).—17α-Methyl-4,9(11)-androstadien-17β-ol-3-one[19] (5.0 g.) was subjected to the action of *Bacillus sphaericus* following the procedure of Stoudt *et al.*[20] The crude extracts were adsorbed onto Florisil (10 g.), dried and chromatographed on Florisil (150 g.). The fractions eluted with ether–hexane (3:1) were crystallized with difficulty from ether–hexane to yield IX (2.1 g.), m.p. 136–139°, $[\alpha]D$ −52°, λ_{max}^{MeOH} 239 mμ (16,900 as ½ ether solvate); λ_{max}^{Nujol} 3.05, 6.04, 6.20, 6.24 μ.

Anal. Calcd. for $C_{20}H_{26}O_2 \cdot 1/2\ C_4H_{10}O$: C, 78.76; H, 9.31. Found: C, 79.01; H, 8.97.

In one experiment this compound was isolated with m.p. 68–70°, λ_{max}^{MeOH} 239 mμ (17,100 as ether solvate); λ_{max}^{Nujol} 2.95, 6.00, 6.16, 6.22 μ.

Anal. Calcd. for $C_{20}H_{26}O_2 \cdot C_4H_{10}O$: C, 77.37; H, 9.74. Found: C, 76.56; H, 9.31.

9α-Bromo-11β-fluoro-17α-methyl-1,4-androstadien-17β-ol-3-one (Xa).—To a solution of 17α-methyl-1,4,9(11)-androstatrien-17β-ol-3-one (IX, 1.0 g.) in diethylacetic acid (50 ml.) was added hydrogen fluoride (1.3 g.) in chloroform–tetrahydrofuran (3:1, 12 ml.) followed immediately by N-bromoacetamide (509 mg.). The reaction mixture was stirred for 1 hour at room temperature, then poured into water (500 ml.) containing sodium carbonate (50 g.) and extracted with methylene chloride. The methylene chloride was washed with 10% aqueous potassium hydroxide and water, dried ($MgSO_4$) and concentrated *in vacuo* to yield white solid. Crystallization from acetone–hexane afforded Xa (525 mg.), m.p. 192–197° dec., $[\alpha]D$ + 55°, λ_{max}^{MeOH} 239 mμ (14,500); λ_{max}^{Nujol} 3.0, 6.02, 6.15, 6.22 μ.

Anal. Calcd. for $C_{20}H_{26}O_2BrF$: C, 60.45; H, 6.60; Br, 20.11; F, 4.78. Found: C, 60.96; H, 6.42; Br, 20.00; F, 5.05.

9α,11β-Dichloro-17α-methyl-1,4-androstadien-17β-ol-3-one (Xb).—To a solution of 17α-methyl-1,4,9(11)-androstatrien-17β-ol-3-one (IX, 800 mg.) in methylene chloride (22 ml.) and pyridine (16 ml.) was added chlorine (285 mg.) in carbon tetrachloride (10 ml.). The mixture was stirred at room temperature for 1 hour, diluted with methylene chloride (100 ml.) and washed with 10% aqueous sulfuric acid, *N* sodium thiosulfate and water, dried ($MgSO_4$) and concentrated to dryness *in vacuo*. The solid residue was crystallized from acetone–hexane to yield Xb (475 mg.), m.p. 210–215°, $[\alpha]D$ + 121°, λ_{max}^{MeOH} 237 mμ (14,600); λ_{max}^{Nujol} 2.98, 6.00, 6.18, 6.22 μ.

Anal. Calcd. for $C_{20}H_{26}O_2Cl_2$: C, 65.04; H, 7.10; Cl, 19.20. Found: C, 64.85; H, 7.25; Cl, 19.03.

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