Steroids. CCVIII.[1] Ring A Modified Hormone Analogs. Part IV. 2-Chloro and 2-Halomethyl-Δ^2-androstenes

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The synthesis of 2-chloro-Δ^2-androstene-17β-ol acetate (Ic) from androstane-17β-ol-2-one acetate (IIf) is described. Syntheses of several 2-halo-methyl-Δ^2-androstenes are also reported and the structures of these compounds are confirmed by nuclear magnetic resonance spectroscopy.

The biological significance of sp^2 hybridization at C-2 and C-3 in the androstane molecule was clearly demonstrated in Part I[2] of this series. As a result of this finding our attention was focused on the preparation of C-2 substituted Δ^2-androstenes in order to evaluate their biological properties. The present paper is a continuation of this general study[1,2,3] and describes the synthesis of 2-chloro and 2-halomethyl derivatives of Δ^2-androstene-17β-ol acetate.

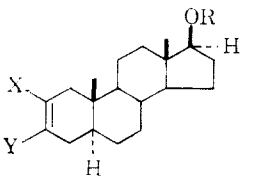
Recently Mamlok and Jacques[4] described a general procedure for the preparation of vinylic chlorides in the androstane series. This method involved the treatment of the steroidal ketone with phosphorus pentachloride in boiling chloroform to afford an uncharacterized intermediate, formulated by the French workers as a *gem*-dichloro compound. Subsequent dehydrohalogenation with collidine led to the vinyl chloride in 40-60% yield. Extension of this reaction to the ester derivatives of androstane-17β-ol-2-one (IIg) appeared to offer a route to 17-hydroxy-2-chloro-Δ^2-androstenes.

Although 2-ketosteroids have received very little attention, a number of procedures have been recorded in the literature for their preparation.[5] The method of Slates and Wendler[5b] appeared to be the most convenient and was adopted for this work.

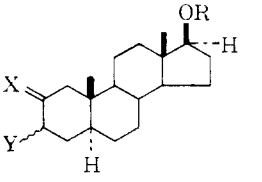
Reaction of Δ^2-androstene-17β-ol benzoate (Ib) with N-bromoacetamide and perchloric acid in tetrahydrofuran solution afforded a crystalline bromohydrin IIa, which was directly converted to 3ξ-bromoandrostane-17β-ol-2-one benzoate (IIb) with chromium trioxide in acetone–sulfuric acid solution.[6] Debromination of the ketone IIb with zinc dust in acetic acid yielded androstane-17β-ol-2-one benzoate (IIc).[7]

In the same manner, Δ^2-androstene-17β-ol acetate (Ic)[8] was converted to androstane-17β-ol-2-one acetate (IIf), without purification of the intermediate bromohydrin IId or the bromoketone IIe. Alkaline hydrolysis of the 2-keto acetate IIf gave androstane-17β-ol-2-one (IIg), identical in all respects with the product obtained by saponification of the 17-benzoate IIc.

Before proceeding with the halogenation of the 2-ketone IIf with phosphorus pentachloride, a preliminary investigation of this reaction was carried out with dihydrotestosterone acetate (IIIa). Treatment of the latter with phosphorus pentachloride according to the reported conditions[4] produced a mixture containing a considerable quantity of starting material. However, when carbon tetrachloride was employed as solvent a



Ia, X = Y = R = H
b, X = Y = H; R = COC_6H_5
c, X = Y = H; R = $COCH_3$
d, X = H; Y = Cl; R = $COCH_3$
e, X = Cl; Y = H; R = $COCH_3$
f, X = CHO; Y = H; R = $COCH_3$
g, X = CH_2OH; Y = H; R = $COCH_3$
h, X = CH_2OH; Y = R = H
j, X = CH_2Cl; Y = H; R = $COCH_3$
k, X = CH_2F; Y = H; R = $COCH_3$
m, X = CHF_2; Y = H; R = $COCH_3$
n, X = CHF_2; Y = R = H



IIa, X = OH, H; Y = H, Br; R = COC_6H_5
b, X = O; Y = ξBr; R = COC_6H_5
c, X = O; Y = H; R = COC_6H_5
d, X = OH, H; Y = H, Br; R = $COCH_3$
e, X = O; Y = ξBr; R = $COCH_3$
f, X = O; Y = H; R = $COCH_3$
g, X = O; Y = R = H
h, X = CH_2; Y = Cl, H; R = $COCH_3$
j, X = CH_2; Y = F, H; R = $COCH_3$

(1) Steroids CCVII and Part III, J. C. Orr, O. Halpern, P. G. Holton, F. Alvarez, I. Delfin, A. de la Roz, A. M. Ruiz and A. Bowers, *J. Med. Chem.*, **6**, 166 (1963).

(2) A. Bowers, A. D. Cross, J. A. Edwards, H. Carpio, M. C. Calzada and E. Denot, *ibid.*, **6**, 156 (1963).

(3) A. D. Cross, J. A. Edwards, J. C. Orr, B. Berköz, L. Cervantes, M. C. Calzada and A. Bowers, *ibid.*, **6**, 162 (1963).

(4) L. Mamlok and J. Jacques, *Bull. soc. chim. France*, 484 (1960).

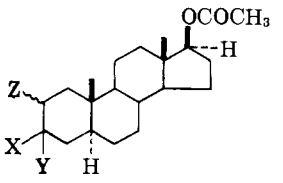
(5) (a) L. Ruzicka, P. A. Plattner, and M. Furrer, *Helv. Chim. Acta.*, **27**, 524 (1944); (b) H. L. Slates and N. L. Wendler, *J. Am. Chem. Soc.*, **78**, 3781 (1956); (c) F. Sondheimer and M. Nussim, *J. Org. Chem.*, **26**, 630 (1961).

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

(7) The preparation of androstane-17β-ol-2-one propionate by the same reaction sequence was reported earlier by R. R. Engle and C. Djerassi, Abstracts of 134th National Meeting of the American Chemical Society, Sept. 7, 1958, p. 15-O.

(8) R. E. Marker, O. Kamm, D. M. Jones and L. W. Mixon, *J. Am. Chem. Soc.*, **59**, 1363 (1937); see also ref. 2.

crystalline monochloro compound, formulated as 3-chloro-Δ^2-androstene-17β-ol acetate (Id), was isolated directly from the reaction mixture. Since the yield of Id was not markedly increased when the crude product was treated with collidine, the 3-chloro-Δ^2-compound is probably the major product of the phosphorus pentachloride reaction, in contrast to the observations of Mamlok and Jacques. It is interesting to note that Braude and Coles[9] have reported results in accord with our findings. These authors obtained 1-chlorocyclohex-1-ene directly from the reaction of phosphorus pentachloride and cyclohexanone.



IIIa, X, Y = O, Z = H
b, X = Y = Z = Cl

The vinyl chloride Id was not isolated, however, after prolonged treatment of dihydrotestosterone acetate (IIIa) with phosphorus pentachloride. Instead a new trichloro compound was obtained which had an analysis consistent with the formula $C_{21}H_{31}Cl_3O_2$. We considered 2ξ,3,3-trichloroandrostane-17β-ol acetate (IIIb) to be the most plausible structure for this substance, since its formation could be rationalized by the reaction of the 3 chloro-Δ^2-intermediate Id with molecular chlorine liberated by the dissociation of phosphorus pentachloride into its trivalent derivative.[10]

The reaction of androstane-17β-ol-2-one acetate (IIf) with phosphorus pentachloride in carbon tetrachloride solution proceeded according to our earlier finding to afford directly 2-chloro-Δ^2-androstene-17β-ol acetate (Ie).

It has been demonstrated previously that the elimination of a 3β-chloro[11] or 3β-tosyl[12] grouping affords predominantly the Δ^2-steroid admixed with a small amount of the Δ^3-isomer.[12] Consequently the possibility that the 3-chloroandrostene Id is contaminated with a small amount of its Δ^3-isomer cannot be ruled out. The assignment of a Δ^2-double bond in the 2-chloroandrostene Ie is based on the greater stability of a Δ^2-olefin compared to the corresponding Δ^1-isomer, as shown by heats of hydrogenation studies[13] and by the enolization of 2-keto-5α-steroids to the Δ^2-enol.[14,15]

2-Hydroxymethyl-Δ^2-androstene-17β-ol acetate (Ig)[1] was considered to be an attractive starting material for the preparation of the 2-halomethyl-Δ^2-androstenes, since such an allylic alcohol should be particularly amenable to a variety of displacement reactions with chloride and fluoride ions.[16]

(9) E. A. Braude and J. A. Coles, *J. Chem. Soc.*, 2014 (1950).

(10) *Cf.* H. Remy, "Treatise on Inorganic Chemistry," Vol. I, Elsevier Publishing Co., Amsterdam, 1956, p. 643.

(11) A. Furst and P. A. Plattner, *Helv. Chim. Acta*, **32**, 275 (1949).

(12) I. Malunowicz, J. Fajkos and F. Sorm, *Collection Czech. Chem. Commun.*, **25**, 1359 (1960).

(13) R. B. Turner, W. R. Meador and R. E. Winkler, *J. Am. Chem. Soc.*, **79**, 4122 (1957).

(14) C. Djerassi and T. Nakano, *Chem. Ind.* (London), 1385 (1960).

(15) Although the 2-chloro-Δ^2-androstene-17β-ol acetate (Ie) behaved as a homogeneous compound, its method of preparation does not preclude the possibility of it being contaminated by a small amount of the Δ^1-isomer.

(16) For a comprehensive summary of the chemistry of allylic compounds see R. H. De Wolfe and W. G. Young, *Chem. Rev.*, **56**, 753 (1956).

The displacement reaction of allylic alcohols with thionyl chloride may proceed with or without rearrangement.[16] In the steroid series, for example, reaction of Δ^1-cholestene-3β-ol with thionyl chloride afforded 3β-chloro-Δ^1-cholestene[17] *via* direct displacement, whereas Δ^5-cholestene-4β-ol and Δ^4-cholestene-6β-ol yielded the rearranged 6β-chloro-Δ^4 and 4β-chloro-Δ^5-cholestenes[18] with the same reagent. These differences in product formation have been attributed to the stereochemistry of the unsaturated alcohol moiety. Rearranged products are formed when the geometry of the initially formed chlorosulfinate ester permits the facile formation of a cyclic transition state, thus enabling the chlorine atom to attack the γ-carbon of the allylic system.[19]

In view of these results, the reaction of 2-hydroxymethyl-Δ^2-androstene-17β-ol acetate (Ig)[1] with thionyl chloride was expected to proceed with rearrangement. Brief treatment of the allylic alcohol Ig with thionyl chloride in benzene solution afforded a homogeneous monochloro compound in 70% yield after chromatography.[20] The infrared and nuclear magnetic resonance data for this substance were consistent with the rearranged structure, 2-methylene-3β-chloroandrostane-17β-ol acetate (IIh). Infrared bands corresponding to the exomethylene grouping occurred at 903 and 1650 cm.$^{-1}$. In the n.m.r. spectrum[21] of the chloro compound IIh, resonance totalling four protons was observed between 260 and 310 c./s., of which a pair of doublets at 284 and 299 c./s. (each showing further splitting) were assigned to the exomethylene protons.[22] The proximity of the 3β-chlorine to one of these protons causes deshielding and accounts for the chemical shift of 15 c./s. between this and the more remote, less deshielded exomethylene proton.[24] Resonance due to the latter exomethylene proton partially overlays the two 1-proton triplets corresponding to the 3α- and 17α-protons.

2-Chloromethyl-Δ^2-androstene-17β-ol acetate (Ij) was obtained from the 2-methylene-3-chloro compound IIh by a second S$_N$2′ displacement by chloride ion in dimethylformamide solution. The infrared and n.m.r. spectral properties of the 2-chloromethyl-Δ^2-compound Ij confirmed the structure. More specifically, the infrared spectrum of the rearrangement product Ij was devoid of the exomethylene absorption bands present in its precursor. Its n.m.r. spectrum showed a multiplet at 345 c./s. for the C-3 olefinic proton and resonance equivalent to two protons at 234 c./s. (inner bands

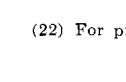
(17) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 3289 (1956).

(18) R. E. Ireland, T. I. Wrigley and W. G. Young, *J. Am. Chem. Soc.*, **80**, 4604 (1958).

(19) W. G. Young, J. D. Roberts and S. Winstein, *ibid.*, **64**, 2157 (1942).

(20) Consistent yields of the allylic halides were only obtained when acetic acid-washed alumina was employed for chromatography.

(21) N.m.r. spectra were taken in deuteriochloroform solution (*ca.* 10% w./v.) with a tetramethylsilane internal reference using Varian A-60 or H.R. 60 spectrometers. Chemical shifts are quoted as c./s. from the reference.

(22) For protons in the environment of  proton–proton coupling occurs with J = 0–3.5 c./s.[23] In the case studied here, broadening of the olefinic proton resonance band by long-range coupling with protons at C-1 and/or at C-3 apparently occurs.

(23) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p. 85.

(24) This evidence supports the β-configuration for the 3-chloro substituent.

of an AB quartet almost coalesced) for the hydrogens of the chloromethyl group.

In view of the reactivity of allylic alcohols with hydrogen bromide and hydrogen chloride,[16] analogous displacements with hydrogen fluoride appeared feasible. When 2-hydroxymethyl-Δ^2-androstene-17β-ol acetate (Ig) was treated with a mixture of anhydrous hydrogen fluoride and tetrahydrofuran[25] at $-20°$, a monofluoro compound was obtained in 33% yield. The elementary analysis of this substance was in good agreement with the structure 2-fluoromethyl-Δ^2-androstene-17β-ol acetate (Ik) or with the isomeric 2-methylene-3-fluoro compound (IIj). While a decision between these two possible structures could not be made on the basis of the infrared data the problem was resolved easily in favor of the 2-fluoromethyl-Δ^2- compound Ik by n.m.r. spectroscopy. A broad multiplet at 346 c./s. is attributed to the olefinic proton at C-3. The protons of the fluoromethyl group give an ill-resolved 8-line resonance pattern between 243 and 322 c./s., which is interpreted as two overlapping quartets (J HF *ca.* 36 c./s. and J HH *ca.* 15 c./s.) each equivalent to one of the protons.[26]

The final compound prepared in this series was 2-difluoromethyl-Δ^2-androstene-17β-ol acetate (Im). This substance was obtained by the difluorination of 2-formyl-Δ^2-androstene-17β-ol acetate (If)[1] with sulfur tetrafluoride.[27] Following the procedure of Tadanier and Cole,[28] conversions of the aldehyde If to the difluoromethyl compound Im were realized in moderate yield, when a reaction period of 24 hours was permitted. In order to remove unchanged aldehyde from the difluorinated product, the crude reaction mixture was reduced with lithium aluminum hydride and the difluoromethyl compound In was separated from the allylic alcohol Ih by chromatography. Final purification was achieved through the 17-acetate. In this manner 2-difluoromethyl-Δ^2-androstene-17β-ol acetate (Im) was obtained in 28% yield. The difluoromethyl-Δ^2- structure follows from its mode of preparation, elementary analysis and n.m.r. spectrum. This last determination clearly demonstrated the presence of the difluoromethyl-Δ^2- moiety by the broad 1-proton multiplet at 355 c./s. (C-3 olefinic proton) and a triplet at 293, 350 and 407 c./s. corresponding to the lone proton of the difluoromethyl group (J_{HF} 57 c./s., proton coupled with two chemically equivalent fluorines).

Biological Activities.—Anabolic–androgenic assays were carried out as described previously.[2] 2-Chloromethyl-Δ^2-androstene-17β-ol acetate (Ij) and the 2-difluoromethyl-Δ^2 analog Im exhibited approximately 10% of the anabolic and androgenic activity of testosterone. 2-Fluoromethyl-Δ^2-androstene-17β-ol acetate (Ik) had twice the anabolic and 0.4 times the androgenic activity of testosterone.

We thank Dr. A. D. Cross for his considerable help in the interpretation of the n.m.r. spectra which were determined at the Universidad Nacional Autónoma de México through the courtesy of Dr. A. Sandoval, and at the Worcester Foundation for Experimental Biology through the kindness of Dr. H. J. Ringold.

Experimental[29]

Δ^2-Androstene-17β-ol Benzoate (Ib).—A mixture of 10 g. of Δ^2-androstene-17β-ol (Ia),[8] 20 ml. of benzoyl chloride and 100 ml. of pyridine was left standing for 13 hr. The solution was diluted with water and extracted with ethyl acetate. The organic extracts were washed with 10% hydrochloric acid, 5% sodium bicarbonate solution and with water to neutrality. Removal of the solvent and crystallization from acetone–hexane afforded 6.7 g. of Ib, m.p. 134–137°. Two additional crystallizations gave the analytical sample, m.p. 141–142°; $[\alpha]_D$ +84°; ν_{max} 1725 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{34}O_2$: C, 82.49; H, 9.05; O, 8.45. Found: C, 82.36; H, 9.21; O, 8.72.

3α-Bromoandrostane-2β,17β-diol 17-Benzoate (IIa).—A solution of 6.1 g. of Δ^2androstene-17β-ol benzoate (Ib) and 3.3 g. of N-bromoacetamide in 122 ml. of dioxane was treated with 7 ml. of 0.79 *N* perchloric acid and the mixture was left standing for 5 hr. Addition of water precipitated 7.1 g. of the bromohydrin IIa, m.p. 80–85°.

3ξ-Bromoandrostane-17β-ol-2-one Benzoate (IIb).—A solution of 7.1 g. of the bromohydrin IIa in 100 ml. of acetone was cooled in ice and treated with 6.6 ml. of 8 *N* chromium trioxide solution.[6] After 3 min. water was added to the reaction and the precipitate was filtered, washed and dried. Crystallization from methanol furnished 3.2 g. of the bromoketone IIb, m.p. 185–187°, unchanged after several additional crystallizations. $[\alpha]_D$ +102°; ν_{max} 1725 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{33}BrO_3$: C, 65.68; H, 7.42. Found: C, 65.35; H, 7.33.

Androstane-17β-ol-2-one Benzoate (IIc).—Zinc dust (2 g.) was added to a solution of 0.7 g. of the bromoketone IIb in 15 ml. of acetic acid and the resulting mixture was heated with stirring for 30 min. on the steam bath. The zinc was removed by filtration, water was added to the filtrate and the product extracted with methylene chloride. The organic extracts were washed with 5% sodium bicarbonate solution and water, dried over sodium sulfate and concentrated. Crystallization of the crude product from methylene chloride–ether provided 0.25 g. of androstane-17β-ol-2-one benzoate (IIc), m.p. 149–152°. The analytical specimen exhibited m.p. 152–156°; $[\alpha]_D$ +74°; ν_{max} 1725 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{34}O_3$: C, 79.15; H, 8.69; O, 12.17. Found: C, 79.05; H, 8.79; O, 12.20.

Androstane-17β-ol-2-one Acetate (IIf).—A solution of 5 g. of Δ^2-androstene-17β-ol acetate (Ic)[8] in 100 ml. of dioxan was treated with 3.5 ml. of 0.6 *N* aqueous perchloric acid solution. N-Bromoacetamide (3.2 g.) was added in 4 portions with stirring during 1 hr. The reaction mixture, after standing for 4 hr., was treated with several drops of 1% sodium bisulfite solution and diluted with water. The precipitate was collected, washed with water and dissolved in methylene chloride. This solution was dried over sodium sulfate and concentrated *in vacuo* at 30–40° to afford the crystalline bromohydrin IId.

A solution of crude IId in 150 ml. of acetone was cooled to 5° and treated with 4.5 ml. of 8 *N* chromium trioxide solution.[6] After 1 min. the reaction mixture was diluted with 1 l. of water and the 3-bromo-2-ketone IIe was isolated with ether. This product, dissolved in 135 ml. of acetic acid, was treated with 10 g. of zinc dust and the mixture was heated on the steam bath with stirring for 30 min. The zinc was removed by filtration through Celite and the product precipitated with water. Crystallization of the crude ketone from acetone–hexane furnished 2.3 g. of IIf, m.p. 136–138° and raised to 148–149° after 3 successive crystallizations, $[\alpha]_D$ +25°; ν_{max} 1730 and 1715 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70; O, 14.44. Found: C, 76.24; H, 9.58; O, 14.38.

Androstane-17β-ol-2-one (IIg). (a) From (IIf).—Androstane-17β-ol-2-one acetate (0.6 g.) in methanol (15 ml.) was

(25) R. F. Hirschmann, R. Miller, J. Wood and R. E. Jones, *J. Am. Chem. Soc.*, **78**, 4956 (1956).

(26) Long range coupling of the fluorine with C-19 angular methyl protons was reported earlier from these laboratories, see A. D. Cross and P. W. Landis, *ibid.*, **84**, 1736 (1962).

(27) W. R. Hasek, W. C. Smith and V. A. Englehardt, *ibid.*, **82**, 543 (1960).

(28) J. Tadanier and W. Cole, *J. Org. Chem.*, **26**, 2436 (1961).

(29) All rotations were determined in chloroform solutions and infrared spectra in potassium bromide disks. The neutral alumina was prepared by treating the commercial material for 24 hr. with 5% aqueous acetic acid solution, followed by filtration, washing with water and methanol, and reactivation (48 hr. at 100° *in vacuo*). Microanalyses were determined by either Mid-West Micro Laboratories, Indianapolis 20, Indiana, or by Dr. A. Bernhardt, Mülheim (Ruhr), Germany.

heated under reflux for 5 hr. with 15 ml. of 10% methanolic potassium hydroxide solution. The excess of base was neutralized with acetic acid and the product precipitated with water. Crystallization of the dried solid from acetone–hexane yielded 0.35 g. of IIg, m.p. 177–179°. The analytical sample prepared from the same solvent pair exhibited m.p. 180–181°; $[\alpha]_D$ +49°; ν_{max} 3450 and 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41; O, 11.02. Found: C, 78.46; H, 10.43; O, 11.28.

(b) **From (IIc).**—Hydrolysis of androstane-17β-ol-2-one benzoate (1 g.) as in (a) afforded 0.6 g. of product, m.p. 174–176°, identical in all respects with androstane-17β-ol-2-one (IIg).

3-Chloro-Δ²-androstene-17β-ol Acetate (Ie).—A solution of 2 g. of dihydrotestosterone acetate (IIIa) in 100 ml. of carbon tetrachloride was heated under reflux for 2 hr. with 3 g. of phosphorus pentachloride. The reaction mixture was washed cautiously with an excess of 5% aqueous sodium bicarbonate solution and with water, dried over sodium sulfate and concentrated. The resulting oil was dissolved in hexane and absorbed on a column of 100 g. of alumina. The semi-crystalline product, eluted with hexane–benzene (4:1), was crystallized from methanol–water to yield 0.4 g. of product m.p. 65–68°. Three additional crystallizations raised the melting point to 88–94°; $[\alpha]_D$ +26°; ν_{max} 1740 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{31}ClO_2$: C, 71.87; H, 8.91; Cl, 10.10. Found: C, 71.64; H, 8.72; Cl, 10.79.

2ξ,3,3-Trichloroandrostane-17β-ol Acetate (IIIb).—A mixture of 10 g. of dihydrotestosterone acetate (IIIa), 15 g. of phosphorus pentachloride and 500 ml. of carbon tetrachloride was boiled for 22 hr. and then processed as in the preceding experiment. The reaction product dissolved in hexane–benzene (4:1), was chromatographed on 400 g. of alumina. The semicrystalline material, eluted with hexane–benzene (1:1), was treated with hexane, and the insoluble fraction (1 g.) collected and crystallized from methylene chloride–acetone to afford 0.6 g. of product m.p. 244–248°. Three additional crystallizations raised the melting point to 246–250°; $[\alpha]_D$ −16°; ν_{max} 1740 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{31}Cl_3O_2$: C, 59.79; H, 7.41; Cl, 25.22. Found: C, 59.98; H, 7.25; Cl, 25.78.

2-Chloro-Δ²-androstene-17β-ol Acetate (Ie).—A solution of 1 g. of androstane-17β-ol-2-one acetate (IIf) in 50 ml. of dry carbon tetrachloride was heated under reflux for 2 hr. with 1.5 g. of phosphorus pentachloride. The reaction mixture was washed with dilute sodium carbonate solution and water, dried over sodium sulfate and concentrated. The crude product was dissolved in hexane and absorbed on a column of 40 g. of alumina. The crystalline fractions eluted with hexane were combined and crystallized from acetone–hexane to yield 0.26 g. of 2-chloro-Δ²-androstene-17β-ol acetate (Ie) m.p. 90–92°; $[\alpha]_D$ +36°; ν_{max} 1740 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{31}ClO_2$: C, 71.87; H, 8.91; Cl, 10.10. Found: C, 71.69; H, 8.73; Cl, 10.03.

2-Methylene-3β-chloroandrostane-17β-ol Acetate (IIh).—From a solution of 0.6 g. of 2-hydroxymethyl-Δ²-androstene-17β-ol acetate (Ig)[1] in 36 ml. of dry benzene, 15 ml. of solvent was distilled to remove moisture. The solution was cooled to 20° and treated with 0.6 ml. of freshly distilled thionyl chloride. After 45 min. the reaction mixture was diluted with ether and the resulting solution was washed with 5% sodium carbonate solution and with water, dried over calcium chloride and concentrated. A hexane solution of the crude product was filtered rapidly through a column of 18 g. of acetic acid-washed alumina. Removal of the solvent provided 0.47 g. of the chloro compound IIh of satisfactory purity for the subsequent transformation. A pure specimen prepared from acetone–hexane, exhibited m.p. 170–172°; $[\alpha]_D$ +57°; ν_{max} 1735, 1660 and 903 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{33}ClO_2$: C, 72.40; H, 9.16; Cl, 9.68; O, 8.67. Found: C, 72.28; H, 9.05; Cl, 9.93; O, 9.01.

2-Chloromethyl-Δ²-androstene-17β-ol Acetate (Ij).—A mixture of 0.2 g. of 2-methylene-3β-chloroandrostane-17β-ol-acetate (IIh), 0.2 g. of lithium chloride and 10 ml. of dimethylformamide was heated for 7 hr. on the steam bath. The solution was diluted with water and the product isolated with ether. The crystalline residue was dissolved in hexane–benzene (9:1) and the resulting solution was filtered rapidly through a column of 8 g. of acetic acid-washed alumina. Removal of the solvent and crystallization from methanol yielded 0.1 g. of Ij, m.p. 115–118°. The analytical sample, prepared from methanol, melted at 128–130°; $[\alpha]_D$ +40°; ν_{max} 1730 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{33}ClO_2$: C, 72.40; H, 9.16; Cl, 9.68. Found: C, 72.88; H, 9.41; Cl, 9.27.

2-Fluoromethyl-Δ²-androstene-17β-ol Acetate (Ik).—A solution of 2 g. of 2-hydroxymethyl-Δ²-androstene-17β-ol acetate (Ig)[1] in 80 ml. of dry methylene chloride was added to a mixture of 8 g. of anhydrous hydrogen fluoride and 14.4 g. of dry tetrahydrofuran, previously cooled to −70°. The mixture was left for 14 hr. at −20° and then poured into an excess of aqueous sodium carbonate solution. Isolation with methylene chloride afforded 2 g. of oil which was adsorbed on a column of 80 g. of acetic acid-washed alumina. Elution with mixtures of pure hexane and hexane–benzene (9:1) yielded 0.6 g. of Ik. Crystallization from methanol gave 0.24 g. of Ik, m.p. 115–116°, and raised to 118–120° after two additional crystallizations, $[\alpha]_D$ +33°; ν_{max} 1735 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{33}FO_2$: C, 75.82; H, 9.54; F, 5.45. Found: C, 75.54; H, 9.39; F, 5.06.

2-Difluoromethyl-Δ²-androstene-17β-ol Acetate (Im).—2-Formyl-Δ²-androstene-17β-ol acetate[1] (5 g.) in chloroform (50 ml.) and ethanol (1 ml.) was treated with sulfur tetrafluoride (approximately 5 g.) for 24 hr. at room temperature in a stainless steel tube. The mixture was cooled in Dry Ice and then poured into an excess of aqueous sodium carbonate solution. Isolation with ethyl acetate afforded 4.8 g. of oil which was dissolved in 50 ml. of ether and treated with 7 ml. of a saturated solution of lithium aluminum hydride in ether. After 30 min. the excess of hydride was destroyed with acetone and 200 ml. of ether added. This solution was washed with dilute hydrochloric acid, sodium bicarbonate solution, and finally with water. Removal of the ether furnished 4.1 g. of semi-crystalline material which was dissolved in benzene and adsorbed on a column of 180 g. of alumina. Elution with benzene–ether (1:1) gave 1.8 g. of impure 2-difluoromethyl-Δ²-androstene-17β-ol (In). Continued elution with pure ether afforded 0.5 g. of 2-hydroxymethyl-Δ²-androstene-17β-ol (Ih)[1] derived from unchanged starting material. The crude difluoro compound In was acetylated with 10 ml. of acetic anhydride–pyridine (1:1) 0.5 hr. on the steam bath and a hexane solution of the resulting acetate was adsorbed on a column of 60 g. of alumina. The fractions eluted with pure hexane were crystallized from methanol to yield 1.4 g. of Im, m.p. 169–171°; $[\alpha]_D$ +54°; ν_{max} 1730 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{32}F_2O_2$: C, 72.08; H, 8.73; F, 10.46. Found: C, 71.84; H, 8.94; F, 9.98.

2-Difluoromethyl-Δ²-androstene-17β-ol (In).—A solution of 0.4 g. of 2-difluoromethyl-Δ²-androstene-17β-ol acetate (Ik) in 20 ml. of ethanol was heated under reflux with 1 g. of potassium hydroxide for 30 min. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic extracts were washed with water, dried over sodium sulfate and concentrated. Crystallization of the resulting solid from acetone hexane provided 0.25 g. of the alcohol In, m.p. 107–109°; $[\alpha]_D$ +55°; ν_{max} 3280 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{30}F_2O$: C, 74.05; H, 9.26; F, 11.71. Found: C, 74.29; H, 8.97; F, 11.63.