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Direct Introduction of Oxygen into the Steroid Nucleus. I. Studies on the Chromic Anhydride Oxidation of Dehydroisoandrosterone Acetate Dibromide[1]

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The incorporation of oxygen-containing functional groups into the steroid nucleus is of considerable interest in connection with the synthesis of corticosteroids and cardioactive substances. The direct introduction of oxygen at non-activated positions in the steroid nucleus, apparently not recorded heretofore, has been accomplished by the chromic anhydride oxidation of dehydroisoandrosterone acetate dibromide. The compound so obtained has been shown to be 3β-acetoxy-14β-hydroxy-5-androsten-17-one. Dehydration yielded 3β-acetoxy-5,14-androstadien-17-one, the 16-benzylidene derivative of which was found to be identical with that synthesized from the known 16-benzylidene of dehydroisoandrosterone acetate. It has also been shown that when the 14-double bond was reduced, compounds of the 14-isoandrostane series were produced.

During the course of an investigation of the stability of dehydroisoandrosterone acetate 5,6-dibromide to oxidizing agents it was observed that this steroid was attacked vigorously under certain conditions by chromic anhydride.[2] To further elucidate the mechanism of the chromic anhydride oxidation of steroids and to determine if compounds with functional groups in the intact ring system were formed an investigation of the oxidation products was undertaken.

When dehydroisoandrosterone acetate 5,6-dibromide was subjected to oxidation with chromic anhydride in acetic acid under the anhydrous conditions of Fieser[3] and the reaction products subsequently debrominated, a new compound was isolated from the neutral fraction in a yield of about 20%. Analytical data indicated that this compound had the empirical formula $C_{21}H_{30}O_4$ and, therefore, contained one additional oxygen atom. Compound Ia was shown to contain one double bond and one acetyl group by perbenzoic acid oxidation and acetyl determination, respectively. The infrared absorption spectra of compound Ia contained the characteristic bands of a 3-acetoxy-5-ene grouping and free hydroxyl group. This free hydroxyl group was resistant to further acetylation. Infrared analysis of the hydrolysis product Ib indicated a 17-keto group and two free hydroxyl groups.

Based on the theory of Fieser[3] and Billeter and Miescher[4] that the steroid side chain is cleaved by the formation and fission of tertiary alcohols during the normal chromic anhydride oxidation, it was postulated that the new alcohol group was on a tertiary carbon atom. This was supported by the fact that it was resistant to acetylation and to oxidation. The presence of the 3-acetoxy-5-ene grouping was confirmed by hydrolysis of the compound Ia to a diol Ib and reacetylation to the original compound, and by the oxidation of compound Ib to an α,β-unsaturated ketone III. The formation of only a monosemicarbazone and reduction of compound Ia to a compound with only one new acylable group confirmed the presence of one keto group. This evidence showed compound Ia to be 3-acetoxy-x-hydroxy-5-androstene-17-one with a tertiary alcohol group either at 8, 9 or 14, thus supporting the above carbinol mechanism of degradation. The Zimmermann color reaction[5] for 17-keto steroids was negative, suggesting that the tertiary alcohol group might be exerting some action on the 17-keto or 16-methylene group, thereby making position 14 a likely site.

Dehydration experiments with thionyl chloride and phosphorus oxychloride in pyridine solution yielded only small amounts of a dehydro compound. However, with acetic anhydride and potassium acid sulfate water was eliminated in 70% yield. The resulting diene VI showed no absorption in the ultraviolet between 215–290 mμ, thus indicating the absence of a conjugated diene system. Furthermore, the newly introduced double bond was found to be very readily catalytically hydrogenated in neutral solution, a fact which would rule out its being a 7-, 8(9)- or 8(14)-double bond. Thus C-8 would seem to be eliminated as the point of attachment for the hydroxyl group, leaving only C-9 and C14 as possibilities.

In order to obtain evidence as to which of these was the more likely, the 16-benzylidene derivative of the unknown compound (IVb) was prepared so that an oxidation similar to that described by Hirschmann[6] could be carried out. In our case, protection of the 5,6-double bond was necessary and, therefore, one mole of bromine was added according to the directions of Velluz and Petit[7] who state that under their experimental conditions such compounds add bromine mainly to the 5,6-double bond. Chromic acid oxidation of the benzylidene dibromide gave, after debromination, a substance identified as Köster's ketone acetate X.[8] Although the yield was quite low (2%), the result of this experiment indicated that the point of attachment must be in ring D of the steroid nucleus and thus the C-14 position would seem to be more likely.

Further structural information was obtained by preparing the benzylidene derivative (V) of the dehydro compound, which was made either from the diene VI or by dehydration of the benzylidene IVb, and comparing it with the same compound synthesized from the known benzylidene derivative (VII) of dehydroisoandrosterone acetate.

Since the presence of the 5,6-double bond might complicate this synthesis, it was saturated by the

(1) Presented before the Organic Division at the Buffalo Meeting of the American Chemical Society, March, 1952.

(2) H. E. Bachofner and W. H. Fischer, unpublished data.

(3) L. F. Fieser, THIS JOURNAL, **70**, 3237 (1948).

(4) J. R. Billeter and K. Miescher, *Helv. Chim. Acta*, **30**, 1409 (1947).

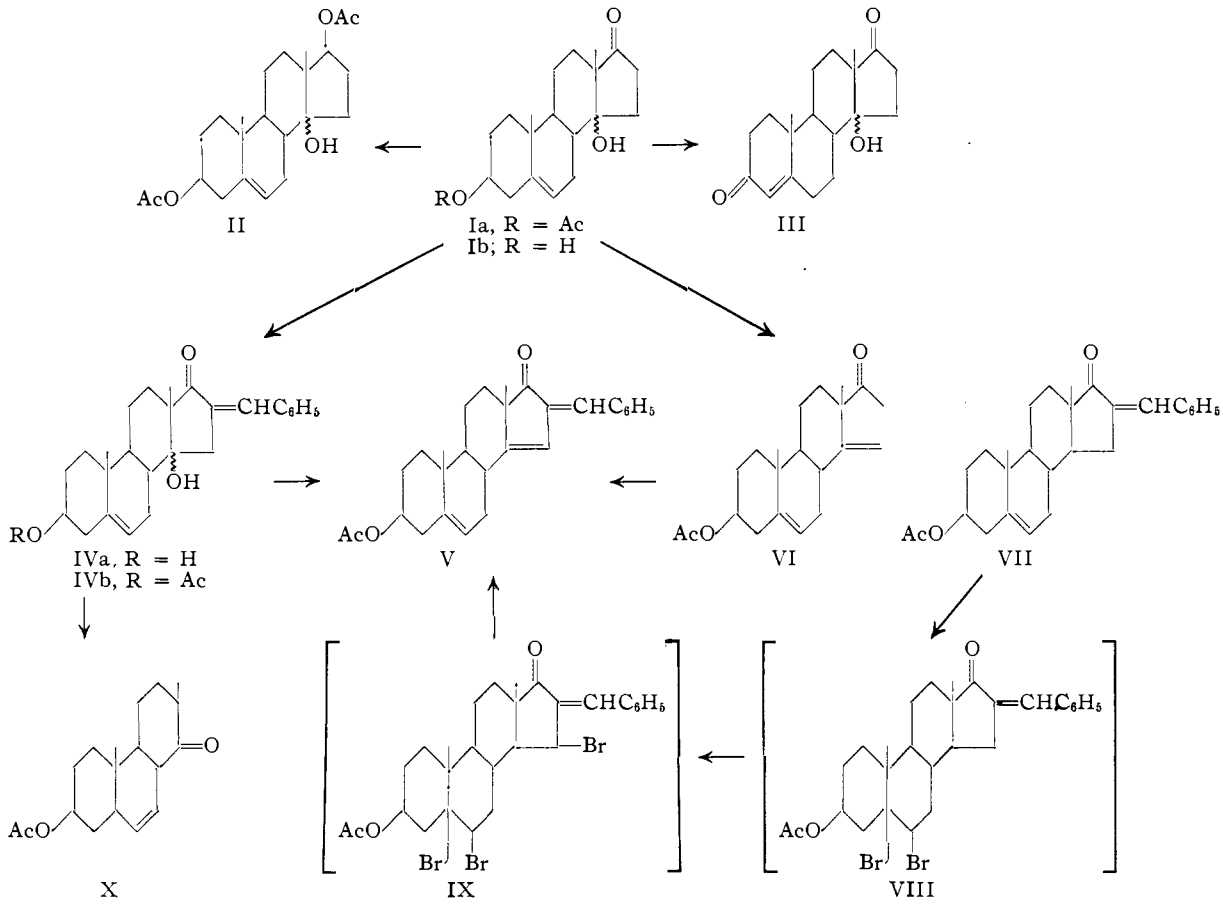
(5) W. Zimmermann, "Vitamine u. Hormone," Akademische Verlagsgesellschaft, m.b.H., Leipzig, **5**, 1 (1944).

(6) H. Hirschmann, *J. Biol. Chem.*, **150**, 363 (1943).

(7) L. Velluz and A. Petit, *Bull. soc. chim.*, **12** 949 (1945).

(8) H. Köster and W. Logemann, *Ber.*, **73**, 298 (1940).

FLOWSHEET I



addition of bromine. Reaction of the crude benzylidene dibromide VIII with N-bromosuccinimide followed by debromination with sodium iodide yielded a halogen-free compound which was shown to be identical with V. Evidently hydrogen bromide was spontaneously eliminated during the bromination reaction.

As an additional check on the structure, the original oxidation product Ia was hydrogenated using a palladium catalyst and yielded the dihydro compound XI. Dehydration produced the substance XIIa, the benzylidene derivative of which XIII was shown to be identical with that synthesized from the known benzylidene derivative of isoandrosterone acetate (XIV) by the series of reactions shown in Flowsheet II.

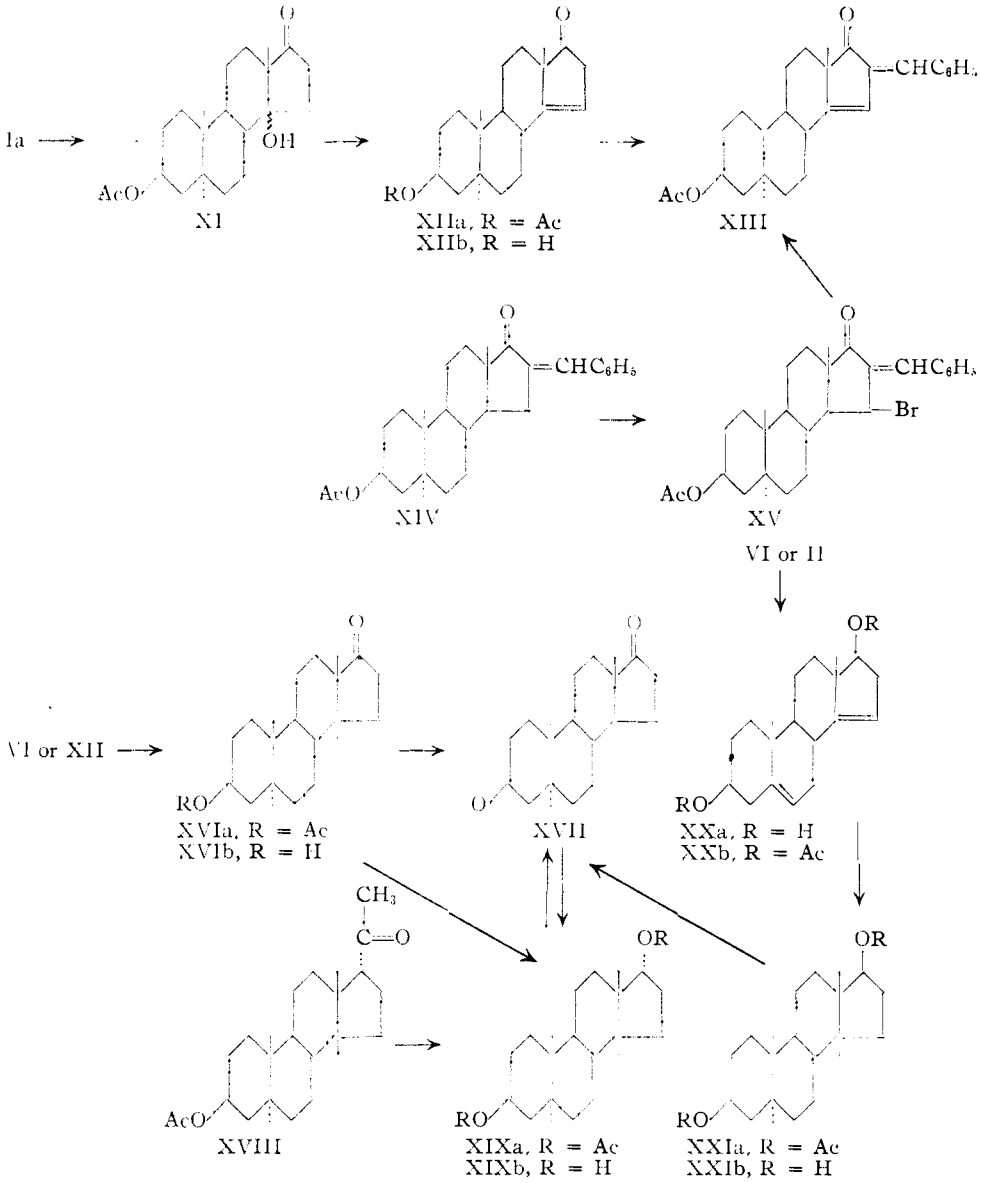
Thus, further evidence was provided showing that in the dehydro compounds (VI, XIIa and by interconversion XXb) the introduced double bond was between carbons 14 and 15. There is the possibility that following dehydration bond migration takes place with the ultimate formation of the 14-double bond. Such migrations are known to occur in sterols under the influence of free mineral acid. However, we do not feel that our dehydration conditions were such as to cause any marked shifting of a preformed double bond. Furthermore, it has recently been reported[9] that when 8(14)-androstene-3β,17β-diol diacetate was subjected to hydrogen chloride treatment no bond migration occurred. It would, therefore, seem unlikely that any rearrangement would have occurred during the dehydration of II to XXb. Thus we feel confident in placing the unknown hydroxyl group at C-14; C-15 having been eliminated by the properties and reactions of the compound.

When compound XIIa was hydrolyzed with alkali two products were isolated, XIIb and a substance melting at 300–305°. The ultraviolet absorption spectrum of this material indicated the presence of an α,β-unsaturated ketone, while the infrared absorption curve showed two carbonyl peaks, a double bond and the expected hydroxyl absorption. When VI was likewise saponified only a high melting compound with similar absorption properties was obtained. Thus, it would seem that when VI and XIIa are subjected to treatment with alkali, some type of rearrangement or bimolecular condensation occurs. Further work will be necessary before the structure of these compounds can be established.

Since the conditions necessary to cause dehydration seemed to be much more vigorous than those reported for the dehydration of most of the known 14β-hydroxyl groups, we believe that, in our case, the hydroxyl group has the α-configuration. This is also supported by the fact that inversion at C-14 would not be expected to take place during chromic anhydride oxidation.

(9) R. Antonucci, S. Bernstein, D. Giancola and K. J. Sax, *J. Org. Chem.*, **16**, 1891 (1951).

Flowsheet II



When either compound VI or XIIa was completely reduced by catalytic hydrogenation a substance was obtained which was not identical with isoandrosterone acetate. Compound XIIa must have rings A and B in the *trans* configuration since its benzylidene derivative XIII was shown to have the same configuration as that derived from isoandrosterone. Therefore, it would seem that the reduction product must be the 14-iso compound. In order to confirm this assumption compound XVIa was saponified to XVIb which on oxidation gave the dione XVII. The same substance was then synthesized from the known 3β-acetoxy-14-iso-17-isoallopregnan-20-one (XVIII)[10] by the steps shown in flowsheet II.[11] The two diketones thus prepared were shown to have the same physical constants and infrared absorption spectra, thus proving the 14-iso configuration for the saturated products.

It is interesting to note that when the 14-iso compounds XVIa and XVII were reduced with sodium borohydride the 17α-hydroxy compound XIXb[12] was formed. Whereas, if the reduction was carried out on Ia or VI subsequent reactions lead to the formation of an isomeric compound XXIb which was not identical with XIXb, and since it was oxidized to XVII it must be the 17β-hydroxy-14-iso derivative. Thus, it would seem that in the 14-iso compounds reduction of the 17-ketone leads predominantly to the 17α-hydroxy epimer in contrast to the formation of mainly the 17β-hydroxy epimer in the normal series.

(10) P. A. Plattner, H. Heusser and A. Segre, *Helv. Chim. Acta*, **31**, 249 (1948).

(11) H. Heusser, K. Eichenberger and A. B. Kulkarni, *ibid.*, **32**, 2145 (1949).

(12) The steric configuration given for this compound seems certain in view of its preparation from the known 17α-pregnane XVIII by treatment with perbenzoic acid. That this oxidation proceeds without inversion at C-17 has been well established. *Cf.* L. H. Sarett, This Journal, **69**, 2899 (1947); P. Wieland and K. Miescher, *Helv. Chim. Acta*, **32**, 1768 (1949); Ref. (11); T. F. Gallagher and T. H. Kritchevsky, This Journal, **72**, 882 (1950).

Table I gives a comparison of the physical properties of the 14-iso compounds prepared in this work with the corresponding 14-normal androstanes.

TABLE I

Substituent		14-Normal			14-Iso		
3	17	M.p., °C.	$[\alpha]_D$	M_D	M.p., °C.	$[\alpha]_D$	M_D
β-ol	one	175	+78°	+226°	162	+81°	+235°
one	one	133	+113	+326	185	+110	+317
β-ol	α-ol	214	−10	−29	189	+36	+105
β-ol	β-ol	164	+4	+12	170	+38	+111

Experimental[13]

3β-Acetoxy-14 ξ-hydroxy-5-androstene-17-one (Ia).—To a solution of 8.34 g. of dehydroisoandrosterone acetate in 480 cc. of glacial acetic acid was added 1.48 cc. (1.1 moles) of bromine dissolved in 20 cc. of acetic acid. The mixture was well stirred and maintained at 15° during the addition. After the bromine solution had been added stirring was continued for 10 minutes during which time the temperature rose to room temperature.

At the end of this time 40 g. of freshly pulverized chromic anhydride was added and the reaction mixture stirred vigorously for one-half hour. A rise of only 2–3° in temperature was noted. The solution was then decanted away from the excess solid chromic anhydride and, after cooling in an ice-bath, 30% sodium bisulfite solution was added until all of the chromic acid was reduced. An equal volume of water was added and the mixture was extracted four times with 250-cc. portions of chloroform. These were combined, washed with water, dried and the solvent removed *in vacuo*.

The oily residue was dissolved in 400 cc. of glacial acetic acid and 33 g. of zinc dust was added portionwise with stirring during 15 minutes. Stirring was continued for six hours at room temperature. At the end of this time the reaction mixture was filtered and the filter cake was washed well with acetic acid. The combined filtrate and washings were concentrated, diluted with water and the oxidation products were extracted with chloroform. The acidic material was removed by washing with 30% sodium hydroxide solution and the neutral fraction (7.0 g.) after removal of the solvent, was taken up in benzene (50 cc.) and hexane added until scratching produced a precipitation. In this way 1.46 g. (16.7%) of material, m.p. 220–225° was obtained. The mother liquor was chromatographed on alumina and yielded an additional 700 mg. of product, giving a total yield of 24.7%.

After recrystallization from methanol it melted at 235.5–237°, $[\alpha]^{22}D$ +4.1°, ultraviolet absorption maximum at 285 mμ (log ε 1.68).

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.8; H, 8.7; acetyl, 12.3. Found: C, 72.9; H, 9.0; acetyl, 12.2.

Semicarbazone, recrystallized from ethanol, m.p. 269–270° (dec.).

Anal. Calcd. for $C_{22}H_{33}N_3O_4$: C, 65.5; H, 8.2; N, 10.4. Found: C, 64.9; H, 8.3; N, 10.8.

3β,14ξ-Dihydroxy-5-androstene-17-one (Ib).—The above acetate (390 mg.) was saponified by refluxing for one hour in 10 cc. of 5% potassium hydroxide in methanol. After working up the mixture and recrystallizing the product from methanol, 250 mg. of material was obtained, m.p. 225–228°, $[\alpha]^{24}D$ 0° (dioxane).

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 75.0; H, 9.3. Found: C, 74.7; H, 9.4.

This material was reconverted to the acetate Ia on acetylation with acetic anhydride in pyridine solution.

14ξ-Hydroxy-4-androstene-3,17-dione (III).—A sample of the above diolone Ib (970 mg.) was subjected to Oppenauer oxidation using aluminum isopropylate and cyclohexanone in toluene solution. After working up the reaction and recrystallizing the product from ethyl acetate 770 mg. of material was obtained, m.p. 257–260°, $[\alpha]^{24}D$ +175.7°, ultraviolet absorption maximum at 240 mμ (log ε 4.18).

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.5; H, 8.7. Found: C, 75.4; H, 9.1.

3β,17β-Diacetoxy-5-androstene-14ξ-ol (II).—To a methanolic solution of 400 mg. of Ia was added 100 mg. of sodium borohydride and the mixture was allowed to stand at room temperature for 18 hours. It was then refluxed for 1 hour and then 15 cc. of 1% aqueous potassium carbonate solution was added and the mixture again refluxed for 1 hour. It was diluted with water and the precipitated material filtered and dried. The crude product was directly acetylated with acetic anhydride in pyridine solution and the resulting diacetate recrystallized from hexane and from dilute acetone, m.p. 174–177°, $[\alpha]^{23}D$ −33°.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.7; H, 8.8. Found: C, 70.9; H, 8.7.

3β-Acetoxy-5,14-androstadien-17-one (VI).—Since compound Ia could not be dehydrated in good yield with alcoholic hydrogen chloride, phosphorus oxychloride in pyridine nor with anhydrous zinc chloride or anhydrous copper sulfate, a 2.0-g. sample was dissolved in 20 cc. of acetic anhydride, 2.0 g. of fused potassium acid sulfate added and the mixture heated at 95–100° for 15 minutes. On isolation and recrystallization of the product from dilute methanol 1.38 g. of a diene was obtained, m.p. 130–132°, $[\alpha]^{27}D$ +54°. No major absorption in the ultraviolet down to 215 mμ was found.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.8; H, 8.6. Found: C, 76.6; H, 8.6.

16-Benzylidene-3β,14-ξ-dihydroxy-5-androsten-17-one (IVa).—To a solution of 2.0 g. of compound Ia in 20 cc. of methanol was added 760 mg. of benzaldehyde and 280 mg. of sodium methoxide and the mixture was refluxed for two hours during which time an additional 280 mg. of methoxide was added. The solution was cooled, diluted with water and the crystalline material filtered and dried (2.12 g.), which on recrystallization from methanol yielded 1.2 g. of product, m.p. 266–268°, $[\alpha]^{23}D$ +46° (alcohol), ultraviolet absorption maxima at 221 mμ (log ε 3.92) and 290 mμ (log ε 4.39).

Anal. Calcd. for $C_{26}H_{32}O_3$: C, 79.6; H, 8.2. Found: C, 79.3; H, 8.3.

The above material was acetylated with acetic anhydride in pyridine solution by heating on the steam-bath for 2 hours. The mixture was then cooled, diluted with water and the product extracted with chloroform. After recrystallization from ethyl acetate 980 mg. of the acetate IVb, m.p. 304–306°, were obtained.

Oxidation of Benzylidene IVb to Köster's Ketone Acetate (X).—To 1.98 g. of the above benzylidene acetate (IVb) in 20 cc. of chloroform was added 0.8 g. of bromine in 50 cc. of chloroform. After allowing the mixture to stand for 1 hour, 100 cc. of glacial acetic acid was added and the chloroform was removed *in vacuo* at 40°. To this solution, with stirring and at 60°, was added 4.14 g. of chromic acid in 40 cc. of 90% acetic acid over a period of 75 minutes. After the mixture was allowed to stir for 5 hours at this temperature, it was cooled, 100 cc. of methanol added and the solvents removed *in vacuo* at 40°. The residue was extracted several times with chloroform, the combined extracts washed with water, dried and the solvent removed *in vacuo*. The residue was taken up in glacial acetic acid and debrominated in the usual manner with zinc dust. After removal of the zinc and evaporation of the solvent the residue was dissolved in chloroform and separated into an acid and a neutral fraction. The neutral fraction (0.630 g.) was chromatographed on alumina. The material eluted with hexane (80 mg.) was sublimed at 0.001 mm. and at 100–130° to give 50 mg. of a sublimate which, when recrystallized from dilute methanol, yielded 25 mg. of a material melting at 124–127°. It did not depress the melting point when mixed with an authentic sample of Köster's ketone acetate.

3β-Acetoxy-16-benzylidene-5,14-androstadien-17-one (V).—A mixture of 60 mg. of the diene VI, 24 mg. of freshly distilled benzaldehyde and 8.4 mg. of sodium methoxide in 3 cc. of methanol was refluxed for two hours. The reaction mixture was diluted with water, and the product taken up in chloroform. The extract was washed, dried and the sol-

(13) All melting points are uncorrected and were taken by the capillary tube method in an aluminum block. Except where noted, all rotations were determined in chloroform solution and the ultraviolet absorption spectra in 95% ethanol solution. We wish to express our thanks to Mr. Louis Dorfman and his associates of our analytical laboratories for the microanalyses, rotations, ultraviolet and some of the infrared spectra. We are also greatly indebted to the late Dr. Konrad Dobriner of the Sloan-Kettering Institute for the infrared data on the original unknown material.

vent was then removed yielding 40 mg. of material, m.p. 165–168°. Repeated crystallizations from ethyl acetate–hexane raised the m.p. to 171–173°. Ultraviolet absorption maxima at 234 mμ (log ε 4.10), 256 mμ (log ε 3.94), 335 mμ (log ε 4.37).

Anal. Calcd. for $C_{28}H_{32}O_3$: C, 80.7; H, 7.7. Found: C, 81.1; H, 8.0.

The same compound could also be prepared by the dehydration of the 14-hydroxybenzylidene IVb with thionyl chloride in pyridine solution. However, the yields were very much lower in this case.

Synthesis of V from Dehydroisoandrosterone.—The 16-benzylidene derivative of dehydroisoandrosterone[14] was prepared as described for compound IVa. It was directly acetylated and yielded an acetate, VII, m.p. 255–256°. Ultraviolet absorption maxima at 223 mμ (log ε 3.92) and 295 mμ (log ε 4.39).

To a solution of 2.85 g. of this material in 50 cc. of chloroform was added 1.1 moles of bromine in 10 cc. of chloroform at 0°. It was then concentrated *in vacuo* at 40° and the residue dissolved in 100 cc. of carbon tetrachloride. After the addition of 1.5 g. of N-bromosuccinimide the mixture was refluxed for 15 minutes and the product worked up in the usual way. The oil remaining after removal of the solvent was debrominated in acetone solution with sodium iodide at room temperature overnight. After recrystallization from methanol the halogen-free product amounted to 1.52 g., m.p. 171–173°, and was shown to be identical with V by mixed melting point and ultraviolet absorption spectra.

Anal. Calcd. for $C_{28}H_{32}O_3$: C, 80.7; H, 7.7. Found: C, 80.5; H, 7.8.

3β-Acetoxy-14ξ-hydroxy-17-androstanone (XI).—Compound Ia (2.0 g.) was hydrogenated at atmospheric pressure in acetic acid solution (60 cc.) using 750 mg. of 5% palladium-on-charcoal as catalyst. Slightly over the theoretical amount of hydrogen was taken up within one hour. The product after recrystallization from methanol–water weighed 1.4 g., m.p. 202–204°, $[\alpha]^{24}D$ +50°.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.4; H, 9.3. Found: C, 72.4; H, 9.3.

3β-Acetoxy-14-androsten-17-one (XIIa).—A 500-mg. sample of the above material was dehydrated as described for the preparation of the diene VI. A yield of 200 mg. of product was obtained after recrystallization from methanol, m.p. 158–159°, $[\alpha]^{22}D$ +116°. The compound had no major absorption in the ultraviolet down to 215 mμ.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.3; H, 9.2. Found: C, 76.1; H, 9.0.

3β-Acetoxy-16-benzylidene-14-androsten-17-one (XIII).—A solution of 250 mg. of compound XIIa in 5 cc. of methanol was refluxed with benzaldehyde and sodium methylate as described above. The oily residue was directly acetylated with acetic anhydride in pyridine solution and 100 mg. of product was obtained after recrystallization from methanol, m.p. 147–149°. Ultraviolet absorption maxima at 234 mμ (log ε 4.1), 256 mμ (log ε 3.93) and 335 mμ (log ε 4.35).

Anal. Calcd. for $C_{28}H_{34}O_3$: C, 80.3; H, 8.2. Found: C, 80.1; H, 8.0.

Synthesis of XIII from Isoandrosterone.—The 16-benzylidene derivative (XIV) of isoandrosterone acetate[6] (2.37 g.) was brominated in carbon tetrachloride solution by refluxing with 1.2 g. of N-bromosuccinimide for 15 minutes. The resulting bromide XV (1.38 g.) was recrystallized from ethyl acetate and yielded an analytical sample, m.p. 158–160°.

Anal. Calcd. for $C_{28}H_{35}O_3Br$: Br, 16.0. Found: Br, 15.9.

About 1 g. of the above crude bromide was refluxed for 15 minutes with 15 cc. of collidine. On cooling, the reaction mixture was diluted with ether and washed with dilute hydrochloric acid and water, dried and the solvent removed. The resulting material (750 mg.) contained some unreacted benzylidene XIV which was removed in the first crop of crystals. The mother liquor material was recrystallized repeatedly from methanol and yielded 520 mg. of product, m.p. 146–148°, which was shown to be identical with XIII by mixed melting point and ultraviolet absorption spectra.

Anal. Calcd. for $C_{28}H_{34}O_3$: C, 80.3; H, 8.2. Found: C, 80.3; H, 8.0.

(14) F. H. Stodola and E. C. Kendall, *J. Org. Chem.*, **7**, 336 (1942).

3β-Acetoxy-14-isoandrostan-17-one (XVIa).—A solution of 30.7 mg. of compound XIIa in 5 cc. of purified ethanol was hydrogenated using 5% palladium-on-charcoal as catalyst. One mole of hydrogen was taken up within 30 minutes. The product was recrystallized from hexane and yielded 23 mg. of material, m.p. 177–178°, $[\alpha]^{24}D$ +65°. Isoandrosterone acetate (polymorphic), m.p. 96 or 116°, $[\alpha]^{24}D$ +82°.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.9; H, 9.7. Found: C, 76.1; H, 10.0.

The same substance was similarly prepared by the reduction of the diene VI in either alcohol or acetic acid solution.

Semicarbazone, m.p. 267–269° (dec.).

Anal. Calcd. for $C_{22}H_{35}N_3O_3$: C, 67.8; H, 9.1; N, 10.8. Found: C, 67.7; H, 9.0; N, 10.8.

3β-Hydroxy-14-isoandrostan-17-one (XVIb).—Upon saponifying 60 mg. of the above substance with potassium carbonate in aqueous methanol, 40 mg. of product was obtained after recrystallization from methanol, m.p. 161–164°, $[\alpha]^{24}D$ +81° (isoandrosterone, m.p. 174–175°, $[\alpha]^{24}D$ +78°).

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.6; H, 10.4. Found: C, 78.3; H, 10.3.

14-Isoandrostane-3,17-dione (XVII).—A solution of 250 mg. of the 3-hydroxy-17-keto compound (XVIb) in 10 cc. of acetic acid was treated with 120 mg. of chromic anhydride in 3 cc. of 90% acetic acid overnight at room temperature. On working up the reaction 150 mg. of dione was obtained after recrystallization from dilute methanol, m.p. 184–186°, $[\alpha]^{25}D$ +110° (androstane-3,17-dione, m.p. 133–134°, $[\alpha]^{23}D$ +113°).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.1; H, 9.8. Found: C, 79.1; H, 10.0.

Disemicarbazone did not melt below 360°.

Anal. Calcd. for $C_{21}H_{34}N_6O_2$: C, 62.6; H, 8.5; N, 20.9. Found: C, 62.6; H, 8.8; N, 19.9.

14-Isoandrostane-3β,17α-diol Diacetate (XIXa).—A solution of 5.4 g. of 3β-acetoxy-14-iso-17-isoallopregnan-20-one[10] in 150 cc. of chloroform containing 40.4 mg./cc. of perbenzoic acid was allowed to stand for three weeks in the dark. At the end of this time the reaction mixture was worked up as described in the literature[11] and 5.2 g. of orange-red oil was obtained. This was chromatographed in 50% benzene–hexane solution on acid washed alumina. The fraction eluted with 100% benzene amounted to 3.75 g., m.p. 95–100°. It was recrystallized from aqueous methanol and yielded pure product, m.p. 102–104°, $[\alpha]^{22}D$ +23°. Since these diols tend to solvate a small sample was sublimed *in vacuo* at 100–115° for analysis.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.4; H, 9.6. Found: C, 73.0; H, 9.6.

14-Isoandrostane-3β,17α-diol (XIXb).—For saponification 3.0 g. of the above diacetate was allowed to stand overnight at room temperature in 5% methanolic potassium hydroxide solution. It was then concentrated to a small volume and diluted with an excess of water. The precipitated material was taken up in chloroform and the solution washed with water until neutral. After drying the solvent was removed and the residue was recrystallized from methanol–water yielding 1.89 g. of material, m.p. 188–189°, $[\alpha]^{23}D$ +36°. A small sample was sublimed for analysis.

Anal. Calcd. for $C_{19}H_{32}O_2$: C, 78.0; H, 11.0. Found: C, 78.3; H, 11.2.

This same substance was also produced when XVIa and XVII were reduced with sodium borohydride in methanol by the usual procedure.

14-Isoandrostane-3,17-dione from XIXb.—A solution of 900 mg. of the above diol in 25 cc. of 90% acetic acid was oxidized with chromic acid overnight at room temperature. The acetic acid was then removed *in vacuo* and the residue diluted with water and extracted with ether. The ether solution was washed with dilute sodium carbonate solution and water, dried and the solvent removed. The residue was recrystallized from methanol and gave 600 mg. of product, m.p. 183–185°, $[\alpha]^{22}D$ +114°.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.1; H, 9.8. Found: C, 79.1; H, 10.0.

A mixture of this compound with that made from XVIb showed no depression of the m.p. and their infrared absorp-

tion curves were identical and quite distinguishable from that of 3,17-androstanedione.

5,14-Androstadiene-3β,17β-diol (XXa).—A 400-mg. sample of the diene VI was dissolved in 25 cc. of methanol and 100 mg. of pulverized sodium borohydride added. The mixture was allowed to stand overnight at room temperature and then refluxed for 2 hours. An aqueous solution of 400 mg. of potassium carbonate was added and refluxing was continued for an additional hour. On cooling, the mixture was diluted with water and the precipitated material extracted with ethyl acetate. After washing neutral the extract was dried and the solvent removed. The residue was recrystallized from ethyl acetate–hexane and yielded 240 mg. of material, m.p. 193–195°, $[\alpha]^{23}D$ −33°. A small sample was sublimed for analysis, m.p. 195–197°.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.1; H, 9.8. Found: C, 79.2; H, 9.8.

5,14-Androstadiene-3β,17β-diol Diacetate (XXb).—On acetylating 50 mg. of the above diol with acetic anhydride in pyridine solution 30 mg. of diacetate was obtained, m.p. 157–158°, $[\alpha]^{22}D$ −51°.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.2; H, 8.7. Found: C, 74.2; H, 8.9.

About 400 mg. of the same diacetate resulted from the dehydration of 630 mg. of II with acetic anhydride and potassium acid sulfate as previously described.

14-Isoandrostane-3β,17β-diol Diacetate (XXIa).—A 220-mg. sample of the above compound (XXb) was reduced in 15 cc. of acetic acid with 100 mg. of 5% palladium-on-charcoal as catalyst at atmospheric pressure and room temperature. On working up the product there was obtained 135 mg., m.p. 171–172°, $[\alpha]^{24}D$ +35°.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.4; H, 9.6. Found: C, 73.3; H, 9.5.

14-Isoandrostane-3β,17β-diol (XXIb).—Saponification of 100 mg. of the above diacetate with aqueous methanolic potassium hydroxide for 2 hours on the steam-bath yielded 60 mg. of diol, m.p. 170–171°, $[\alpha]^{22}D$ +38° after recrystallization from dilute methanol. A small sample was sublimed for analysis.

Anal. Calcd. for $C_{19}H_{32}O_2$: C, 78.0; H, 11.0. Found: C, 77.8; H, 11.3.

The same diol was also obtained from the catalytic reduction of the diene diol XXa.

14-Isoandrostane-3,17-dione from XXIb.—The above diol (40 mg.) was oxidized with chromic acid in 90% acetic acid solution overnight at room temperature. On working up the reaction 28 mg. of product, m.p. 178–181°, was obtained after recrystallization from aqueous methanol. A mixture of this material with that made from the 17α-epimer (XIXb) showed no depression of the melting point.

3β,17β-Diacetoxyandrostan-14ξ-ol.—To 350 mg. of 3β-acetoxy-14ξ-hydroxyandrostan-17-one (XI) in 15 cc. of methanol was added 250 mg. of sodium borohydride. The mixture was refluxed for two hours, 350 mg. of potassium carbonate was then added along with enough water to dissolve the insoluble material and the solution refluxed for an additional hour. After cooling water was added to precipitate the steroid which was filtered, washed neutral and dried. It was recrystallized from aqueous methanol and from ethyl acetate–hexane, m.p. 181–183°. Since this trihydroxy compound could not be obtained in an analytically pure state, it was acetylated with acetic anhydride in pyridine solution. After working up the mixture and recrystallizing the product from dilute methanol 175 mg. of material was obtained, m.p. 189.5–191°, $[\alpha]^{25}D$ +11°.

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 70.4; H, 9.3. Found: C, 70.6; H, 9.4.

14-Androstene-3β,17β-diol.—Two hundred milligrams of 3β-acetoxy-14-androsten-17-one (XIIa) was reduced with sodium borohydride as described above. The product (100 mg.) was recrystallized from aqueous methanol, m.p. 140–141°, $[\alpha]^{25}D$ +36°.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.6; H, 10.4. Found: C, 78.3; H, 10.4.

Diacetate.—A sample of the above material was acetylated with acetic anhydride in pyridine solution and the product recrystallized from dilute methanol, m.p. 160–161°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.8; H, 9.2. Found: C, 73.9; H, 9.1.

3β-Hydroxy-14-androsten-17-one (XIIb).—A mixture of 420 mg. of XIIa, 40 cc. of methanol and 2 cc. of 50% aqueous potassium hydroxide solution was refluxed for 1 hour. The alcoholic solution was concentrated to one-third its volume and diluted with an excess of water. The precipitated yellowish material was extracted with chloroform and the extracts washed until neutral. The solution was dried and after removal of the solvent 400 mg. of neutral oil remained. About 5 cc. of acetone was added whereupon a white crystalline substance separated. This was filtered and after recrystallization from ethyl acetate yielded 70 mg. of material, m.p. 300–305°; ultraviolet absorption maximum at 244 mμ ($E^{1\%}_{1\ cm.}$ 129); infrared spectrum bands at 1622 cm.$^{-1}$ (double bond), 1696 and 1734 cm.$^{-1}$ (carbonyl) and 3558 cm.$^{-1}$ (hydroxyl) ($CHCl_3$).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.1; H, 9.8. Found: C, 79.1; H, 9.9.

The acetone mother liquor after removal of the above material was concentrated to dryness and chromatographed in benzene solution on 8.0 g. of acid-washed alumina. The fractions eluted with 10–20% ether in benzene (95 mg.) were recrystallized from methanol–water and yielded 50 mg. of compound XIIb, m.p. 130–131°. Ultraviolet absorption maximum 292 mμ (log ε 1.62). Infrared absorption bands at 1639 cm.$^{-1}$ (double bond); 1736 cm.$^{-1}$ (carbonyl) and 3552 cm.$^{-1}$ (hydroxyl) ($CHCl_3$).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.1; H, 9.8. Found: C, 78.8; H, 9.8.

Saponification of 3β-Acetoxy-5,14-androstadien-17-one (VI).—Two hundred milligrams of VI was refluxed for two hours with 10 cc. of methanol containing 1% potassium hydroxide. The mixture was then diluted with water and the precipitated material extracted with chloroform. The extract was washed, dried and the solvent was removed. The residue was recrystallized from aqueous methanol and then from ethyl acetate and yielded 10 mg. of material, m.p. 280–282° $[\alpha]^{23}D$ +78°. Ultraviolet absorption maximum at 245 mμ ($E^{1\%}_{1\ cm.}$ 142). Infrared bands at 1733 and 1700 cm.$^{-1}$ (carbonyl) and a hydroxyl band.

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