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ISOMERIC ESTRANE DERIVATIVES

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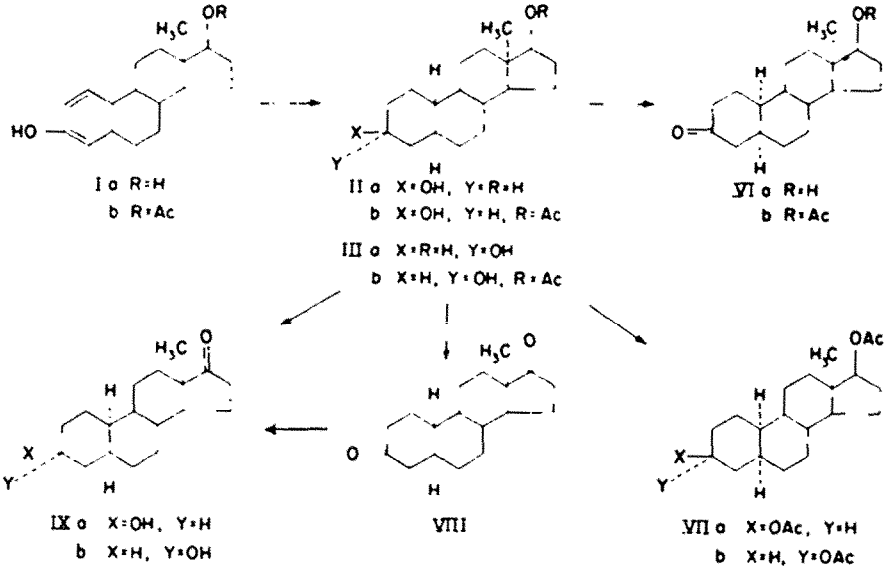
Abstract -Various 3,17-oxygenated isomeric estrane derivatives have been synthesized as possible metabolites of 19-norsteroids. Methods employed to establish configurations are described and biological data on some of the more pertinent compounds is presented.

TESTOSTERONE and its esters have been used in therapy for their anabolic effects in many disease processes but treatment has been limited by the inherent androgenicity of the molecule. In 1953 Hershberger *et al.*[1] demonstrated that 19-nortestosterone (17β-hydroxyestr-4-en-3-one) retained the anabolic potency but was much less androgenic than testosterone propionate. In the past few years a number of modifications of 19-nortestosterone have been made in an effort to produce more potent anabolic agents possessing minimal androgenicity.[2-4] One approach to this problem involves the possibility that some metabolite of 19-nortestosterone may be the anabolicly active agent. As a consequence, the 19-nor analogs (estranes) of the *in vivo* metabolites of testosterone[5] were synthesized for biological evaluation. Since this work was initiated, a number of isomeric estrane derivatives have been synthesized[6-12] as well as isolated in metabolic studies.[13,14] This paper confirms the work of these investigators and attempts to clarify some of the structural discrepancies found in the literature as well as to describe the synthesis of other possible estrogen and norsteroid metabolites.

One path to the synthesis of the estranes is by catalytic hydrogenation of the aromatic "A" ring of the steroid estrogens. Hydrogenation with platinum catalyst has been employed for this purpose but causes extensive hydrogenolysis to monooxygenated products.[6,15] In their work on steroid total synthesis, Johnson and coworkers[16] reported that hydrogenations with ruthenium dioxide as catalyst reduced phenols with a minimum amount of hydrogenolysis. As a consequence, this catalyst was selected for the hydrogenation of the aromatic "A" ring.

[1] L. G. Hershberger, E. G. Shipley and R. K. Meyer, *Proc. Soc. Exp. Biol. Med.* **83**, 175 (1953).
[2] F. B. Colton, L. N. Nysted, B. Riegel and A. L. Raymond, *J. Amer. Chem. Soc.* **79**, 1123 (1957).
[3] J. Iriarte, C. Djerassi and H. J. Ringold, *J. Amer. Chem. Soc.* **81**, 436 (1959).
[4] B. Camerino, B. Patelli and A. Vercellone, *J. Amer. Chem. Soc.* **78**, 3540 (1956).
[5] *cf.* R. I. Dorfman and R. A. Shipley, *Androgens* p. 68. John Wiley, New York (1956).
[6] C. Chen, *Tetrahedron* **3**, 43 (1958).
[7] R. T. Rapala and E. Farkas, *J. Amer. Chem. Soc.* **80**, 1008 (1958).
[8] R. T. Rapala and E. Farkas, *J. Org. Chem.* **23**, 1404 (1958).
[9] A. Bowers, H. J. Ringold and R. I. Dorfman, *J. Amer. Chem. Soc.* **79**, 4556 (1957).
[10] A. Bowers, H. J. Ringold and E. Denot, *J. Amer. Chem. Soc.* **80**, 6115 (1958).
[11] D. Kupfer, E. Forchielli and R. I. Dorfman, *J. Org. Chem.* **25**, 1674 (1960).
[12] D. Kupfer, E. Forchielli and R. I. Dorfman, *J. Amer. Chem. Soc.* **82**, 1257 (1960).
[13] L. L. Engel, J. Alexander and M. Wheeler, *J. Biol. Chem.* **231**, 159 (1958).
[14] D. Kupfer, E. Forchielli and R. I. Dorfman, *J. Biol. Chem.* **235**, 1968 (1960).
[15] R. E. Marker and E. Rohrmann, *J. Amer. Chem. Soc.* **62**, 73 (1940).
[16] W. S. Johnson, E. R. Rogier and J. Ackerman, *J. Amer. Chem. Soc.* **78**, 6322 (1956).

Of the four possible steric arrangements for the A/B rings in the estrane series, hydrogenation of estradiol (Ia) over ruthenium afforded the 5α,10α isomer (*cis-syn-trans*)[17] in excellent yield with no apparent hydrogenolysis. A similar finding was recently reported by Rapala and Farkas.[8] Thus, 5α,10α-estrane-3β,17β-diol (IIa) was obtained in 78 per cent yield. Chromatography of the mother liquors showed that the 3α epimer (IIIa) and 5β-estrane-3α,17β-diol (Va) were also formed in minor amounts. Although no 5β-estrane-3β,17β-diol (IVa) was isolated in this experiment, it was probably present in trace amounts (see below). IIa was also prepared by similar treatment of 17β-hydroxy-estr-5(10)-en-3-one. Considering that 19-nortestosterone is reduced by ruthenium catalysis to give products of the 5β,10β series,[7] it was conjectured that this catalyst may promote the hydrogenation of the difficultly reducible 5(10) double bond of estr-5(10)-ene-3,17-diol.[19] All attempts to reduce this compound, however, were unsuccessful.

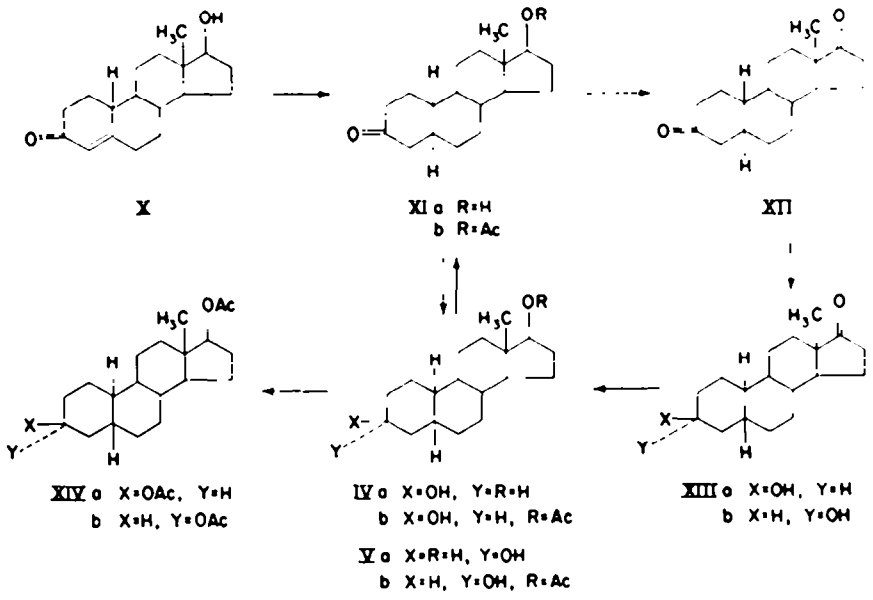


Four isomeric 17-monoacetates (IIb, IIIb, IVb and Vb) were obtained when estradiol 17-monoacetate was similarly hydrogenated. In this instance, 5β-estrane-3β,17β-diol 17-monoacetate (IVb), the isomer not obtained in the reduction of estradiol, was isolated and characterized. Hydrolysis of these monoacetates afforded the corresponding four isomeric diols, while oxidation by the Jones procedure[20] gave 5α,10α-estran-17β-ol-3-one acetate (VIb) and 5β-estran-17β-ol-3-one acetate (XIb) respectively. 5α,10α-Estrane-3,17-dione (VIII) was prepared by oxidation of the diol IIa.

Selective reduction of the C-3 carbonyl of VIII with non-pyrophoric W-2 Raney nickel catalyst according to the method of Djerassi[21] gave 5α,10α-estran-3β-ol-17-one

[17] The *trans-syn-trans* arrangement is energetically unfavored as it would require the "B" ring to assume a boat conformation.[18]
[18] W. S. Johnson, *Experientia* 7, 315 (1951).
[19] J. A. Hartman, *J. Amer. Chem. Soc*, 77, 5151 (1955).
[20] K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* 39, (1946).
[21] C. Djerassi, A. J. Manson and M. Gorman, *J. Amer. Chem Soc.* 77, 4925 (1955).

(IXa). Surprisingly, none of the 3α-epimer (IXb) could be isolated by this procedure. This isomer was prepared from 5α,10α-estrane-3α,17β-diol 17-monoacetate (IIIb) by initial formation of the 3-tetrahydropyranyl ether followed by basic hydrolysis of the 17-acetate group. The resulting product was oxidized and the 3α-hydroxyl group regenerated by acid hydrolysis of the pyranyl ether to give 5α,10α-estran-3α-ol-17-one (IXb). Acetylation of the 17-monoacetates IIb and IIIb gave the diacetates VIIa and VIIb, respectively.

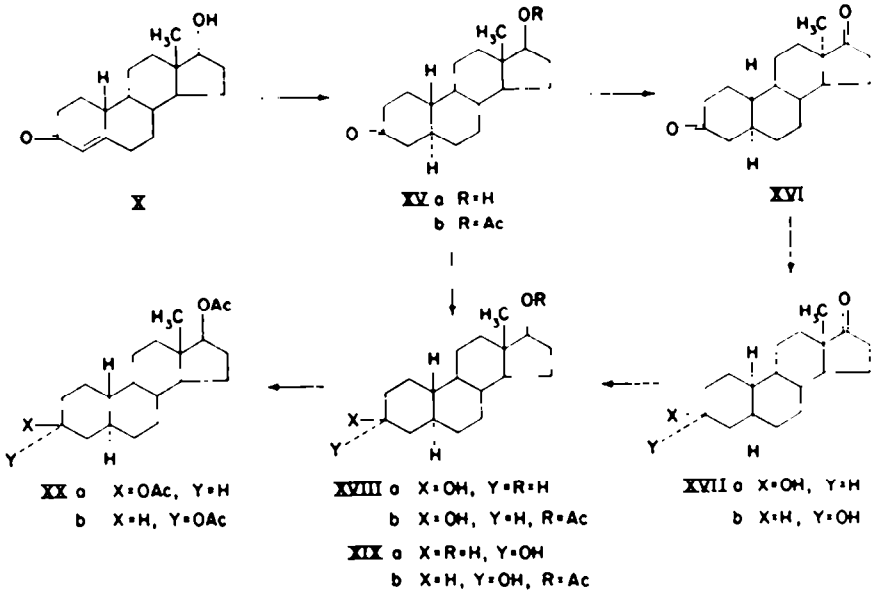


19-nortestosterone (X) was employed as the starting material for the preparation of the 5β and 5α-estranes. Low pressure hydrogenation over palladium-on-carbon gave 5β-estran-17β-ol-3-one (XIa) in good yield. A small amount 5β-estrane-3α,17β-diol (Va) was isolated by chromatography and found to be identical with Marker's estranediol B, of unknown configuration, isolated from human non-pregnancy urine.[22] Acetylation of this diol gave the diacetate XIVb in agreement with that of Marker's while oxidation of XIa gave 5β-estrane-3,17-dione (XII) identical with the reported estranedione B.[22] Reduction of this diketone with Raney nickel in ethanol gave the epimeric 5β-estran-3β-ol-17-one (XIIIa) and 5β-estran-3α-ol-17-one (XIIIb) (19-noretiocholanolone). Sodium borohydride reduction of these products furnished the diols IVa and Va which proved to be identical with those obtained by the hydrolysis of the corresponding 17-monoacetates.

5α-Estran-17β-ol-3-one (XVa) was prepared by reduction of 19-nortestosterone with lithium and liquid ammonia in a manner similar to that described by Bowers *et al.*[9,10] 5α-Estrane-3β,17β-diol (XVIIIa) was isolated as a minor by-product of this reduction. Oxidation of either of these two products or the crude reduction mixture gave 5α-estrane-3,17-dione (XVI). Selective reduction of this diketone with Raney nickel furnished 5α-estran-3β-ol-17-one (XVIIa) (19-norepiandrosterone) and 5α-estran-3α-ol-17-one (XVIIb) (19-norandrosterone). The latter was isolated by Engel

[22] R. E. Marker, E. Rohrmann, E. L. Wittle and E. J. Lawson, *J. Amer. Chem. Soc.* **60**, 1512 (1938).

and co-workers[13] from the urine of a patient after administration of 19-nortestosterone. An alternate synthesis of both these products was recently reported by Kupfer *et al.*[11,12] Reduction of 5α-estran-17β-ol-3-one (XVa) and its acetate (XVb) with Raney



nickel gave the epimeric diols XVIIIa and XIXa and their corresponding 17-monoacetates XVIIIb and XIXb. Acetylation furnished the diacetates XXa and XXb of which the former agrees with the product of unassigned configuration prepared by Hartman[19] by catalytic hydrogenation of estr-4-ene-3β,17β-diol diacetate.

The stereochemistry of the A/B ring fusion in the isomeric estranes has already

TABLE 1.—M_D INCREMENTS FOR CHANGES AT C-3

	Type	Δ Ac (acetylation)	Δ Ket (ketonization)
5α	3α OH	+29 (+17)*	+57 (+66)
	3β OH	−30 (−29)	−67 (−73)
5β	3α OH	+113 (+82)	−16 (+7)
	3β OH	+15 (+17)	+20 (+36)

* The values for the 19 methyl steroids are in parentheses.[24]

been established.[7-9] The axial or equatorial configurations at C-3 were assigned on the basis of: (a) order of elution from the chromatographic column[23] (b) molecular rotation differences (c) position of C-O frequencies between 1050 and 1000 cm^{-1} in the infrared and (d) nuclear magnetic resonance spectra.

Table 1 shows the molecular rotation differences (M_D) upon conversion of the

[23] The less polar axial isomer is followed by the more polar equatorial isomer upon elution.
[24] L. F. Fieser, *Steroids* p. 180. Reinhold, New York (1959).

epimeric C—3 alcohols into their acetates or corresponding ketones. It will be seen that the values obtained for isomeric 5α and 5β estranes are in good agreement with those obtained for the corresponding epimers in steroids possessing the C—19 angular methyl group.

The infrared spectra of the six isomeric estran-3-ol-17-ones gave further support to the configurational assignments at C—3. As noted by Cole and coworkers[25] equatorial

TABLE 2. HYDROXYL ABSORPTION BY AXIAL AND EQUATORIAL SUBSTITUENTS

Compound	Type	Conformation of C - O	ν(C—O) cm^{-1}
XVIIb	5α 3α OH	Axial	1010
XVIIa	5α 3β OH	Equatorial	1028
XIIIb	5β 3α OH	Equatorial	1032
XIIIa	5β 3β OH	Axial	995
IXb	5α, 10α 3α OH	Equatorial	1052
IXa	5α, 10α 3β OH	Axial	Complex

hydroxyl groups give rise to bands near 1040 cm^{-1} whereas for axial hydroxyl groups the C—O frequencies are near 1000 cm^{-1}. Table 2 shows the C—O frequencies for the isomeric estranolones. Whereas the values obtained for the 5α and 5β estranes support the assignments, the complex bands exhibited by 5α,10α-estran-3β-ol-17-one in this region made it impossible to draw conclusions for this series. The equatorial isomer, however, did exhibit an intense band at 1052 cm^{-1}.

Final proof of the configuration of the C—3 hydroxyls in the 5α,10α series was furnished by nuclear magnetic resonance studies.[26] Table 3 lists the τ values obtained for the C—3 proton of the six isomeric estranolones. These values are in agreement with those reported by Shoolery and Rogers for C—3 axial and equatorial protons in 3-hydroxy steroids.[27] The τ values for androsterone and epiandrosterone are shown for comparison.

The estrogen antagonistic action of some of these compounds has been published by our Biological Division.[28] Table 4 shows the androgenic and anabolic activities obtained for several of the more interesting compounds. The compounds exhibited a low order of activity compared to testosterone propionate, but it is interesting to note that the 3α-hydroxy compound (XIXb) in the A/B *trans* series is more active than the β-isomer (XIXa) as is the case in the normal series.[29] The compounds in the

[25] A. R. H. Cole, R. N. Jones and K. Dobriner, *J. Amer. Chem. Soc.* **74**, 5571 (1952).
[26] I am indebted to Dr. McNiven, Worcester Foundation for Experimental Biology for the NMR data. The instrument employed for these measurements was a Varian High Resolution NMR Spectrophotometer Model V-4300B. The compounds were analyzed as 0·1 to 0·3 M. solutions in deuterochloroform using tetremethylsilane as the internal reference.
[27] J. N. Shoolery and M. T. Rogers, *J. Amer. Chem. Soc.* **80**, 5121 (1958).
[28] R. A. Edgren, D. W. Calhoun, R. L. Elton and F. B. Colton, *Endocrinology* **65**, 265 (1959).
[29] R. I. Dorfman and R. A. Shipley, *Androgens* p. 118 John Wiley, New York (1956).

TABLE 3. NMR SHIFTS FOR PROTON ON 3-HYDROXY ESTRANES

Compound	Type	Proton Conformation	τ Value
XVIIb	3α OH	Equatorial	5·92
	5α		
XVIIa	3β OH	Axial	6·47
XIIIb	3α OH	Axial	6·41
	5β		
XIIIa	3β OH	Equatorial	5·89
IXb	3α OH	Axial	6·29
	5α, 10α		
IXa	3β OH	Equatorial	5·94
Androsterone	3α OH	Equatorial	5·87
	5α		
Epiandrosterone	3β OH	Axial	6·42

TABLE 4. ANDROGENIC-ANABOLIC ACTIVITY OF SOME ISOMERIC ESTRANE DERIVATIVES

Compound	Androgenic	Anabolic
Testosterone propionate	100	100
VIa	Inactive	Inactive
XIa	5	Inactive
XVa	10	20
XVIIIa	2	2
XIXa	5	5

5α,10α series were inactive in a variety of endocrinological assays including antiandrogenic, estrogenic, antiestrogenic, progestational, and antiprogestational.[30]

EXPERIMENTAL[31]

Hydrogenation of estradiol. To a solution of estradiol (20 g) in ethanol (500 ml) containing 40% sodium hydroxide solution (1 ml) was added ruthenium dioxide (5 g) and the mixture hydrogenated at elevated pressure (1475 lb/in²) and 65°. After hydrogen uptake ceased (2 hr), the catalyst was removed by filtration and washed well with ethanol. The filtrate was neutralized with acetic acid and the solvent removed by distillation under reduced pressure. Crystallization of the crude product from methanol–water afforded needles (11·9 g), m.p. 177–179°. Sublimation gave an analytical sample of

[30] Private communication from our Endocrinology Division.

[31] All melting points are uncorrected and all rotations were taken in chloroform. The infrared spectra were obtained with a Beckman model IR 4 spectrophotometer using 3% chloroform solutions. I am indebted to Dr. R. T. Dillon and Dr. H. W. Sause of our company for the analytical and microanalytical data.

5α,10α-estrane-3β,17β-diol (IIa), m.p. 180–182° (reported[8] 179–181°), $[\alpha]_D^{26}$ 12°. (Found: C, 77·3; H, 10·7. Calc. for $C_{18}H_{30}O_2$: C, 77·6; H, 10·9%). Adsorption of the residue on silica gel and elution with benzene–ethyl acetate (15%) gave an additional 4·0 g of the above diol. This was followed by minor amounts of the epimeric 5α,10α-estrane-3α,17β-diol (IIIa) m.p. 223–225°, $[\alpha]_D^{25}$ 6°. (Found: C, 77·5; H, 10·6. $C_{18}H_{30}O_2$ requires: C, 77·6; H, 10·9%) and 5β-estrane-3α,17β-diol (Va) (see below).

Hydrogenation of estradiol 17-monoacetate. To a solution of estradiol 17-monoacetate (20 g) in ethanol (1) was added ruthenium dioxide (7·0 g) and the mixture hydrogenated at 900 lb in^2 and 55°. After hydrogen uptake ceased (2 hr), the catalyst was removed by filtration, washed well with ethanol, and the solvent removed from the filtrate. The residue was dissolved in a minimum amount of benzene and adsorbed onto silica gel (1700 g). Elution with benzene–ethyl acetate (5%) gave 5α,10α-estrane-3β,17β-diol 17-monoacetate (IIb, 12·1 g), m.p. 118–120° as the major product. Recrystallization from methanol–water gave an analytical sample, m.p. 125·5–127°, $[\alpha]_D^{26}$ 25°. (Found: C, 75·3; H, 10·0. $C_{20}H_{32}O_3$ requires: C, 75·0; H, 10·1%). Further elution gave 5β-estrane-3β,17β-diol-17-monoacetate (IVb, 0·95 g), m.p. 159–160·5°, $[\alpha]_D^{25}$ +15°. (Found: C, 74·6; H, 10·1). These were followed by the more polar 5α,10α-estrane-3α,17β-diol 17-monoacetate (IIIb, 2·25 g), m.p. 126·5–128·5°, $[\alpha]_D^{25}$ −24°. (Found: C, 75·2; H, 10·0), and 5β-estrane-3α,17β-diol-17-monoacetate (Vb, 2·4 g), m.p. 120–122°, $[\alpha]_D^{25}$ +26°. (Found: C, 75·0; H, 9·9).

5α,10α-*Estran*-17β-*ol*-3-*one acetate* (VIb). 5α,10α-Estrane-3β,17β-diol 17-monoacetate (IIb, 2·0 g) was dissolved in acetone (20 ml) and standard chromium trioxide reagent[20] added dropwise with stirring to the cooled solution until a faint color of the reagent persisted. Isopropanol was added to destroy the excess reagent and the supernatant solution poured slowly into ice-water. The resulting precipitate was removed by filtration and washed with water. Recrystallization of the crude product from ethanol water afforded an analytical sample m.p. 112–112·5°, $[\alpha]_D^{25}$ 58·5° (reported[8] m.p. 110–111°, $[\alpha]_D^{22}$ 55·4 [acetone]). (Found: C, 75·3; H, 9·5. Calc. for $C_{20}H_{30}O_3$: C, 75·4; H, 9·5%).

5α,10α-*Estran*-17β-*ol*-3-*one* (VIa). The acetate VIb (2·0 g) was dissolved in methanol (49 ml) and water (1 ml). Potassium hydroxide flakes (1·0 g) was added and the solution refluxed for 1 hr. After allowing the solution to cool, water was added slowly with stirring. The resulting precipitate was removed by filtration and washed with water to give 1·8 g of product. Alternate recrystallizations from acetone–Skellysolve B and methanol–water produced an analytical sample, m.p. 149·5–150·5°, $[\alpha]_D^{25}$ −53°.[21] (Found: C, 78·2; H, 10·2. Calc. for $C_{18}H_{28}O_2$: C, 78·2; H, 10·2%).

5α,10α-*Estrane*-3β,17β-*diol diacetate* (VIIa). 5α,10α-Estrane-3β,17β-diol 17-monoacetate (IIb, 0·5 g) was dissolved in a mixture of pyridine (9 ml) and acetic anhydride (1 ml). The solution was heated on the steam bath for 4 hr and allowed to stand overnight at room temperature. The solution was poured slowly into ice-water and the resulting gum extracted with ether. The ether extract was washed with 2 N hydrochloric acid, 5% sodium carbonate solution, and water. After drying the solution over anhydrous potassium carbonate, the solvent was removed by distillation. Two recrystallizations of the crystalline residue from ethanol–water afforded needles, m.p. 103–104°, $[\alpha]_D^{26}$ 25°. (Found: C, 73·1; H, 9·6. $C_{22}H_{34}O_4$ requires: C, 72·9; H, 9·5%).

5α,10α-*Estrane*-3α,17β-*diol diacetate* (VIIb). Acetylation of 5α,10α-estrane-3α,17α-diol 17-monoacetate (IIIb) with acetic anhydride–pyridine gave, after several crystallizations from ethanol–water, the diacetate, m.p. 110·5–111°, $[\alpha]_D^{25}$ −30°. (Found: C, 72·6; H, 9·2. $C_{22}H_{34}O_4$ requires: C, 72·9; H, 9·5%).

5α,10α-*Estrane*-3,17-*dione* (VIII). 5α,10α-Estrane-3β-17β-diol (IIa, 5·0 g) was dissolved in acetone (200 ml) and oxidized with standard chromium trioxide reagent as described above. This resulted in 3·9 g of product m.p. 157–160° and recrystallization from methanol–water gave an analtyical sample, m.p. 158–161°, $[\alpha]_D^{24}$ +24° (reported 8 m.p. 163–165°, $[\alpha]_D$ +27·5° [Dioxane]). (Found: C, 78·6; H, 9·4. Calc. for $C_{18}H_{28}O_2$: C, 78·8; H, 9·5%).

5α,10α-*Estran*-3β-*ol*-17-*one* (IXa). To a solution of 5α,10α-estran-3,17-dione (VIII, 2·4 g) in ethanol (200 ml) was added a slurry of aged W-2 Raney nickel catalyst (5 g) in ethanol. The mixture was refluxed with stirring for 4 hr and the catalyst removed by filtration. The solvent was removed from the filtrate and the residue dissolved in benzene (25 ml). Adsorption on silica gel (220 g) and elution with benzene–ethyl acetate (5%) afforded starting dione (0·44 g) followed by 5α,10α-estran-3β-ol-17-one (1·18 g). Alternate recrystallization from ethanol–water and Skellysolve C afforded an

[21] Rapala and Farkas[8] reported m.p. 192–194°, $[\alpha]_D$ −31·1° for this compound. Our constants are in more agreement with those of Chen[9] who reported m.p. 135°/146°, $[\alpha]_D^{22}$ −54·1° (acetone).

analytical sample, m.p. 152-154°, $[\alpha]_D^{25}$ + 64°. (Found: C, 78·4; H, 10·0. $C_{18}H_{30}O_2$ requires: C, 78·2; H, 10·2%). Further elution with benzene–acetate (10%) gave a trace of 5α,10α-estrane-3β,17β-diol (IIa) identical with an authentic sample. This product was also prepared by reduction of IXa with sodium borohydride.

5α,10α-*Estran*-3α-*ol*-17-*one* (IXb). 5α,10αEstran-3α,17β-diol 17-monoacetate (IIIb, 2·0 g), dihydropyran (3 ml), and *p*-toluene sulfonic acid monohydrate (0·03 g) were dissolved in benzene (30 ml). After allowing the solution to stand overnight at room temperature, ether (100 ml) was added and the resulting solution washed successively with 5%-sodium bicarbonate solution and water. The organic phase was dried over anhydrous sodium sulfate and the solvent removed by distillation. The residue was dissolved in methanol (58 ml) and water (2 ml), sodium hydroxide flakes (1·0 g) added, and the solution refluxed for 1 hr. Glacial acetic acid (1·5 ml) was added and the solution concentrated to one third its original volume. Ether (100 ml) was added and the solution washed with water, 2 N hydrochloric acid, 10% sodium bicarbonate solution, and water respectively. After drying over anhydrous sodium sulfate, the solvent was removed and the oily residue dissolved in acetone (40 ml). Oxidation with chromium trioxide reagent in the usual manner afforded a gum when the solution was poured into ice-water. The product was extracted with methylene chloride and ether and the solvents removed by distillation. The residue was dissolved in methanol (30 ml), *p*-toluene sulfonic acid monohydrate (0·3 g) added, and the solution allowed to stand overnight at room temperature. The solution was poured slowly into ice-water and the resulting crystalline product removed by filtration. The crude product (1·6 g) was dissolved in benzene and the solution adsorbed on silica gel (85 g). Elution with benzene-ethyl acetate (10%) afforded 5α,10α-estran-3α-ol-17-one, m.p. 149·5–151°, $[\alpha]_D^{26}$ + 64° after crystallization from acetone Skellysolve C. (Found: C, 78·3; H, 10·1. $C_{18}H_{30}O_2$ requires: C, 78·2; H, 10·2%). Admixture with the 3β-epimer (Xa) caused a marked depression in the melting point (115 125).

5β-*Estran*-17β-*ol*-3-*one* (XIa). To a solution of 19-nortestosterone (8·0 g) in ethanol (50 ml) containing potassium hydroxide (0·2 g) was added a slurry of 5% palladium-on-carbon (4 g) in ethanol (50 ml). Hydrogenation was carried out in a Parr low pressure hydrogenator at room temperature and the catalyst removed by filtration. The filtrate was neutralized with acetic acid and concentrated to one half its original volume. This solution was added dropwise with stirring to ice-water and the product removed by filtration. Adsorption of the residue from benzene onto silica gel and elution with benzene ethyl acetate (20%) gave 5β-estran-17β-ol-3-one, m.p. 98–106°. Several recrystallizations from ether–Skellysolve B raised the m.p. to 108–110°, $[\alpha]_D^{25}$ + 39° (reported[7] m.p. 106–108°; $[\alpha]_D$ + 29·7° [Dioxane]). (Found: C, 78·0; H, 9·9. Calc. for $C_{18}H_{30}O_2$: C, 78·2; H, 10·2%). Further elution with benzene–ethyl acetate (40%) afforded a small amount of 5β-estrane-3α,17β-diol (Va) m.p. 204–206°, undepressed by admixture with an analytical sample (see below).

5β-*Estran*-17β-*ol*-3-*one acetate* (XIb). 5β-Estran-17β-ol-3-one (XIa) was acetylated by treatment with pyridine and acetic anhydride overnight at room temperature. The solution was poured slowly into ice-water and the crude product collected by filtration. Crystallization from methanol–water gave needles, m.p. 115 116/130 131·5°, $[\alpha]_D^{25}$ + 29°.[25] (Found: C, 75·5; H, 9·6. Calc. for $C_{20}H_{32}O_3$: C, 75·4; H, 9·5%). This product was also obtained by oxidation of IVb and Vb with chromium trioxide reagent.

5β-*Estrane*-3,17-*dione* (XII). Oxidation of crude XIa (3·0 g) with chromium trioxide reagent in the usual manner and crystallization of the crude product from methanol–water gave 1·5 g of product, m.p. 181 183°. Alternate recrystallization from acetone–Skellysolve B and methanol–water gave an analytical sample, m.p. 182·5 185°, $[\alpha]_D^{24}$ + 113° (reported[7] 179 181°, $[\alpha]_D$ + 111·6°). (Found: C, 78·3; H, 9·4. Calc. for $C_{18}H_{28}O_2$: C, 78·8; H, 9·5%). An additional 0·8 g of product was obtained by chromatography of the residue from the mother liquor on silica gel.

Raney nickel reduction of 5β-*estrane*-3,17-*dione*. To 5β-estrane-3,17-dione (4·0 g) in ethanol (300 ml) was added aged W 2 Raney nickel catalyst (10 g) in the form of a slurry in ethanol. The mixture was refluxed with stirring for 2 hr and the catalyst removed by filtration. The solvent was removed from the filtrate and the residue taken up in benzene (40 ml) and placed on a column of silica gel (400 g). Elution with benzene ethyl acetate (10%) gave a trace of starting material (0·5 g) followed by 5β-estran-3β-ol-17-one (XIIIa, 2·0 g) m.p. 157–164°. Several recrystallizations from ethanol water gave an analytical sample m.p. 165–166·5°, $[\alpha]_D^{26}$ + 108·5°. (Found: C, 78·1; H, 10·0.

[25] This product agrees with the compound obtained by Chen[6] (m.p. 114°/132·5°, $[\alpha]_D^{15}$ + 28·2° [acetone]) to which the 5α configuration was assigned.

$C_{18}H_{28}O_2$ requires: C, 78·2; H, 10·2%). Further elution with benzene–ethyl acetate (15%) gave 5β-estran-3α-ol-17-one (XIIIb, 1·1 g), m.p. 167–167·5°, $[\alpha]_D^{26}$ −114·2° after recrystallization from ethanol–water. (Found: C, 78·2; H, 10·3. $C_{18}H_{28}O_2$ requires: C, 78·2; H, 10·2%). Admixture with the 3β epimer caused a marked depression in the melting point.

5β-Estrane-3β,17β-diol (IVa). To a solution of 5β-estran-3β,17β-diol-17-monoacetate (IVa, 0·2 g) in methanol (9·8 ml) and water (0·2 ml) was added potassium hydroxide flakes (0·1 g). The solution was refluxed for 1 hr and allowed to cool to room temperature. Water was added slowly with stirring and the resulting precipitate removed by filtration. Crystallization from acetone-Skellysolve C gave the diol (IVa) m.p. 127–131°, raised by recrystallization from methanol ethyl acetate to 131–133°/154–157°, $[\alpha]_D^{25}$ −21·8°.[24] (Found: C, 77·7; H, 10·6. $C_{18}H_{30}O_2$ requires: C, 77·6; H, 10·9%). This product was also obtained by sodium borohydride reduction of XIIIa.

5β-Estrane-3α,17β-diol (Va). To a solution of 5β-estran-3α-ol-17-one (XIIIb, 0·05 g) in ethanol (10 ml) was added sodium borohydride (0·05 g) and the solution was allowed to stand overnight at room temperature. The solution was poured slowly into ice-water and the resulting precipitate removed by filtration and washed with 2 N hydrochloric acid and water. Recrystallization of the crude product from ethanol–water afforded an analytical sample, m.p. 207–208°, $[\alpha]_D^{25}$ +29·8° (reported[7] m.p. 211–212°, $[\alpha]_D$ +10·2°). (Found: C, 77·6; H, 10·9. Calc. for $C_{18}H_{30}O_2$: C, 77·6; H, 10·9%). This product was also obtained by hydrolysis of the monoacetate Vb and as a by-product in the catalytic hydrogenation of 19-nortestosterone.

5β-Estrane-3β,17β-diol diacetate (XIVa). A solution of 5β-estrane-3β,17β-diol (IVa, 0·25 g) in acetic anhydride (1 ml) and pyridine (9 ml) was heated on a steam bath for 2 hr. The cooled reaction mixture was poured slowly into ice-water and the resulting precipitate removed by filtration. Recrystallization from Skellysolve C gave an analytical sample, m.p. 113·5–115°, $[\alpha]_D^{26}$ +17°. (Found: C, 73·2; H, 9·5. $C_{22}H_{34}O_4$ requires: C, 72·9; H, 9·5%).

5β-Estrane-3α,17β-diol diacetate (XIVb). Acetylation of 5β-estrane-3α,17β-diol as described above afforded after several crystallizations from Skellysolve C needles, m.p. 160–162°, $[\alpha]_D^{25}$ +54°. (Found: C, 72·9; H, 9·3. $C_{22}H_{34}O_4$ requires: C, 72·9; H, 9·5%).

5α-Estran-17β-ol-3-one (XVa). 19-nortestosterone was reduced with lithium in liquid ammonia essentially as described by Bowers *et al.*[10] except that tetrahydrofuran previously distilled from methyl magnesium iodide was used as solvent. The crude product was adsorbed from benzene onto silica gel and eluted with benzene containing increasing amounts of ethyl acetate. Elution with benzene–ethyl acetate (15%) and crystallization of the product from acetone-Skellysolve C gave 5α-estran-17-β-ol-3-one, m.p. 133–134°, $[\alpha]_D^{25}$ +59·5° (reported[10] m.p. 130–132°, $[\alpha]_D$ +60°). (Found: C, 77·9; H, 10·2. Calc. for $C_{18}H_{32}O_2$: C, 78·2; H, 10·2%). Further elution with benzene–acetate (25%) gave a trace of 5α-estrane-3β,17β-diol (XVIIIa) m.p. 163–166°, raised by several crystallizations from ethanol–water to 171–173°, $[\alpha]_D^{26}$ +26°.[25] (Found: C, 77·8; H, 10·6. $C_{18}H_{30}O_2$ requires: C, 77·7; H, 10·9%).

5α-Estrane-3,17-dione (XVI). Oxidation of either XVa or XVIIIa with chromium trioxide reagent in the usual manner gave 5α-estran-3,17-dione. Recrystallization from Skellysolve B afforded an analytical sample m.p. 73–75°, $[\alpha]_D^{25}$ +139°.[26] (Found: C, 79·0; H, 9·5 $C_{18}H_{28}O_2$ requires: C, 78·8; H, 9·5%).

Raney nickel reduction of 5α-estrane-3,17-dione. 5α-Estran-3,17-dione (4·2 g) was dissolved in ethanol (300 ml) and refluxed with aged W-2 Raney Nickel catalyst as described above. Chromatography of the residue on silica gel (400 g) gave upon elution with benzene-ethyl acetate (10%) 5α-estran-3α-ol-17-one (XVIIb), m.p. 170–171·5°, $[\alpha]_D^{25}$ +115° (reported[11] m.p. 148°, 164·5–167°, $[\alpha]_D^{21.7}$ +110°) after crystallization from ethanol water. (Found: C, 77·9; H, 9·9. Calc. for $C_{18}H_{32}O_2$: C, 78·2; H, 10·2%). Further elution with the same solvent system afforded the more polar 5α-estran-3β-ol-17-one (XVIIa). Crystallization from acetone Skellysolve C gave an analytical sample, m.p. 181·5–184°, $[\alpha]_D^{26}$ +106° (reported[12] m.p. 177–179°, $[\alpha]_D^{20}$ +108°. (Found: C, 78·5; H, 10·2. Calc. for $C_{18}H_{32}O_2$: C, 78·2; H, 10·2%).

Raney nickel reduction of 5α-estran-17β-ol-3-one. Reduction of 5α-estran-17β-ol-3-one with aged

[24] Rapala and Farkas[7] reported the preparation of 5β-estran-3β,17β-diol by sodium borohydride reduction of the 3,17-diketone. Their physical constants (m.p. 202–204°, $[\alpha]_D$ +7·2°), however, are different from those obtained in this laboratory.

[25] This product has been reported as the solvate with two moles of acetone, m.p. 168–170°, $[\alpha]_D$ +16°.[10]

[26] This product agrees with that described by Chen[6] (m.p. 70°, $[\alpha]_D^{25.6}$ +127·3° [acetone]) to which the 5β configuration was assigned.

W-2 Raney Nickel catalyst as described above gave a mixture of the C—3 epimeric diols. Chromatography on silica gel and elution with benzene–ethyl acetate (20%) gave 5α-estran-3α,17β-diol (XIXa) m.p. 187–192°, raised by recrystallization from ethyl acetate to 191·5–193°, $[\alpha]_D^{26}$ + 31·5 (reported[11] m.p. 191–193°, $[\alpha]_D^{21\cdot1}$ + 23·7°). (Found: C, 77·7; H, 10·4. Calc. for $C_{18}H_{30}O_2$: C, 77·7; H, 10·9%). This product was also obtained by reduction of XVIIb with sodium borohydride. Further elution with the same solvent system afforded the epimeric 5α-estrane-3β,17β-diol (XVIIIa) identical with that described above.

5α-Estran-17β-ol-3-one acetate (XVb). A solution of 5α-estran-17β-ol-3-one (5·0 g) in pyridine (25 ml) and acetic anhydride (5 ml), was allowed to stand at room temperature overnight and then poured slowly into ice-water. The resulting precipitate was removed by filtration and washed with 2 N hydrochloric acid, 2·5% sodium carbonate solution, and water. Recrystallization from Skellysolve C afforded 5α-estran-17β-ol-3-one acetate m.p. 103–105°. An additional recrystallization from methanol–water gave an analytical sample, m.p. 104–106°, $[\alpha]_D^{25}$ + 47°.[37] (Found: C, 75·3; H, 9·4. $C_{20}H_{30}O_3$ requires: C, 75·4; H, 9·5%). Recrystallization from absolute methanol gave the dimethyl ketal, m.p. 135–137°, $[\alpha]_D^{25}$ + 20°. (Found: C, 72·5; H, 9·9. $C_{22}H_{34}O_4$ requires: C, 72·5; H, 10·0%).

Raney nickel reduction of 5α-estran-17β-ol-3-one acetate. 5α-Estrane-17β-ol-3-one acetate (XVb, 2·0 g) was dissolved in ethanol (150 ml) and refluxed for 2 hr with aged W-2 Raney Nickel catalyst (5·0 g) as described above. Adsorption of the residue on silica gel (200 g) and elution with benzene–ethyl acetate (5%) gave starting material (0·79 g) followed by 5α-estrane-3α,17β-diol 17-monoacetate (XIXb, 0·50 g), m.p. 163–167°. Recrystallization from acetone-Skellysolve C gave an analytical sample, m.p. 166–167°, $[\alpha]_D^{25}$ + 18°. (Found: C, 74·6; H, 9·8. $C_{20}H_{32}O_3$ requires: C, 74·9; H, 10·1%). Further elution produced the epimeric 5α-estrane-3β,17β-diol 17-monoacetate (XVIIIb, 0·33 g) which upon crystallization from Skellysolve C afforded an analytical sample, m.p. 121–121·5°, $[\alpha]_D^{25}$ + 15°. (Found: C, 74·8; H, 10·0. $C_{20}H_{32}O_3$ requires: C, 74·9; H, 10·1%).

5α-Estrane-3β,17β-diol diacetate (XXa). Acetylation of 5α-estrane-3β,17β-diol with acetic anhydride–pyridine at room temperature gave the corresponding diacetate (XXa). Crystallization from Skellysolve B gave an analytical sample, m.p. 142–145°, $[\alpha]_D^{25}$ + 5°. (Found: C, 72·9; H, 9·5. $C_{22}H_{34}O_4$ requires: C, 72·9; H, 9·5%).

5α-Estrane-3α,17β-diol diacetate (XXb). Acetylation of 5α-estrane-3α,17β-diol (0·4 g) was accomplished by warming on the steam bath for 2 hr with pyridine (9 ml) and acetic anhydride (1 ml). Work up in the usual manner and crystallization from ethanol afforded needles, m.p. 142–143·5°, $[\alpha]_D^{24}$ + 24°. (Found: C, 72·9; H, 9·5. $C_{22}H_{34}O_4$ requires: C, 72·9; H, 9·5%).

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[37] This product agrees with the acetate described by Chen[6] m.p. 102–103° $[\alpha]_D^{23\cdot6}$ + 39° (acetone) to which the 5β configuration was assigned.