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STEROIDS—XCIV*

SYNTHESIS OF 2-METHYL- AND 1,2-DIMETHYL-ESTROGENS

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Abstract—2-Methyl-and 1,2-dimethyl-estrogens have been derived from 2-methyltestosterone via the $\Delta^{1,4}$ and ^{1,4,6} compounds. Ultraviolet, rotatory and biological influences of alkyl substituents in the phenolic steroids series are discussed.

IN continuation of our program to determine the effect of alkyl substitution on steroidal hormone biological activity,[1,2] we have prepared a number of 2-methyl and 1,2-dimethyl substituted derivatives of estrone and of estradiol. The only known derivatives of this type are the 1-methyl derivatives of estrone first prepared by Djerassi *et al.*[3] by "dienone-phenol rearrangement" of a $\Delta^{1,4,6}$-trien-3-one and 1,4-dimethylestradiol recently reported by Sondheimer and Mazur[4] by "dienone-phenol rearrangement" of 4-methyl-$\Delta^{1,4}$-androstadien-17β-ol-3-one. A compound of the natural estrogen structure but partly inactivated biologically (i.e., a non-estrogenic estrogen) by the presence of additional alkyl groups could possibly possess a number of important applications.

Our starting material, 2α-methyltestosterone (I),[1] on treatment with selenium dioxide,[5,6,7,8] preferably in *tert.*-butanol,[6,7] was readily converted to the $\Delta^{1,4}$-dienone (II) in over 80 per cent yield. While comparable yields with selenium dioxide have been reported[6] in dehydrogenations in the cortical hormone series, the yields in general in the testosterone and substituted testosterone series are very low[4,5,6,7] (ca. 35 per cent or less), owing primarily to formation of a selenium complex of the derived $\Delta^{1,4}$-dienone. Such a complex has been reported in the selenium dioxide dehydrogenation of testosterone,[8] 17α-methyltestosterone[6] and 4-methyltestosterone.[4] The exceptionally high yield in the case of the C-2 methyl-substituted (II) and the absence of selenium complexes prompts us to postulate that the selenium–dienone compounds formed in the above-mentioned cases have at least one linkage at C-2.

The dienone (II), after chromic acid oxidation to 2-methyl-$\Delta^{1,4}$-androstadien-3, 17-dione (VII), was identical with the product obtained by dibromination of

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2α-methylandrostane-3,17-dione (VI) followed by collidine dehydrobromination of the 2,4-dibromo compound. Pyrolysis of (II) in mineral oil at 600° as described previously [9,10] gave 2-methylestradiol (IIIa). 2-Methylestrone (IVa) was readily prepared by Schotten–Baumann benzoylation of (IIIa), chromic acid oxidation of the resultant 3-monobenzoate (IIIb) and alkaline hydrolysis.

It has been previously shown[11] that Δ^4-3-oxosteroids may be dibrominated at C-2 and C-6 in ether–acetic acid solution and that the subsequent $\Delta^{1,4,6}$-trienones derived by dehydrobromination readily undergo acid-catalyzed "dienone–phenol rearrangement" in acetic anhydride solution to give the 3-acetate of the 1-methyl-Δ^6-dehydroestrogens. Ether–acetic acid dibromination of 2α-methyltestosterone did not proceed smoothly, but the crystalline 2,6-dibromide was readily obtained by similar bromination of the corresponding 17-ketone, 2α-methyl-Δ^4-androstene-3,17-dione (VIII). The intermediate 2,6-dibromo compound (IX) probably possesses the 6β-bromo (axial) configuration in view of the high position of the ultraviolet maximum[12] (251 mμ; log ε 4·11). Dehydrobromination of (IX) in boiling collidine gave the desired $\Delta^{1,4,6}$-trienone (X). Under milder dehydrobromination conditions it was possible to stop the reaction at the 6-bromo-$\Delta^{1,4}$-dienone (XV) stage (λ_{max} 246 mμ; log ε 4·20), thereby establishing that the order of elimination of the halogens is reversed* in the presence of a 2-methyl group, a not surprising finding, since the 2-bromine is a tertiary bromide in this case.

The trienone (XI) smoothly underwent rearrangement and aromatization in hot acetic anhydride–toluene-*p*-sulfonic acid solution to yield 1,2-dimethyl-Δ^6-dehyrdoestrone 3-acetate (XIb). Catalytic hydrogenation of this 6-dehydro compound followed by alkaline hydrolysis furnished 1,2-dimethylestrone (XII), while sodium borohydride reduction of (XI) and (XII), respectively, gave the estradiol derivatives 1,2-dimethyl-Δ^6-dehydroestradiol (XIII) and 1,2-dimethyl-estradiol (XIV).

Inspection of molecular-rotation differences (Table 1) reveals that, as one might expect, the contribution of a planar 2-methyl group is insignificant (+5 to +126). On the other hand, the 1-methylestrogens exhibit a somewhat greater positive molecular rotation increment varying from +104 to +271, this shift very likely being due to a minor interaction between the C-1 methyl and the C-11 methylene group of the type already noted in certain 1-methyl-19-norsteroids.[13]

It may be seen from Table 1 that the ultraviolet bathochromic shift attributable to the C-2 methyl group is very slight, varying from 1 to 5 mμ in the different examples. The shift due to a C-1 methyl is slightly greater (+3 to +7 mμ,) although it is of interest to note that the 306 mμ maximum in the Δ^6-dehydroestrogens is essentially unaltered by C-1 methyl substitution or C-1 and C-2 dimethyl substitution.

Biologically† it may be stated as a first approximation that an individual methyl group at C-1 or C-2, as in 1-methylestrone or 2-methylestrone, decreases estrogenic

* Unpublished observation : 2,6-dibromo-Δ^4-androstene-3,17-dione has been dehydrobrominated stepwise in these laboratories, thereby establishing that the 6-bromo atom is eliminated first.

† Bioassays by Dr. R. I. Dorfman, The Worcester Foundation, Shrewsbury, Mass.

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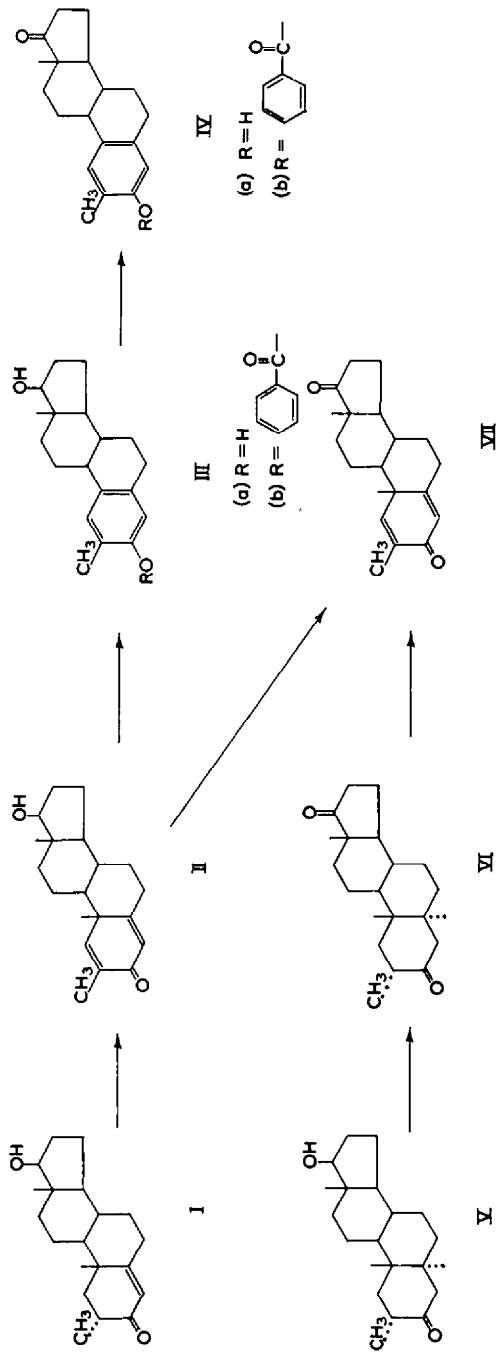
I
II
III
(a) R = H
(b) R =
IV
(a) R = H
(b) R =
V
VI
VII

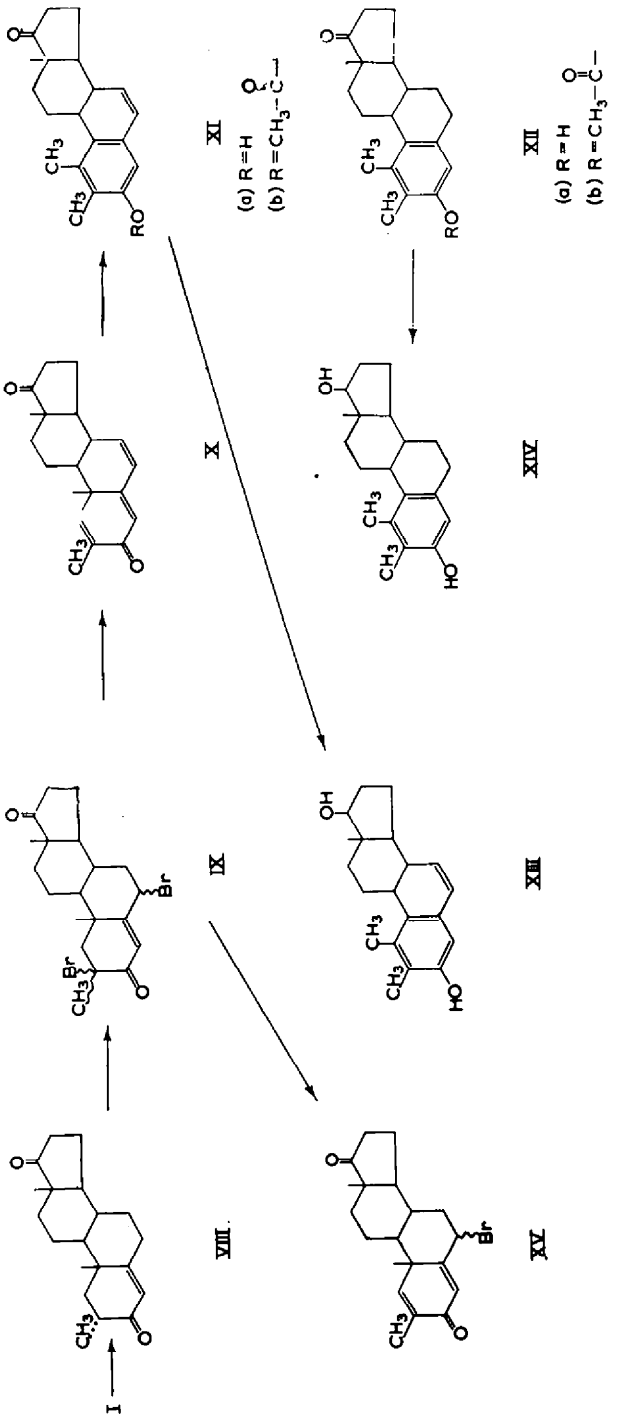
I
VIII
IX
X
XI
(a) R=H
(b) R=CH3—C(=O)—
XII
(a) R=H
(b) R=CH3—C(=O)—
XIII
XIV
XV

TABLE 1. OPTICAL DATA FOR SUBSTITUTED ESTRONES AND ESTRADIOLS

Compound	$[\alpha]_D$ (dioxane)*	$[M]_D$	$\Delta[M]_D$		λ_{max} in alcohol	log ε*
			1-Methyl	2-Methyl		
Estrone	+163°	+460			280	3·37
1-Methylestrone	+247°	+731	+271		287	3·23
2-Methylestrone	+198°	+586		+126	283	3·41
1,2-Dimethylestrone	+258°	+800		+69	288	3·36
6-Dehydroestrone	−124°	−347			221, 262, 306	4·49, 3·95, 3·40
1-Methyl-6-dehydroestrone	−77°	−226	+121		228, 267, 276, 304	4·49, 3·92, 3·82 3·29
1,2-Dimethyl-6-dehydroestrone	−44°	−136		+90	231, 272, 306	4·45, 3·94, 3·38
Estradiol	+80°	+227			280	3·33
1-Methylestradiol	+146°	+435	+208		284	3·28
2-Methylestradiol	+78°	+232		+5	284	3·38
1,2-Dimethylestradiol	+149°	+465		+30	288	3·25
6-Dehydroestradiol	−169°	−477			222, 263, 306	4·50, 3·98, 3·52
1-Methyl-6-dehydroestradiol	−126°	−373	+104		227, 266, 276, 305	4·57, 3·95, 3·74 3·20
1,2-Dimethyl-6-dehydroestradiol	−110°	−328		+40	230, 271, 307	4·49, 3·99, 3·41

* Constants determined in these laboratories.

activity by a factor of up to 200*. The activity decrease for two methyl groups is not completely cumulative, but 1,2-dimethylestrone (XII) and 1,2-dimethyl-Δ^6-dehydroestrone (XI) exhibit less than 1/2000 the uterotrophic activity of estrone in the mouse assay. Despite their low estrogenic activity these two compounds are rather potent anti-androgens as determined by their antagonism to testosterone in the chick comb assay.†

EXPERIMENTAL‡

2-*Methyl*-$\Delta^{1,4}$-*androstadien*-17β-*ol*-3-*one* (*II*)

A solution of 2α-methyltestosterone (I) (2·2 g) in 75 ml of *tert.*-butanol was treated with 2·2 g of selenium dioxide and 2 ml of acetic acid and the mixture was boiled in a nitrogen atmosphere for 72 hr. The cooled suspension after dilution with ethyl acetate was filtered through Celite and concentrated to dryness *in vacuo*, and the residue was treated with water and finally extracted with ethyl acetate. The ethyl

* Considerable variation has been encountered in the assay of the 1-methyl estrogens (see Djerassi *et al.*[3]) particularly in the case of the diesters of 1-methylestradiol, the activity varying with the particular dosage and assay utilized.

† Bioassay by Dr. R. I. Dorfman. The Worcester Foundation, Shrewsbury, Mass.

‡ Melting points are uncorrected. Rotations were determined at 20° and ultraviolet absorption spectra in 95% ethanol solution. We are grateful to Srita. Ma. Luisa Franco for technical assistance and to Sr. E. Avila for rotation and ultraviolet spectral data.

acetate solution was washed successively with dilute sodium carbonate solution, cold ammonium sulfide, cold ammonia solution water, dilute hydrochloric acid and water. Concentration of the dried solution and trituration with ether furnished 1·5 g of *dienone* (II), m.p. 203–209°. Chromatography of the mother liquors on neutral alumina gave an additional 0·25 g of material, m.p. 209–210°, for an overall yield of 80 per cent. The analytical specimen, from ether, exhibited m.p. 211–212°; $[\alpha]_D$ +6° (chloroform); λ_{max} 248 mμ; log ε 4·23. *Anal.* Calcd. for $C_{20}H_{28}O_2$: C, 79·95; H, 9·39. Found: C, 79·90; H, 9·27.

2-*Methylestradiol* (IIIa)

Δ^1-Dehydrotestosterone (II) was pyrolyzed by passing a solution of 3 g of compound in 1·5 l. of mineral oil through a heated (600°) Pyrex-glass tube packed with glass-beads. The cooled mineral-oil solution was diluted with hexane and the phenolic material was separated by extraction with 5% sodium hydroxide solution. Acidification gave crude (IIIa), which was purified by chromatography on 80 g of silica gel. Crystallization of the benzene–ether (9 + 1) fractions from ether–hexane gave 0·5 g of 2-*methylestradiol* (IIIa), m.p. 180–182°. The pure product from ether recrystallization (silky needles) melted at 185–186°; $[\alpha]_D$ +78° (dioxan), λ_{max} 284 mμ; log ε 3·38. *Anal.* Calcd. for $C_{19}H_{26}O_2$: C, 79·68; H, 9·15; Found: C, 79·98; H, 9·13.

2-*Methylestradiol* 3-*monobenzoate* (IIIb)

Treatment of an aqueous sodium hydroxide solution of the phenol (IIIa) with benzoyl chloride (Schotten–Baumann technique) and crystallization from ether of the precipitate thus formed gave the *benzoate* (IIIb), m.p. 187–190°; λ_{max} 226, 270 mμ; log ε 4·37, 3·58. *Anal.* Calcd. for $C_{26}H_{30}O_3$; C, 79·97; H, 7·74; O, 12·29. Found C, 79·56; H, 7·83; O, 12·53.

2-*Methylestrone benzoate* (IVb)

Chromic acid (0·25) g in 2·5 ml of glacial acetic acid was added to a solution of 0·125 g of (IIIb) in 5 ml of acetic acid and the solution (slow deposition of crystals) was set aside for 1 hr at 25°. Water was added, and the crystalline precipitate filtered off, washed, air-dried and recrystallized from ether, to yield plates (0·08 g), m.p. 212°; $[\alpha]_D$ +183° (dioxan); λ_{max} 226, 270 mμ; log ε 4·36, 3·54. *Anal.* Calcd. for $C_{26}H_{28}O_3$: C, 80·38; H, 7·26; O, 12·36. Found: C, 80·15; H, 7·58; O, 12·65.

2-*Methylestrone* (IVa)

The benzoate (IVb) (0·1 g) was added to 5 ml of 1% methanolic potassium hydroxide, and the solution was boiled for 1 hr neutralized with acetic acid, concentrated and treated with salt solution. The precipitate thus obtained was taken up in ether, the solution was decolorized with charcoal and pure 2-*methylesterone* (0·05 g) was obtained by ether–hexane crystallization, m.p. 221–225°; $[\alpha]_D$ +198° (dioxan); λ_{max} 283 mμ; log ε 3·41. *Anal.* Calcd. for $C_{19}H_{24}O_2$: C, 80·24; H, 8·51. Found: C, 80·06; H, 8·49.

2α-*Methylandrostane*-3,17-*dione* (VI)

2α-Methylandrostan-17β-ol-3-one (V)[1] (3 g) in 40 ml of glacial acetic acid was treated over a 10 min period with a solution of 1·5 g of chromic acid in 10 ml of water

and 40 ml of acetic acid. The oxidation was allowed to proceed for 1 hr in addition at 25°, and the solution was then poured into water and the crystalline precipitate was filtered off, washed and dried. Recrystallization from ether–hexane gave 2·3 g (77 per cent) of (VI), m.p. 148–149°. The analytical sample, from ether, melted at 152–153°; $[\alpha]_D$ +110° (chloroform). *Anal.* Calcd. for $C_{20}H_{30}O_2$; C, 79·42; H: 10·00. Found C, 79·28, H, 9·95.

2-Methyl-$\Delta^{1,4}$-androstadiene-3,17-dione (VII) *from* (VI)

The dione (VI) (1·0 g) dissolved in 30 ml of glacial acetic acid was dibrominated at 18° by the slow addition of 15·2 ml of a solution of bromine in acetic acid (0·07 g/ml) (2·0 equivalents). Bromine uptake was rapid, but the solution was set aside for 1 hr and then poured into 300 ml of ice–water. The crude 2,4-dibromo compound was filtered off, thoroughly washed with water and dried *in vacuo*; the yield was 1·25 g of product, m.p. 140–145° (dec.). Without further purification the crude bromo compound was dehydrobrominated by being heated with 20 ml of boiling γ-collidine for 4 hr with exclusion of moisture. The mixture was cooled, diluted with ether and the precipitated amine hydrobromide (0·87 g) was removed and washed with ether. The filtrate was washed with excess of 5% hydrochloric acid, water and sodium bicarbonate solution and was then dried and evaporated. The residue was purified by chromatography on 20 g of neutral alumina, the benzene–ether (2 + 1) fractions yielding 0·56 g of (VII), m.p. 183–188°. Analytical sample from ether, m.p. 198–200°; $[\alpha]_D$ +100° (chloroform); λ_{max} 247 mμ; log ε 4·20. *Anal.* Calcd. for $C_{20}H_{26}O_2$; C, 80·49; H, 8·78. Found: C, 80·33; H, 8·75.

(VII) *from* (II)

Chromic acid oxidation (as described in the preparation of (VI)) of 1 g of (II) gave 0·8 g of 2-methyl-$\Delta^{1,4}$-androstadiene-3,17-dione (VII), m.p. 198–200°, the product being identical in all respects with the dienone obtained by bromination and dehydrobromination of 2α-methylandrostane-3,17-dione (VI).

2α-Methyl-Δ^4-androstene-3,17-dione (VIII)

To a solution of 10 g of 2α-methyltestosterone (I) in 100 ml of glacial acetic acid was added over a 10 min period a solution of 5 g of chromic acid in 25 ml of water and 150 ml of acetic acid. After being set aside at room temperature for 1 hr the mixture was poured into water and the precipitate was collected, washed well with water and dried, to yield 8·6 g of (VIII), m.p. 155–159°. A sample further purified by ether crystallization showed m.p. 159–160°; $[\alpha]_D$ +190° (chloroform); λ_{max} 242 mμ; log ε 4·22. *Anal.* Calcd. for $C_{20}H_{28}O_2$: C, 79·95; H, 9·36. Found C, 80·10; H, 9·43.

2,6-Dibromo-2-methyl-Δ^4-androstene-3,17-dione (IX)

2α-Methyl-Δ^4-androstene-3,17-dione (VIII) (10 g) was dissolved in 500 ml of anhydrous ether and the solution was cooled to 0°. With agitation and exclusion of moisture, while the temperature was maintained at 0° with an ice–salt bath, a solution of 12 g of bromine (2·0 equivalents) in 20 ml of glacial acetic acid was added dropwise. A slight induction period was noted, but thereafter bromine uptake was smooth and rapid. The reaction mixture was then allowed to come to room temperature, water (200 ml) was added and the ether was removed by distillation *in vacuo* at 25°. The

resultant precipitate was filtered off, washed with water and finally with 5 ml of cold methanol, to yield 10·6 g (69 per cent) of crude 2,6-*dibromo compound*, m.p. 115–120° (dec.). This material was satisfactory for the subsequent step. The pure compound was prepared by recrystallization from methanol, m.p. 128–132° (dec.); $[\alpha]_D$ +49° (chloroform); λ_{max} 251 mμ; log ε 4·11. *Anal.* Calcd. for $C_{20}H_{26}O_2Br_2$: C, 52·42; H, 5·72; Br, 34·88. Found: C, 52·42; H, 5·75; Br, 32·20.

2-*Methyl*-$\Delta^{1,4,6}$-*androstatriene*-3,17-*dione* (X)

A solution of 6 g of crude dibromo compound (IX) in 25 ml of γ-collidine was boiled under reflux for 1 hr with exclusion of moisture. It was then cooled, diluted with ethyl acetate and the collidine hydrobromide (4·8 g) was filtered off and washed with ethyl acetate. The filtrate was washed with dilute hydrochloric acid and water, dried and concentrated, to leave 3·5 g of a semi-crystalline residue. This material was chromatographed on 150 g of neutral alumina, the benzene–ether extracts yielding, after recrystallization from ethyl acetate–ether, 2.1 g (54 per cent) of *trienone* (X), m.p. 197·5–199°; $[\alpha]_D$ +60° (chloroform); λ_{max} 266, 301 mμ; log ε 4·04, 3·98. *Anal.* Calcd. for $C_{20}H_{24}O_2$; C, 81·04; H, 8·16. Found: C, 80·82; H, 8·17.

6-*Bromo*-2-*methyl*-$\Delta^{1,4}$-*androstadiene*-3,17-*dione* (XV)

A solution of 1·1 g of 2,6-dibromo compound (IX) in 7 ml of γ-collidine–xylene (1 + 1) was boiled under reflux for 20 min. Ethyl acetate was added to the cooled solution, the separated collidine hydrobromide (0·56 g) was filtered off, and the filtrate was washed with dilute hydrochloric acid and water, and then evaporated to dryness *in vacuo*. Crystallization of the residue from methanol gave 0·28 g of 6-*bromo*-2-*methyl*-$\Delta^{1,4}$-*androstadiene*-3,17-*dione* (XV), m.p. 211–213° (dec.). Recrystallization from the same solvent gave the analytical sample as shiny plates, m.p. 216–218°; $[\alpha]_D$ +32° (chloroform); λ_{max} 246 mμ; log ε 4·20. *Anal.* Calcd. for $C_{20}H_{25}O_2Br$: C, 63·66; H, 6·68; Br, 21·18. Found: C, 62·96; H, 6·76; Br. 21·20.

1,2-*Dimethyl*-Δ^6-*dehydroestrone acetate* (XIb)

A mixture of 5 g of trienone (X), 100 ml of acetic anhydride and 2 g of toluene-*p*-sulfonic acid hydrate was heated at 90° for 5 hr. The cooled solution was poured into ice–water and stirred until the excess of anhydride had hydrolyzed, and the crystalline precipitate was filtered off, thoroughly washed with water and air-dried. Recrystallization from methanol gave 4·34 g per cent (76 per cent) of the *acetate* (XIb), m.p. 178–180°. The analytical specimen from the same solvent melted at 180–181°; $[\alpha]_D$ −53° (dioxan); λ_{max} 225, λ_{max} 225, 266 mμ; log ε 4·45, 3·11 266 mμ; log ε 4·45 3·11, *Anal.* Calcd. for $C_{22}H_{26}O_3$: C, 78·07; H, 7·74. Found: C, 77·80; H, 7·70.

1,2-*Dimethyl*-Δ^6-*dehydroestrone* (XI)a

The acetate (XIb) (1·7 g) was added to 400 ml of 1% methanolic potassium hydroxide and the mixture was boiled for 30 min in a nitrogen atmosphere. Acetic acid (10 ml) was added, the solution was concentrated to ca. 30 ml and salt and water were added. The crude precipitate thus formed (1·6 g) was recrystallized from ethyl acetate and then from methanol to yield 1·1 g (74 per cent) of pure 1,2-*dimethyl*-Δ^6-*dehydroestrone* (XIa), m.p. 254–255°; $[\alpha]_D$ −44° (dioxan); λ_{max} 231, 272, 306 mμ;

log ε 4·45, 3·92, 3·38. *Anal.* Calcd. for $C_{20}H_{24}O_2$: C, 81·04; H, 8·16. Found: C, 81·29; H, 8·17.

1,2-*Dimethylestrone acetate* (XIIb)

The dehydroestrone acetate (XIa) (1·13) g was added to 50 ml of ethyl acetate containing 50 mg of prehydrogenated 10% palladium–carbon catalyst and the compound was hydrogenated at atmospheric pressure (570 mm) and 25°. In 1 hr 122 ml (1·1 moles) of hydrogen were adsorbed; the catalyst was filtered off and the solution was evaporated to dryness. The crude product (1·1 g), m.p. 204–206°, was crystallized from methanol, whereby the melting point rose to 210–211°; $[\alpha]_D$ +223° (dioxan); λ_{max} 272, 280 mμ; log ε 2·73, 2·73. *Anal.* Calcd. for $C_{22}H_{28}O_3$: C, 77·61; H, 8·29. Found: C, 77·64; H, 8·32.

1,2-*Dimethylestrone* (XIIa)

Hydrolysis of 0·5 g of acetate (XIIb) as described for the preparation of (XIa) gave 0·41 g (94 per cent) of 1,2-*dimethylestrone* (XIIa), m.p. 267–275°. The analytical sample, from methanol, exhibited m.p. 274–275°; $[\alpha]_D$ +257° (chloroform), 270° (dioxan); λ_{max} 288 mμ; log ε 3·36. *Anal.* Calcd. for $C_{20}H_{26}O_2$: C, 80·49; H, 8·78. Found: C, 80·38; H, 8·73.

1,2-*Dimethyl*-Δ^6-*dehydroestradiol* (XIII)

A solution of 0·52 g of 1,2-dimethyl-Δ^6-dehydroestrone acetate (XIb) in 100 ml of methanol was treated with 0·7 g of sodium borohydride dissolved in 2 ml of water. The solution was boiled for 10 min and then set aside at room temperature for 1 hr. Acetic acid (5 ml) was added, and the solution was partly concentrated *in vacuo*, cooled, poured into ice-water and extracted with ethyl acetate. Evaporation to dryness of the ethyl acetate solution gave 0·43 g (94 per cent) of (XIII), m.p. 229–231.° The analytical sample was obtained by recrystallization from methanol and it showed m.p. 231–232°; $[\alpha]_D$ −110°; λ_{max} 230, 270–272, 306–308 mμ; log ε 4·49, 3·99, 3·41. *Anal.* Calcd. for $C_{20}H_{26}O_2$: C, 80·49; H, 8·78. Found: C, 80·94; H, 8·85.

1,2-*Dimethylestradiol* (XIV)

A solution of 0·22 g of 1,2-dimethylestrone (XIIa) in 100 ml of methanol was treated with 0·25 g of sodium borohydride in a few millilitres of water and the solution was set aside at room temperature for 16 hr. Acetic acid (2 ml) was added, and the solution was concentrated *in vacuo* to a gummy residue, water was added and the steroid was extracted with ethyl acetate. Evaporation of the extract gave an oil that, on treatment with hexane, was converted to an amorphous powder (XIV), m.p. 120–125°; $[\alpha]_D$ +149° (dioxan); λ_{max} 288 mμ; log ε 3·25. *Anal.* Calcd. for $C_{20}H_{28}O_2 \cdot \frac{1}{2}H_2O$: C, 77·63; H: 9·45. Found: C, 77·15, H, 9·47.