Tetrahedron, 1965, Vol. 21, pp. 2501 to 2508. Pergamon Press Ltd. Printed in Northern Ireland

CONFORMATION OF RING A IN SOME 2β-METHYL- AND 2β-ACETOXY-19-NORTESTOSTERONES

Y. YAMATO and H. KANEKO
Research Laboratory of Dainippon Pharmaceutical Co., Ltd.,
Fukushima-ku, Osaka, Japan

(*Received* 8 *April* 1965)

Abstract—The synthesis of 2β-methyl-19-norsteroids are described. By means of optical rotatory dispersion and NMR spectroscopy it is shown that the introduction of 2β-methyl and 2β-acetoxy substituents into 19-nortestosterones changes the normal half chair conformation of A ring to a twist form as cited in the cholestane series.

RECENTLY it has been reported[1,2] that the A ring in some 2β-hydroxy- and 2β-acetoxy-Δ⁴-3-ketosteroids can be taken as a twist conformation, owing to a 1,3-diaxial interaction between the 2β-substituent and the 19-methyl group. It is interesting to discuss whether ring A in 2β-substituted 19-nor-Δ⁴-3-ketosteroids, lacking the 1,3-diaxial interaction, have the normal half-chair conformation.

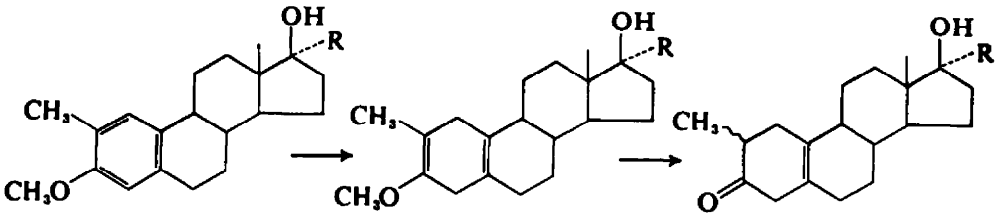
In a previous communication[3] we reported the synthesis of some 2β-methyl-estr-4-en-3-ones which show abnormal optical dispersion curves (ORD). This paper presents evidence based on ORD measurements and NMR spectroscopy that ring A in 2β-methyl- and 2β-acetoxy-19-nor-Δ⁴-3-ketosteroids has a twist conformation.

Since, acid treatment of the Birch reduction products of aromatic steroids affords the thermodynamically more stable Δ⁴-3-ketosteroids with β-configuration at C–10,[4] two isomeric 2-methyl-17β-hydroxy-estr-4-en-3-ones (2-methyl-19-nor-testosterones) prepared from 2-methylestradiol-3-methylether (Ia) by Birch reduction followed by hydrolysis with methanolic hydrochloric acid should be α and β isomers at C–2. Actually, one isomer having a higher m. p. (IVa) is readily isomerized to another stable isomer (Va) on treatment with methanolic potassium hydroxide.

Further reduction of the 2α-methyl and 2β-methyl compounds (IVa and Va) with lithium–liquid ammonia affords 2α-methyl- and 2β-methyl-17β-hydroxyestrane-3-one (VIa and VIIa), respectively. In a similar manner 2α- and 2β,17α-dimethyl-17β-hydroxyestrane-3-one (VIb and VIIb) have been synthesized.

The 2β-methyldihydro compounds (VIIa and VIIb) are also readily isomerized to the 2α isomers (VIa and VIb) by methanolic potassium hydroxide. The ring A/B *trans* configuration[5] in these compounds was established by their ORD which indicates that the ring A is in a normal chair conformation.

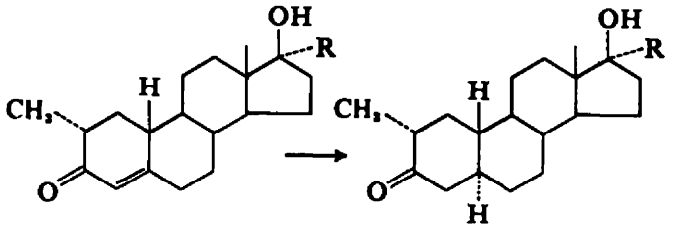
[1] K. Kuriyama, E. Kondo and K. Tori, *Tetrahedron Letters* No. 22, 1485 (1963).
[2] S. Burstein and H. L. Kimball, *Steroids* **2**, 1 (1963).
[3] H. Kaneko, M. Hashimoto, Y. Mitta and K. Kawase, *Chem. Pharm. Bull., Japan* **11**, 264 (1963).
[4] A. Sandoval, G. H. Thomas, C. Djerassi, G. Rosenkranz and F. Sandheimer, *J. Amer. Chem. Soc.* **77**, 148 (1955); C. Djerassi, A. E. Lippman and J. Grossman, *Ibid.* **78**, 2479 (1956).
[5] F. Sondheimer, R. Vasin, G. Rosenkranz and C. Djerassi, *J. Amer. Chem. Soc.* **74**, 2696 (1952).



Ia R = H
b R = CH_3

IIa R = H
b R = CH_3

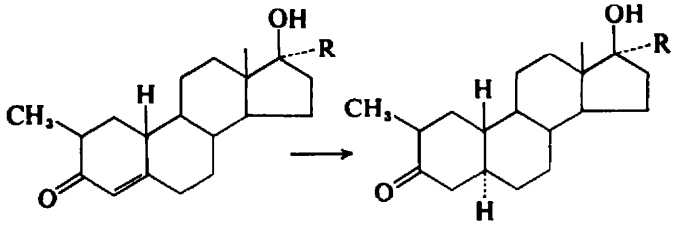
IIIa R = H
b R = CH_3



IVa R = H, IVb R = CH_3

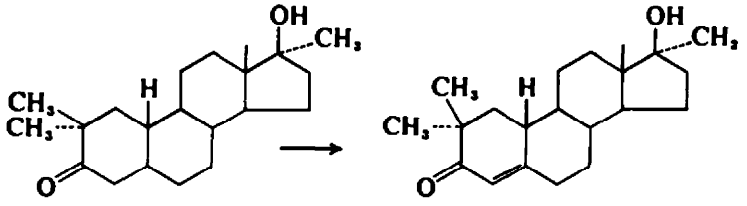
VIa R = H, VIb R = CH_3

IIIa,b



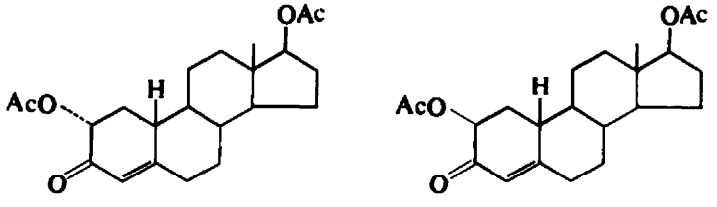
Va R = H, Vb R = CH_3

VIIa R = H, VIIb R = CH_3



VIII

IX



X

XI

Recently Bhacca *et al.*[6] pointed out that the shift induced by benzene on the methyl group adjacent to a carbonyl group is dependent upon the axial or the equatorial nature of the methyl group and that the axial methyl resonance suffers an up-field shift ($\Delta = \partial CDCl_3 - \partial C_6H_6 = +0{\cdot}2 \sim +0{\cdot}3$ ppm), whereas the equatorial methyl resonance suffers a small downfield shift ($\Delta = \partial CDCl_3 - \partial C_6H_6 = -0{\cdot}06 \sim -0{\cdot}1$ ppm). The solvent effect in the NMR of two isomeric 2-methyl-19-nordihydrotestosterones given in Table 1 is in good agreement with Bhacca's value.

TABLE 1. SOLVENT EFFECTS ON C_2–CH_3 IN SOME SATURATED 3-KETOSTEROIDS

Compound	Chemical shift on C_2–CH_3 (τ) in $CDCl_3$	in benzene	Difference in chemical shifts $\delta CDCl_3$-benzene
2α-Methyl-17β-hydroxy-estran-3-one (VIa)	8·99	8·91	−0·08
2α,17α-Dimethyl-17β-hydroxy-estran-3-one (VIb)	8·99	8·91	−0·08
2β-Methyl-17β-hydroxy-estran-3-one (VIIa)	8·83	9·04	+0·21
2β,17α-Dimethyl-17β-hydroxy-estran-3-one (VIIb)	8·83	9·03	+0·20
2,2,17α-Trimethyl-17β-hydroxy-estran-3-one (VIII)	α8·96 β8·83	α8·85 β9·05	−0·11 +0·22

The ORD curve shown for 2α-methyl-17β-hydroxyestr-4-en-3-one (IVa) is essentially the same as that of unsubstituted 19-nortestosterone. However, in contrast the curve of 2β-methyl-17β-hydroxyester-4-en-3-one (Va) exhibits the abnormal multiple Cotton effect given in Fig 1. Djerassi *et al.*[7] have reported that the ORD curve of 6β-methyl-17β-hydroxyandrost-4-en-3-one shows abnormality, whereas that of 6β-methyl-17β-hydroxyestr-4-en-3-one is similar to the parent steroid, and that this difference is attributable to a conformational distortion due to the 1,3-diaxial interaction between the 6β-methyl group and the 19-methyl group. On the other hand, it has been noted[8] that the presence of an axial 2β-methyl group in 2,2-dimethyl-17β-hydroxyandrost-4-en-3-one does not affect the shape of the ORD curve to any extent and that such 1,3-diaxial steric interaction is not serious in the ring A.

The abnormality attributed to the 2β-methyl group in 2β-methyl-17β-hydroxyestr-4-en-3-one is therefore inconsistent with the above inference, although there seems to be no significant steric interaction in this case. The discrepancy between 2,2-dimethyl 17β-hydroxyandrost-4-en-3-one and 2β-methyl-17β-hydroxyestr-4-en-3-one can not be explained without the following consideration. The ORD curve of Δ^4-3-ketosteroid is rather sensitive to conformational distortion,[9] hence a slight 1,3-interaction between the axial 2β-methyl group and the 10β-hydrogen in 2β-methyl-17β-hydroxyestr-4-en-3-ones forces the A ring into a twist conformation. Such an alternate conformation

[6] N. S. Bhacca and D. H. Williams, *Tetrahedron Letters* No. 42, 3127 (1964); N. S. Bhacca and D. H. Williams, *Applications of NMR Spectroscopy in Organic Chemistry* P 159. Holden-Day, San Francisco.

[7] R. Villotti, C. Djerassi and H. J. Ringold, *J. Amer. Chem. Soc.* **81**, 4566 (1959).

[8] C. Djerassi, O. Halpern, V. Halpern and B. Riniker, *J. Amer. Chem. Soc.* **80**, 4001 (1958).

[9] C. Djerassi, R. Riniker and B. Riniker, *J. Amer. Chem. Soc.* **78**, 6377 (1956).

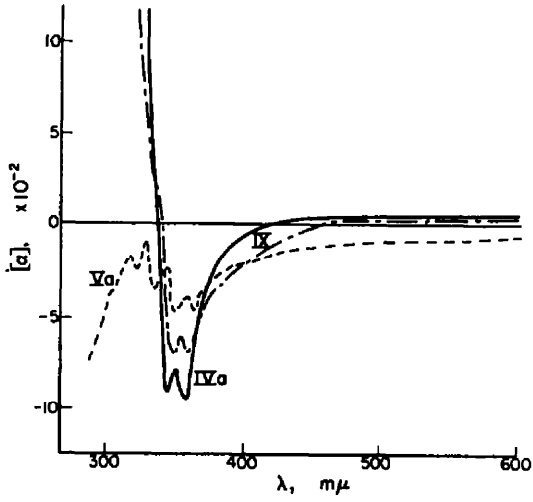


FIG. 1 Optical rotatory dispersion curves of IVa, Va and IX.

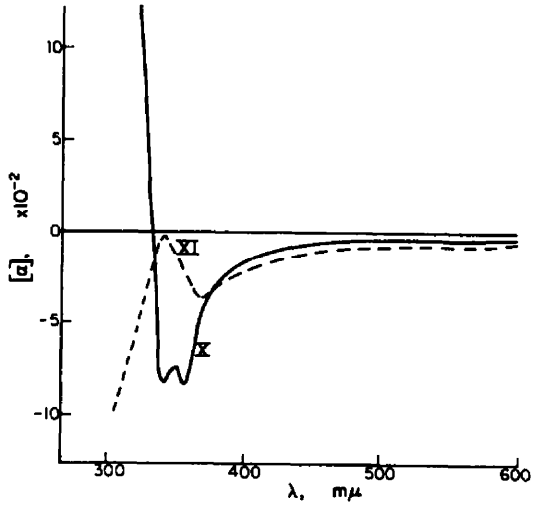


FIG. 2 Optical rotatory dispersion curves of X and XI.

in the case of 2,2-dimethyl-17β-hydroxyandrost-4-en-3-one is disturbed by the interaction between the equatorial 2α-methyl group and the 9α-hydrogen, consequently the A ring has a slightly distorted conformation having the same chirality of the C=C—C=O grouping as the parent ketone.[10] Furthermore, the ring A of 2,2,17α-trimethyl-17β-hydroxyestr-4-en-3-one (IX) exists in a similar conformation, since its ORD curve is of the same type as that of 2,2-dimethyl-17β-hydroxyandrost-4-en-3-one.

This consideration may also be interpreted from NMR spectroscopy. Table 2 shows that in the 2α-methyl-17β-hydroxyestr-4-en-3-ones (IVa and IVb) having normal transoid conformation the down-field shifts on passing from deuteriochloroform to benzene solution are comparable to androstane-3-one derivatives having an equatorial methyl group adjacent to a carbonyl group at C—3. However, in the 2β-methyl-17β-hydroxyestr-4-en-3-ones (Va and Vb) such solvent effect observed is

[10] C. Djerassi, R. Records, E. Bunnenberg, K. Mislow and A. Moscowitz, *J. Amer. Chem. Soc.* **84**, 870 (1962).

less than that of the normal 2β-axial methyl group. This result implies that the axial 2β-methyl group decreasing the anisotropic shielding effect of benzene is slightly laterally distorted by an interaction with 10β-hydrogen.

The ORD curve of 2β,17β-diacetoxyestr-4-en-3-one (XI)[11] given in Fig. 2 shows the same abnormality as that of 2β-methyl-17β-hydroxyestr-4-en-3-one. The NMR

TABLE 2. SOLVENTS EFFECTS ON C_2–CH_3 IN SOME Δ^4-3-KETOSTEROIDS

Compound	Chemical shift on C_2–CH_3 (τ) in $CDCl_3$	in benzene	Difference in chemical shifts $CDCl_3$-benzene
2α-Methyl-17β-hydroxy estr-4-en-3-one (IVa)	8·90	8·80	−0·10
2α,17α-Dimethyl-17β-hydroxy-estr-4-en-3-one (IVb)	8·89	8·80	−0·09
2β-Methyl-17β-hydroxy-estr-4-en-3-one (Va)	8·91	8·92	+0·01
2β,17α-Dimethyl-17β-hydroxy-estr-4-en-3-one (Vb)	8·91	8·91	0
2,2,17α-Trimethyl-17β-hydroxy-estr-4-en-3-one (IX)	α8·90 β8·95	α8·76 β9·00	−0·14 +0·05

signal of the 2α-proton in this compound appears as a quartet with peaks at 337, 330, 327 and 230 c/s. This quartet is similar to that of the 2 proton in 2β-acetoxy-19-methyl-Δ^4-3-ketosteroids.[1] These data indicate that the A ring in the 2β,17β-diacetoxyestr-4-en-3-one is of the same twist conformation as the latter compounds. Coupling constants derived on the basis of a first order approximation are $J_{2\alpha,1\alpha} = 9{\cdot}3$ c/s and $J_{2\alpha,1\beta} = 6{\cdot}9$ c/s. Dihedral angles calculated by the Karplus equation with parameters as modified by Williamson and Johnson[12] were $\theta_{2\alpha,1\beta} =$ 131–135° and $\theta_{2\alpha,1\alpha} =$ 11–15°, respectively. These values are not consistent with a normal half-chair conformation for the ring A but do fit a twist conformation.

EXPERIMENTAL*

Preparation of 2α- and 2β-methyl-17β-hydroxyestr-4-en-3-one (2α- and 2β-methyl-19-nortestosterone) (IVa *and* Va). To a solution of 500 mg of Ia[13] prepared from 2-methylestradiol in 100 ml dry ether was added 100 ml liquid ammonia followed by 2·0 g Li. After stirring for an additional 20 min, 20 ml absolute EtOH was added dropwise over 30 min. The ammonia was allowed to evaporate at room temp and the product taken up in ether, washed with water and dried over Na_2SO_4. Evaporation of the ethereal solution afforded 500 mg of an impure *2-methyl-1,4-dihydroestradiol-3-methyl-ether* (IIa) containing 7·8% unchanged aromatic compound (estimate based on UV absorption spectrum).

The *enol ether* (IIa) prepared from 500 mg of Ia was refluxed with 2 ml of conc. HCl in 40 ml MeOH for 5 min. The mixture was diluted with water and extracted with ether. Evaporation of the solvent afforded an oily residue (480 mg) which was chromatographed on silica gel. Elution with

* Mps were determined in a Kofler block. IR spectra were determined in $CHCl_3$ or KBr disk, and UV spectra in EtOH solution. NMR spectra were recorded on a Varian A-60 Spectrometer in $CDCl_3$ containing tetramethyl silane as an internal standard. Specific rotations were measured in $CHCl_3$ solution at room temperature (*ca* 20°) unless otherwise indicated. ORD curves were obtained in dioxan solution. Microanalysis were carried out by Mr. Y. Utsui and colleague in this laboratory.

[11] P. N. Rao and L. R. Axelord, *Tetrahedron* **10**, 144 (1960).
[12] K. L. Williamson and W. S. Johnson, *J. Amer. Chem. Soc.* **83**, 4623 (1961).
[13] H. Kaneko, M. Hashimoto and A. Kobayashi, *Chem. Pharm. Bull., Japan* **12**, 196 (1964).

benzene–ether (9:1) gave 230 mg of IVa which on crystallization from hexane–ether furnished needles, m.p. 175–178°, $[\alpha]_D$ +81·3° (*c*, 0·89), undepressed on admixture with an authentic specimen[14] (lit.: m.p. 176–178°, $[\alpha]_D$ +93°) prepared from 19-nortestosterone via 2-oxalate, λ_{max} 237·5 mμ (ε 15,600), $\nu_{max}^{CHCl_3}$ 1664 (C=O) and 1623 cm^{-1} (C=C), NMR: 9·19τ (18-H), 8·90τ (J = 6·2, 2-CH_3), 6·29τ (17α-H), 4·20τ (4-H). (Found: C, 78·89; H, 9·58. Calc. for $C_{19}H_{28}O_2$: C, 79·12; H, 9·79%.)

Further elution with benzene–ether (4:1) followed by crystallization from hexane–ether gave 114 mg of *2β-methyl-17β-hydroxyestr-4-en-3-one* (Va) as needles, m.p. 155–158° $[\alpha]_D$ −34·3° (*c*, 1·05), λ_{max} 240·5 mμ (ε 16,840), $\nu_{max}^{CHCl_3}$ 1658 (C=O) and 1626 cm^{-1} (C=C), NMR: 9·18τ (18-H), 8·91τ (J = 7·0, 2-CH_3), 6·43τ (17α-H), 4·28τ (4-H). (Found: C, 78·89; H, 9·80. $C_{19}H_{28}O_2$ requires: C, 79·12; H, 9·79%.)

ORD of IVa[15] (Fig. 1): $[\alpha]_{650}$ +48°, $[\alpha]_{589}$ +57°, $[\alpha]_{358}$ −952°, $[\alpha]_{350}$ −805°, $[\alpha]_{345}$ −920°, $[\alpha]_{325}$ +1445° (*c*, 0·55). ORD of Va (Fig. 1): $[\alpha]_{650}$ −64·8°, $[\alpha]_{589}$ −77·7°, $[\alpha]_{365}$ −477°, $[\alpha]_{359}$ −405°, $[\alpha]_{350}$ −499°, $[\alpha]_{341}$ −203°, $[\alpha]_{335}$ −332°, $[\alpha]_{328}$ −90·7°, $[\alpha]_{322}$ −244°, $[\alpha]_{316}$ −179°, $[\alpha]_{308}$ −341° (sh), $[\alpha]_{270}$ −1480° (*c*, 0·46).

2ξ-Methyl-17β-hydroxyestr-5(10)-en-3-one (IIIa). A solution of 500 mg of crude *1,4-dihydroestradiol-3-methylether* (IIa) in 40 ml MeOH and 1 ml acetic acid was refluxed for 15 min. The mixture was diluted with water and extracted with ether. The organic layer was washed with sat. $NaHCO_3$ aq and water. After drying (Na_2SO_4) and evaporating the solvent, the residue was chromatographed on silica gel in benzene. Elution with benzene–ether (5:1) gave 300 mg of IIIa as an oil which failed to crystallize. This oil exhibited a single spot different from those of the conjugated ketones (IVa and Va) by thin-layer chromatography.

Acetylation of IIIa with pyridine and acetic anhydride at room temp and chromatography of the product on silica gel with benzene–acetone (97:3) afforded 170 mg of the *acetate of* IIIa as prisms from MeOH, m.p. 144–147°, $[\alpha]_D$ +180° (*c*, 1·18), ν_{max}^{KBr} 1715 (C=O) and 1731 cm^{-1} ($OCOCH_3$), NMR: 9·18τ (18-H), 8·91τ (J = 6·0, 2-CH_3), 7·95τ ($OCOCH_3$). (Found: C, 76·58; H, 9·12. $C_{21}H_{30}O_3$ requires: C, 76·32, H, 9·15%.)

Isomerization of 2β-methyl-17β-hydroxyestr-4-en-3-one (Va) *to 2α-isomer* (IVa). A solution of 50 mg of Va in 10 ml MeOH and 2 ml 7·5% KOH aq was refluxed for 2 hr. The mixture was diluted with water, extracted with ether and chromatographed on silica gel. Elution with benzene–ether (9:1) yielded 40 mg of a solid which crystallized from hexane–ether as needles, m.p. 170–174°, and was identical with IVa by comparison of IR spectrum and mixed m.p. determination.

Preparation of 2α,17α- and 2β,17α-dimethyl-17β-hydroxyestr-4-en-3-one (IVb *and* Vb). To a solution of 500 mg of Ib[13] in 100 ml dry ether was added 100 ml of liquid ammonia followed by 1·5 g Li wire. After stirring for 30 min, 20 ml abs. EtOH was added dropwise during 30 min. Evaporation of the ammonia and extraction with ether yielded 470 mg of crude *enol ether* (IIb). It was refluxed with 40 ml MeOH and 2·1 ml conc. HCl in 10 ml water for 5 min, yielding 450 mg of an oily product which was chromatographed on silica gel. Elution with benzene–ether (9:1) afforded 250 mg of IVa which crystallized from hexane–ether to give needles, m.p. 125–127°, $[\alpha]_D$ +59° (*c*, 0·95) undepressed on admixture with an authentic specimen[16] (lit: m.p. 114–115°, $[\alpha]^{28}$ +35°), prepared from 17α-methyl-19-nortestosterone via 2-oxalate sequence, λ_{max} 237·5 mμ (ε 15,400), $\nu_{max}^{CHCl_3}$ 1667 (C=O) and 1623 cm^{-1} (C=C), NMR: 9·08τ (18-H), 8·89τ (J = 6·0, 2-CH_3), 8·78τ (17α-CH_3), 4·19τ (4-H). (Found: C, 79·39; H, 9·99. Calc. for $C_{20}H_{30}O_2$ C, 79·42; H, 10·00%.)

Further elution with benzene–ether (20:3) followed by crystallization from hexane–ether gave 70 mg of *2β,17α-dimethyl-17β-hydroxyestr-4-en-3-one* (IVb) as needles, m.p. 138–140°, $[\alpha]_D$ −72° (*c*, 1·01), λ_{max} 240·5 mμ (ε 19,000), $\nu_{max}^{CHCl_3}$ 1661 (C=O) and 1626 cm^{-1} (C=C), NMR: 9·08τ (18-H), 8·91τ (J = 7·0, 2-CH_3), 8·79τ (17-CH_3), 4·28τ (4-H). (Found: C, 79·16; H, 9·97. $C_{20}H_{30}O_2$ requires: C, 79·42; H, 10·00%.) ORD of IVb: $[\alpha]_{500}$ +118°, $[\alpha]_{365}$ −1273°, $[\alpha]_{360}$ −1056°, $[\alpha]_{353}$ −1181°, $[\alpha]_{325}$ +2220° (*c*, 0·22).

ORD of Vb: $[\alpha]_{500}$ −56·8°, $[\alpha]_{372}$ −600°, $[\alpha]_{364}$ −478°, $[\alpha]_{356}$ −716°, $[\alpha]_{345}$ −216°, $[\alpha]_{325}$ −455°, $[\alpha]_{327}$ −34·0°, $[\alpha]_{319}$ −353°, $[\alpha]_{315}$ −193°, $[\alpha]_{303-304}$ −500°, $[\alpha]_{270}$ −1270° (*c*, 0·22).

2ξ,17α-Dimethyl-17β-hydroxyestr-5(10)-en-3-one (IIIb). A solution of 560 mg of IIb in 30 ml MeOH and 1 ml acetic acid was treated as described above for the 1,4-dihydro compound. The

[14] R. Villotti, H. J. Ringold and C. Djerassi, *J. Amer. Chem. Soc.* **82**, 5693 (1960).
[15] The observed curve is similar to the data previously reported in Ref. 14.
[16] Organon Inc., USP 2,997,488.

resulting oily product was dissolved in hexane and chromatographed on silica gel. Elution with benzene–ether (9:1–4:1) gave 152 mg of 2ξ,17α-*dimethyl*-17β-*hydroxyestr*-5(10)-*en*-3-*one* (IIIb) which was crystallized from hexane–ether as prisms, m.p. 128–131°, $[\alpha]_D$ +155° (*c*, 0·89), ν_{max}^{KBr} 3584 (OH) and 1718 cm^{-1} (C=O), NMR: 9·13τ (18 H), 8·93τ (J = 6·0, 2-CH_3), 8·73τ (17-CH_3). (Found: C, 79·46; C, 9·71. $C_{20}H_{30}O_2$ requires: C, 79·42; H, 10·00%.) ORD: $[\alpha]_{650}$ +114°, $[\alpha]_{589}$ +147°, $[\alpha]_{308}$ +134·6°, $[\alpha]_{276}$ +639° (*c*, 0·28).

Isomerization of 2β,17α-*dimethyl*-17β-*hydroxyestr*-4-*en*-3-*one* (Vb) *to* 2α *isomer* (IVb). Isomerization was carried out as for Va with KOH and MeOH, and afforded IVb, m.p. 123–126°, undepressed on admixture with the sample prepared as above.

2α-*Methyl*-17β-*hydroxyestran*-3-*one* (VIa). Compound IVa (300 mg) was reduced with 70 ml Li in 30 ml liquid ammonia as reported by Bowers *et al.*[14] m.p. 133–136°, $[\alpha]_D$ +47·6° (lit: m.p. 135–137°, $[\alpha]_D$ +66°), NMR: 9·23τ (18-H), 8·99τ (J = 6·3, 2-CH_3), 6·34τ (17-H). ORD: $[\alpha]_{700}$ +18·3°, $[\alpha]_{589}$ +55·0°, $[\alpha]_{314}$ +997°, $[\alpha]_{275}$ −720°, $[\alpha]_{260}$ −580° (*c*, 0·60).

2β-*Methyl*-17β-*hydroxyestran*-3-*one* (VIIa). Compound Va (171 mg) was reduced with 70 mg Li in 30 ml liquid ammonia. The resulting crude product was chromatographed on silica gel. Elution with benzene–ether (10:1) afforded 100 mg of 2β-*methyl*-17β-*hydroxyestran*-3-*one* (VIIa) as needles, crystallized from acetone–hexane, m.p. 152–154°, $[\alpha]_D$ +129° (*c*, 0·59), ν_{max}^{KBr} 3485 (OH), 1707 (C=O), NMR: 9·22τ (18-H), 8·83τ (J = 7·0, 2-CH_3), 6·34τ (17-H). (Found: C, 78·18; H, 10·45. $C_{19}H_{30}O_2$ requires: C, 78·57; H, 10·41%.) ORD: $[\alpha]_{700}$ +80·3°, $[\alpha]_{589}$ +110°, $[\alpha]_{316}$ +2340°, $[\alpha]_{278}$ −1660°, $[\alpha]_{260}$ −1290° (*c*, 0·51).

2α,17α-*Dimethyl*-17β-*hydroxyestran*-3-*one* (VIb). Compound IVb (100 mg) was reduced with 70 mg Li in 20 ml liquid ammonia. The chromatography of the resulting product with benzene–ether (9:1) yielded 80 mg of 2α,17α-*dimethyl*-17β-*hydroxyestran*-3-*one* (VIb), which was crystallized from hexane as needles, m.p. 149–151°, $[\alpha]_D$ +49° (*c*, 0·96), ν_{max}^{KBr} 3378 (OH) and 1712 cm^{-1} (C=O), NMR: 9·11τ (18-H), 8·99τ (J = 6·3, 2-CH_3), 8·79τ (17-CH_3). (Found: C, 78·93; H, 10·53. $C_{20}H_{32}O_2$ requires: C, 78·89; H, 10·59%.) ORD: $[\alpha]_{589}$ +69·3°, $[\alpha]_{316}$ +1340, $[\alpha]_{278}$ −956, $[\alpha]_{260}$ −698° (*c*, 0·49).

2β,17α-*Dimethyl*-17β-*hydroxyestran*-3-*one* (VIIb). Compound Vb (90 mg) was reduced with 50 mg Li in 20 ml liquid ammonia. The crude product was chromatographed on silica gel and elution with benzene–ether (9:1) afforded 60 mg of 2β,17α-*dimethyl*-17β-*hydroxyestran*-3-*one* (VIIb), crystallized from hexane, m.p. 156·5–159°, $[\alpha]_D$ +98° (*c*, 0·56), ν_{max}^{KBr} 3378 (OH) and 1712 cm^{-1} (C=O), NMR: 9·11τ (18-H), 8·83τ (J = 7·0, 2-CH_3), 8·78τ (17-CH_3). (Found: C, 78·85; H, 10·64. $C_{20}H_{32}O_2$ requires: C, 78·89; H, 10·58%.) ORD: $[\alpha]_{589}$ +113·2°, $[\alpha]_{316}$ +2142°, $[\alpha]_{278}$ −1680°, $[\alpha]_{260}$ −1340° (*c*, 0·38).

2,2,17α-*Trimethyl*-17β-*hydroxyestran*-3-*one* (VIII) was prepared from 17α-methyl-17β-hydroxyestran-3-one according to the method reported by Bowers *et al.*[17] m.p. 142–145°, $[\alpha]_D$ +96° (*c*, 0·52) (lit: m.p. 140–142°, $[\alpha]_D$ +102°), $\nu_{max}^{CHCl_3}$ 1706 cm^{-1} (C=O), NMR: 9·10τ (18-H), 8·96τ (2α-CH_3), 8·83τ (2β-CH_3), 8·78τ (17-CH_3).

2,2,17α-*Trimethyl*-17β-*hydroxyestr*-4-*en*-3-*one* (IX). To a solution of VIII (300 mg) in 13·5 ml acetic acid was added dropwise with stirring a solution of 155 mg Br_2 and 70 mg anhydrous sodium acetate in 1 ml acetic acid. The solution was poured slowly into ice water (70 ml) containing 700 mg sodium acetate and the resulting precipitate was extracted with ether. The ethereal solution was washed with $NaHCO_3$ aq, water, dried and evaporated *in vacuo*. The crude product (300 mg) was dehydrobrominated by refluxing with 70 mg LiCl and 40 mg $LiCO_3$ in 5 ml dimethylformamide for 2·5 hr. Extraction with ether, washing with water and removal of the solvent yielded 250 mg of an oil, which was chromatographed on silica gel. Elution with benzene–ether (20:1) afforded 100 mg crude crystals, m.p. 140–146°. Recrystallization from ether–hexane gave 70 mg of 2,2,17α-*trimethyl*-17β-*hydroxyestr*-4-*en*-3-*one* (IX). m.p. 150–153°, $[\alpha]_D$ +34° (*c*, 0·53), λ_{max} 239 mμ (ε 15,800), $\nu_{max}^{CHCl_3}$ 1661 (C=O) and 1626 cm^{-1} (C=C), NMR: 9·06τ (18-H), 8·95τ (2β-CH_3), 8·90τ (2α-CH_3), 8·78τ (17α-CH_3), 4·25τ (4-H). (Found: C, 79·48; H, 10·06. $C_{21}H_{32}O_2$ requires: C, 79·70; H, 10·19%.) ORD (Fig. 1): $[\alpha]_{700}$ +14·3°, $[\alpha]_{589}$ +11·9°, $[\alpha]_{365}$ −633°, $[\alpha]_{354}$ −588°, $[\alpha]_{340}$ −719°, $[\alpha]_{309}$ +1924° (*c*, 0·42).

2α,17β- *and* 2β,17α-*Diacetoxyestr*-4-*en*-3-*one* (X and XI). The preparation of X and XI was carried out according to the procedure reported by Rao *et al.*[18] 17β-Acetoxyestr-4-en-3-one (5·38 g)

[17] A. Bowers and H. J. Ringold, *J. Amer. Chem. Soc.* **81**, 424 (1959).

was treated with 12 g lead tetra-acetate to afford a mixture of X and XI, which was separated by fractional crystallization.

Recrystallization from MeOH gave 0·68 g (11%) of X, m.p. 240–242°, $[\alpha]_D$ +25° (*c*, 1·0) (lit:[11] m.p. 235–237°, $[\alpha]_D$ +24°), λ_{max} 240·5 mμ (ε 17·210), $\nu_{max}^{CHCl_3}$ 1722–1740 ($OCOCH_3$), 1680 (C=O) and 1622 cm^{-1} (C=C), NMR in C_6D_6: 9·25τ (18-H), 8·24τ (17-$OCOCH_3$), 8·06τ (2α-$OCOCH_3$), 5·33τ (17-H), 4·63τ ($J_{2,1\alpha}$ = 13·8, $J_{2,1\beta}$ = 5·5, 2β-H), 4·26τ (4-H). (Found: C, 70·69; H, 8·04. Calc. for $C_{32}H_{50}O_6$: C, 70·56; H, 8·08%.)

Recrystallization from hexane gave 0·14 g (2·2%) of XI, m.p. 188–190·5°, $[\alpha]_D$ −101·3° (*c*, 0·71) (lit:[11] m.p. 185–186°, $[\alpha]_D$ −101·6°), λ_{max} 243 (ε 16,780), $\nu_{max}^{CHCl_3}$ 1723–1738 ($OCOCH_3$), 1683 (C=O) and 1626 cm^{-1} (C=C), NMR in C_6D_6: 9·29τ (18-H), 8·24τ (17-$OCOCH_3$), 8·13τ (2β-$OCOCH_3$), 5·30τ (17-H), 4·52τ ($J_{2,1\alpha}$ = 9·3, $J_{2,1\beta}$ = 6·9, 2α-H), 4·21τ (4-H). (Found: C, 70·29; H, 7·91. Calc. for $C_{32}H_{50}O_6$: C, 70·56; H, 8·08%.)

ORD of IX (Fig. 2): $[\alpha]_{700}$ −62·5°, $[\alpha]_{589}$ −52·5°, $[\alpha]_{356}$ −728°, $[\alpha]_{343}$ −835°, $[\alpha]_{310}$ +1880° (*c*, 0·4).

ORD of X (Fig. 2): $[\alpha]_{700}$ −12·8°, $[\alpha]_{589}$ −38·5°, $[\alpha]_{378}$ −398°, $[\alpha]_{340}$ −12·8°, $[\alpha]_{370}$ −2950° (*c*, 0·39).

Acknowledgements—The authors are very grateful to Dr. S. Ose, Director of this laboratory, for his encouragement and to Dr. H. Takamatsu, Director of Chemical Division, and Dr. H. Nishimura for their advice and also to the members of Analytical Center of this laboratory for the NMR measurements. They wish to thank Dr. K. Kuriyama and Dr. K. Tori, Shionogi Research Laboratory, for their helpful discussion.