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Syntheses of 15α-Hydroxyestrone and 15α-Hydroxyestradiol[1]

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The titled compounds (**1**, **2**) have been prepared from estrone by the new synthetic routes. Introduction of a hydroxyl group into the 15α-position was readily attained by hydroboration of the 14,15- or 15,16-double bond with diborane and subsequent oxidation of the organoborane with alkaline hydrogen peroxide. In the preparation of **1** the dimethyl-*tert*-butylsilyl function was conveniently employed for the purpose of protecting the 3,17β-hydroxyl groups.

15α-Hydroxyestrone (**1**) and 15α-hydroxyestradiol (**2**) isolated from human pregnancy urine[3] are of particular interest in connection with the biosynthesis of 15α-hydroxyestriol (estetrol).[4] During the course of our biochemical studies on the female hormone the availability of the 15α-hydroxylated estrogens has become an essential prerequisite. Although microbial transformation of estrone or estradiol is widely used for this purpose,[5] the preparation of these compounds by chemical means has not yet been reported. The present paper deals with the syntheses of **1** and **2** starting from estrone.

It has already been reported that nucleophilic addition of benzyl alcohol to the Δ^{15}-17-ketone affords the 15β-hydroxyl derivative[6] and reductive cleavage of the 17β-acetoxy-15α, 16α-epoxide with lithium aluminum hydride results in regiospecific formation of the 16α,17β-diol.[7] Therefore hydroboration of the Δ^{14} or Δ^{15} compound with diborane followed by oxidation of the organoborane with alkaline hydrogen peroxide appeared to be promising to introduce a hydroxyl function into the 15α-position.[8] An initial effort was directed to hydration of the Δ^{15}-17β-hydroxyl derivative. Estra-1,3,5(10),15-tetraene-3,17β-diol (**4**) was prepared by metal hydride reduction of the 17-ketone (**3**) which is readily obtainable from estrone by the known method.[9] The preparation of **1** from the 3,15α,17β-triol required the protection of the hydroxyl functions in **4** prior to hydration of the 15,16-double bond. Derivatization into the dimethyl-*tert*-butylsilyl ether was chosen for this purpose since the silylation would proceed quantitatively under the mild conditions[10] and the facile separation of the desired product from the possible isomers would be expected.[11] Being treated with dimethyl-*tert*-butylsilyl

1) Part CV of "Studies on Steroids" by T. Nambara; Part CIV: T. Nambara, K. Shimada, and R. Hanabuchi, *Chem. Pharm. Bull.* (Tokyo), **23**, 2458 (1975). In this paper the following trivial names were used: estrone, 3-hydroxyestra-1,3,5(10)-trien-17-one; estradiol, estra-1,3,5(10)-triene-3,17β-diol; estriol, estra-1,3,5(10)-triene-3,16α,17β-triol.
2) Location: *Aobayama, Sendai.*
3) R. Knuppen, O. Haupt, and H. Breuer, *Biochem. J.*, **96**, 33c (1965); B.P. Lisboa, U. Goebelsmann, and E. Diczfalusy, *Acta Endocrinol.*, **54**, 467 (1967); R. Knuppen and H. Breuer, *Z. Physiol. Chem.*, **348**, 581 (1967).
4) E.V. YoungLai and S. Solomon, *J. Clin. Endocrinol. Metab.*, **28**, 1611 (1968).
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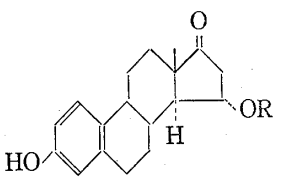
6) E.W. Cantrall, R. Littell, and S. Bernstein, *J. Org. Chem.*, **29**, 214 (1964).
7) J. Fishman and H. Guzik, *J. Org. Chem.*, **33**, 3133 (1968).
8) *a*) M. Nussim, Y. Mazur, and F. Sondheimer, *J. Org. Chem.*, **29**, 1120 (1964); *b*) R.W. Kelly and P.J. Sykes, *J. Chem. Soc.* (*C*), **1968**, 416.
9) T. Nambara, K. Sudo, and M. Sudo, *Steroids*, in press.
10) E.J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).
11) H. Hosoda, K. Yamashita, H. Sagae, and T. Nambara, *Chem. Pharm. Bull.* (Tokyo), **23**, 2118 (1975).

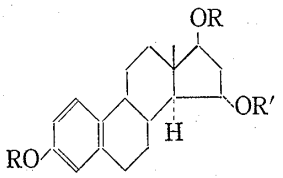
chloride in dimethylformamide in the presence of imidazole, **4** was transformed into the 3,17-bis(dimethyl-*tert*-butylsilyl) ether (**5**).

Hydration of **5** with diborane and alkaline hydrogen peroxide afforded two isomeric products whose separation could be attained by preparative thin-layer chromatography (TLC). The major product was identified as estriol 3,17-bis(dimethyl-*tert*-butylsilyl) ether (**6**), which on acid hydrolysis was led to estriol (**7**). On the other hand the nuclear magnetic resonance (NMR) spectrum of the minor product exhibited a characteristic sextet signal[12] at 4.16 ppm and a triplet (J=8 Hz) at 3.88 ppm, attributable to 15β- and 17α-protons, respectively. These evidences lent a support to assign the structure 15α-hydroxyestradiol 3,17-bis(dimethyl-*tert*-butylsilyl) ether (**8**) to the minor product. Upon exposure to 5N hydrochloric acid in acetone **8** underwent elimination of the silyl group to provide the desired 15α-hydroxyestradiol in a quantitative yield.

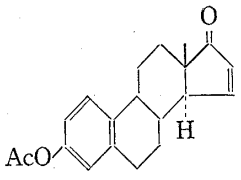
Thus it has proved that hydration of the Δ^{15}-olefin is not necessarily favorable for preparation of the 15α-hydroxysteroid because of its undesirable regioselectivity. Hereupon, the preparation of the desired compound was undertaken by utilizing hydration of estra-1,3,-5(10),14-tetraene-3,17β-diol bis(dimethyl-*tert*-butylsilyl) ether (**11**). On treatment with isopropenyl acetate in the presence of *p*-toluenesulfonic acid as a catalyst **3** was converted into the $\Delta^{14,16}$-dien-17-ol acetate (**9**) in a satisfactory yield. Reduction of the enol acetate with sodium borohydride in aqueous ethanol furnished estra-1,3,5(10),14-tetraene-3,17β-diol (**10**),[13] which in turn was transformed into the 3,17-disilyl ether (**11**) in the manner as described above. Hydration of **11** afforded the desired 15α-hydroxyl derivative (**8**) in 70% yield. The structure



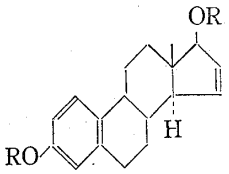
1: R=H
15: R=Ac



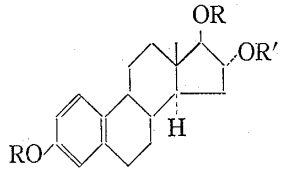
2: R=R′=H
8: R=Si(CH$_3$)$_2$-*t*-Bu, R′=H
13: R=Si(CH$_3$)$_2$-*t*-Bu, R′=Ac
14: R=H, R′=Ac



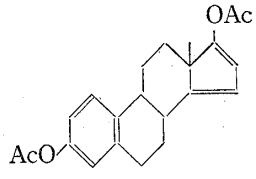
3



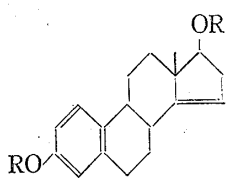
4: R=H
5: R=Si(CH$_3$)$_2$-*t*-Bu



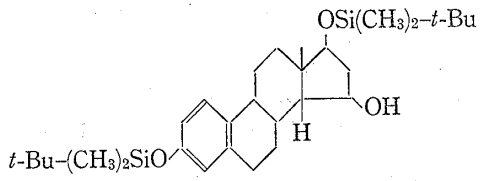
6: R=Si(CH$_3$)$_2$-*t*-Bu, R′=H
7: R=R′=H



9



10: R=H
11: R=Si(CH$_3$)$_2$-*t*-Bu



12

Chart 1

12) J.E. Bridgeman, P.C. Cherry, A.S. Clegg, J.M. Evans, E.R.H. Jones, A. Kasal, V. Kumar, G.D. Meakins, Y. Morisawa, E.E. Richards, and P.D. Woodgate, *J. Chem. Soc.* (*C*), **1970**, 250.
13) B. Belleau and T.F. Gallagher, *J. Am. Chem. Soc.*, **73**, 4458 (1951); G.H. Rasmusson and G.E. Arth, *Steroids*, **22**, 107 (1973).

of the by-product hereby obtained was tentatively assigned to 14β-estra-1,3,5(10)-triene-3,15β,-17β-triol 3,17-bis(dimethyl-*tert*-butylsilyl) ether (**12**). It has been previously demonstrated that hydration of the Δ^{14}-17β-ol yields two epimeric *cis*-adducts in an approximately equal amount.[8b] Therefore it seems very likely that the presence of the bulky silyloxy group at the 17β-position would favor the preferential attack of the reagent from the α-face of a molecule toward the 14,15-double bond.

From the necessity of 15α-hydroxyestrone **8** was led to the 15-acetate (**13**) by usual acetylation with acetic anhydride and pyridine. Removal of the silyl group without disturbance of the acetate in **13** was effected by brief exposure to hydrogen chloride in acetone to yield 15α-acetoxyestradiol (**14**). Subsequent oxidation with Jones reagent provided 15α-acetoxyestrone (**15**) in a fairly good yield. An attempt for saponification of **15** with potassium bicarbonate resulted in failure even under the mild conditions due to the presence of the highly susceptible β-ketol system. Hydrolytic cleavage of the 15α-acetoxyl group, however, was accomplished by treatment with hydrochloric acid in acetone to furnish the desired 15α-hydroxyestrone in 80% yield.

It is hoped that the availability of the titled compounds will provide the more precise knowledge on the biosynthesis of estetrol in the feto-placental unit.

Experimental[14]

Estra-1,3,5(10),15-tetraene-3,17β-diol (**4**)——To a solution of 3-hydroxyestra-1,3,5(10),15-tetraen-17-one acetate (**3**)[9] (150 mg) in anhydrous ether (40 ml) was added $LiAlH_4$ (62 mg) and allowed to stand at 0° for 30 min. After addition of moist ether to decompose the excess reagent the resulting solution was diluted with 25% Rochelle salt solution and extracted with AcOEt. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization from aq. MeOH gave **4** (140 mg) as colorless needles. mp 195—198° (lit. mp 200—201.5°).[9]

Estra-1,3,5(10),15-tetraene-3,17β-diol Bis(dimethyl-*tert*-butylsilyl) Ether (**5**)——To a solution of **4** (360 mg) in dimethylformamide (3 ml) were added imidazole (1.2 g) and dimethyl-*tert*-butylsilyl chloride (1 g) and allowed to stand at room temperature for 2 hr. The resulting solution was diluted with ether, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization from MeOH gave **5** (453 mg) as colorless prisms. mp 89.5—90.5°. $[\alpha]_D^{22}$ +12.3° (c=0.37). NMR ($CDCl_3$) δ: 0.08 (6H, s, 17-OSi$(CH_3)_2$), 0.18 (6H, s, 3-OSi$(CH_3)_2$), 0.81 (3H, s, 18-CH_3), 0.91 (9H, s, 17-OSi-*t*-Bu), 0.97 (9H, s, 3-OSi-*t*-Bu), 4.33 (1H, broad s, 17α-H), 5.60 (1H, m, 15-H), 5.95 (1H, broad d, 16-H), 6.45—6.75 (2H, 2- and 4-H), 7.12 (1H, d, J= 8 Hz, 1-H). *Anal.* Calcd. for $C_{30}H_{50}O_2Si_2$: C, 72.23; H, 10.10. Found: C, 72.56; H, 10.20.

Hydration of 5——To a stirred solution of **5** (350 mg) and $LiAlH_4$ (700 mg) in anhydrous ether (15 ml) was added BF_3-etherate (3.5 g) in anhydrous ether (10 ml) dropwise at 0° over a period of 30 min under a N_2 gas stream. The ice-bath was then removed and the reaction mixture was stirred at room temperature for 30 min. After addition of moist ether to decompose the excess reagent the resulting solution was extracted with ether. The organic layer was washed with 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. To the residue dissolved in tetrahydrofuran (12 ml) were added 30% H_2O_2 (4 ml) and 10% NaOH (6 ml) and stirred at 0° for 1 hr. The resulting solution was diluted with H_2O and extracted with ether. The organic layer was washed with 5% $NaHSO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product obtained was purified by preparative TLC using hexane–AcOEt (10: 1) as developing solvent. Recrystallization of the major product from MeOH gave **6** (185 mg) as colorless leaflets. mp 140—143.5°. $[\alpha]_D^{22}$ +33.2° (c=0.11). NMR ($CDCl_3$) δ: 0.12 (6H, s, 17-OSi$(CH_3)_2$), 0.20 (6H, s, 3-OSi$(CH_3)_2$), 0.78 (3H, s, 18-CH_3), 0.92 (9H, s, 17-OSi-*t*-Bu), 0.97 (9H, s, 3-OSi-*t*-Bu), 3.51 (1H, d, J=6 Hz, 17α-H), 4.09 (1H, m, 16β-H), 6.48—6.72 (2H, 2- and 4-H), 7.13 (1H, d, J=8 Hz, 1-H). *Anal.* Calcd. for $C_{30}H_{52}O_3Si_2$: C, 69.71; H, 10.14. Found: C, 69.54; H, 10.07. The minor product obtained from the more polar fraction was recrystallized from MeOH to give **8** (24 mg) as colorless needles. mp 146—149.5°. $[\alpha]_D^{22}$ +93.0° (c=0.41). NMR ($CDCl_3$) δ: 0.05 (6H, s, 17-OSi$(CH_3)_2$), 0.20 (6H, s, 3-OSi$(CH_3)_2$), 0.78 (3H, s, 18-CH_3), 0.90 (9H, s, 17-OSi-*t*-Bu), 0.98 (9H, s, 3-OSi-*t*-Bu), 3.88 (1H, t, J=8 Hz, 17α-H), 4.16 (1H, sx, J=9, 9, 4 Hz,

14) All melting points were taken on a micro hot-stage apparatus and are uncorrected. Optical rotations were measured in $CHCl_3$ unless otherwise specified. Infrared (IR) spectra were obtained on a JASCO Model IR-S spectrometer. NMR spectra were recorded on a Hitachi Model R-20A spectrometer at 60 MHz or a JEOL Model PS-100 spectrometer at 100 MHz using tetramethylsilane as an internal standard. Abbreviation used s=singlet, d=doublet, t=triplet, sx=sextet, and m=multiplet. For preparative TLC silica gel HF_{254} (E. Merck AG, Darmstadt) was used as an adsorbent.

15β-H), 6.50—6.70 (2H, 2- and 4-H), 7.12 (1H, d, J=8 Hz, 1-H). *Anal.* Calcd. for $C_{30}H_{52}O_3Si_2$: C, 69.71; H, 10.14. Found: C, 69.55; H, 10.36.

Acid-Catalyzed Hydrolysis of 6——To a solution of **6** (30 mg) in acetone (4 ml) was added 5N HCl (1.5 ml) and allowed to stand at room temperature for 3 hr. The resulting solution was diluted with H_2O and extracted with AcOEt. The organic layer was washed with 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization from acetone gave estriol (**7**) (13 mg) as colorless prisms. mp 283—285°. Mixed melting point on admixture with the authentic sample showed no depression and the IR spectra of two samples were entirely identical.

Estra-1,3,5(10),14,16-pentaene-3,17-diol Diacetate (9)——To a solution of **3** (750 mg) in isopropenyl acetate (18 ml) was added anhydrous *p*-TsOH (50 mg) and refluxed for 1 hr. The resulting solution was concentrated to its half volume by slow distillation over a period of 1 hr. Additional isopropenyl acetate (8 ml) and anhydrous *p*-TsOH (20 mg) were added and concentrated again to its half volume during 1 hr. The reaction mixture was diluted with ether, washed with ice-cooled 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization from MeOH gave **9** (805 mg) as colorless prisms. mp 147—149.5°. $[\alpha]_D^{14}$ +287.3° (c=0.15). NMR ($CDCl_3$) δ: 1.16 (3H, s, 18-CH_3), 2.30, 2.36 (each 3H, s, 3- and 17-$OCOCH_3$), 6.04 (1H, broad s, 15-H), 6.22 (1H, d, J=2.5 Hz, 16-H), 6.90—7.12 (2H, 2- and 4-H), 7.48 (1H, d, J=8 Hz, 1-H). *Anal.* Calcd. for $C_{22}H_{24}O_4$: C, 74.97; H, 6.86. Found: C, 75.42; H, 6.94. Pataki, *et al.* prepared **9** by the different route (lit. mp 151—152.5°).[15]

Estra-1,3,5(10),14-tetraene-3,17β-diol (10)——To a solution of **9** (512 mg) in EtOH (40 ml) was added $NaBH_4$ (1.2 g) in EtOH (20 ml)–H_2O (8 ml) at 0° and stirred at room temperature for 3 hr. After addition of 10% AcOH (5 ml) to decompose the excess reagent the resulting solution was concentrated to its half volume under the reduced pressure, diluted with AcOEt, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product obtained was purified by preparative TLC using hexane–AcOEt (2: 1) as developing solvent. Recrystallization from acetone-hexane gave **10** (380 mg) as colorless needles. mp 179—182°. $[\alpha]_D^{22}$ +140.6° (c=0.11, EtOH). NMR (acetone-d_6) δ: 1.00 (3H, s, 18-CH_3), 4.00 (1H, t, J=8 Hz, 17α-H), 5.20 (1H, m, 15-H), 6.40—6.72 (2H, 2- and 4-H), 7.10 (1H, d, J=8 Hz, 1-H). *Anal.* Calcd. for $C_{18}H_{22}O_2 \cdot 1/2H_2O$: C, 77.38; H, 8.30. Found: C, 77.19; H, 8.30.

Estra-1,3,5(10),14-tetraene-3,17β-diol Bis(dimethyl-*tert*-butylsilyl) Ether (11)——To a solution of **10** (380 mg) in dimethylformamide (3 ml) were added imidazole (1.5 g) and dimethyl-*tert*-butylsilyl chloride (1.2 g) and allowed to stand at room temperature for 2 hr. The resulting solution was diluted with ether, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization from MeOH gave **11** (555 mg) as colorless leaflets. mp 106.5—108.5°. $[\alpha]_D^{22}$ +90.0° (c=0.10). NMR ($CDCl_3$) δ: 0.07 (6H, s, 17-$OSi(CH_3)_2$), 0.20 (6H, s, 3-$OSi(CH_3)_2$), 0.90 (9H, s, 17-OSi-*t*-Bu), 0.98 (12H, s, 18-CH_3 and 3-OSi-*t*-Bu), 4.00 (1H, t, J=8 Hz, 17α-H), 5.15 (1H, m, 15-H), 6.47—6.72 (2H, 2- and 4-H), 7.12 (1H, d, J=8 Hz, 1-H). *Anal.* Calcd. for $C_{30}H_{50}O_2Si_2$: C, 72.23; H, 10.10. Found: C, 71.87; H, 10.20.

Hydration of 11——Hydroboration of **11** (220 mg) with diborane and subsequent oxidation of the organoborane with H_2O_2–NaOH were carried out in the manner as described with **5**. The crude product obtained was purified by preparative TLC using hexane–AcOEt (10: 1) as developing solvent. Recrystallization of the major product from MeOH gave **8** (160 mg) as colorless needles. mp 147—149°. The IR spectrum was identical with that of the sample prepared from **5**. The minor product obtained from the less polar fraction was recrystallized from MeOH to give **12** (20 mg) as colorless needles. mp 171—175°. $[\alpha]_D^{16}$ +80.2° (c=0.12). NMR ($CDCl_3$) δ: 0.08 (6H, s, 17-$OSi(CH_3)_2$), 0.20 (6H, s, 3-$OSi(CH_3)_2$), 0.93 (9H, s, 17-OSi-*t*-Bu), 0.99 (9H, s, 3-OSi-*t*-Bu), 1.08 (3H, s, 18-CH_3), 3.63 (1H, d, J=4 Hz, 17α-H), 4.14 (1H, m, 15α-H), 6.40—6.68 (2H, 2- and 4-H), 7.06 (1H, d, J=8 Hz, 1-H). *Anal.* Calcd. for $C_{30}H_{52}O_3Si_2$: C, 69.71; H, 10.14. Found: C, 70.06; H, 10.10.

15α-Acetoxyestra-1,3,5(10)-triene-3,17β-diol 3,17-Bis(dimethyl-*tert*-butylsilyl) Ether (13)——A solution of **8** (140 mg) in pyridine (3 ml) and Ac_2O (1 ml) was allowed to stand at room temperature overnight. The resulting solution was diluted with ice-water and extracted with ether. The organic layer was washed with 10% AcOH, ice-cooled 5% $NaHCO_3$, and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product obtained was purified by preparative TLC using hexane–AcOEt (30: 1) as developing solvent. Recrystallization from MeOH gave **13** (115 mg) as colorless plates. mp 70—74°. $[\alpha]_D^{22}$ +100.0° (c=0.20). NMR ($CDCl_3$) δ: 0.05 (6H, s, 17-$OSi(CH_3)_2$), 0.20 (6H, s, 3-$OSi(CH_3)_2$), 0.79 (3H, s, 18-CH_3), 0.89 (9H, s, 17-OSi-*t*-Bu), 0.97 (9H, s, 3-OSi-*t*-Bu), 3.81 (1H, t, J=8 Hz, 17α-H), 4.96 (1H, m, 15β-H), 6.40—6.72 (2H, 2- and 4-H), 7.11 (1H, d, J=8 Hz, 1-H). *Anal.* Calcd. for $C_{32}H_{54}O_4Si_2$: C, 68.77; H, 9.74. Found: C, 68.12; H, 9.60.

Estra-1,3,5(10)-triene-3,15α,17β-triol 15-Acetate (14)——To a solution of **13** (50 mg) in acetone (0.5 ml) was added HCl (170 mg) in acetone (2 ml) and allowed to stand at room temperature for 3 hr. The resulting solution was diluted with AcOEt, washed with 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product obtained was purified by preparative TLC using hexane–AcOEt (2: 1) as developing solvent to give **14** (25 mg) as colorless oil. NMR ($CDCl_3$) δ: 0.82 (3H, s, 18-CH_3), 2.07 (3H, s,

15) J. Pataki and G. Siade B, *J. Org. Chem.*, 37, 2127 (1972).

15α-$OCOCH_3$), 3.94 (1H, t, J=8 Hz, 17α-H), 5.00 (1H, m, 15β-H), 6.48—6.84 (2H, 2- and 4-H), 7.17 (1H, d, J=8 Hz, 1-H).

3,15α-Dihydroxyestra-1,3,5(10)-trien-17-one 15-Acetate (15)——To a solution of **14** (25 mg) in acetone (1.5 ml) was added Jones reagent (50 μl) at 0° and allowed to stand at 0° for 15 min. After addition of MeOH to decompose the excess reagent the resulting solution was extracted with AcOEt. The organic layer was washed with 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product obtained was purified by preparative TLC using hexane–AcOEt (3: 1) as developing solvent. Recrystallization from MeOH gave **15** (18 mg) as colorless needles. mp 140—141°. $[\alpha]_D^{22}$ +205.6° (c=0.09). NMR ($CDCl_3$) δ: 1.00 (3H, s, 18-CH_3), 2.12 (3H, s, 15α-$OCOCH_3$), 5.31 (1H, m, 15β-H), 6.44—6.76 (2H, 2- and 4-H), 7.12 (1H, d, J=8 Hz, 1-H). *Anal.* Calcd. for $C_{20}H_{24}O_4 \cdot 1/2H_2O$: C, 71.19; H, 7.47. Found: C, 71.36; H, 7.53.

3,15α-Dihydroxyestra-1,3,5(10)-trien-17-one (15α-Hydroxyestrone) (1)——To a solution of **15** (13 mg) in acetone (2 ml) was added 5N HCl (1.2 ml) and allowed to stand at room temperature for 20 hr. The resulting solution was diluted with AcOEt, washed with 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product obtained was purified by preparative TLC using benzene–ether (2: 1) as developing solvent. Recrystallization from $CHCl_3$–AcOEt gave **1** (9 mg) as colorless needles. mp 226—228°. Mixed melting point on admixture with the authentic sample prepared from estrone by microbial transformation showed no depression and the IR spectra of two samples were entirely identical.

Estra-1,3,5(10)-triene-3,15α,17β-triol (15α-Hydroxyestradiol) (2)——To a solution of **8** (21 mg) in acetone (4 ml) was added 5N HCl (1.8 ml) and allowed to stand at room temperature for 2 hr. The resulting solution was diluted with AcOEt, washed with 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product obtained was purified by preparative TLC using $CHCl_3$–EtOH (10: 1) as developing solvent. Recrystallization from acetone gave **2** (11 mg) as colorless prisms. mp 247—250°. Mixed melting point on admixture with the authentic sample prepared from **1** by $NaBH_4$ reduction showed no depression and the IR spectra of two samples were entirely identical.

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