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Studies on Steroid Conjugates. III. New Syntheses of 2-Methoxyestrogens[1]

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The new synthetic routes leading to the 2-methoxyestrogens from the readily available compounds have been investigated. Utilization of both Friedel–Crafts and Baeyer–Villiger reactions with estrone and estradiol 3-methyl ethers gave the desired 2-methoxyestrogens in overall yield of *ca.* 50%. Fries rearrangement with estrone acetate and Friedel–Crafts reaction with 2-methoxy-3-deoxyestrogens were also undertaken. The chemical shifts of the aromatic protons of the 2,3-substituted estratrienes are collected in Table I and II.

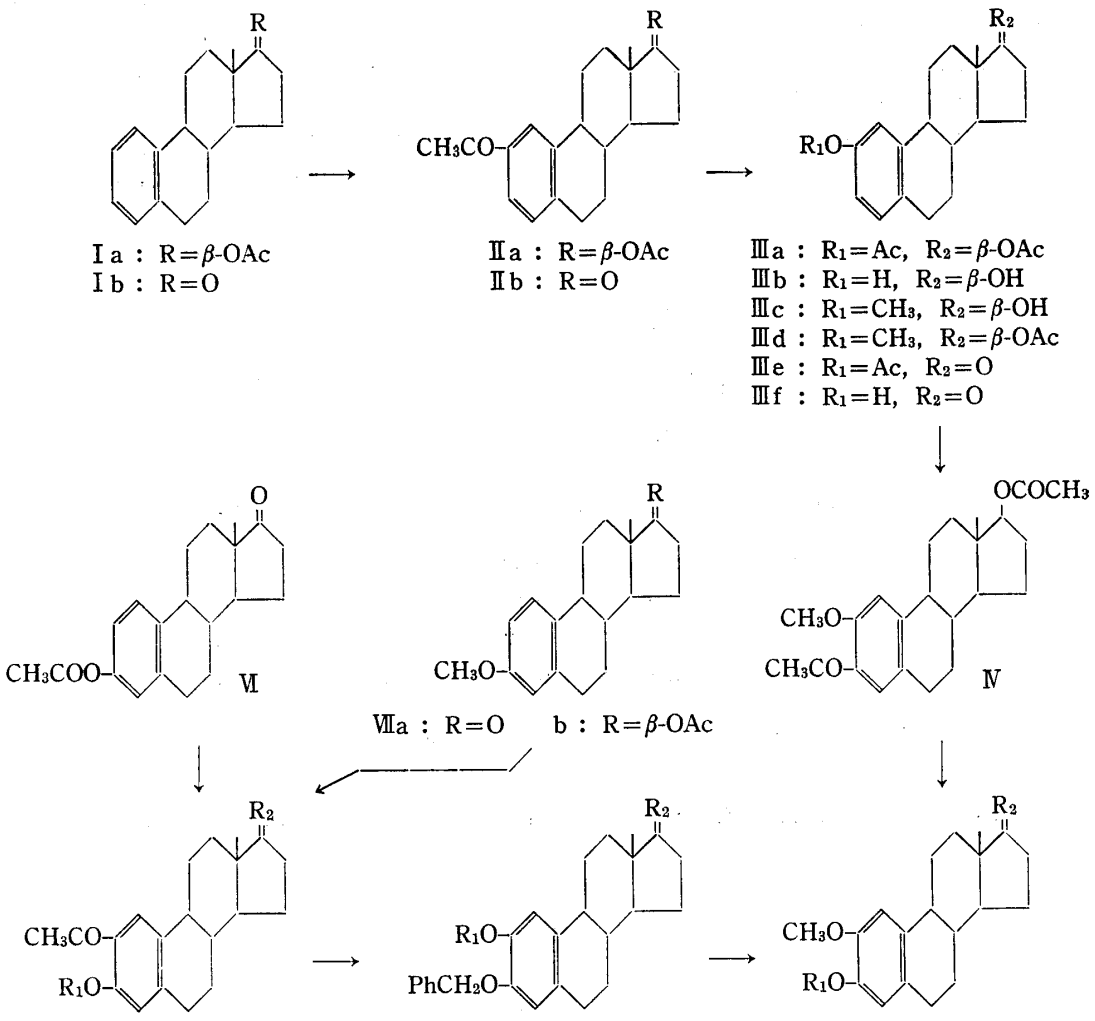
In 1957 Gallagher and his co-worker reported first the occurrence of 2-methoxyestrone in human urine after the administration of estradiol or estrone.[3] The physiological significance of this biotransformation is still an attractive subject. Since the discovery of this novel metabolite, several methods for preparation of the catechol estrogens and their methyl ethers have been proposed.[4] However, the synthetic methods hitherto proposed are not necessarily satisfactory in respect of feasibility and/or yield. The present paper describes new synthetic routes leading to the 2-methoxyestrogens with more advantages.

An initial attempt was directed to the utilization of Friedel–Crafts reaction starting from 2-hydroxy-3-deoxyestradiol, since the exclusive acetylation at C-3 would be anticipated. The starting compound was obtained with ease from 3-deoxyestrogens by the method of Sakakibara.[5,6] When 3-deoxyestradiol acetate (Ia) was treated with acetyl chloride in the presence of anhydrous aluminum chloride as catalyst, condensation reaction proceeded to give 2-acetylestra-1,3,5(10)-trien-17β-ol acetate (IIa) accompanied with a small amount of the 3-acetylated isomer. The structures of these products were established by inspection of the nuclear magnetic resonance (NMR) spectra of the ring proton region.[7] Treatment of IIa with perbenzoic acid in chloroform gave 2-hydroxy-3-deoxyestradiol 2,17-diacetate (IIIa) in satisfactory yield. The preparation of 2-hydroxy-3-deoxyestrone (IIIf) was also attempted employing the same reaction sequence. As was expected 3-deoxyestrone (Ib) also underwent Friedel–Crafts and Baeyer–Villiger reactions without any difficulties resulting in formation of IIIf. Hereupon the result promised the success, with which the subsequent elaborations would also be applicable to the 17-oxo series.

The alkaline hydrolysis of IIIa followed by methylation with dimethyl sulfate furnished 2-methoxy-3-deoxyestradiol (IIIc), which in turn was led to the 17-acetate (IIId). The 2-methoxy-3-deoxysteroid thus obtained being submitted again to Friedel–Crafts reaction with acetyl chloride, 2-methoxy-3-acetylestra-1,3,5(10)-trien-17β-ol acetate (IV) was afforded

1) This paper constitutes Part XXXIII of the series entitled "Analytical Chemical Studies on Steroids"; Part XXXII: T. Nambara, H. Hosoda, and T. Shibata, *Chem. Pharm. Bull.* (Tokyo), **17**, 2599 (1969).
2) Location: *Aobayama, Sendai.*
3) S. Kraychy and T.F. Gallagher, *J. Am. Chem. Soc.*, **79**, 754 (1957).
4) *a*) J. Fishman, *J. Am. Chem. Soc.*, **80**, 1213 (1958); *b*) J. Fishman, M. Tomasz, and R. Lehman, *J. Org. Chem.*, **25**, 585 (1960); *c*) P.N. Rao and L.R. Axelrod, *Tetrahedron*, **10**, 144 (1960).
5) K. Sakakibara, M. Sawai, and K. Chuma, Japan Patent 9279 (1963) [*C.A.*, **59**, 14060 (1963)].
6) K. Sakakibara, Japan Patent 16887 (1963) [*C.A.*, **60**, 592 (1964)].
7) J. Fishman and J.S. Liang, *Tetrahedron*, **24**, 2199 (1968).

in 80% yield. The NMR spectral pattern of the aromatic protons revealed the position of the introduced acetyl group. Two singlets at 6.85 and 7.44 ppm were assignable to C-1 and C-4 protons, respectively. Then Baeyer–Villiger reaction with per-acid in the manner as mentioned above and subsequent alkaline hydrolysis gave the desired 2-methoxyestradiol (Vb), which proved to be identical with the authentic sample prepared by Fishman's method.[4a]



Ia : R=β-OAc
Ib : R=O

IIa : R=β-OAc
IIb : R=O

IIIa : R1=Ac, R2=β-OAc
IIIb : R1=H, R2=β-OH
IIIc : R1=CH3, R2=β-OH
IIId : R1=CH3, R2=β-OAc
IIIe : R1=Ac, R2=O
IIIf : R1=H, R2=O

VI

IV

VIIa : R=O b : R=β-OAc

VIIIa : R1=CH3, R2=O
VIIIb : R1=H, R2=O
VIIIc : R1=CH2Ph, R2=O
VIIId : R1=CH3, R2=β-OAc
VIIIe : R1=H, R2=β-OAc
VIIIf : R1=CH2Ph, R2=β-OH
VIIIg : R1=CH2Ph, R2=β-OAc

IXa : R1=Ac, R2=O
IXb : R1=H, R2=O
IXc : R1=CH3, R2=O
IXd : R1=Ac, R2=β-OAc
IXe : R1=H, R2=β-OH
IXf : R1=CH3, R2=β-OH

Va : R1=Ac, R2=β-OAc
Vb : R1=H, R2=β-OH
Vc : R1=H, R2=O

Chart 1

The present method requires only four steps to prepare the 2-methoxyestrogens from the known compounds, but it suffers from disadvantages in availability of the starting compound. Therefore the next project was focused to development of an alternative way with more convenience starting from estrone acetate (VI). When VI was treated with anhydrous aluminum chloride in tetrachloroethane, Fries rearrangement did take place to furnish 2-acetylestrone (VIIIb) in 54% yield. Orientation of the migrated group was established on the basis of NMR spectral data. It is now to be noted that the acyl group transfers preferentially toward C-2 rather than C-4 probably due to the steric hindrance with C-6 hydrogen.

Indeed the use of Fries reaction fulfilled the requirement for facile availability of the starting material, but the satisfactory yield could not be attained. Hence the next project

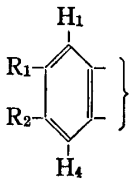
was directed to Friedel–Crafts reaction with estrone 3-methyl ether (VIIa). The starting compound being stirred with acetyl chloride in the presence of anhydrous aluminum chloride, the 2-acetyl derivative (VIIIa) was provided as a single product in excellent yield. The aromatic ring protons appeared as two singlets at 7.72 and 6.68 ppm supporting the assignment of the newly introduced acetyl group at C-2. It is noteworthy that orientation of the acetyl group is consistent with that of Fries rearrangement. Removal of the methyl group at C-3 with hydrogen bromide in acetic acid gave 2-acetylestrone (VIIIb), which was identical with the sample yielded by Fries reaction. The free hydroxylic compound was then converted into the 3-benzyl ether (VIIIc) by treatment with benzyl chloride and potassium carbonate. Subsequent oxidation with perbenzoic acid gave rise to formation of 2-acetoxyestrone 3-benzyl ether (IXa). Alkaline hydrolysis provided the 2-hydroxy compound (IXb), which on treat-

Table I. Chemical Shifts of Aromatic Protons of 2- and 3-Monosubstituted Estratrienes

R	δH_1	δH_4	$\Delta\delta(H_1-H_4)$	$\delta H_1'$	$\delta H_4'$	$\Delta\delta(H_1'-H_4')$
OH	7.00	6.40	0.60	6.67	6.82	−0.15
OAc	7.17	6.70	0.47	6.71	6.97	−0.26
OCH_3	7.02	6.40	0.62	6.65	6.82	−0.17
Ac	7.60	7.23	0.37	7.78	7.03	0.75

The free phenols were measured in DMSO, while others in CCl_4.

Table II. Chemical Shifts of Aromatic Protons of 2,3-Disubstituted Estratrienes



R_1	R_2	δH_1	δH_4	$\Delta\delta(H_1-H_4)$
OH	OH	6.78	6.57	0.21
OAc	OAc	7.01	6.83	0.18
OH	OAc	6.92	6.74	0.18
OAc	OH	6.92	6.65	0.27
OCH_3	OCH_3	6.80	6.57	0.23
OH	OCH_3	6.88	6.57	0.31
OCH_3	OH	6.75	6.60	0.15
OCH_2Ph	OCH_2Ph	6.88	6.62	0.26
OH	OCH_2Ph	6.90	6.63	0.27
OCH_2Ph	OH	6.84	6.62	0.22
OH	Ac	6.87	7.38	−0.51
Ac	OH	7.60	6.70	0.90
OCH_3	Ac	6.85	7.44	−0.59
Ac	OCH_3	7.72	6.68	1.04

All the spectra were obtained in $CDCl_3$.

ment with diazomethane was led to the 2-methoxy derivative (IXc). Upon hydrogenation over palladium–on–charcoal the desired 2-methoxyestrone (Vc) was obtained in 78% yield.

Then, 2-methoxyestradiol (Vb) was prepared from estradiol 3-methyl ether 17-acetate (VIIb) in similar fashion as mentioned above. As was expected Friedel–Crafts reaction with acetyl chloride furnished the 2-acetylated derivative (VIIId). Demethylation with hydrogen bromide gave 2-acetylestradiol 17-acetate (VIIIe), which in turn was converted to the 3-benzyl ether (VIIIf) and its acetate (VIIIg). When treated with *m*-chloroperbenzoic acid in chloroform, VIIIg was easily transformed into the 2-acetoxyl derivative (IXd). Usual saponification afforded the 2-hydroxy compound (IXe), which on treatment with diazomethane was led to the 2-methoxy derivative (IXf). Hydrogenolysis over palladium–on–charcoal gave finally the desired 2-methoxyestradiol (Vb). The synthetic route leading to the desired compound from VIIb was thus established with overall yield of *ca.* 50%.

The chemical shifts of the aromatic protons of 2-, 3-monosubstituted and 2,3-disubstituted estratrienes[8] are listed in Table I and II, respectively. With the 3-mono- and 2,3-dioxygenated derivatives C-1 proton resonates downfield than C-4 proton. The reverse relationship can be seen with the estratrienes having oxygen function at C-2. These properties have already been reported by Fishman, *et al.*,[7] but the present result with the various substrates do confirm the previous finding. In addition these data may readily permit the structural assignment to a limited amount of estrogen available from biological sources.

It is hoped that the facile availability of the 2-methoxyestrogens may be helpful for promoting the biochemical studies associated with the catechol estrogens.

Experimental[9]

2-Acetylestra-1,3,5(10)-trien-17β-ol Acetate (IIa)——Anhydrous $AlCl_3$ (21 g) was dissolved in CS_2 (160 ml) containing AcCl (32 ml) by stirring for 10 min. To this solution was added a solution of Ia (16 g) in CH_2Cl_2 (160 ml) over a period of 10 min and stirred for 1 hr at room temperature. The reaction mixture was poured into cold dil. HCl and extracted with ether. The organic phase was washed with 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the crude product obtained was recrystallized from MeOH to give IIa (13.2 g) as colorless needles. mp 134—135°. $[\alpha]_D^{25}$ +152.2° (c=0.21). (Reported mp 125—126°).[5] From mother liquor isomeric 3-acetylestra-1,3,5(10)-trien-17β-ol (0.48 g) was afforded. Recrystallization from acetone gave it as colorless needles. mp 173—175°. $[\alpha]_D^{24}$ +93.6° (c=0.14). *Anal.* Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.50; H, 8.49.

Estra-1,3,5(10)-triene-2,17β-diol Diacetate (IIIa)——To a solution of IIa (13 g) in $CHCl_3$ (40 ml) was added $C_6H_5CO_3H$–$CHCl_3$ solution (0.5M, 120 ml) and allowed to stand at room temperature for 1 week. The reaction mixture was diluted with ether, washed with cold 5% NaOH, H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the crude product obtained was recrystallized from hexane to give IIIa (12 g) as colorless needles. mp 168—169°. $[\alpha]_D^{25}$ +60.5° (c=0.10). *Anal.* Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 73.87; H, 7.97. (Reported mp 157—158°).[6]

Estra-1,3,5(10)-triene-2,17β-diol (IIIb)——To a solution of IIIa (1 g) in MeOH (60 ml) was added 10% KOH (40 ml) and refluxed for 2 hr. The resulting solution was acidified with dil. HCl and extracted with ether. The organic phase was washed with 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the crude product obtained was recrystallized from benzene to give IIIb (820 mg) as colorless prisms. mp 213—215°. $[\alpha]_D^{25}$ +108.2° (c=0.12, MeOH). *Anal.* Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.23; H, 8.64. (Reported mp 222—224°, $[\alpha]_D^{27}$ +101°).[10]

2-Acetylestra-1,3,5(10)-trien-17-one (IIb)——Anhydrous $AlCl_3$ (4 g) was dissolved in CS_2 (20 ml) containing AcCl (6 ml) by stirring for 10 min. To this solution was added slowly a solution of Ib (3 g) in CH_2Cl_2 (20 ml) over a period of 10 min and stirred for 1 hr at room temperature. The reaction mixture was poured into cold dil. HCl and extracted with ether. The organic phase was washed with 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the crude product obtained was recrystallized

8) Synthesis of the samples which have not mentioned above will be reported elsewhere.

9) All melting points were taken on a micro hot-stage apparatus and are uncorrected. Optical rotations were measured in $CHCl_3$ unless otherwise stated. NMR spectra were measured on Hitachi Model H-60 spectrometer at 60 Mc; the chemical shifts are quoted as ppm downfield from $(CH_3)_4Si$, an internal standard.

10) J. Fishman and M. Tomasz, *J. Org. Chem.*, **27**, 365 (1962).

from MeOH to give IIb (590 mg) as colorless needles. mp 134—136°. $[\alpha]_D^{16}$ +183.9° (c=0.11). *Anal.* Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 80.87; H, 8.03.

2-Hydroxyestra-1,3,5(10)-trien-17-one Acetate (IIIe)——To a solution of IIb (527 mg) in $CHCl_3$ (2 ml) was added $C_6H_5CO_3H$–$CHCl_3$ solution (0.36M, 10 ml) and allowed to stand at room temperature for 1 week. The reaction mixture was diluted with ether, washed with cold 5% NaOH, H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the crude product obtained was recrystallized from MeOH to give IIIe (380 mg) as colorless needles. mp 188.5—190°. $[\alpha]_D^{25}$ +152.2° (c=0.21). *Anal.* Calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 77.07; H, 7.89.

2-Hydroxyestra-1,3,5(10)-trien-17-one (IIIf)——To a solution of IIIe (2.89 g) in MeOH (120 ml) was added 30% KOH (20 ml) and refluxed for 2 hr. The resulting solution was concentrated, acidified with HCl and extracted with ether. On usual work-up a crystalline product was obtained. Recrystallization from MeOH gave IIIf (1.39 g) as colorless prisms. mp 205—208°. (Reported mp 202—204°).[10]

2-Methoxyestra-1,3,5(10)-trien-17β-ol (IIIc)——To a stirred solution of IIIb (3.3 g) in MeOH (150 ml) containing $(CH_3)_2SO_4$ (20 ml) was added slowly 30% KOH (20 ml) at 0°, and then heated at 40° for 1 hr. The reaction mixture was poured into ice-water and the precipitate was collected by filtration. Recrystallization from hexane gave IIIc (3.13 g) as colorless needles. mp 132—133°. $[\alpha]_D^{25}$ +94.5° (c=0.14). *Anal.* Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.78; H, 9.07. (Reported mp 131—133°, $[\alpha]_D^{25}$ +90°).[10]

2-Methoxyestra-1,3,5(10)-trien-17β-ol Acetate (IIId)——Treatment of IIIc (3 g) with Ac_2O (30 ml) and pyridine (30 ml) in usual manner and recrystallization from MeOH gave IIId (2.67 g) as colorless needles. mp 106.5—107.5°. $[\alpha]_D^{26}$ +56.3° (c=0.12). *Anal.* Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.45; H, 8.58.

2-Methoxy-3-acetylestra-1,3,5(10)-trien-17β-ol Acetate (IV)——Anhydrous $AlCl_3$ (3.65 g) was dissolved in CS_2 (17 ml) containing AcCl (5 ml) by stirring for 10 min. To this solution was added a solution of IIId (2.6 g) in CH_2Cl_2 (17 ml) over a period of 10 min and stirred for 1 hr at room temperature. The reaction mixture was poured into cold dil. HCl and extracted with ether. The organic phase was washed with 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the crude product obtained was recrystallized from MeOH to give IV (2.1 g) as colorless needles. mp 221—225°. $[\alpha]_D^{25}$ +40.2° (c=0.14). *Anal.* Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.23; H, 7.91.

2-Methoxyestra-1,3,5(10)-triene-3,17β-diol Diacetate (Va)——To a solution of IV (370 mg) in $CHCl_3$ (2 ml) was added $C_6H_5CO_3H$–$CHCl_3$ solution (0.35M, 8 ml) and allowed to stand at room temperature for 13 days. The reaction mixture was diluted with ether, washed with 5% NaOH, H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the crude product was recrystallized from MeOH to give Va (230 mg) as colorless leaflets. mp 165.5—166.5°. $[\alpha]_D^{26}$ +44.8° (c=0.12). *Anal.* Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.55; H, 7.58. (Reported mp 165—166°, $[\alpha]_D^{26.5}$ +53°).[4a]

2-Methoxyestra-1,3,5(10)-triene-3,17β-diol (Vb)——i) A solution of Va (150 mg) dissolved in 4% methanolic NaOH was refluxed for 40 min. The resulting solution was concentrated, diluted with H_2O and acidified with dil. H_2SO_4. The solution was extracted with ether, washed with 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the crude product obtained was recrystallized from MeOH to give Vb (77 mg) as colorless prisms. mp 187—188°. The product was identical in all respects with that (mp 188—190°) prepared by Fishman's method.[4a]

ii) A solution of IXf (80 mg) dissolved in EtOH (40 ml) was shaken with 5% Pd/C (20 mg) under a stream of H_2 at room temperature for 5 hr. After removal of catalyst by filtration the filtrate was concentrated to give a crystalline product. Recrystallization from benzene gave Vb (54 mg) as colorless prisms. mp 188—191°. Mixed mp on admixture with the sample obtained in i) showed no depression.

2-Acetyl-3-hydroxyestra-1,3,5(10)-trien-17-one (VIIIb)——i) Anhydrous $AlCl_3$ (340 mg) was dissolved in $C_2H_2Cl_4$ (10 ml) by stirring at 80—90° for 10 min. To this solution was added slowly a solution of VI (300 mg) in CH_2Cl_2 (2 ml) and stirred at 120° for 45 min. The reaction mixture was poured into cold dil. HCl and extracted with ether. The organic phase was washed with 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the crude product obtained was recrystallized from MeOH to give VIIIb (163 mg) as colorless leaflets. mp 138—140°/148—150°. $[\alpha]_D^{28}$ +152.5° (c=0.10). *Anal.* Calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.39; H, 7.64.

ii) A solution of VIIIa (700 mg) in AcOH (5 ml)–48% HBr (5 ml) was heated on water-bath for 2 hr. The reaction mixture was poured into ice-water and extracted with ether. The organic phase was washed with 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the crude product obtained was recrystallized from MeOH to give VIIIb (500 mg) as colorless leaflets. mp 138—140°. Mixed mp on admixture with the sample obtained in i) showed no depression.

2-Acetyl-3-methoxyestra-1,3,5(10)-trien-17-one (VIIIa)——Anhydrous $AlCl_3$ (2.6 g) was dissolved in CS_2 (20 ml) containing AcCl (4 ml) by stirring for 1 hr. To this solution was added slowly a solution of VIIa (2 g) in CH_2Cl_2 (20 ml) and stirred for 1 hr at room temperature. The reaction mixture was poured into cold dil. HCl and extracted with ether. The organic phase was washed with 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the crude product obtained was recrystallized from MeOH to give VIIIa (1.62 g) as colorless leaflets. mp 189—190°. $[\alpha]_D^{28}$ +155.1° (c=0.11). *Anal.* Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.56; H, 7.90.

2-Acetyl-3-benzyloxyestra-1,3,5(10)-trien-17-one (VIIIc)——To a solution of VIIIb (3.4 g) in EtOH (300 ml) were added benzyl chloride (3 ml) and anhydrous K_2CO_3 (7 g) and refluxed for 7 hr. The reaction mixture was concentrated and extracted with CH_2Cl_2. The organic phase was washed with H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the crude product obtained was recrystallized from MeOH to give VIIIc (3.4 g) as colorless needles. mp 208—211°. $[\alpha]_D^{26}$ +134.1° (c=0.16). *Anal.* Calcd. for $C_{27}H_{30}O_3$: C, 80.56; H, 7.51. Found: C, 80.88; H, 7.65.

2-Hydroxy-3-benzyloxyestra-1,3,5(10)-trien-17-one Acetate (IXa)——To a solution of VIIIc (3 g) in $CHCl_3$ (15 ml) was added $C_6H_5CO_3H$–$CHCl_3$ solution (0.4M, 90 ml) and allowed to stand at room temperature for 1 week. The reaction mixture was diluted with ether, washed with cold 5% NaOH, H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the crude product obtained was recrystallized from MeOH to give IXa (2.35 g) as colorless needles. mp 162—165°. $[\alpha]_D^{25}$ +131.8° (c=0.12). *Anal.* Calcd. for $C_{27}H_{30}O_4$: C, 77.48; H, 7.23. Found: C, 77.20; H, 7.06.

2-Hydroxy-3-benzyloxyestra-1,3,5(10)-trien-17-one (IXb)——To a solution of IXa (858 mg) in MeOH (60 ml) was added 5% KOH (30 ml) and refluxed for 2.5 hr. The reaction mixture was poured into cold dil. HCl and the precipitate was collected by filtration. Recrystallization of the crude product from MeOH gave IXc (630 mg) as colorless needles. mp 210—212°. $[\alpha]_D^{25}$ +123.1° (c=0.11). *Anal.* Calcd. for $C_{25}H_{28}O_3$: C, 79.75; H, 7.50. Found: C, 79.85; H, 7.62.

2-Methoxy-3-benzyloxyestra-1,3,5(10)-trien-17-one (IXc)——To a solution of IXb (80 mg) in EtOH (30 ml) was added excess amount of CH_2N_2–ether solution and allowed to stand at 0° for 48 hr. After decomposition of excess CH_2N_2 with AcOH the resulting solution was concentrated to give a crystalline product. Recrystallization from MeOH gave IXc (72 mg) as colorless needles. mp 152—154°. $[\alpha]_D^{25}$ +135.5° (c=0.01). *Anal.* Calcd. for $C_{26}H_{30}O_3$: C, 79.96; H, 7.74. Found: C, 79.86; H, 7.91.

2-Methoxy-3-hydroxyestra-1,3,5(10)-trien-17-one (Vc)——A solution of IXc (760 mg) dissolved in EtOH (80 ml) was shaken with 5% Pd/C (200 mg) under a stream of H_2 at room temperature for 24 hr. After removal of catalyst by filtration the filtrate was concentrated to give a crystalline product. Recrystallization from MeOH gave Vc (430 mg) as colorless needles. mp 190—192°. The product was identical in all respects with that (mp 188—191°) prepared by Fishman's method.[4a]

2-Acetyl-3-methoxyestra-1,3,5(10)-trien-17β-ol Acetate (VIIId)——Anhydrous $AlCl_3$ (20 g) was dissolved in CS_2 (80 ml) containing AcCl (20 ml) by stirring for 10 min. To this solution was added slowly a solution of VIIb (12 g) in CS_2 (100 ml) over a period of 10 min and stirred for 1 hr at room temperature. The reaction mixture was poured into cold dil. HCl and extracted with ether. The organic phase was washed with 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the crude product obtained was recrystallized from MeOH to give VIIId (10.3 g) as colorless needles. mp 192—194°. $[\alpha]_D^{19}$ +63.8° (c=0.13). *Anal.* Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.55; H, 7.86.

2-Acetylestra-1,3,5(10)-triene-3,17β-diol 17-Acetate (VIIIe)——A solution of VIIId (5 g) in AcOH (120 ml)–48% HBr (80 ml) was heated on water-bath for 2 hr. The reaction mixture was poured into ice–water and extracted with ether. The organic phase was washed with 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the crude product obtained was recrystallized from MeOH to give VIIIe (3.82 g) as colorless leaflets. mp 202—204°. $[\alpha]_D^{21}$ +53.3° (c=0.24). *Anal.* Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 73.89; H, 8.03.

2-Acetyl-3-benzyloxyestra-1,3,5(10)-trien-17β-ol (VIIIf)——To a solution of VIIIe (3 g) in EtOH (200 ml) were added benzyl chloride (3 ml) and anhydrous K_2CO_3 (6 g) and refluxed for 10 hr. The resulting solution was concentrated and extracted with CH_2Cl_2. The organic phase was washed with H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the crude product obtained was recrystallized from MeOH to give VIIIf (3.05 g) as colorless needles. mp 158—160°. $[\alpha]_D^{25}$ +92.5° (c=0.12). *Anal.* Calcd. for $C_{27}H_{32}O_3$: C, 80.16; H, 7.97. Found: C, 80.30; H, 8.08.

2-Acetyl-3-benzyloxyestra-1,3,5(10)-trien-17β-ol Acetate (VIIIg)——Treatment of VIIIf (400 mg) with Ac_2O (4 ml) and pyridine (4 ml) in usual manner and recrystallization from MeOH gave VIIIg (360 mg) as colorless needles. mp 170—172°. $[\alpha]_D^{28}$ +61.3° (c=0.11). *Anal.* Calcd. for $C_{29}H_{34}O_4$: C, 77.99; H, 7.67. Found: C, 78.13; H, 7.87.

3-Benzyloxyestra-1,3,5(10)-triene-2,17β-diol Diacetate (IXd)——To a solution of VIIIg (358 mg) in $CHCl_3$ was added *m*-chloroperbenzoic acid (280 mg) and allowed to stand at room temperature for 10 days. On usual work-up a crystalline product was obtained. Recrystallization from MeOH gave IXd (241 mg) as colorless needles. mp 157—159°. $[\alpha]_D^{18}$ +40.1° (c=0.14). *Anal.* Calcd. for $C_{29}H_{34}O_5$: C, 75.30; H, 7.41. Found: C, 75.15; H, 7.00.

3-Benzyloxyestra-1,3,5(10)-triene-2,17β-diol (IXe)——A solution of IXd dissolved in MeOH–5% NaOH (2:1) was refluxed for 2.5 hr. On usual work-up a crystalline product was obtained. Recrystallization from MeOH gave IXe as colorless needles. mp 227—228°. $[\alpha]_D^{25}$ +83.8° (c=0.02). *Anal.* Calcd. for $C_{25}H_{30}O_3$: C, 79.33; H, 7.99. Found: C, 79.09; H, 7.98.

2-Methoxy-3-benzyloxyestra-1,3,5(10)-trien-17β-ol (IXf)——To a solution of IXe (220 mg) in EtOH (60 ml) was added excess amount of CH_2N_2–ether solution and allowed to stand at 0° for 48 hr. After

decomposition of excess CH_2N_2 with AcOH the resulting solution was concentrated to give a crystalline product. Recrystallization from benzene–hexane gave IXf (204 mg) as colorless needles. mp 89—90°. $[\alpha]_D^{28}$ +78° (c=0.10). *Anal.* Calcd. for $C_{26}H_{32}O_3$: C, 79.55; H, 8.22. Found: C, 79.25; H, 8.39.

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