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A Stereoselective Synthesis and Nuclear Magnetic Resonance Spectral Study of Four Epimeric 17-Hydroxy-16-ethylestranes

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Four epimeric 17-hydroxy-16-ethylestr-4-en-3-ones (**11**) having potent antiandrogenic activity were prepared stereoselectively starting from 16α-ethyl-16β,17β-diol monoacetate (**2**). The nuclear magnetic resonance spectra of the four epimers and other 16-substituted estranes and androstanes were investigated in order to elucidate the possibility for the assignment of the unknown configurations at the positions of 16 and 17. The data of the coupling constants ($J_{16,17}$) and the chemical shifts (13-methyl protons and 17-proton) can be used for the determination of the configuration at the positions of 16 and 17.

Keywords——16-substituted estrane; 16-substituted androstane; NMR-spectrometry; structure-activity relationship; antiandrogen

In a previous paper,[2] we reported that the introduction of alkyl substituent at the position of 16 in testosterone and 19-nortestosterone resulted in the considerable reduction of their androgenic activity leading to a new group of androgen antagonist. Among the 16-alkyl-testosterone and 19-nortestosterone derivatives, 17β-hydroxy-16β-ethylestr-4-en-3-one (**11a**) was found to have the most potent antiandrogenic activity with very weak side effects.[2] We interested in the structure-activity relationships and the nuclear magnetic resonance (NMR) spectra of four epimeric 17-hydroxy-16-ethylestr-4-en-3-ones. This paper describes a stereoselective synthesis of the four epimers and the possibility for the configurational assignment of 16,17-disubstituents on the basis of the NMR spectral data.

Serini reaction of *β-cis* diol monoacetate (**2**)[3] gave stereospecifically 16β-ethyl-17-oxo steroid (**3**)[4] in 95% yield. Its 16α-isomer was prepared as follows. A reductive elimination[5] of **2** with zinc in acetic acid afforded 16-ethyl-Δ^{16}-steroid (**4**) in 92% yield. Oxidation of **4** with osmium tetraoxide in ether-pyridine, after treatment of the resulting osumate with hydrogen sulfide, gave 16α,17α-dihydroxy derivative (**5**) in 96% yield. The *α-cis* diol configuration of **5** derives from the comparison of the spectral data with those of *β-cis* diol isomer (**1**),[3] coupled with the rule[6] that the preference for reagents to attack the 16,17-double bond is on the α-face. Acetylation of **5** with acetic anhydride in pyridine at 0° yielded *α-cis*-diol monoacetate (**6**). **6** was heated with zinc in toluene for 8 hr to afford stereospecifically 16α-ethyl-17-oxo steroid (**7**)[2] in 92% yield. Epimerization of a 16-ethyl-17-ketone with sulfuric acid in methanol gave a mixture of **3** and **7** in a ratio of 6:4.[7] This means that 16β-ethyl-17-ketone (**3**) is thermodynamically more stable than its 16α-isomer (**7**).

1) Location: *Juso-Honmachi, Yodogawa-ku, Osaka, 532, Japan.*
2) K. Yoshioka, G. Goto, H. Mabuchi, K. Hiraga, and T. Miki, *Chem. Pharm. Bull.* (Tokyo), **23**, 3203 (1975), and references cited therein.
3) G. Goto, K. Yoshioka, and K. Hiraga, *Tetrahedron*, **30**, 2107 (1974).
4) G. Goto, K. Yoshioka, K. Hiraga, and T. Miki, *Chem. Pharm. Bull.* (Tokyo), **21**, 1393 (1973).
5) G. Goto, *Bull. Chem. Soc. Japan*,**50**, 186 (1977).
6) L.F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, 1959, pp. 467—468.
7) The separation of the equilibration mixture was difficult due to their very close *Rf* values. The ratio of the mixture was estimated by the NMR spectra.

Reduction of **3** with sodium borohydride gave 17β-hydroxy-16β-ethyl derivative (**8a**) in good yield. When **7** was treated with sodium dihydro-bis(2-methoxyethoxy)aluminate in benzene, 17α-hydroxy-16α-ethyl isomer (**8b**) was obtained in satisfactory yield together with a small amount of 17β-hydroxy isomer (**8c**).

In addition, the preparation of the 16,17-*trans* isomers were undertaken. Treatment of **7** with sodium borohydride in methanol afforded 17β-hydroxy-16α-ethyl isomer (**8c**) in 98% yield. No trace amount of 17α-hydroxyl compound (**8b**) was detected by thin-layer chromatographic analysis. The synthesis of the remaining 17α-hydroxy-16β-ethyl isomer (**8d**) was achieved by the followings. Reaction of **4** with *m*-chloroperbenzoic acid in dichloromethane gave the desired 16α,17α-epoxy compound (**10**) as a sole product by selective epoxidation of the 16,17 double bond from the α-side. Reductive opening of the epoxide (**10**) was effected by hydrogenolysis with Raney-Ni in 1-butanol[8] at 30° to afford exclusively 17α-hydroxy-16β-ethyl isomer (**8d**)[9] in 96% yield.

Birch reduction of the four isomeric 17-hydroxy-16-ethylestranes (**8**) with lithium in ammonia-tetrahydrofuran in the presence of ethanol as a proton donnor, followed by acid hydrolysis gave the corresponding 17-hydroxy-16-ethylestr-4-en-3-ones (**11**) in good yield. The corresponding acetates (**9, 12**) were also prepared for the purpose of the NMR study.

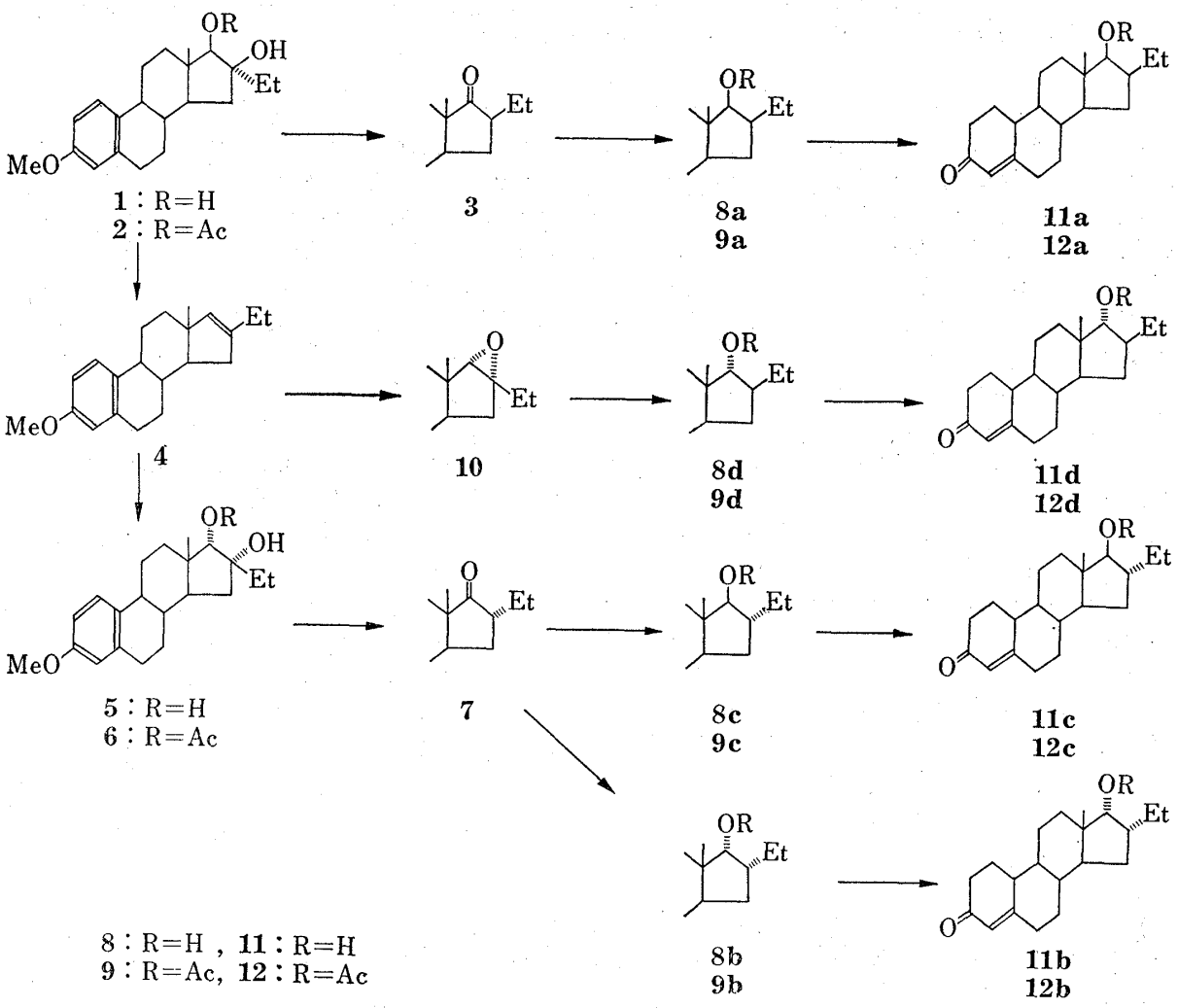
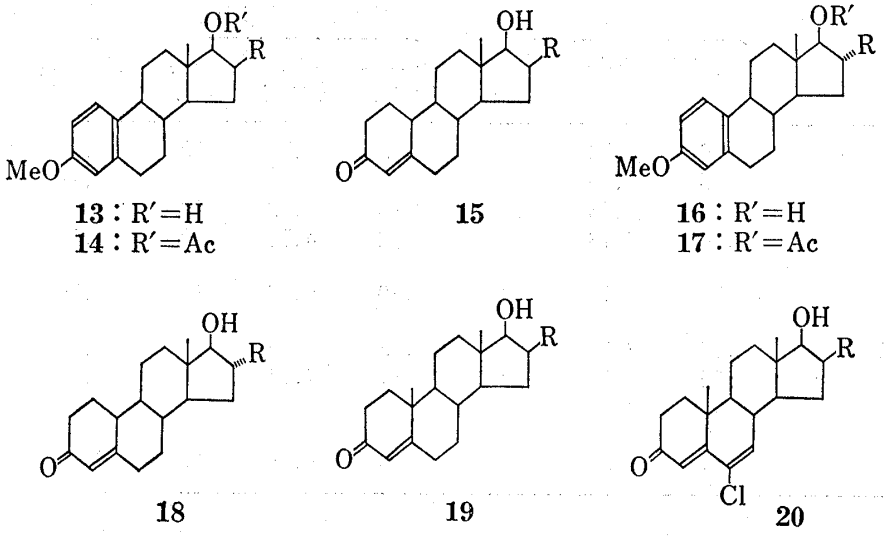


Chart 1

8) Y. Nagahisa, Y. Sugi, and S. Mitsui, *Chem. Ind.* (London), **1975**, 38.
9) H. Mori, K. Yasuda, K. Shibata, R. Oouchi, N. Yamakoshi, and K. Nakanowatari, *Japan Kokai* 50-123655.

The epimers (**11b—d**) were subjected to the biological test and found to show considerable antiandrogenic activity. It is interesting that **11a** has the most potent antiandrogenic activity than the other isomers (**11b—d**).

Introduction of substituents at the position of 16 in steroid can lead to changes in the conformation of ring D.[10] As a result, the coupling constants of 17-proton ($J_{16,17}$), the chemical shifts of 13-methyl protons and 17-proton can vary considerably according to the nature of the substituents.[11] In this connection, we investigated the NMR spectra of 16, 17-disubstituted estranes and androstanes in order to elucidate the possibility for the assignment of the unknown configuration at the positions of 16 and 17.



13 : R′=H
14 : R′=Ac

15

16 : R′=H
17 : R′=Ac

18 **19** **20**

Chart 2

TABLE I. Chemical Shifts of 13-CH_3 and 17-H and Coupling Constants of 17-H for the four Epimers of **8, 9, 11** and **12**

Configuration of substituents	Compound	13-CH_3 (ppm)	17-H (ppm)	$J_{16,17}$ (Hz)
16β, 17β	**8a**	0.75	3.70	9
	9a	0.81	4.73	10
	11a	0.77	3.64	9
	12a	0.85	4.67	10
16α, 17α	**8b**	0.79	3.68	5
	9b	0.83	4.95	5
	11b	0.80	3.64	5
	12b	0.86	4.98	5
16α, 17β	**8c**	0.78	3.23	6
	9c	0.82	4.58	7
	11c	0.83	3.21	6
	12c	0.83	4.56	7
16β, 17α	**8d**	0.72	3.43	0
	9d	0.81	4.61	1
	11d	0.75	3.42	1
	12d	0.85	4.62	1

10) A.D. Cross and P. Crabbé, *J. Am. Chem. Soc.*, **86**, 1221 (1964).
11) A.D. Cross and C. Beard, *J. Am. Chem. Soc.*, **86**, 5317 (1964).

The coupling constants of 17-proton and the chemical shifts of 13-methyl protons and 17-proton were measured in the four epimeric 17-hydroxy-16-ethylestranes (**8**, **9**, **10** and **11**) obtained above. The results are summarized in Table I. The NMR data of the other 16-substituted estranes (**13**, **14**, **15**, **16**, **17** and **18**)[12] and androstanes (**19** and **20**)[12] are given in Tables II, III and IV.

The coupling constants of 16αH-17αH (16βH-17αH) were found to be larger than those of 16βH-17βH (16αH-17βH) in spite of their similar dihedral angles. The megnitude and

Table II. Chemical Shifts of 13-CH_3 and 17-H and Coupling Constants of 17-H for 16β-Substituted Estranes (**13**, **14** and **15**)

R	Compound (**13**)			Compound (**14**)			Compound (**15**)		
	13-CH_3 (ppm)	17-H (ppm)	$J_{16,17}$ (Hz)	13-CH_3 (ppm)	17-H (ppm)	$J_{16,17}$ (Hz)	13-CH_3 (ppm)	17-H (ppm)	$J_{16,17}$ (Hz)
CH_3	0.76	3.73	9	0.82	4.71	10	0.80	3.65	9
CH_2CF_3	0.75	3.79	9	—	—	—	0.79	3.77	9
$CH{=}CH_2$	0.75	3.73	10	0.83	4.72	10	—	—	—
n-C_3H_7	0.76	3.73	9	0.82	4.76	10	0.79	3.64	10
$CH(CH_3)_2$	0.75	3.77	9	0.80	5.02	10	0.79	3.76	9
$CH_2CH{=}CH_2$	0.78	3.76	9	0.82	4.75	10	0.80	3.71	9
$CH_2CH_2CH{=}CH_2$	0.76	3.73	10	0.81	4.74	10	0.79	3.71	10
	0.76	3.83	10	—	—	—	0.79	3.76	9
C_6H_5	0.81	3.92	11	1.00	5.03	11	0.85	3.88	11

Table III. Chemical Shifts of 13-CH_3 and 17-H and Coupling Constants of 17-H for 16-α Substituted Estranes (**16**, **17** and **18**)

R	Compound (**16**)			Compound (**17**)			Compound (**18**)		
	13-CH_3 (ppm)	17-H (ppm)	$J_{16,17}$ (Hz)	13-CH_3 (ppm)	17-H (ppm)	$J_{16,17}$ (Hz)	13-CH_3 (ppm)	17-H (ppm)	$J_{16,17}$ (Hz)
CH_3	0.79	3.22	7	0.83	4.55	7	0.83	3.16	7
$CH{=}CH_2$	0.80	3.42	8	0.86	4.60	8	0.85	3.37	8
n-C_3H_7	0.77	3.27	6	0.81	4.62	7	0.84	3.17	7
$CH_2CH{=}CH_2$	0.80	3.26	6	0.83	4.63	7	0.82	3.16	7
$CH_2CH_2CH{=}CH_2$	0.80	3.29	7	0.83	4.64	7	0.82	3.22	6

Table IV. Chemical Shifts of 13-CH_3 and 17-H and Coupling Constants of 17-H for 16β-Substituted Testosterones (**19** and **20**)

R	Compound (**19**)			Compound (**20**)		
	13-CH_3 (ppm)	17-H (ppm)	$J_{16,17}$ (Hz)	13-CH_3 (ppm)	17-H (ppm)	$J_{16,17}$ (Hz)
CH_3	0.81	3.65	9	0.83	3.65	9
C_2H_5	0.77	3.64	9	0.79	3.65	10
n-C_3H_7	0.76	3.62	10	—	—	—
$CH(CH_3)_2$	0.78	3.76	9	0.83	3.81	9
C_6H_5	0.84	3.85	10	0.87	3.89	10

12) G. Goto, submitted.

the order of the coupling constants are as follows:[4] $J_{16\alpha H-17\alpha H}$=9—11 Hz, $J_{16\beta H-17\alpha H}$=6—8 Hz, $J_{16\beta H-17\beta H}$=5 Hz, $J_{16\alpha H-17\beta H}$=0—1 Hz. These data are in good agreement with those of the other steroid derivatives having 16-substituents such as deuterio,[13] hydroxyl,[14] bromo,[15] azido,[15] and acetamide[15] groups. It is worthy to note that the coupling constants of 17-proton in 16-substituted steroids show no significant variation depending on the nature of 16-substituents.

The chemical shifts of 17α-proton (17β-proton) in 17-hydroxy-16β- and 16α-substituted steroids appear around 3.6—3.9 (*ca.* 3.4) and 3.2—3.4 ppm (*ca.* 3.7 ppm), respectively. The values of δ_{13-CH_3} in 16β-substituted steroids are consistently shifted upfield by *ca.* 0.03—0.07 ppm relative to the 16α-isomers. The change from 17-hydroxyl group to 17-acetoxyl group lead to reduction of the difference in the chemical shifts between 16β- and 16α-substituted steroids.

The investigation revealed that the data of the coupling constants ($J_{16,17}$) and the chemical shifts (δ_{17-H} and δ_{13-CH_3}) may have the applicability for the determination of the unknown configurations at the positions of 16 and 17. It should be emphasized, however, that the NMR data are applicable to only steroidal ring D bearing a hydroxyl group[15,16] which is free or esterified.

Experimental[17]

16β-Ethyl-3-methoxyestra-1,3,5(10)-triene-16α,17α-diol (5)——To a solution of **4** (620 mg) in ether–pyridine (10: 1) (5 ml) was added OsO_4 (580 mg) and allowed to stand at room temperature for 2 days. To the resulting solution was added H_2S in dioxane (5%, 10 ml) and the solution was stirred for 30 min. The dark precipitate was filtered off and the filtrates were evaporated to give crude crystals. Recrystallization from ether–hexane (1: 1) gave **5** (664 mg), mp 141°. *Anal.* Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.40; H, 9.08. IR ν_{max}^{KBr} cm^{-1}: 3450, 1610. NMR δ_{ppm}: 0.81 (3H, s, 13-CH_3), 1.00 (3H, t, J=7 Hz, CH_3), 3.42 (1H, s, 17β-H), 3.74 (3H, s, OCH_3), 6.6—7.3 (3H, m, Ar). Mass Spectrum *m/e*: 330 (M^+), 312.

17α-Acetoxy-16β-ethyl-3-methoxyestra-1,3,5(10)-trien-16α-ol (6)——To a solution of **5** (735 mg) in pyridine (10 ml) was added acetic anhydride (1 ml) and allowed to stand at 0° for 12 hr. The reaction mixture was poured into water and extracted with ether. The ether layer was washed with 5% $NaHCO_3$ solution and dried over Na_2SO_4. The solvent was evaporated to give a resinous material. Recrystallization from hexane–ether (10: 1) yielded **6** (710 mg), mp 105°. *Anal.* Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.21; H, 8.55. IR ν_{max}^{KBr} cm^{-1}: 3500, 1730. NMR δ_{ppm}: 0.92 (3H, s, 13-CH_3), 2.16 (3H, s, OAc), 3.76 (3H, s, OCH_3), 4.62 (1H, s, 17β-H), 6.6—7.3 (3H, m, Ar). Mass Spectrum *m/e*: 372 (M^+), 312.

16α-Ethyl-3-methoxyestra-1,3,5(10)-trien-17-one (7)——To a solution of **6** (450 mg) in dry toluene (10 ml) was added freshly activated zinc powder (0.9 g) and the mixture was refluxed with stirring for 5 hr. The zinc was removed by filtration and the solid was washed with toluene thoroughly. The combined filtrates were evaporated under vacuum to give crude crystals. Recrystallization from hexane–ether (2: 1) afforded **7**[2] (347 mg).

16α,17α-Epoxy-16β-ethyl-3-methoxyestra-1,3,5(10)-triene (10)——To a solution of **4** (1.42 g) in CH_2Cl_2 (50 ml) was added *m*-chloroperbenzoic acid (1.2 g) and allowed to stand at room temperature for 2 hr. The solution was washed with 10% Na_2CO_3 solution and dried over Na_2SO_4. The solvent was evaporated to afford crude crystals. Recrystallization from ether gave **10** (1.23 g), mp 138—140°. *Anal.* Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.74; H, 8.96. IR ν_{max}^{KBr} cm^{-1}: 1610. NMR δ_{ppm}: 0.74 (3H, s, 13-CH_3), 0.96 (3H, t, J=7 Hz, CH_3), 3.71 (1H, s, 17β-H), 3.73 (3H, s, OCH_3), 6.6—7.3 (3H, m, Ar). Mass Spectrum *m/e*: 312 (M^+), 296.

13) *a*) J. Fishman, *J. Am. Chem. Soc.*, **87**, 3455 (1965); *b*) R. Robbiani and J. Seibl, *Helv. Chim. Acta*, **57**, 674 (1974).
14) M.G. Combe, W.A. Denny, G.D. Meakins, Y. Morisawa, and E.E. Richards, *J. Chem. Soc.* (*C*), **1971**, 2300.
15) B. Schönecker, D. Tresselt, and K. Ponsold, *Tetrahedron*, **31**, 2845 (1975).
16) The NMR studies of pregnane series, see references 10 and 11.
17) All melting points were determined on a micro hot stage apparatus and are uncorrected. Ultraviolet (UV) spectra were measured in EtOH on a Hitachi EPS-3T spectrophotometer. Infrared (IR) spectra were recorded with a Hitachi 215 spectrophotometer. NMR spectra were recorded on a Varian HA-100 (100 MHz) spectrometer using $CDCl_3$ as a solvent; chemical shifts (δ) are given in ppm relative to internal TMS. The mass spectra were determined on a Hitachi RMU-6D mass spectrometer equipped with a direct inlet system.

16β-Ethyl-3-methoxyestra-1,3,5(10)-trien-17β-ol (8a)——To a solution of **3** (4.3 g) in MeOH (60 ml) was added $NaBH_4$ (0.5 g). After stirring for 1 hr, the reaction mixture was poured into water and the crude crystals separated were taken out by filtration. Recrystallization from hexane-ether (2: 1) gave **8a** (4.2 g), mp 97°. *Anal.* Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 79.96; H, 9.83. IR ν_{max}^{KBr} cm^{-1}: 3450. NMR δ_{ppm}: 0.96 (3H, t, J=7 Hz, CH_3), 3.72 (3H, s, OCH_3), 6.6—7.3 (3H, m, Ar). Mass Spectrum *m/e*: 314 (M^+), 296, 286.

16α-Ethyl-3-methoxyestra-1,3,5(10)-trien-17α-ol (8b)——To a solution of **7** (680 mg) in dry benzene (20 ml) was added 70% benzene solution of $NaAlH_2(OCH_2CH_2OCH_3)_2$ (0.2 ml) and the mixture was stirred at room temperature for 2 hr. The excess reagent was decomposed by careful addition of H_2O. The organic layer was washed with H_2O, dried over Na_2SO_4 and evaporated to give an oily product. Separation of the mixture by preparative TLC (E. Merk) using benzene–ether (5: 1) as an eluent gave **8b**[2] (464 mg, *Rf*: 0.50), mp 98—100° and **8c** (205 mg, *Rf*: 0.31).

16α-Ethyl-3-methoxyestra-1,3,5(10)-trien-17β-ol (8c)——To a solution of **7** (1.6 g) in MeOH (30 ml) was added $NaBH_4$ (0.3 g). After stirring for 1 hr, the reaction mixture was poured into water and the crude crystals separated were taken out by filtration. Recrystallization from hexane–ether (2: 1) gave **8c** (1.45 g), mp 74°. *Anal.* Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.29; H, 9.66. IR ν_{max}^{KBr} cm^{-1}: 3450. NMR δ_{ppm}: 0.94 (3H, t, J=7 Hz, CH_3), 3.72 (3H, s, OCH_3), 6.6—7.3 (3H, m, Ar). Mass Spectrum *m/e*: 314 (M^+), 296.

16β-Ethyl-3-methoxyestra-1,3,5(10)-trien-17α-ol (8d)——**10** (1.2 g) in 1-butanol (50 ml) was hydrogenated over Raney-Ni catalyst (W-3, 0.7 g) at 30°. After H_2 absorption ceased, the catalyst was filtered off and the solvent was evaporated to give crystals. Recrystallization from hexane–ether (2: 1) afforded **8d** (1.15 g), mp 89°. *Anal.* Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.04; H, 9.52. IR ν_{max}^{KBr} cm^{-1}: 3450. NMR δ_{ppm}: 0.96 (3H, t, J=7 Hz, CH_3), 3.72 (3H, s, OCH_3), 6.6—7.3 (3H, m, Ar). Mass Spectrum *m/e*: 314 (M^+), 296.

Acetylation of **8**: Acetylation of **8** with acetic anhydride in pyridine was performed by the usual way. Recrystallization from hexane–ether (5: 1) gave **9**. The following compounds were prepared.

17β-Acetoxy-16β-ethyl-3-methoxyestra-1,3,5(10)-triene (9a)——mp 134°. *Anal.* Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.51; H, 9.01. IR ν_{max}^{KBr} cm^{-1}: 1725. NMR δ_{ppm}:0.87 (3H, t, J=7 Hz, CH_3), 2.05 (3H, s, OAc), 3.72 (3H, s, OCH_3), 6.6—7.3 (3H, m, Ar). Mass Spectrum *m/e*: 356 (M^+), 296.

17α-Acetoxy-16α-ethyl-3-methoxyestra-1,3,5(10)-triene (9b)——mp 127°. *Anal.* Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.48; H, 9.06. IR ν_{max}^{KBr} cm^{-1}: 1725. NMR δ_{ppm}: 0.86 (3H, t, J=7 Hz, CH_3), 2.06 (3H, s, OAc), 3.72 (3H, s, OCH_3), 6.6—7.3 (3H, m, Ar). Mass Spectrum *m/e*: 356 (M^+), 296.

17β-Acetoxy-16α-ethyl-3-methoxyestra-1,3,5(10)-triene (9c)——mp 114°. *Anal.* Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.60; H, 9.05. IR ν_{max}^{KBr} cm^{-1}: 1725. NMR δ_{ppm}: 0.87 (3H, t, J=7 Hz, CH_3), 2.02 (3H, s, OAc), 3.71 (3H, s, OCH_3), 6.6—7.3 (3H, m, Ar). Mass Spectrum *m/e*: 356 (M^+), 296.

17α-Acetoxy-16β-ethyl-3-methoxyestra-1,3,5(10)-triene (9d)——mp 108°. *Anal.* Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.36; H, 9.02. IR ν_{max}^{KBr} cm^{-1}: 1725. NMR δ_{ppm}: 0.93 (3H, t, J=7 Hz, CH_3), 2.04 (3H, s, OAc), 3.74 (3H, s, OCH_3), 6.6—7.3 (3H, m, Ar). Mass Spectrum *m/e*: 356 (M^+), 296.

Birch Reduction of **8**: To a solution of **8** (1.2 g) in EtOH (5 ml), tetrahydrofuran (30 ml) and liq. NH_3 (200 ml) was added Li ribbon (2.6 g) in *ca.* 0.3 g portion at −50° by appropriate dry ice-acetone cooling. After an additional 1 hr, NH_3 was evaporated in a slow stream of N_2 and the residue was extracted with ether. The extracts were washed with H_2O, dried over Na_2SO_4 and concentrated to dryness to give crude crystals. To a stirred solution of this material in MeOH (30 ml) was added 6N HCl (4 ml). After stirring for 30 min, the mixture was extracted with ether and worked up in the usual manner to give crude crystals. Recrystallization from ether gave **11** in 75—85% yield. The following compounds were prepared.

17β-Hydroxy-16β-ethylestr-4-en-3-one (11a)——mp 152—153°. *Anal.* Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.53; H, 10.01. UV λ_{max} nm (ε): 240 (16800). IR ν_{max}^{KBr} cm^{-1}: 3450, 1665, 1620. NMR δ_{ppm}: 0.88 (3H, t, J=7 Hz, CH_3), 5.80 (1H, s, 4-H). Mass Spectrum *m/e*: 302 (M^+), 284.

17α-Hydroxy-16α-ethylestr-4-en-3-one (11b)——mp 188—190°. *Anal.* Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.53; H, 9.99. UV λ_{max} nm (ε): 240 (16800). IR ν_{max}^{KBr} cm^{-1}: 3450, 1660, 1620. NMR δ_{ppm}: 1.04 (3H, t, J=7 Hz, CH_3), 5.82 (1H, s, 4-H). Mass Spectrum *m/e*: 302 (M^+), 284.

17β-Hydroxy-16α-ethylestr-4-en-3-one (11c)——mp 123°. *Anal.* Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.61; H, 10.09. UV λ_{max} nm (ε): 240 (16800). IR ν_{max}^{KBr} cm^{-1}: 3450, 1660, 1620. NMR δ_{ppm}: 0.94 (3H, t, J=7 Hz, CH_3), 5.81 (1H, s, 4-H). Mass Spectrum *m/e*: 302 (M^+), 284.

17α-Hydroxy-16β-ethylestr-4-en-3-one (11d)——mp 182°. *Anal.* Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.23; H, 9.85. UV λ_{max} nm (ε): 240 (16800). IR ν_{max}^{KBr} cm^{-1}: 3450, 1660, 1620. NMR δ_{ppm}: 0.94 (3H, t, J=7 Hz, CH_3), 5.79 (1H, s, 4-H). Mass Spectrum *m/e*: 302 (M^+), 284.

Acetylation of **11**: Acetylation of **11** with acetic anhydride in pyridine was performed by the usual way. Recrystallization from ether gave **12**. The following compounds were prepared.

17β-Acetoxy-16β-ethylestr-4-en-3-one (12a)——mp 138—140°. *Anal.* Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.44; H, 9.28. UV λ_{max} nm (ε): 240 (17000). IR ν_{max}^{KBr} cm^{-1}: 1730, 1670, 1620. NMR δ_{ppm}: 0.85 (3H, t, J=7 Hz, CH_3), 2.05 (3H, s, OAc), 5.79 (1H, s, 4-H). Mass Spectrum *m/e*: 344 (M^+), 285.

17α-Acetoxy-16α-ethylestr-4-en-3-one (12b)——mp 142—143°. *Anal.* Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.59; H, 9.35. UV λ_{max} nm (ε): 240 (17000). IR ν_{max}^{KBr} cm^{-1}: 1730, 1670, 1620. NMR δ_{ppm}:0.84 (3H, t, J=7 Hz, CH_3), 2.03 (3H, s, OAc), 5.83 (1H, s, 4-H). Mass Spectrum *m/e*: 344 (M^+), 285.

17β-Acetoxy-16α-ethylestr-4-en-3-one (12c)——mp 116°. *Anal.* Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.69; H, 9.38. UV λ_{max} nm (ε): 240 (17000). IR ν_{max}^{KBr} cm^{-1}: 1730, 1670, 1620. NMR δ_{ppm}:0.86 (3H, t, J=7 Hz, CH_3), 2.04 (3H, s, OAc), 5.82 (1H, s, 4-H). Mass Spectrum *m/e*: 344 (M^+), 285.

17α-Acetoxy-16β-ethylestr-4-en-3-one (12d)——mp 113°. *Anal.* Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.01; H, 9.33. UV λ_{max} nm (ε): 240 (17000). IR ν_{max}^{KBr} cm^{-1}: 1730, 1670, 1620. NMR δ_{ppm}: 0.93 (3H, t, J=7 Hz, CH_3), 2.03 (3H, s, OAc), 5.84 (1H, s, 4-H). Mass Spectrum *m/e*: 344 (M^+), 285.

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