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Total Synthesis of Estrone *via* Estriol Dimethyl Ether[1]

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Meerwein–Ponndorf reduction of 3-methoxy-8,14-secoestra-1,3,5(10),9,15-pentaene-14,17-dione (III) yielded a mixture of *rac*-17α- and 17β-hydroxy-3-methoxy-8,14-secoestra-1,3,5(10),9,15-pentaen-14-one (XI and XII). Cyclization of 17β-benzoate of XII gave 3,16α-dimethoxy estra-1,3,5(10),8,14-pentaen-17β-ol 17-benzoate (XV), which was further transformed to *rac*-estrone (XXI).

This report is concerned with further synthetic studies for an advantageous route to estrone.

Wendler, *et al.*[3] described synthesis of *rac*-8-isoestrone methyl ether (V) by the route shown in Chart 1, where 4-acetoxy-2-methylcyclopentane-1,3-dione (IIb) was used as one of the starting material. We had independently been performing similar work and found a novel synthesis of estrone via estriol derivatives.

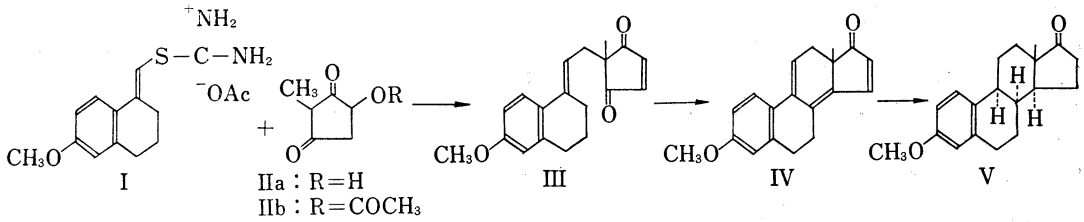


Chart 1

With 4-hydroxy-2-methylcyclopentane-1,3-dione (IIa),[4] in our case, was treated 6-methoxy-1-vinyl-1-tetralol or its isothiuronium salt (I) to obtain 3-methoxy-8,14-secoestra-1,3,5(10),9,15-pentaene-14,17-dione (III) in a yield of 68%. Cyclization of III with acid gave hexaenone (IV), which was reduced with sodium borohydride to afford the corresponding 17β-ol (VI). On catalytic hydrogenation VI was converted to *rac*-3-methoxyestra-1,3,5(10),8-tetraen-17β-ol-(VII)[5] after uptake of two moles of hydrogen. This finding let us to undertake a new route to estrogen, that is, reduction of one carbonyl group of III and cyclization of the reduced product followed by successive reduction of the double bond.

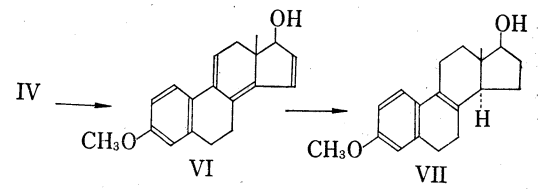
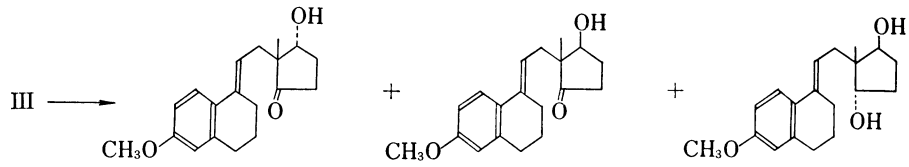


Chart 2

1) Part of this work was reported by K. Hiraga, T. Asako, and T. Miki, *Chem. Comm.*, **1969**, 1013.
2) Location: *Juso-Nishinocho, Higashiyodogawa-ku, Osaka.*
3) R.D. Hoffsomer, D. Taub, and N.L. Wendler, *J. Org. Chem.*, **32**, 3074 (1967).
4) *a*) M. Orchin and L.W. Butz, *J. Am. Chem. Soc.*, **65**, 2296 (1943); *b*) Japan. Patent, Pub., 5738 (1966).
5) P. Morand and J. Lyall, *Chem. Rev.*, **68**, 85 (1968), and references cited therein.

Reduction of a carbonyl group of III with sodium borohydride simultaneously saturated the double bond of the ring D to give *rac*-17α-hydroxy-3-methoxy-8,14-secoestra-1,3,5(10),9-tetraen-14-one[6] (VIII[7]: 53%), *rac*-17β-hydroxy analog of VIII (IX[7]: 26.5%) and *rac*-3-methoxy-8,14-secoestra-14α,17β-diol (X[8]: 8.8%).



VIII IX X

Chart 3

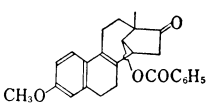
On the other hand Meerwein–Ponndorf reduction of III, *i.e.* reduction with aluminum isopropoxide and isopropyl alcohol, afforded a mixture of crystalline and oily products. The crystalline substance collected by filtration melted at 115° and showed hydroxyl and carbonyl bands at 3320 cm^{-1} and 1687 cm^{-1} in the infrared (IR) spectrum and signals of olefinic protons at 6.10 ppm (C_{15}-H) and 6.4—7.5 ppm (aromatic protons and C_{16}-H) in the nuclear magnetic resonance (NMR) spectrum. The structure of this substance was assigned to *rac*-17α-hydroxy-3-methoxy-8,14-secoestra-1,3,5(10),9,15-pentaen-14-one (XI) since this was transformed to *rac*-3-methoxyestra-1,3,5(10),8,14-pentaen-17α-ol by the successive reactions as reported in the following paper,[9] 9,14-epoxydation, reduction of the double bond at C-15 and cyclization. The oily substance obtained from the mother liquor was benzoylated to obtain the 17-benzoates, which apparently showed the presence of two products due to the difference of the configuration at C-17 on thin-layer chromatography (TLC). Therefore, we isolated the 17α-benzoate (XIII: oil) and the 17β-benzoate (XIV: mp 112°), respectively, by means of chromatographic separation on silicagel. The ratio of the 17α to the 17β isomer produced in the above reduction was found to be about 6: 4 on the basis of the yield of XI and the esters (XIII and XIV). An attempt to cyclize XIII under an acidic condition resulted in formation of resinous products.

Treatment of XIV with methanolic hydrochloric acid, however, yielded three products, *i.e.* two crystalline substances (mp 144° and mp 135°[10]) and an oily compound as a minor product. These were separated by column chromatography on silica gel. The NMR spectrum of the former substance (mp 144°) showed signals of two methoxy groups at 3.29 ppm and 3.70 ppm and one olefinic proton at 5.47 ppm as multiplet. The absorption maximum at 313 mμ in the ultraviolet (UV) spectrum indicated the presence of 3-methoxy-1,3,5(10),8,14-pentaen system in this molecule. The NMR and UV spectra of the latter (oily material) were quite similar to those of the former, showing absorptions at 3.26 (3H), 3.70 (3H) and 5.71 ppm (1H) in the NMR and absorption maximum at 312 mμ in the UV spectrum. These data show that both are cyclization products and isomers due to the difference in the configuration of methoxy group at C-16. It appeared that this reaction proceeded by attack of MeOH

6) T. Asako, K. Hiraga, and T. Miki, *Chem. Pharm. Bull.* (Tokyo), **21**, 107 (1973).

7) These compounds were converted to *rac*-3-methoxy-9,14-epoxy-8,14-secoestra-1,3,5(10)-trien-17-one[9] and *rac*-3-methoxyestra-1,3,5-(10),8,14-pentaen-17β-ol[5] with acid respectively and identified with the authentic samples.

8) Reduction of (+)-17α-hydroxy-3-methoxy-8,14-secoestra-1,3,5(10),9-tetraen-14-one[6] with sodium borohydride gave two tetraene-diol compounds, which consist of 14α,17α-diol (meso form $[\alpha]_D=0$) and 14β,-17α-diol ($[\alpha]_D=+21.1°$). On thin-layer chromatography, *Rf* value of X was the same as that of the latter.



XXVIII

9) T. Asako, K. Hiraga, and T. Miki, *Chem. Pharm. Bull.* (Tokyo), **21**, 703 (1973).

10) This compound seems to be of the structure (XXVIII) shown on the right.

at C-16 of the postulated intermediate (XVIII). The chemical shifts of the C_{13}-methyl group indicate that the former (XV: 1.02 ppm) may have a methoxy group at C-16α and the latter (XVI: 1.28 ppm) at C-16β, because crowding of the β-face of the ring D is known to cause substantial downfield shifts of angular methyl protons.[11]

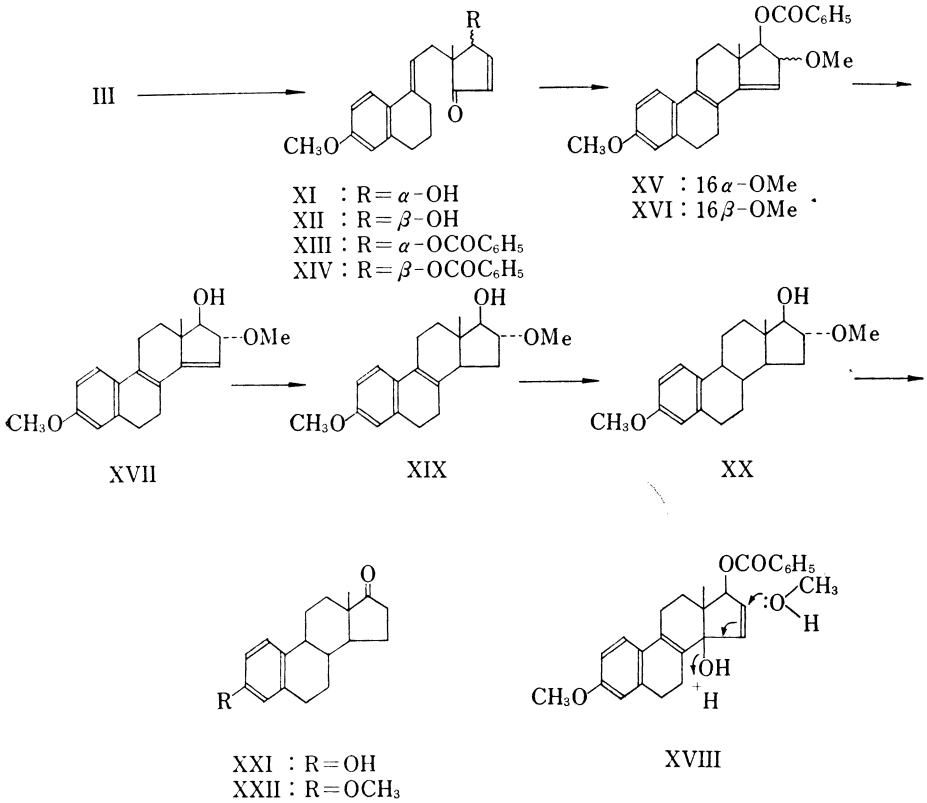


Chart 4

The structure of the former was assigned to 3,16α-dimethoxyestra-1,3,5(10),8,14-pentaen-17β-ol 17-benzoate (XV) and the latter to the corresponding 16β-methoxy compound (XVI). This assignment could be also supported by the interpretation that XV may have been obtained as a major product due to the attack of MeOH from less hindered α side.

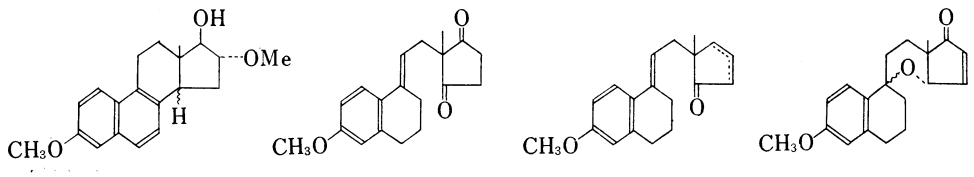
Hydrogenation of XV over Raney Ni did not proceed smoothly. Addition of the catalyst in quantities resulted in formation of an equilenine derivative[12] (XXIII) as a major product. The 16β-isomer (XVI) was also resistant to catalytic reduction, giving a result similar to XV. Whereas hydrolyzed product XVII was smoothly hydrogenated to give XIX in the yield of 70%.

Further reduction of XIX with potassium in liquid ammonia gave *rac*-estriol 3,16α-dimethyl ether (XX), which was subsequently converted into *rac*-estrone (XXI) by fusion with pyridinium chloride at 200—250°[13] and the structure was confirmed by comparison with the authentic sample. The total yield from XIX to XXI was 80%.

11) A.D. Cross and P. Crabbe, *J. Am. Chem. Soc.*, **86**, 1221 (1964).
12) *a*) S.N. Ananchenko and I.V. Torgov, *Tetrahedron Letters*, **1963**, 1553; *b*) C, Rufer. E. Schroder, and H. Gibian, *Ann. Chem.*, **705**, 211 (1967).
13) J.C. Sheehan, W.F. Erman, and P.A. Cruickshank, *J. Am. Chem. Soc.*, **79**, 147 (1957).

In the following is described another work we conducted in this field.

Treatment of III with zinc and acetic acid or hydrogenation over Raney Ni saturated the double bond at C-15 in good yield to give the diketone (XXIV). Whereas treatment of XI with zinc and acetic acid yielded *rac*-3-methoxy-8,14-secoestra-1,3,5(10),9,16-pentaen-14-one (XXV: 33%), *rac*-3-methoxy-8,14-secoestra-1,3,5(10),9,15-pentaen-14-one (XXVI: 2.5%), XXIV (3.1%) and *rac*-3-methoxy-9,14-epoxy-8,14-secoestra-1,3,5(10),15-tetraen-17-one (XXVII: 5%). The structure of XXV and XXVI was supported by the following data. The IR spectra had no absorption band ascribable to hydroxyl group but showed carbonyl bands at 1748 cm^{-1} and 1710 cm^{-1}, respectively. Further the NMR spectra displayed the signals of three olefinic protons and a UV absorption maximum characteristic to 3-methoxy-8,14-secoestra-1,3,5(10),9-tetraene system was observed at 267 mμ.



XXIII XXIV XXV : Δ^{16}-14-one XXVI : Δ^{15}-14-one XXVII

Chart 5

Experimental

3-Methoxy-8,14-secoestra-1,3,5(10),9,15-pentaene-14,17-dione (III)——A solution of 6 g of isothiuronium salt of 6-methoxy-1-vinyl-1-tetralol[3] (I) and 2.9 g of 4-hydroxy-2-methylcyclopentane-1,3-dione[4] (IIa) in 100 ml of MeOH was refluxed for 1 hr. After addition of water to this solution, the resulting mixture was extracted with ether. The ether layer was shaken with a 5% aqueous KOH solution and allowed to stand for 15 min. The ether layer was washed with water, dried over Na_2SO_4 and concentrated to yield 3.9 g of III. mp 84° (from MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3075, 1743, 1705, 1610, 1575, 1500. NMR δ ppm ($CDCl_3$): 1.20 (3H, singlet, C_{13}–CH_3), 3.76 (3H, singlet, OCH_3), 5.51 (1H, triplet, $J=7$ Hz), 7.2 (2H, singlet, C_{15} & C_{16}–H), 7.4—6.55 (3H, multiplet, aromatic H).

***rac*-3-Methoxyestra-1,3,5(10),8(14),9,15-hexaen-17β-ol (VI)**——To a solution of 1.1 g of *rac*-3-methoxyestra-1,3,5(10),8(14),9,15-hexaen-17-one (IV)[3] in 50 ml of MeOH and 50 ml of tetrahydrofuran was added $NaBH_4$ at −20° with stirring and the reaction was monitored by TLC. When the spot of IV on TLC disappeared, water was added to the reaction mixture. The resulting mixture was extracted with ether. The ether layer was washed with water, dried and concentrated to yield 0.8 g of *rac*-VI. mp 125—130° (from MeOH). UV λ_{max}^{EtOH} mμ (ε): 273 (3.3×10^4). *Anal.* Calcd. for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19. Found: C, 81.05; H, 7.20.

***rac*-3-Methoxyestra-1,3,5(10),8-tetraen-17β-ol (VII)**——A solution of 0.8 g of *rac*-VI in 50 ml of dioxane was shaken under a stream of hydrogen in the presence of 3 g of Raney Ni. After absorption of 145 ml of hydrogen catalyst was filtered off and the filtrate was concentrated to yield 0.6 g of *rac*-VII. mp 115°. This compound was identified by the comparison of mp, IR with the authentic sample.

Reduction of III with $NaBH_4$——To a solution of 1.7 g of III in 100 ml of MeOH was added 0.14 g of $NaBH_4$ at −20° with stirring. After stirring for 2 hr, water was added to this solution and the resulting mixture was extracted with ether. The ether layer was washed with water, dried over Na_2SO_4 and evaporated to yield 1.7 g of an oily material. This oily product was separated to afford 1.5 g of hydroxy ketone compound (VIII and IX) and 0.15 g of diol (X) by column chromatography on silica gel using ether–benzene (1: 9 and 1: 3). A solution of 1 g of the former (VIII and IX) in MeOH was treated with conc. HCl. After addition of water, the resulting mixture was extracted with ether and the ether layer was washed with an aqueous $NaHCO_3$ solution and water, dried and concentrated to yield 1 g of an oily material. From this oily material, 0.6 g of *rac*-3-methoxy-9,14-epoxy-8,14-secoestra-1,3,5(10)-trien-17-one and 0.3 g of *rac*-3-methoxyestra-1,3,5(10),8,14-pentaen-17β-ol were isolated by chromatographic separation. On the other hand, 0.05 g of *rac*-3-methoxy-14β,17α-dihydroxy-8,14-secoestra-1,3,5(10),9-tetraene (X) was obtained from the latter diol fraction. mp 108.5—111° (from MeOH–H_2O).

***rac*-17α-Hydroxy-3-methoxy-8,14-secoestra-1,3,5(10),9,15-pentaene-14-one (XI)**——To a solution of 0.5 g of 3-methoxy-8,14-secoestra-1,3,5(10),8,15-pentaen-14,17-dione (III) in 50 ml of iso-PrOH was added

3 g of Al(iso-PrO)$_3$. The reaction mixture was heated at 80° for 1 hr, removing acetone formed and iso-PrOH. After cooling, aqueous solution of Rochelle salt was added into the reaction mixture and the resulting solution was extracted with ether. The organic layer was washed with water, dried over Na_2SO_4 and concentrated to yield 0.5 g of an oily product. This oil was crystallized by triturating with MeOH. Recrystallization from MeOH gave 0.25 g of *rac*-XI. mp 114.5—115°. IR ν_{max}^{Nujol} cm^{-1}: 3320, 1687, 1610, 1500, 1241. UV λ_{max}^{EtOH} mμ (ε): 265 (1.78×10^4). NMR δ ppm (CCl_4): 1.12 (3H, singlet, C_{13}–CH_3), 3.66 (3H, singlet, OCH_3), 4.08 (1H, doublet, C_{17}–H), 5.70 (1H, triplet, C_{11}–H, J=7 Hz), 6.10 (1H, multiplet, C_{15}–H), 6.4—7.5 (4H, multiplet, aromatic H and C_{16}–H). *Anal.* Calcd. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.57; H, 7.51.

rac-XI could be transformed to *rac*-3-methoxyestra-1,3,5(10),8,14-pentaen-17α-ol and identified. *rac*-17β-hydroxy-3-methoxy-8,14-secoestra-1,3,5(10),9,15-pentaen-14-one (XII) was obtained as an oily material by hydrolysis of ester XIV. NMR δ ppm (CCl_4): 1.02 (3H, singlet, C_{13}–CH_3), 3.61 (3H, singlet, OCH_3), 4.54 (1H, multiplet, C_{17}–H), 5.56 (1H, triplet, C_{11}–H, J=7 Hz), 5.98 (1H, doublet, C_{15}–H, J=6 Hz), 6.3—7.4 (4H, multiplet, aromatic H and C_{16}–H).

***rac*-17α-Hydroxy-3-methoxy-8,14-secoestra-1,3,5(10),9,15-pentaen-14-one 17-Benzoate (XIII) and *rac*-17β-Hydroxy-3-methoxy-8,14-secoestra-1,3,5(10),9,15-pentaen-14-one 17-Benzoate (XIV)**——1 g of the crude oily product obtained above by Meerwein–Ponndorf reduction of III was dissolved in 20 ml of pyridine. To this solution was gradually added 1.5 g of benzoylchloride with ice-cooling and the mixture was stirred at room temperature for 2 hr and poured into water. The resulting solution was extracted with ether. Organic layer was washed with a 5% aqueous H_2SO_4 solution, a 5% aqueous $NaHCO_3$ solution and water, dried and concentrated. The oily product was chromatographed on silica gel and eluted with benzene to afford 0.4 g of *rac*-XIV as crystals. mp 110—112° (from MeOH). IR ν_{max}^{Nujol} cm^{-1}: 1713. NMR δ ppm (in CCl_4): 1.09 (3H, singlet, C_{13}–CH_3), 3.64 (3H, singlet, OCH_3), 5.55 (1H, triplet, C_{11}–H, J=7 Hz), 5.87 (1H, multiplet, C_{17}–H), 6.24 (1H, quartet, C_{15}–H, J=8 Hz), 7.3—8.02 (6H, multiplet, C_{16}–H and aromatic protons). *Anal.* Calcd. for $C_{26}H_{26}O_4$: C, 77.59; H, 6.51. Found: C, 77.57; H, 6.53. Further elution with benzene gave 0.5 g of *rac*-XIII as an oil. IR ν_{max}^{film} cm^{-1}: 1726. UV λ_{max}^{EtOH} mμ (ε): 265 (1.25×10^4). NMR δ ppm ($CDCl_3$): 1.31 (3H, singlet, C_{13}–CH_3), 3.68 (3H, singlet, OCH_3), 5.74 (1H, triplet, C_{11}–H, J=7 Hz), 5.87 (1H, multiplet, C_{17}–H), 6.32 (1H, quartet, C_{15}–H, J=6 Hz & 1 Hz), 6.4—6.66 (2H, multiplet, C_2 & C_4–H), 7.1—8.1 (7H, multiplet, C_1–H, C_{16}–H & other aromatic protons).

***rac*-17α-Acetate of XI**——mp 64.5—65.5°. IR ν_{max}^{Nujol} cm^{-1}: 1710, 1743. UV λ_{max}^{EtOH} mμ (ε): 265 (1.75×10^4). NMR δ ppm (CCl_4): 1.98 (3H, singlet, –OCOCH$_3$). *Anal.* Calcd. for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 74.49; H, 7.21.

***rac*-17β-Acetate of XII**——Oily material. IR ν_{max}^{film} cm^{-1}: 1720, 1740. NMR δ ppm (CCl_4): 2.02 (3H, singlet, –OCOCH$_3$).

***rac*-3,16α-Dimethoxyestra-1,3,5(10),8,14-pentaen-17β-ol 17-Benzoate (XV) and *rac*-3,16β-Dihydroxyestra-1,3,5(10),8,14-pentaen-17β-ol 17-Benzoate (XVI)**——1 ml of conc. HCl was added to a solution of 0.5 g of *rac*-XIV in 50 ml of MeOH and the mixture was refluxed for 15 min. After cooling, this solution was poured into water and extracted with ether. The organic layer was washed with a 5% aqueous $NaHCO_3$ solution and water, dried and concentrated. At this time, 0.1 g of crystals of mp 135°[10] was obtained. After this crystals were removed by filtration, 0.4 g of the oily residue obtained from the filtrate was chromatographed over silica gel and eluted with benzene. From first fraction, 0.08 g of the crystals of mp 135°[10] was obtained. Second fraction gave 0.15 g of *rac*-XV. mp 142—144°. IR ν_{max}^{Nujol} cm^{-1}: 1723. UV λ_{max}^{EtOH} mμ (ε): 313 (2.74×10^4). NMR δ ppm (CCl_4): 1.02 (3H, singlet, C_{13}–CH_3), 3.29 (3H, singlet, $C_{16\alpha}$–OCH_3), 3.70 (3H, singlet, C_3–OCH_3), 4.66 (1H, multiplet, $C_{16\beta}$–H), 5.17 (1H, doublet, C_{17}–H, J=6.5 Hz), 5.47 (1H, multiplet, C_{15}–H), 6.4—7.2 (3H, multiplet, protons of ring A), 7.2—8.1 (5H, aromatic protons of ester part). *Anal.* Calcd. for $C_{27}H_{28}O_4$: C, 77.86; H, 6.78. Found: C, 77.75; H, 6.44.

Mother liquor of *rac*-XV was again chromatographed on silica gel and carefully eluted with benzene. At this time, 0.04 g of *rac*-XVI was obtained as an oil showing the same *Rf* value on TLC as *rac*-XV. UV λ_{max}^{EtOH} mμ (ε): 312 (2.10×10^4). NMR δ ppm (CCl_4): 1.28 (3H, singlet, C_{13}–CH_3), 3.26 (3H, singlet, $C_{16\beta}$–OCH_3), 3.70 (3H, singlet, C_3–OCH_3), 4.28 (1H, quartet, $C_{16\alpha}$–H, J=6 Hz & 2.5 Hz), 4.81 (1H, doublet, C_{17}–H, J=6 Hz), 5.71 (1H, doublet, C_{15}–H, J=2.5 Hz).

***rac*-3,16α-Dimethoxyestra-1,3,5(10),8,14-pentaen-17β-ol (XVII)**——To a solution of 0.3 g of *rac*-XV in 8 ml of MeOH and 8 ml of tetrahydrofuran was added 4 ml of 1N KOH methanolic solution. The mixture was allowed to stand for 1.5 hr at room temperature and then poured into water. After extracting with ether, the organic layer was washed with water, dried and concentrated to afford 0.2 g of *rac*-XVII. mp 143—148°. NMR δ ppm ($CDCl_3$): 0.99 (3H, singlet, C_{13}–CH_3), 3.43 (3H, singlet, C_{16}–OCH_3), 3.73 (3H, singlet, C_3–OCH_3), 3.78 (1H, doublet, C_{17}–H, J=7 Hz), 4.37 (1H, doublet, C_{16}–H, J=7 Hz), 5.51 (1H, singlet, C_{15}–H), 6.5—7.2 (3H, multiplet, aromatic protons).

***rac*-3,16α-Dimethoxyestra-1,3,5(10),8-tetraen-17β-ol (XIX)**——A solution of 0.15 g of *rac*-XVII in 30 ml of dioxane was stirred under a stream of hydrogen over Raney Ni. After absorption of an equivalent of hydrogen, catalyst was filtered off and the filtrate was concentrated to give 0.12 g of *rac*-XIX. mp 142—144° (from AcOEt–*n*-hexane). *Anal.* Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.16; H, 8.28.

***rac*-3,16α-Dimethoxyestra-1,3,5(10)-trien-17β-ol (XX)**——To a solution of 0.3 g of *rac*-XIX in 40 ml of tetrahydrofuran and 80 ml of liq. NH_3 was added 0.7 g of potassium at −50°. The mixture was stirred for 2 hr at the same temperature. After addition of 1 g of NH_4Cl, NH_3 was removed at room temperature. Water was poured into the residue and the precipitate was extracted with ether. The organic layer was washed with water, dried and concentrated to give 0.25 g of an oily product. Recrystallization from ether–hexane of crude crystals, which were obtained by trituration with ether, afforded 0.2 g of *rac*-XX. mp 166—168°. UV λ_{max}^{EtOH} mμ (ε): 278 (1.4×10^3), 287 (1.38×10^3). *Anal.* Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: Found: C, 75.63; H, 8.75.

***rac*-Estrone (XXI) and Its 3-Methyl Ether (XXII)**——0.15 g of *rac*-XX was fused with 7 g of pyridinium chloride at 200—250° under a stream of nitrogen and allowed to stand for 1 hr. After cooling, the mixture was triturated with 30 ml of a 5% aqueous HCl solution and extracted with ether. The organic layer was extracted with a 1N aqueous NaOH solution. This alkaline aqueous layer was acidified with conc. HCl and extracted with ether. The organic layer was washed with water, dried and concentrated to give 0.1 g of *rac*-estrone (XXI). mp 240°. XXI was methylated with KOH-dimethyl sulfate to afford XXII. mp 142° (from MeOH). Comparison with authentic sample of XXII by mp showed the identity.

***rac*-3-Methoxy-8,14-secoestra-1,3,5(10),9,16-pentaen-14-one (XXV), *rac*-3-Methoxy-8,14-secoestra-1,3,5(10),9,15-pentaen-14-one (XXVI), *rac*-3-Methoxy-9,14-epoxy-8,14-secoestra-1,3,5(10),15-tetraen-17-one (XXVII)[9] and XXIV**——To a solution of 2 g of *rac*-XI in 30 ml of AcOH was added 10 g of Zn and the mixture was stirred at room temperature. After 1 hr, 12 g of Zn was added and stirring was further continued for 2 hr. Zinc was filtered off and the filtrate was poured into 300 ml of water, then extracted with ether. The organic layer was washed with a 5% aqueous $NaHCO_3$ solution and water, dried and evaporated to yield oily products, which were separated into the following four compounds by column chromatography on silica gel using *n*-hexane–benzene (1: 1) as eluant and their physical properties are shown below.

rac-XXV (0.65 g): UV λ_{max}^{EtOH} mμ (ε): 267 (1.58×10^4). IR ν_{max}^{film} cm^{-1} 1748, 1610, 1500, 1042. NMR δ ppm (CCl_4): 1.08 (3H, singlet, C_{13}–CH_3), 3.65 (3H, singlet, –OCH_3), 5.60 (1H, triplet, C_{11}–H, $J=10$ Hz), 5.94 (2H, multiplet, C_{16} & C_{17}–H). Semicarbazone of *rac*-XXV. mp 197—200°. *Anal.* Calcd. for $C_{20}H_{25}O_2N_3$: C, 70.77; H, 7.43; N, 12.38. Found: C, 70.47; H, 7.43; N, 11.77.

rac-XXVI (0.05 g): IR ν_{max}^{film} cm^{-1}: 1710, 1610, 1500, 1035. NMR δ ppm (CCl_4): 1.06 (3H, singlet, C_{13}–CH_3), 3.64 (3H, singlet, OCH_3), 5.50 (1H, triplet, C_{11}–H), 6.0 (1H, doublet, C_{15}–H), 6.3—6.6 (2H, multiplet, C_2 & C_4–H), 7.20 (1H, doublet, C_1–H), 7.43 (1H, quartet, C_{16}–H).

rac-XXVII (0.1 g): IR ν_{max}^{film} cm^{-1}: 1720, 1611, 1503. Comparison with authentic sample of *rac*-XXVII by TLC, IR, NMR showed the identity.

rac-XXIV (0.07 g): mp 73—77°. Comparison with authentic sample of *rac*-XXIV by TLC, IR, NMR showed the identity.

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