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Methylation of Catechol Estrogen with Diazomethane

MASANORI TERANISHI,*,[a] YOUICHI FUJII,[a] MITSURU YAMAZAKI[a]
and SUSUMU MIYABO[b]

*School of Pharmacy, Hokuriku University,[a] 3 Ho, Kanagawa-machi,
Kanazawa 920–11, Japan and School of Medicine, Kanazawa
University,[b] 13–1, Takara-machi, Kanazawa 920, Japan*

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Dynamic aspects of methylation of catechol estrogen with diazomethane were investigated by means of thin-layer chromatography. The methylation rate of the hydroxyl group at the C-3 position was almost the same as that of the C-2 hydroxyl group in the reaction of 2-hydroxyestrogen, and 2—3 times that of the C-4 hydroxyl group in the reaction of 4-hydroxyestrogen. In these experiments, the maximum yields of 2-methoxyestrone, 2-hydroxyestrone 3-methyl ether, 4-methoxyestrone and 4-hydroxyestrone 3-methyl ether were 32, 39, 13 and 70%, respectively. In addition, demethylation of catechol estrogen dimethyl ethers with boron tribromide and synthesis of 4-hydroxyestrone monomethyl ethers are described.

Keywords——catechol estrogen; guaiacol estrogen; 2-methoxyestrone; 4-methoxyestrone; 2-hydroxyestrone 3-methyl ether; 4-hydroxyestrone 3-methyl ether; 4-benzyloxyestrone 3-methyl ether; 4-methoxyestrone 3-benzyl ether; rate constant; thin-layer chromatography

Catechol estrogen, the major metabolite of the female sex hormone in man and other species, is physiologically potent,[1)] and a number of *in vivo* and *in vitro* experiments have demonstrated that this active substance undergoes further metabolism.[2)] Both 2- and 4-hydroxyestrogens are rapidly converted to the corresponding guaiacol estrogens by the enzyme catechol-*O*-methyltransferase.[3)] Several synthetic procedures for the preparation of guaiacol estrogens have been proposed,[4)] but are not always satisfactory with respect to the simplicity of the synthetic route. In the reaction of catechol estrogen with a methylating reagent, two isomeric monomethyl derivatives were usually obtained.[5)] In this work, we examined in detail the methylation of catechol estrogen with diazomethane (CH_2N_2), and the demethylation of its dimethyl ether with boron tribromide (BBr_3) by using thin-layer chromatography (TLC) and densitometry. Furthermore, 4-hydroxyestrogen monomethyl ethers were prepared *via* the monobenzyl ethers.

Our initial study was focused on the TLC separation of catechol estrogens and their methyl ethers on silica gel layers. When the $CHCl_3$–MeOH system was employed as a developing solvent for 2-hydroxyestrogens (I) and their derivatives II, III and IV, and the cyclohexane–AcOEt–EtOH–AcOH system for 4-hydroxyestrogens (V) and their derivatives VI, VII and VIII, the separation of these compounds was sufficiently good and reproducible to permit quantitative work (Table I).

The direct methylation of catechol estrogens with CH_2N_2 was then undertaken. The methylation of I and V with CH_2N_2 gave isomeric monomethyl ethers (II and III, VI and VII) along with dimethyl ethers (IV and VIII), respectively (Chart 1), and no other product was detected in the reaction mixture. The relative amounts of products were calculated from the peak areas on TLC (Fig. 1). The reaction of Ia gave about 32% of IIa and 39% of IIIa (maximum yields), and that of Ib gave 25% of IIb and 36% of IIIb. On the other hand, the maximum yields for VIa, VIIa, VIb and VIIb were 13, 70, 19 and 65%, respectively.

The shapes of the reaction plots reflected typical competitive and successive reaction.

Table I. Relative Response Factors and *Rf* Values of Catechol Estrogens and Their Methyl Ethers in Thin-Layer Chromatography[a] and Densitometry[b]

Compound	Relative response factor[c] At 288 nm	Relative response factor[c] At 280 nm	*Rf* Value	Developing solvent
2-Hydroxyestrone (Ia)	1.347		0.10	$CHCl_3$–MeOH (99:1)
2-Methoxyestrone (IIa)	1.068		0.66	
2-Hydroxyestrone 3-methyl ether (IIIa)	1.000		0.58	
2-Hydroxyestrone 2,3-dimethyl ether (IVa)	0.928		0.79	
4-Hydroxyestrone (Va)		1.026	0.32	Cyclohexane–AcOEt–EtOH–AcOH (70:27:2:1)
4-Methoxyestrone (VIa)		1.394	0.41	
4-Hydroxyestrone 3-methyl ether (VIIa)		1.000	0.52	
4-Hydroxyestrone 3,4-dimethyl ether (VIIIa)		1.327	0.60	
2-Hydroxyestradiol (Ib)	1.418		0.09	$CHCl_3$–MeOH (98:2)
2-Methoxyestradiol (IIb)	1.010		0.51	
2-Hydroxyestradiol 3-methyl ether (IIIb)	1.000		0.41	
2-Hydroxyestradiol 2,3-dimethyl ether (IVb)	0.909		0.63	
4-Hydroxyestradiol (Vb)		1.070	0.41	Cyclohexane–AcOEt–EtOH–AcOH (70:27:2:1) Development twice
4-Methoxyestradiol (VIb)		1.511	0.52	
4-Hydroxyestradiol 3-methyl ether (VIIb)		1.000	0.59	
4-Hydroxyestradiol 3,4-dimethyl ether (VIIIb)		1.314	0.65	

a) Adsorbent: Merck TLC plate, Silica gel 60.
b) Measuring mode: reflection-absorption photometry; scanning range: *X* 12 mm, *Y* 180 mm; chart speed: 24 mm/min.
c) Each value is relative to catechol estrogen 3-monomethyl ether within each group.

Thus, the rates can be expressed by the following equations.

$$
\begin{array}{rl}
-d[\mathrm{A}]/dt=(k_1+k_2)[\mathrm{A}][\mathrm{CH_2N_2}] & \mathrm{A}\text{: Ia, Ib, Va or Vb} \\
d[\mathrm{B}]/dt=k_1[\mathrm{A}][\mathrm{CH_2N_2}]-k_3[\mathrm{B}][\mathrm{CH_2N_2}] & \mathrm{B}\text{: IIa, IIb, VIa or VIb} \\
d[\mathrm{C}]/dt=k_2[\mathrm{A}][\mathrm{CH_2N_2}]-k_4[\mathrm{C}][\mathrm{CH_2N_2}] & \mathrm{C}\text{: IIIa, IIIb, VIIa or VIIb} \\
d[\mathrm{D}]/dt=k_3[\mathrm{B}][\mathrm{CH_2N_2}]+k_4[\mathrm{C}][\mathrm{CH_2N_2}] & \mathrm{D}\text{: IVa, IVb, VIIIa or VIIIb}
\end{array}
$$

Here, k_1 is the rate constant for the conversion from catechol estrogen to 2 (or 4)-monomethyl ether, and k_2, k_3 and k_4 correspond to the processes of conversion from catechol estrogen to 3-monomethyl ether, from 2 (or 4)-monomethyl ether to 2,3 (or 3,4)-dimethyl ether and from 3-monomethyl ether to 2,3 (or 3,4)-dimethyl ether, respectively, as shown in Chart 1. In the present study, the change in $[CH_2N_2]$ can be neglected in the above equations, because the initial concentration of CH_2N_2 was 20—50 times that of catechol estrogen. Therefore, the equations, which can be regarded as representing pseudo-first order reactions, were integrated, and then the individual rate constants were determined by the multi-lines fitting method. The values of the rate constants are compiled in Table II.

Yoshizawa and Kimura reported on the chemical reactivity of the two phenolic hydroxyl groups of 2-hydroxyestrogen.[6] They concluded that the C-2 position is more nucleophilic than the C-3 position. Our results show that the two hydroxyl groups of 2-hydroxyestrogen have the same reactivity toward CH_2N_2 and that the C-3 phenolic functional group is more reactive than the C-2 phenolic group in the methylation of guaiacol estrogens. On the other hand, in the case of 4-hydroxyestrogen, the rate constant k_2 was 2—3 times k_1 and k_3 was 10—15 times k_4. These results show that the hydroxyl group at the C-3 position is more reactive than that at the C-4 position.

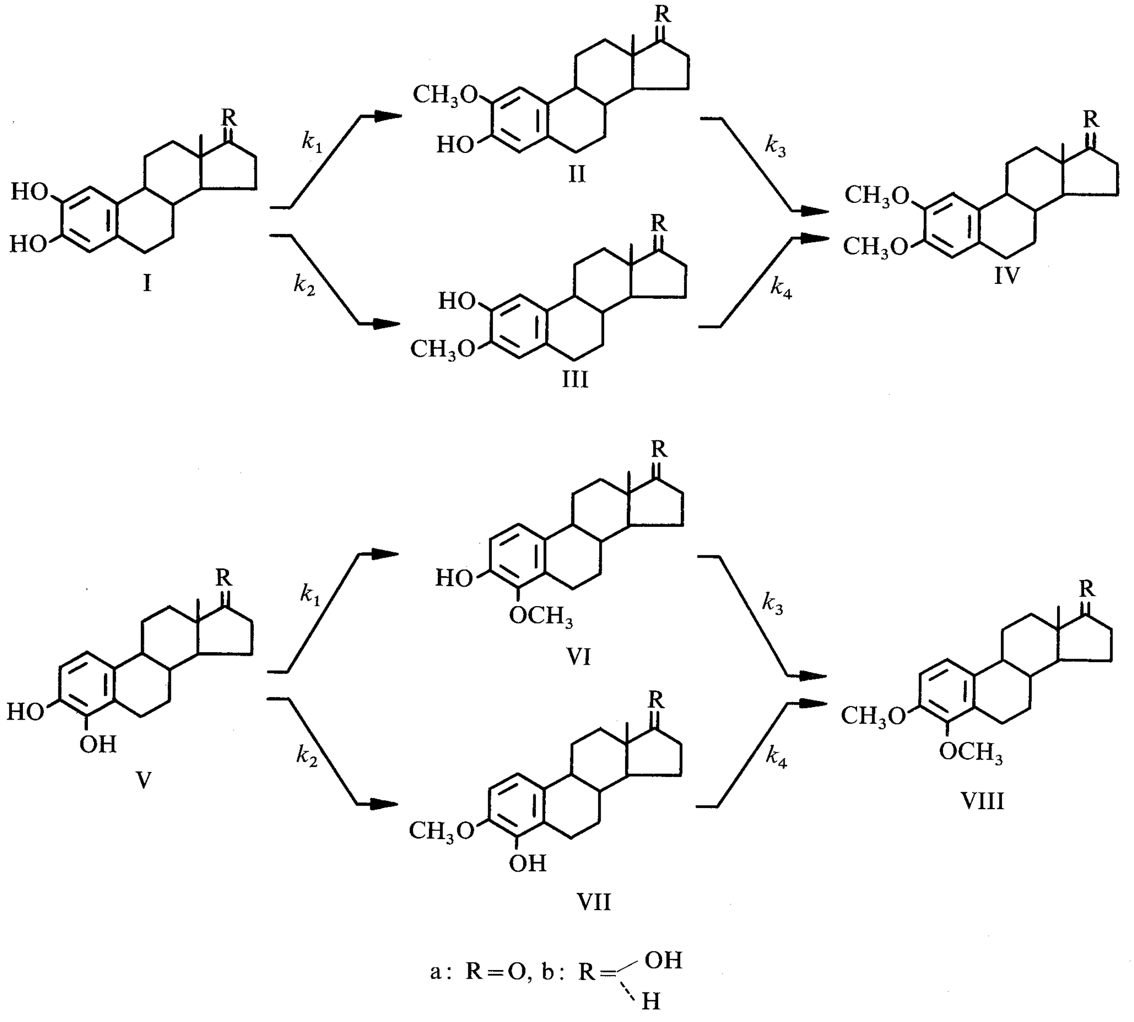


Chart 1

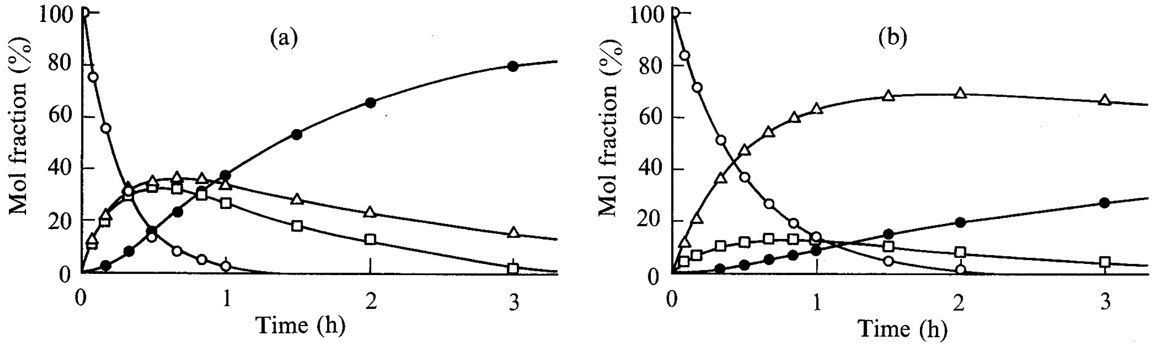


Fig. 1. Time Courses of the Methylation of (a) 2-Hydroxyestrone and (b) 4-Hydroxyestrone with Diazomethane in Ether–MeOH (2 : 1) at 30 °C

—○—, (a) Ia, (b) Va; —□—, (a) IIa, (b) VIa; —△—, (a) IIIa, (b) VIIa; —●—, (a) IVa, (b) VIIIa. Initial concentrations: (a) Ia, 2.33 mmol/l; CH_2N_2, 46.7 mmol/l; (b) Va, 2.35 mmol/l; CH_2N_2, 48.7 mmol/l. The methylation patterns of 2-hydroxyestradiol and 4-hydroxyestradiol with CH_2N_2 were similar to those of 2-hydroxyestrone and 4-hydroxyestrone, respectively.

Next, the demethylation of dimethyl ethers (IVa, VIIIa) with BBr_3 was carried out (Fig. 2). The demethylation of IVa produced similar amounts of two isomeric methyl ethers (IIa, IIIa), and that of VIIIa gave 3-monomethyl ether (VIIa) with a negligibly small amount of the other isomer (VIa). However, improvement in the yield of each monomethyl ether could

Table II. Rate Constants for the Methylation of Catechol Estrogen with Diazomethane

Compound	Rate constant[a] ($l \cdot mol^{-1} \cdot h^{-1}$)			
	k_1	k_2	k_3	k_4
Ia	44.7	45.2	19.4	11.3
Ib	19.1	24.5	16.5	9.91
Va	9.90	31.7	16.3	1.10
Vb	11.8	25.6	13.8	1.29

a) Accuracy: ±3%.

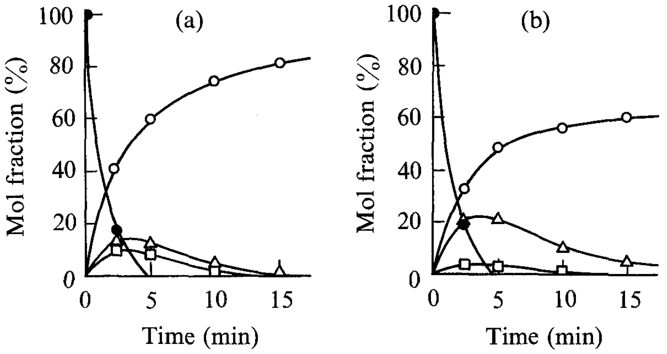
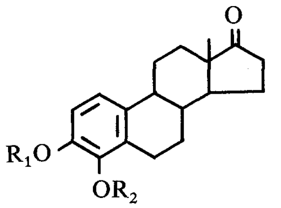


Fig. 2. Time Courses of the Demethylation of (a) 2-Hydroxyestrone 2,3-Dimethyl Ether and (b) 4-Hydroxyestrone 3,4-Dimethyl Ether with Boron Tribromide in CH_2Cl_2 at 30 °C

—○—, (a) Ia, (b) Va; —□—, (a) IIa, (b) VIa; —△—, (a) IIIa, (b) VIIa; —●—, (a) IVa, (b) VIIIa. Initial concentrations: (a) IVa, 4.1 mmol/l; BBr_3, 14.3 mmol/l; (b) VIIIa, 4.0 mmol/l; BBr_3, 14.3 mmol/l.



IXa : $R_1=CH_2C_6H_5$, $R_2=H$
IXb : $R_1=H$, $R_2=CH_2C_6H_5$
IXc : $R_1=R_2=CH_2C_6H_5$
IXd : $R_1=CH_2C_6H_5$, $R_2=CH_3$
IXe : $R_1=CH_3$, $R_2=CH_2C_6H_5$

Chart 2

not be expected owing to the difficulty of controlling the reaction.

The benzylation of Va with benzyl chloride (equivalent to steroid) gave the isomeric monobenzyl ethers (IXa, IXb) with a small amount of dibenzyl ether (IXc). The ratio of IXa to IXb was 1.3 : 1, with a slight predominance of 3-substituted derivative. Treatment of IXa and IXb with CH_2N_2 provided 4-methoxyestrone 3-benzyl ether (IXd) and 4-benzyloxyestrone 3-methyl ether (IXe), which on hydrogenolysis were led to VIa and VIIa, respectively. The total yields from Va were 25% for VIa and 21% for VIIa. In this connection, the preparation of monomethyl ethers *via* monobenzyl ethers had been proposed by Stubenrauch *et al.*,[7] but insufficient physical data were given. We present further details concerning the synthesis of 4-hydroxyestrone monomethyl ethers.

It is hoped that kinetic studies on the methylation of catechol estrogen may be useful for the synthesis of its monomethyl ethers.

Experimental

All melting points were taken on a Yanagimoto micro hot-stage apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-4 digital polarimeter in $CHCl_3$. Ultraviolet (UV) spectra were obtained with a Hitachi 323 recording spectrophotometer and infrared (IR) spectra with a JASCO DS-701G diffraction grating infrared spectrophotometer. Mass spectral (MS) measurements were run on a JEOL JMS-D 100 instrument. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded using tetramethylsilane as an internal standard on a JEOL FX-100 spectrometer at 100 MHz. The steroidal materials, Ia, Ib, Va and Vb were prepared from estrone using the procedure of Stubenrauch and Knuppen.[8] Their mono- and dimethyl ethers were synthesized by direct methylation with CH_2N_2. The structures of these methyl ethers were confirmed by the NMR data and also by alternative syntheses according to the methods of Kraychy[4a] and Nambara *et al.*[4c] TLC was performed with Merck precoated Silica gel 60 plates (10 × 20 cm) with a thickness of 0.25 mm. The steroids on a TLC plate were determined with a Shimadzu high-speed zig-zag TLC scanner (CS-920).

Separation and Determination of Steroids by TLC——A standard mixture solution of Ia, IIa, IIIa and IVa (or Ib, IIb, IIIb and IVb) was carefully prepared. Aliquots (about 10 μl) of this solution were placed on a TLC plate and developed with $CHCl_3$–MeOH (99 : 1) (or 98 : 2). After development, the TLC plate was dried at room temperature and scanned at 288 nm with a TLC scanner. Similarly, a mixture of Va, VIa, VIIa and VIIIa (or Vb, VIb, VIIb and VIIIb) was subjected to TLC using cyclohexane–AcOEt–EtOH–AcOH (70 : 27 : 2 : 1) and the spots were detected at 280 nm. The relative response factor of each steroid was determined from the recorded peak area (Table I).

Kinetic Study of the Methylation of Catechol Estrogen——The molar concentration of CH_2N_2 ether solution (redistilled twice) was determined volumetrically by adding excess benzoic acid and then titrating with 0.2 N $Ba(OH)_2$.[9] A solution of Ia (10.0 mg, 34.9 μmol) in ether (5.0 ml)–MeOH (5.0 ml) was held in a closed container at 30 ± 1 °C and methylation was started by adding CH_2N_2 ether solution (5.0 ml, 140 μmol/ml). At suitable time intervals, aliquots (about 10 μl) of the reaction mixture were subjected to TLC. The reaction products and the unchanged material were identified from the *Rf* values, and their peak areas were obtained by use of the TLC scanner. The areas were corrected by the relative response factor of each steroid, and the results were converted into mole fractions. In a similar manner, the methylations of Ib, Va and Vb with CH_2N_2 were followed as a function of time.

Time Course of the Demethylation of Catechol Estrogen Dimethyl Ether——A solution of BBr_3 (17.9 mg) in anhydrous CH_2Cl_2 (5.0 ml)[10] was added to a solution of IVa (13.0 mg) or VIIIa (13.0 mg) in anhydrous CH_2Cl_2 (5.0 ml), and the reaction mixture was allowed to stand at room temperature. The progress of the reaction was followed in the same manner as described for methylation.

Benzylation of Va——Benzyl chloride (0.42 ml) and anhydrous K_2CO_3 (2.0 g) were added to a solution of Va (1.0 g) in $CHCl_3$ (20 ml)–EtOH (150 ml), and the mixture was refluxed for 8 h. The resulting solution was concentrated and then extracted with $CHCl_3$. The organic phase was washed with H_2O and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude products were chromatographed on silica gel (110 g). Elution with cyclohexane–AcOEt–EtOH–AcOH (80 : 18 : 1 : 1) and recrystallization of the eluate from cyclohexane–CH_2Cl_2 gave 3,4-dibenzyloxy-1,3,5(10)-estratrien-17-one (IXc) (300 mg) as colorless needles. mp 111—112 °C. $[\alpha]_D^{25}$ +91.1 ° (c=0.39). *Anal.* Calcd for $C_{32}H_{34}O_3$: C, 82.37; H, 7.35. Found: C, 82.14; H, 7.33. MS *m/e*: 466 (M^+), 375 ($M^+-CH_2C_6H_5$). UV $\lambda_{max}^{CHCl_3}$ nm (ε): 277 (2140). IR ν_{max}^{KBr} cm^{-1}: 1740 (>C=O), 1490 (aromatic). ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, s, 18-CH_3), 5.02 (2H, s, 3- or 4-$OC\underline{H}_2C_6H_5$), 5.11 (2H, s, 4- or 3-$OC\underline{H}_2C_6H_5$), 6.85 (1H, d, J=8.6 Hz, 2-H), 6.99 (1H, d, J=8.6 Hz, 1-H), 7.20—7.50 (10H, m, 3- and 4-$OCH_2C_6\underline{H}_5$). Subsequent elution and recrystallization of the product from CH_2Cl_2–MeOH gave 3-benzyloxy-4-hydroxy-1,3,5(10)-estratrien-17-one (IXa) (420 mg) as colorless needles. mp 148—150 °C. $[\alpha]_D^{25}$ +111.4 ° (c=0.85). *Anal.* Calcd for $C_{25}H_{28}O_3$: C, 79.76; H, 7.50. Found: C, 79.70; H, 7.44. MS *m/e*: 376 (M^+). UV $\lambda_{max}^{CHCl_3}$ nm (ε): 281 (2130). IR ν_{max}^{KBr} cm^{-1}: 3500—3300 (–OH), 1760 (>C=O), 1490 (aromatic). ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, s, 18-CH_3), 5.08 (2H, s, $-OC\underline{H}_2C_6H_5$), 6.77 (2H, s, 1-H and 2-H), 7.30—7.45 (5H, m, $-OCH_2C_6\underline{H}_5$). These data for IXa are identical with those reported by Shimada *et al.*[11] The final eluate was rechromatographed on silica gel (50 g) using hexane–AcOEt (4 : 1) to give 4-benzyloxy-3-hydroxy-1,3,5(10)-estratrien-17-one (IXb) (330 mg) as a colorless oil. $[\alpha]_D^{25}$ +116.7 ° (c=0.29). *Anal.* Calcd for $C_{25}H_{28}O_3$: C, 79.76; H, 7.50. Found: C, 79.45; H, 7.59. MS *m/e*: 376 (M^+), 285 ($M^+-CH_2C_6H_5$). UV $\lambda_{max}^{CHCl_3}$ nm (ε): 281 (2070). IR ν_{max}^{KBr} cm^{-1}: 3500—3300 (–OH), 1730 (>C=O), 1490 (aromatic). ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, s, 18-CH_3), 4.89 (2H, d, J_{gem}=16.2 Hz, $-OC\underline{H}_2C_6H_5$), 6.79 (1H, d, J=8.5 Hz, 2-H), 6.98 (1H, d, J=8.5 Hz, 1-H), 7.30—7.50 (5H, m, $-OCH_2C_6\underline{H}_5$).

3-Benzyloxy-4-methoxy-1,3,5(10)-estratrien-17-one (IXd)——A excess amount of CH_2N_2 ether solution was added to a solution of IXa (310 mg) in CH_2Cl_2 (5 ml)–MeOH (20 ml), and the mixture was allowed to stand at room temperature for 48 h. After decomposition of excess CH_2N_2 with AcOH, the resulting solution was concentrated to give a crystalline product. Recrystallization from CH_2Cl_2–MeOH gave IXd (280 mg) as colorless leaflets. mp 117—

118 °C. $[\alpha]_D^{25}$ +106.3° (c=0.42). *Anal.* Calcd for $C_{26}H_{30}O_3$: C, 79.97; H, 7.74. Found: C, 80.17; H, 7.81. MS *m/e*: 390 (M^+), 299 ($M^+ - CH_2C_6H_5$). UV $\lambda_{max}^{CHCl_3}$ nm (ε): 277 (1380). IR ν_{max}^{KBr} cm^{-1}: 1740 (>C=O), 1490 (aromatic). ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, s, 18-CH_3), 3.86 (3H, s, -OCH_3), 5.09 (2H, s, -$OC\underline{H}_2C_6H_5$), 6.80 (1H, d, J=8.6 Hz, 2-H), 6.95 (1H, d, J=8.6 Hz, 1-H), 7.20—7.50 (5H, m, -$OCH_2C_6\underline{H}_5$).

4-Benzyloxy-3-methoxy-1,3,5(10)-estratrien-17-one (IXe)——IXb (220 mg) was treated with CH_2N_2 in the manner described for IXd. After the usual work-up, the crude product was chromatographed on silica gel (70 g) using hexane–AcOEt (5:1). The eluate was concentrated to give IXe (222 mg) as a colorless oil. $[\alpha]_D^{25}$ +99.0° (c=0.40). *Anal.* Calcd for $C_{26}H_{30}O_3$: C, 79.97; H, 7.74. Found: C, 79.60; H, 7.80. MS *m/e*: 390 (M^+), 299 ($M^+ - CH_2C_6H_5$). UV $\lambda_{max}^{CHCl_3}$ nm (ε): 278 (1860). IR ν_{max}^{KBr} cm^{-1}: 1740 (>C=O), 1490 (aromatic). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, s, 18-CH_3), 3.84 (3H, s, -OCH_3), 4.98 (2H, s, -$OC\underline{H}_2C_6H_5$), 6.79 (1H, d, J=8.6 Hz, 2-H), 7.00 (1H, d, J=8.6 Hz, 1-H), 7.20—7.56 (5H, m, -$OCH_2C_6\underline{H}_5$).

Transformation of IXd into VIa——A solution of IXd (190 mg) dissolved in CH_2Cl_2 (2 ml)–EtOH (40 ml) was shaken with 5% Pd/C (70 mg) under a stream of H_2 at room temperature for 24 h. After removal of catalyst by filtration, the filtrate was concentrated to give a crystalline product. Recrystallization from CH_2Cl_2–MeOH gave VIa (130 mg) as colorless plates. mp 222—223 °C (lit.,[4a)] 224—225 °C). Mixed mp on admixture with the sample obtained by the direct methylation of Va showed no depression, and the ^{1}H-NMR spectra of the two samples were identical.

Transformation of IXe into VIIa——Treatment of IXe (92 mg) with 5% Pd/C (40 mg) in the manner described above and recrystallization of the product from CH_2Cl_2–MeOH gave VIIa (60 mg) as colorless plates. mp 218—220 °C (lit.,[4a)] 220—224 °C). Mixed mp on admixture with the sample obtained by the direct methylation of Va showed no depression, and the ^{1}H-NMR spectra of the two samples were identical. Further, the identity of this compound was confirmed by comparison with a sample prepared by the method of Kraychy.[4a)]

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