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Synthesis of 1,2- and 2,3-Dimethoxy-4-methylestratrienes[1]

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The synthesis of 1,2- and 2,3-dimethoxy-4-methylestra-1,3,5(10)-trien-17β-ols (XIIIc, VIIIc) from androsta-1,4-diene-3,17-dione (I), which is readily available as the microbial transformation product derived from cholesterol, has been undertaken. The desired compounds could be obtained by introducing an oxygen function into 1- and 3-methoxy-4-methylestratrienes (XIc, VId) employing Friedel–Crafts reaction with acetyl chloride followed by Baeyer–Villiger oxidation as shown in Chart 1 and 2.

It has recently been found that cholesterol is transformed into C_{19}-steroids in excellent yield with loss of the side chain by the enzyme system in some microorganisms.[3] The facile availability of androsta-1,4-diene-3,17-dione (I) prompted us to obtain a new class of modified steroids utilizing this biotransformation product. As a part of this program we have attempted to prepare the methoxyestrogens, which may possibly exhibit the lipid-shifting[4] or analgesic efficacy[5,6] as the non-endocrine functions. The present paper deals with synthesis of 1,2- and 2,3-dimethoxy-4-methylestratrien-17β-ols starting from I.

In our previous paper a feasible method to introduce an acetoxyl group into the aromatic ring by Friedel–Crafts reaction and subsequent Baeyer–Villiger reaction has been reported.[7] Employing this method the preparation of the 2,3-dimethoxy derivatives from 4-methylestratrien-17β-ol acetate (II), derivable from I in three steps,[8] was first undertaken. When II was treated with acetyl chloride in the presence of anhydrous aluminum chloride, the condensation reaction proceeded to give the 3- and 2-acetyl derivatives (III, IV) in a ratio of *ca.* 1 to 3 accompanied with a small amount of the 1-acetylated isomer (V).[9] These positional isomers could be efficiently separated by preparative thin-layer chromatography (TLC). The 2-acetylated product (IV) was readily distinguishable from III and V by the inspection of the aromatic proton signal on the nuclear magnetic resonance (NMR) spectrum.

Upon exposure to *m*-chloroperbenzoic acid III underwent Baeyer–Villiger oxidation resulting in the formation of the known 4-methylestradiol diacetate (VIa) in 27% yield. The alkaline hydrolysis and subsequent methylation with dimethyl sulfate gave 4-methylestradiol 3-methyl ether (VIc) and its 17-acetate (VId). Then VId was further submitted to Friedel–Crafts reaction with acetyl chloride in the manner as described above. The chromato-

1) This paper constitutes Part I of the series entitled "Studies on Microbial Transformation Products Derived from Steroids."
2) Location: *a) Aobayama, Sendai; b) Noda-shi, Chiba.*
3) M. Nagasawa, M. Bae, G. Tamura, and K. Arima, *Agr. Biol. Chem.* (Tokyo), **33**, 1644 (1969).
4) S. Gordon, E.W. Cantrall, W.P. Cekleniak, H.J. Albers, S. Mauer, S.M. Stolar, and S. Bernstein, *Steroids*, **4**, 267 (1964).
5) L.R. Axelrod, P.N. Rao, and D.H. Baeder, *J. Am. Chem. Soc.*, **88**, 856 (1966); L.R. Axelrod and D.H. Baeder, *Proc. Soc. Exptl. Biol. Med.*, **121**, 1184 (1966).
6) D.R. VanDeripe, G.B. Hoey, W.R. Teeters, and T.W. Tusing, *J. Am. Chem. Soc.*, **88**, 5365 (1966).
7) T. Nambara, S. Honma, and S. Akiyama, *Chem. Pharm. Bull.* (Tokyo), **18**, 474 (1970).
8) M.J. Gentles, J.B. Moss, H.L. Herzog, and E.B. Hershberg, *J. Am. Chem. Soc.*, **80**, 3702 (1958).
9) Dannenberg, *et al.* have also carried out Friedel–Crafts reaction of II with acetic anhydride, whereby the 2-acetylated derivative was solely obtained (H. Dannenberg, D. Dannenberg-von Dresler, and T. Köhler, *Chem. Ber.*, **93**, 1989 (1960)).

graphic separation of the reaction product gave the expected 2-acetyl-3-methoxy-4-methylestratriene (VIIb) together with the 2-acetylated 3-hydroxy and 3-acetoxy derivatives (VIIa, VIIc). On treatment with potassium bicarbonate VIIc underwent partial hydrolysis to give VIIa. The structures of these two by-products were confirmed by leading to VIIb *via* the 3,17β-diol (VIId) and its 3-monomethyl ether (VIIe) by hydrolysis, methylation and acetylation. The position of an acetyl group newly introduced was deduced to be C-2 from the infrared (IR) spectrum of VIIa indicating the formation of the hydrogen bond. Treatment of VIIb with the per-acid afforded the 2,17-diacetate (VIIIa), which on alkaline hydrolysis and subsequent methylation was led to the desired 2,3-dimethoxy-4-methylestra-1,3,5(10)-trien-17β-ol (VIIIc) in satisfactory yield.

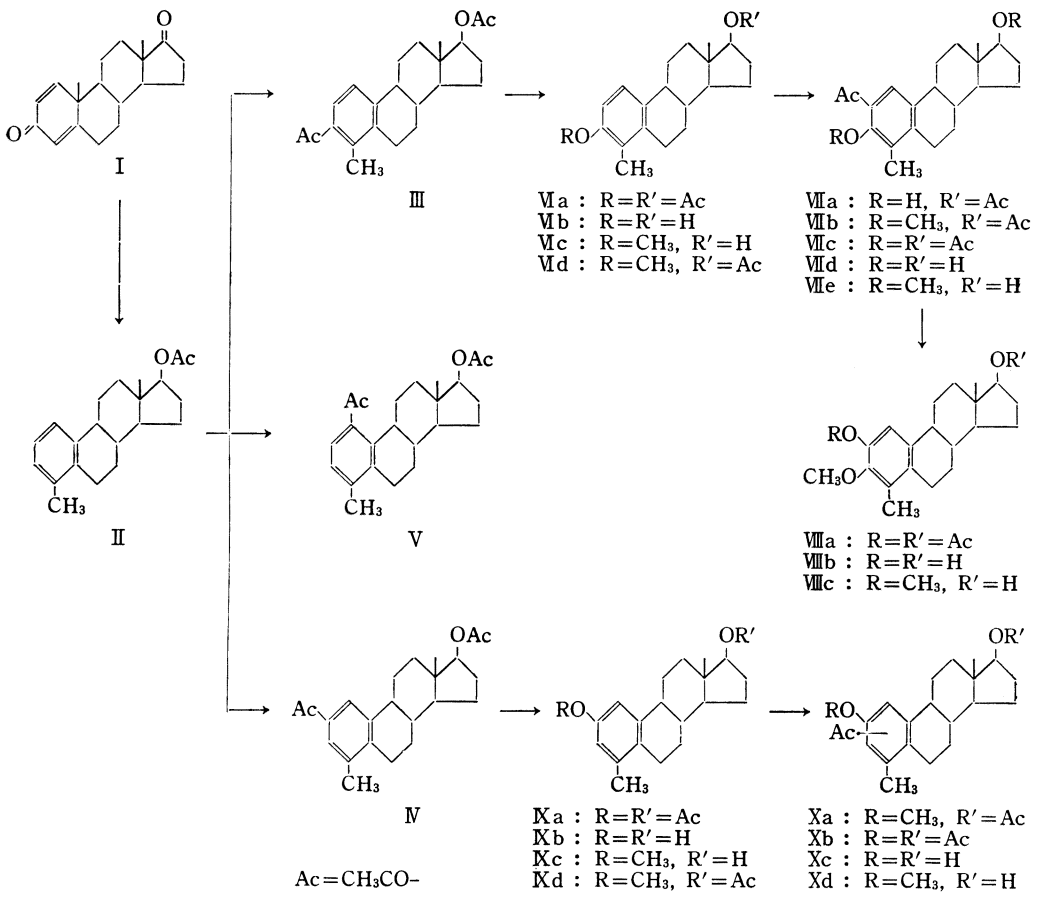

Chart 1

The second product (IV) obtained by Friedel–Crafts reaction was similarly treated with *m*-chloroperbenzoic acid yielding the 2-acetoxy derivative (IXa), which in turn was transformed into 4-methylestratriene-2,17β-diol (IXb) by alkaline hydrolysis. Methylation with dimethyl sulfate followed by the usual acetylation provided the 2-methyl ether 17-acetate (IXd). Further introduction of an acetyl group into IXd was also effected by Friedel–Crafts reaction yielding the acetyl derivatives of the 2-methyl ether and the 2,17β-diol diacetate (Xa, Xb). Correlation of these two products was rationalized by leading the latter to the former according to the above-mentioned reaction sequence. However, the position of the newly introduced acetyl group could not definitely be determined. In addition the difficulties were

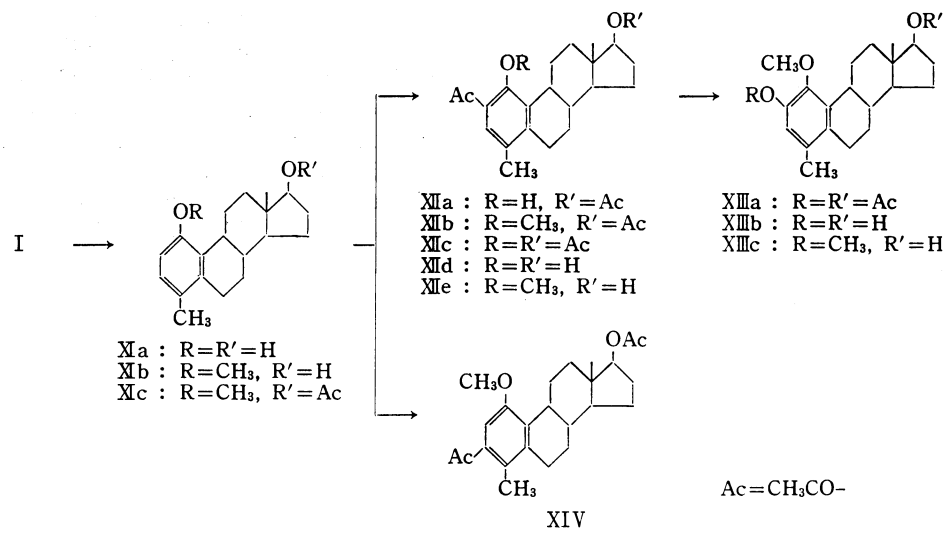

Chart 2

encountered with Baeyer–Villiger reaction with Xa presumably because the reaction center would be crowded with the neighboring substituents. With regard to the remaining 1-acetyl derivative (V) further elaboration could not be performed because of very small amount available and the inertness toward the per-acid treatment.

The next project was directed to the synthesis of the 1,2-dimethoxy derivative employing 4-methylestratriene-1,17β-diol (XIa) as a starting material obtained from I by the method of Tsuda, *et al.*[10] The Friedel–Crafts reaction with XIc under the similar conditions as mentioned above gave the 2-acetylated products (XIIa, XIIb, XIIc) together with a trace amount of the positional isomer. The mutual relationship between XIIb and XIIc was elucidated by the chemical means as usual. The orientation of the acetyl group in XIIb was elucidated to be C-2 by correlating with the 1,17β-diol 17-monoacetate (XIIa), whose IR spectrum showed the carbonyl absorption at the lower wavenumber due to the formation of the hydrogen bond. The remaining isomer was therefore unequivocally assinged to the structure 3-acetyl-1-methoxy-4-methylestratrien-17β-ol acetate (XIV). Oxidation of XIIb with *m*-chloroperbenzoic acid gave the 2,17-diacetate (XIIIa), which on hydrolysis followed by methylation was led to the desired 1,2-dimethoxy-4-methylestra-1,3,5(10)-trien-17β-ol (XIIIc) in a reasonable yield.

The results of the biological examination on dimethoxy-4-methylestratrienes thus prepared will be reported elsewhere in the near future.

Experimental[11]

Friedel-Crafts Reaction of 4-Methylestra-1,3,5(10)-trien-17β-ol Acetate (II)——Anhydrous $AlCl_3$ (2.3 g) was dissolved in CS_2 (17 ml) containing AcCl (3.4 ml) by stirring for 10 min. To this solution was added a solution of II (1.65 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

10) K. Tsuda, E. Ohki, and S. Nozoe, *J. Org. Chem.*, **28**, 783 (1963).

11) All melting points were taken on a micro hot-stage apparatus and are uncorrected. Optical rotations were measured in $CHCl_3$ unless otherwise stated. IR spectra were obtained on JASCO Model DS-403G spectrometer. NMR spectra were measured on Hitachi Model H-60 spectrometer at 60 Mc; the chemical shifts are quoted as ppm downfield from tetramethylsilane used as an internal standard. Abbreviation used s=singlet and d=doublet. TLC was carried out on Silica gel G (E. Merck AG) by the following systems: TL-I=benzene–AcOEt (10:1); TL-II=benzene–AcOEt (5:1), and *Rf* values are given.

with 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent the crude product obtained was submitted to preparative TLC using benzene–AcOEt (50: 1) as developing solvent. After multiple development the adsorbent corresponding to the most non-polar spot was eluted with AcOEt. Recrystallization of the eluate from MeOH gave 3-acetyl-4-methylestra-1,3,5(10)-trien-17β-ol acetate (III) (353 mg) as colorless prisms. mp 184—185.5°. $[\alpha]_D^{25}$+22.3° (c=0.16). *Anal.* Calcd. for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 78.15; H, 8.65. NMR (5% solution in CCl_4) δ: 0.79 (3H, s, 18-CH_3), 1.98 (3H, s, 17β-OCOCH_3), 2.23 (3H, s, 4-CH_3), 2.43 (3H, s, 3-COCH_3), 7.03 (1H, d, J=8.5 cps, 1 or 2-H), 7.23 (1H, d, J=8.5 cps, 2 or 1-H). TL-I: 0.56.

The adsorbent corresponding to the secondly polar spot was eluted with AcOEt. Recrystallization of the eluate from MeOH gave 2-acetyl-4-methylestra-1,3,5(10)-trien-17β-ol acetate (IV) (997 mg) as colorless leaflets. mp 188—189.5°. NMR (5% solution in CCl_4) δ: 0.80 (3H, s, 18-CH_3), 1.98 (3H, s, 17β-OCOCH_3), 2.23 (3H, s, 4-CH_3), 2.45 (3H, s, 2-COCH_3), 7.41 (1H, s, 1 or 3-H), 7.60 (1H, s, 3 or 1-H). TL-I: 0.49. Dannenberg, *et al.* prepared this compound by Friedel–Crafts reaction (reported: mp 188°).[9]

The adsorbent corresponding to the most polar spot was eluted with AcOEt. Recrystallization of the eluate from MeOH gave 1-acetyl-4-methylestra-1,3,5(10)-trien-17β-ol acetate (V) (82 mg) as colorless needles. mp 128—131°. $[\alpha]_D^{22}$+216.0° (c=0.15). *Anal.* Calcd. for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 77.77; H, 8.60. NMR (8% solution in CCl_4) δ: 0.80 (3H, s, 18-CH_3), 1.96 (3H, s, 17β-OCOCH_3), 2.21 (3H, s, 4-CH_3), 2.46 (3H, s, 1-COCH_3), 6.84 (1H, d, J=7 cps, 2 or 3-H), 7.09 (1H, d, J=7 cps, 3 or 2-H). TL-I: 0.44.

4-Methylestra-1,3,5(10)-triene-3,17β-diol Diacetate (VIa)——To a solution of III (858 mg) in $CHCl_3$ (45 ml) was added *m*-chloroperbenzoic acid (1 g) and allowed to stand at room temperature for 10 days. The resulting solution 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 submitted to preparative TLC using benzene–AcOEt (50: 1) as developing solvent. After multiple development the adsorbent corresponding to the spot was eluted with AcOEt. Recrystallization of the eluate from acetone–hexane gave VIa (235 mg) as colorless prisms. mp 155—157°. NMR (5% solution in CCl_4) δ: 0.79 (3H, s, 18-CH_3), 1.96 (3H, s, 17β-OCOCH_3), 2.20 (3H, s, 4-CH_3), 6.61 (1H, d, J=8.5 cps, 1 or 2-H), 7.00 (1H, d, J=8.5 cps, 2 or 1-H). TL-I: 0.58. Frei, *et al.* prepared this compound by the different method (reported: mp 153—155°).[12]

4-Methylestra-1,3,5(10)-triene-3,17β-diol (VIb)——To a solution of VIa (138 mg) in MeOH (10 ml) was added 10% KOH (4 ml) and refluxed for 1 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 usual work-up the crude product was recrystallized from MeOH to give VIb (114 mg) as colorless needles. mp 218—220°. Kaneko, *et al.* prepared this compound by the different method (reported: mp 218—223°).[13]

3-Methoxy-4-methylestra-1,3,5(10)-trien-17β-ol (VIc)——To a stirred solution of VIb (114 mg) in MeOH (8 ml)–30% KOH (2.5 ml) was added slowly Me_2SO_4 (2.5 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 acetone–hexane gave VIc (91 mg) as colorless needles. mp 168.5—170°. Johns prepared this compound by the different method (reported: mp 170—172°).[14]

3-Methoxy-4-methylestra-1,3,5(10)-trien-17β-ol Acetate (VId)——Treatment of VIc (91 mg) with Ac_2O (1 ml) and pyridine (2 ml) in the usual manner and recrystallization from MeOH gave VId (76 mg) as colorless prisms. mp 195.5—197.5°. $[\alpha]_D^{25}$+43.2° (c=0.42). *Anal.* Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.24; H, 8.95. NMR (5% solution in $CDCl_3$) δ: 0.81 (3H, s, 18-CH_3), 2.05 (3H, s, 17β-OCOCH_3), 2.11 (3H, s, 4-CH_3), 3.80 (3H, s, 3-OCH_3), 6.70 (1H, d, J=9 cps, 1 or 2-H), 7.13 (1H, d, J=9 cps, 2 or 1-H).

Friedel-Crafts Reaction of VId——Anhydrous $AlCl_3$ (330 mg) was dissolved in CS_2 (2.4 ml) containing AcCl (0.6 ml) by stirring for 10 min. To this solution was added a solution of VId (217 mg) in CH_2Cl_2 (2.4 ml) over a period of 10 min and stirred for 1 hr under ice-cooling. 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 submitted to preparative TLC using benzene–AcOEt (50: 1) as developing solvent. The adsorbent corresponding to the most non-polar spot was eluted with AcOEt. Recrystallization of the eluate from MeOH gave 2-acetyl-4-methylestra-1,3,5(10)-triene-3,17β-diol 17-acetate (VIIa) (10.3 mg) as colorless prisms. mp 224—226°. $[\alpha]_D^{25}$+31.6° (c=0.17). *Anal.* Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.29; H, 8.18. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1632 (C=O). NMR (5% solution in $CDCl_3$) δ: 0.82 (3H, s, 18-CH_3), 2.03 (3H, s, 17β-OCOCH_3), 2.09 (3H, s, 4-CH_3), 2.56 (3H, s, 2-COCH_3), 7.41 (1H, s, 1-H). TL-I: 0.68.

The adsorbent corresponding to the secondly polar spot was eluted with AcOEt. Recrystallization of the eluate from MeOH gave 2-acetyl-3-methoxy-4-methylestra-1,3,5(10)-trien-17β-ol acetate (VIIb) (156 mg)

12) J. Frei, C. Ganter, D. Kägi, K. Kocsis, M. Miljković, A. Siewinski, R. Wenger, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **49**, 1049 (1966).
13) H. Kaneko, M. Hashimoto, and A. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **12**, 196 (1964).
14) W.F. Johns, *J. Org. Chem.*, **30**, 3993 (1965).

as colorless leaflets. mp 153.5—155°. $[\alpha]_D^{22}$+53.2° (c=0.15). *Anal.* Calcd. for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 74.80; H, 8.39. NMR (4% solution in $CDCl_3$) δ: 0.83 (3H, s, 18-CH_3), 2.05 (3H, s, 17β-OCOCH_3), 2.18 (3H, s, 4-CH_3), 2.62 (3H, s, 2-COCH_3), 3.69 (3H, s, 3-OCH_3), 7.44 (1H, s, 1-H). TL-I: 0.56.

The adsorbent corresponding to the most polar spot was eluted with AcOEt. Recrystallization of the eluate from MeOH gave 2-acetyl-4-methylestra-1,3,5(10)-triene-3,17β-diol diacetate (VIIc) (37.5 mg) as colorless plates. mp 206—208°. $[\alpha]_D^{22}$+46.2° (c=0.18). *Anal.* Calcd. for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.87; H, 7.86. NMR (6% solution in $CDCl_3$) δ: 0.82 (3H, s, 18-CH_3), 2.04 (6H, s, 3- and 17β-OCOCH_3), 2.34 (3H, s, 4-CH_3), 2.50 (3H, s, 2-COCH_3), 7.57 (1H, s, 1-H). TL-I: 0.41.

Transformation of VIIc into VIIa——To a soution of VIIc (200 mg) in MeOH (40 ml) was added 4% $KHCO_3$ (8 ml) and allowed to stand at room temperature for 24 hr. The resulting solution was extracted with ether, washed with H_2O and dried over anhydrous Na_2SO_4. After usual work-up the crude product obtained was recrystallized from MeOH to give VIIa (120 mg) as colorless prisms. mp 225—226.5°. Mixed mp on admixture with the sample obtained by Friedel-Crafts reaction showed no depression and IR spectra of the two samples were entirely identical in every respect.

2-Acetyl-4-methylestra-1,3,5(10)-trien-3,17β-diol (VIId)——VIIc (170 mg) was treated with methanolic KOH in the manner as described in VIb. Recrystallization from MeOH gave VIId (132 mg) as colorless needles. mp 174—175°. $[\alpha]_D^{22}$+63.0° (c=0.30). *Anal.* Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.75; H, 8.76. NMR (5% solution in $CDCl_3$) δ: 0.77 (3H, s, 18-CH_3), 2.06 (3H, s, 4-CH_3), 2.56 (3H, s, 2-COCH_3), 7.42 (1H, s, 1-H).

2-Acetyl-3-methoxy-4-methylestra-1,3,5(10)-trien-17β-ol (VIIe)——VIId (120 mg) was treated with Me_2SO_4 (5 ml) and 30% KOH (9 ml) in MeOH (16 ml) in the manner as described in VIc. After usual work-up the crude product obtained was submitted to preparative TLC using benzene–AcOEt (25: 1) as developing solvent. The adsorbent corresponding to the spot was eluted with AcOEt to give VIIe (65 mg) as a pale yellow oil. NMR (5% solution in $CDCl_3$) δ: 0.78 (3H, s, 18-CH_3), 2.18 (3H, s, 4-CH_3), 2.63 (3H, s, 2-COCH_3), 3.70 (3H, s, 3-OCH_3), 7.49 (1H, s, 1-H). TL-I: 0.15.

Transformation of VIIe into VIIb——Treatment of VIIe (65 mg) with Ac_2O (1 ml) and pyridine (2 ml) in the usual manner and recrystallization from MeOH gave VIIb (60 mg) as colorless leaflets. mp 154—156°. Mixed mp on admixture with the sample obtained by Friedel-Crafts reaction showed no depression and IR spectra of the two samples were entirely identical in every respect.

3-Methoxy-4-methylestra-1,3,5(10)-triene-2,17β-diol Diacetate (VIIIa)——VIIb (200 mg) was treated with *m*-chloroperbenzoic acid (230 mg) in $CHCl_3$ (5.5 ml) for 9 days in the manner as described in VIa. Recrystallization from MeOH gave VIIIa (134 mg) as colorless needles. mp 188.5—190°. $[\alpha]_D^{18}$+33.4° (c=0.16). *Anal.* Calcd. for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.91; H, 8.08. NMR (5% solution in $CDCl_3$) δ: 0.81 (3H, s, 18-CH_3), 2.02 (3H, s, 17β-OCOCH_3), 2.12 (3H, s, 2-OCOCH_3), 2.29 (3H, s, 4-CH_3), 3.68 (3H, s, 3-OCH_3), 6.78 (1H, s, 1-H).

3-Methoxy-4-methylestra-1,3,5(10)-triene-2,17β-diol (VIIIb)——VIIIa (134 mg) was treated with methanolic KOH in the manner as described in VIb. Recrystallization from acetone–hexane gave VIIIb (95 mg) as colorless prisms. mp 175.5—177°. $[\alpha]_D^{18}$+60.9° (c=0.16). *Anal.* Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.80; H, 9.05. NMR (5% solution in $CDCl_3$) δ: 0.77 (3H, s, 18-CH_3), 2.11 (3H, s, 4-CH_3), 3.69 (3H, s, 3-OCH_3), 6.73 (1H, s, 1-H).

2,3-Dimethoxy-4-methylestra-1,3,5(10)-trien-17β-ol (VIIIc)——VIIIb (95 mg) was treated with Me_2SO_4 (2 ml) and 30% KOH (2 ml) in MeOH (6 ml) in the manner as described in VIc. Recrystallization from acetone–hexane gave VIIIc (83 mg) as colorless needles. mp 111.5—112.5°. $[\alpha]_D^{22}$+71.0° (c=0.20). *Anal.* Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.41; H, 9.22. NMR (4% solution in $CDCl_3$) δ: 0.78 (3H, s, 18-CH_3), 2.11 (3H, s, 4-CH_3), 3.70 (3H, s, 2 or 3-OCH_3), 3.78 (3H, s, 3 or 2-OCH_3), 6.68 (1H, s, 1-H).

4-Methylestra-1,3,5(10)-triene-2,17β-diol Diacetate (IXa)——IV (4.2 g) was treated with *m*-chloroperbenzoic acid (4.8 g) in $CHCl_3$ (60 ml) for 4 days in the manner as described in VIa. Recrystallization from acetone–hexane gave IXa (3.7 g) as colorless needles. mp 144—145°. $[\alpha]_D^{26}$+37.5° (c=0.27). *Anal.* Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.32; H, 8.21. NMR (5% solution in CCl_4) δ: 0.80 (3H, s, 18-CH_3), 1.98 (3H, s, 17β-OCOCH_3), 2.18 (6H, s, 4-CH_3 and 2-OCOCH_3), 6.60 (1H, s, 1 or 3-H), 6.72 (1H, s, 3 or 1-H). Dutler, *et al.* prepared this compound by the different method (reported: mp 141—142°).[15]

4-Methylestra-1,3,5(10)-trien-2,17β-diol (IXb)——IXa (980 mg) was treated with methanolic KOH in the manner as described in VIb. Recrystallization from MeOH gave IXb (850 mg) as colorless prisms. mp 254—256°. $[\alpha]_D^{25}$+75.5° (c=0.25, MeOH). *Anal.* Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.51; H, 9.36. Clarke prepared this compound by the different method (reported: mp 257—259°).[16]

2-Methoxy-4-methylestra-1,3,5(10)-trien-17β-ol (IXc)——IXb (100 mg) was treated with Me_2SO_4 (0.6 ml) and 30% KOH (0.6 ml) in MeOH (5 ml) in the manner as described in VIc. After usual work-up the crude

15) H. Dutler, C. Ganter, H. Ryf, E.C. Utzinger, K. Weinberg, K. Schaffner, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **45**, 2346 (1962).

16) R.L. Clarke, *J. Am. Chem. Soc.*, **84**, 467 (1962).

product obtained was recrystallized from acetone–hexane to give IXc (82 mg) as colorless needles. mp 115.5—116.5°. $[\alpha]_D^{26}$+67.8° (c=0.30). *Anal.* Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 80.10; H, 9.47. NMR (5% solution in $CDCl_3$) δ: 0.76 (3H, s, 18-CH_3), 2.19 (3H, s, 4-CH_3), 3.75 (3H, s, 2-OCH_3), 6.60 (1H, s, 1 or 3-H), 6.72 (1H, s, 3 or 1-H). Clarke prepared this compound by the different method (reported: mp 114.5—116°).[16]

2-Methoxy-4-methylestra-1,3,5(10)-trien-17β-ol Acetate (IXd)——Prepared from IXc by the method of Dannenberg, *et al.* mp 102—104° (reported: mp 104°).[9]

Friedel-Crafts Reaction of IXd——Anhydrous $AlCl_3$ (577 mg) was dissolved in CS_2 (5 ml) containing AcCl (0.9 ml) by stirring for 10 min. To this solution was added a solution of IXd (415 mg) in CH_2Cl_2 (5 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 submitted to preparative TLC using benzene–AcOEt (50: 1) as developing solvent. The adsorbent corresponding to the less polar spot was eluted with AcOEt. Recrystallization of the eluate from MeOH gave 1 (or 3)-acetyl-2-methoxy-4-methylestra-1,3,5(10)-trien-17β-ol acetate (Xa) (289 mg) as colorless needles. mp 198—200°. $[\alpha]_D^{20}$+35.4° (c=0.34). *Anal.* Calcd. for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 75.24; H, 8.62. NMR (4% solution in CCl_4) δ: 0.80 (3H, s, 18-CH_3), 1.98 (6H, s, 4-CH_3 and 17β-$OCOCH_3$), 2.31 (3H, s, 1 or 3-$COCH_3$), 3.73 (3H, s, 2-OCH_3), 6.59 (1H, s, 3 or 1-H). TL-I: 0.34.

The adsorbent corresponding to the more polar spot was eluted with AcOEt. Recrystallization of the eluate from MeOH gave 1 (or 3)-acetyl-4-methylestra-1,3,5(10)-triene-2,17β-diol diacetate (Xb) (42 mg) as colorless needles. mp 217—220°. $[\alpha]_D^{20}$+33.2° (c=0.11). *Anal.* Calcd. for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.86; H, 8.03. NMR (7% solution in $CDCl_3$) δ: 0.79 (3H, s, 18-CH_3), 2.02 (3H, s, 17β-$OCOCH_3$), 2.08 (3H, s, 2-$OCOCH_3$), 2.20 (3H, s, 4-CH_3), 2.40 (3H, s, 1 or 3-$COCH_3$), 6.83 (1H, s, 3 or 1-H). TL-I: 0.29.

Transformation of Xb into Xa——Xb was treated with methanolic KOH in the manner as described in VIb to give 1 (or 3)-acetyl-4-methylestra-1,3,5(10)-triene-2,17β-diol (Xc). Treatment of Xc with Me_2SO_4 and 30% KOH in MeOH in the manner as described in VIc gave 1 (or 3)-acetyl-2-methoxy-4-methylestra-1,3,5(10)-trien-17β-ol (Xd). Usual acetylation of Xd with Ac_2O and pyridine followed by recrystallization from MeOH gave Xa as colorless needles. mp 198.5—200°. Mixed mp on admixture with the sample obtained by Friedel-Crafts reaction showed no depression.

1-Methoxy-4-methylestra-1,3,5(10)-trien-17β-ol (XIb)——4-Methylestra-1,3,5(10)-triene-1,17β-diol (XIa)[17] (85 mg) was treated with Me_2SO_4 (3.5 ml) and 30% KOH (3.5 ml) in MeOH (8 ml) in the manner as described in VIc. After usual work-up the crude product was recrystallized from MeOH to give XIb (70 mg) as colorless needles. mp 112—114°. Dodson, *et al.* prepared this compound by the different method (reported: mp 116.5—117.5°).[18]

1-Methoxy-4-methylestra-1,3,5(10)-trien-17β-ol Acetate (XIc)——Prepared from XIb by usual acetylation with Ac_2O and pyridine. Recrystallization from MeOH gave XIc as colorless prisms. mp 146—148° (reported: mp 148.5—150°).[18]

Friedel-Crafts Reaction of XIc——Anhydrous $AlCl_3$ (480 mg) was dissolved in CS_2 (4 ml) containing AcCl (0.84 ml) by stirring for 10 min. To this solution was added a solution of XIc (297 mg) in CH_2Cl_2 (4 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 submitted to preparative TLC using benzene–AcOEt (50: 1) as developing solvent. The adsorbent corresponding to the most non-polar spot was eluted with AcOEt. Recrystallization of the eluate from MeOH gave 2-acetyl-4-methylestra-1,3,5(10)-triene-1,17β-diol 17-acetate (XIIa) (23 mg) as colorless leaflets. mp 176.5—177.5°. $[\alpha]_D^{22}$+214.1° (c=0.09). *Anal.* Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.46; H, 8.07. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1628 (C=O). NMR (5% solution in $CDCl_3$) δ: 0.85 (3H, s, 18-CH_3), 2.01 (3H, s, 17β-$OCOCH_3$), 2.16 (3H, s, 4-CH_3), 2.54 (3H, s, 2-$COCH_3$), 7.21 (1H, s, 3-H). TL-I: 0.53.

The adsorbent corresponding to the thirdly polar spot was eluted with AcOEt. Recrystallization of the eluate from MeOH gave 3-acetyl-1-methoxy-4-methylestra-1,3,5(10)-trien-17β-ol acetate (XIV) (13 mg) as colorless prisms. mp 102.5—103.5°. $[\alpha]_D^{22}$+149.7° (c=0.14). *Anal.* Calcd. for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 75.16; H, 8.51. NMR (4% solution in $CDCl_3$) δ: 0.82 (3H, s, 18-CH_3), 1.99 (3H, s, 17β-$OCOCH_3$), 2.21 (3H, s, 4-CH_3), 2.49 (3H, s, 3-$COCH_3$), 3.72 (3H, s, 1-OCH_3), 6.71 (1H, s, 2-H). TL-I: 0.42.

The adsorbent corresponding to the secondly polar spot was eluted with AcOEt. Recrystallization of the eluate from MeOH gave 2-acetyl-1-methoxy-4-methylestra-1,3,5(10)-trien-17β-ol acetate (XIIb) (151 mg) as colorless needles. mp 139—140.5°. $[\alpha]_D^{20}$+107.2° (c=0.21). *Anal.* Calcd. for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 74.95; H, 8.49. NMR (5% solution in CCl_4) δ: 0.82 (3H, s, 18-CH_3), 1.98 (3H, s, 17β-$OCOCH_3$), 2.16 (3H, s, 4-CH_3), 2.47 (3H, s, 2-$COCH_3$), 3.60 (3H, s, 1-OCH_3), 7.08 (1H, s, 3-H). TL-I: 0.38.

17) E. Caspi, E. Cullen, and P.K. Grover, *J. Chem. Soc.*, **1963**, 212.
18) R.M. Dodson and R.D. Muir, *J. Am. Chem. Soc.*, **80**, 5004 (1958); **83**, 4627 (1961).

The adsorbent corresponding to the most polar spot was eluted with AcOEt. Recrystallization of the eluate from MeOH gave 2-acetyl-4-methylestra-1,3,5(10)-triene-1,17β-diol diacetate (XIIc) (43 mg) as colorless plates. mp 147.5—149°. $[\alpha]_D^{23}$+153.5° (c=0.27). *Anal.* Calcd. for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.95; H, 7.74. NMR (5% solution in $CDCl_3$) δ: 0.84 (3H, s, 18-CH_3), 2.02 (3H, s, 17β-OCOCH_3), 2.22 (3H, s, 1-OCOCH_3), 2.28 (3H, s, 4-CH_3), 2.48 (3H, s, 2-COCH_3), 7.31 (1H, s, 3-H). TL-I: 0.24.

Transformation of XIIc into XIIa——Treatment of XIIc (131 mg) with 4% $KHCO_3$ (6 ml)–MeOH (30 ml) in the manner as described in VIIa. After usual work-up the crude product obtained was recrystallized from MeOH to give XIIa (90 mg) as colorless leaflets. mp 177—178°. Mixed mp on admixture with the sample obtained by Friedel–Crafts reaction showed no depression and IR spectra of the two samples were entirely identical in every respect.

2-Acetyl-4-methylestra-1,3,5(10)-triene-1,17β-diol (XIId)——XIIc (141 mg) was treated with methanolic KOH in the manner as described in VIb. Recrystallization from acetone–hexane gave XIId (95 mg) as colorless prisms. mp 195—196°. $[\alpha]_D^{24}$+246.1° (c=0.09). *Anal.* Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.52; H, 8.83. NMR (5% solution in $CDCl_3$) δ: 0.80 (3H, s, 18-CH_3), 2.17 (3H, s, 4-CH_3), 2.56 (3H, s, 2-COCH_3), 7.29 (1H, s, 3-H).

2-Acetyl-1-methoxy-4-methylestra-1,3,5(10)-trien-17β-ol (XIIe)——XIId (102 mg) was treated with Me_2SO_4 (11 ml) and 30% KOH (18 ml) in MeOH (18 ml) in the manner as described in VIc. After usual work-up the crude product obtained was submitted to preparative TLC using benzene–AcOEt (25: 1) as developing solvent. The adsorbent corresponding to the main spot was eluted with AcOEt. Recrystallization of the eluate from MeOH gave XIIe (37 mg) as colorless needles. mp 189.5—190.5°. $[\alpha]_D^{23}$+132.9° (c=0.15). *Anal.* Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 76.98; H, 8.94. NMR (5% solution in $CDCl_3$) δ: 0.81 (3H, s, 18-CH_3), 2.19 (3H, s, 4-CH_3), 2.60 (3H, s, 2-COCH_3), 3.68 (3H, s, 1-OCH_3), 7.28 (1H, s, 3-H). TL-II: 0.46.

Transformation of XIIe into XIIb——Treatment of XIIe (18 mg) with Ac_2O (1 ml) and pyridine (2 ml) in the usual manner and recrystallization from MeOH gave XIIb (12 mg) as colorless needles. mp 138.5—140.5°. Mixed mp on admixture with the sample obtained by Friedel–Crafts reaction showed no depression and IR spectra of the two samples were entirely identical in every respect.

1-Methoxy-4-methylestra-1,3,5(10)-triene-2,17β-diol Diacetate (XIIIa)——XIIb (200 mg) was treated with *m*-chloroperbenzoic acid (230 mg) in $CHCl_3$ (5.5 ml) for 6 days in the manner as described in VIa. Recrystallization from MeOH gave XIIIa (157 mg) as colorless needles. mp 150.5—152°. $[\alpha]_D^{18}$+138.9° (c=0.22). *Anal.* Calcd. for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 72.05; H, 8.21. NMR (5% solution in CCl_4) δ: 0.82 (3H, s, 18-CH_3), 1.95 (3H, s, 17β-OCOCH_3), 2.10 (3H, s, 2-OCOCH_3), 2.18 (3H, s, 4-CH_3), 3.51 (3H, s, 1-OCH_3), 6.49 (1H, s, 3-H).

1-Methoxy-4-methylestra-1,3,5(10)-triene-2,17β-diol (XIIIb)——XIIIa (158 mg) was treated with methanolic KOH in the manner as described in VIb. Recrystallization from acetone–hexane gave XIIIb (120 mg) as colorless needles. mp 177—179°. $[\alpha]_D^{21}$+149.9° (c=0.18). *Anal.* Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.09; H, 9.17. NMR (5% solution in $CDCl_3$) δ: 0.79 (3H, s, 18-CH_3), 2.10 (3H, s, 4-CH_3), 3.61 (3H, s, 1-OCH_3), 6.57 (1H, s, 3-H).

1,2-Dimethoxy-4-methylestra-1,3,5(10)-trien-17β-ol (XIIIc)——XIIIb (33 mg) was treated with Me_2SO_4 (1 ml) and 30% KOH (1 ml) in MeOH (5 ml) in the manner as described in VIc. Recrystallization from acetone–hexane gave XIIIc (25 mg) as colorless needles. mp 97—98°. $[\alpha]_D^{24}$+136.1° (c=0.24). *Anal.* Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.25; H, 9.24. NMR (5% solution in $CDCl_3$) δ: 0.80 (3H, s, 18-CH_3), 2.17 (3H, s, 4-CH_3), 3.71 (3H, s, 1 or 2-OCH_3), 3.79 (3H, s, 2 or 1-OCH_3), 6.62 (1H, s, 3-H).