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Bile Acids and Steroids. XXXV.[1] Some A-Ring Aromatic Steroids having Oxygen Functions at C-16 and Their Pharmacological Activities. (1)

KATSUO SASAKI, TOMOKO IMAI, HITOSHI MINATO and KEN'ICHI TAKEDA

Shionogi Research Laboratory, Shionogi & Co., Ltd.[2]

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In order to achieve the desired separation of cholesterol-lowering and estrogenic effect, some A-ring aromatic 16-keto steroids were synthesised. All of these compounds lacked estrogenic effect and their lipid-shifting activities were also weak.

It is known that in general A-ring aromatic steroids have an estrogenic effect as well as cholesterol-lowering activity, and it has been the purpose of a number of studies to find compounds which have only cholesterol-lowering activity. Although it is very difficult to achieve the desired separation of the two effects, estra-1,3,5(10)-trien-17-one (I) is actually used medicinally as a cholesterol-lowering agent.

Kondo and Mitsugi[3] in our laboratory have reported a new method for converting diosgenone into androsta-1,4-diene-3,16-dione (II) in one step by micro organisms. Even if the A-ring of the 16-keto steroid (II) were aromatised, the product would be expected to lack or have a very weak estrogenic effect. Moreover Goldkamp, *et al.*[4] reported that removal of the hydroxy group of estrone reduces both the estrogenic and lipid-shifting effects of this substance.

Therefore, in order to investigate whether A-ring aromatic 16-oxygenated steroids have cholesterol-lowering activity; and whether they lack altogether, or have only a very weak estrogenic effect, the following compounds were synthesised. Firstly, some phenol derivatives; and secondly, derivatives having either methyl substituents or no substituent in the A-ring, were synthesised from the 16-keto steroid (II). For these syntheses, the well-known dienone-phenol[5] and dienol-benzene rearrangements[6] were used.

3-Hydroxyestra-1,3,5(10)-trien-16-one (IV), mp 246°, was obtained through the ethylene ketal (III) by Kondo's method.[3]

3-Hydroxy-1-methylestra-1,3,5(10)-trien-16-one (V), mp 265°, and 1-hydroxy-4-methyl-estra-1,3,5(10)-trien-16-one (VIa), mp 297°, were obtained in a ratio of *ca.* 1:1.3 by treatment of II with 47% hydrobromic acid[7] at 55—65° for 6 hr. Treatment of a solution of II in acetic anhydride with 5% zinc chloride-acetic acid[8] at room temperature gave the acetate (VIb), mp 169—170°, of VIa in a quantitative yield. Moreover, when II was heated under reflux with zinc dust[9] in pyridine for 40 hr, it also afforded compound (VIa). Its methyl ether (VIc) was obtained as crystals, mp 190—192°, by methylation with dimethyl sulphate in an alkali

1) Part XXXIV: K. Takeda, T. Komeno, S. Ishihara, and H. Itani, *Chem. Pharm. Bull.* (Tokyo), **14**, 1096 (1966).
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3) E. Kondo and T. Mitsugi, *J. Am. Chem. Soc.*, **88**, 4737 (1966).
4) A.H. Goldkamp, W.M. Hoehn, R.A. Mikulee, E.F. Nutting, and D.L. Cook, *J. Med. Chem.*, **8**, 409 (1965).
5) C. Djerassi, "Steroid Reactions," Holden-Day, Inc., San Francisco, 1963, p. 373.
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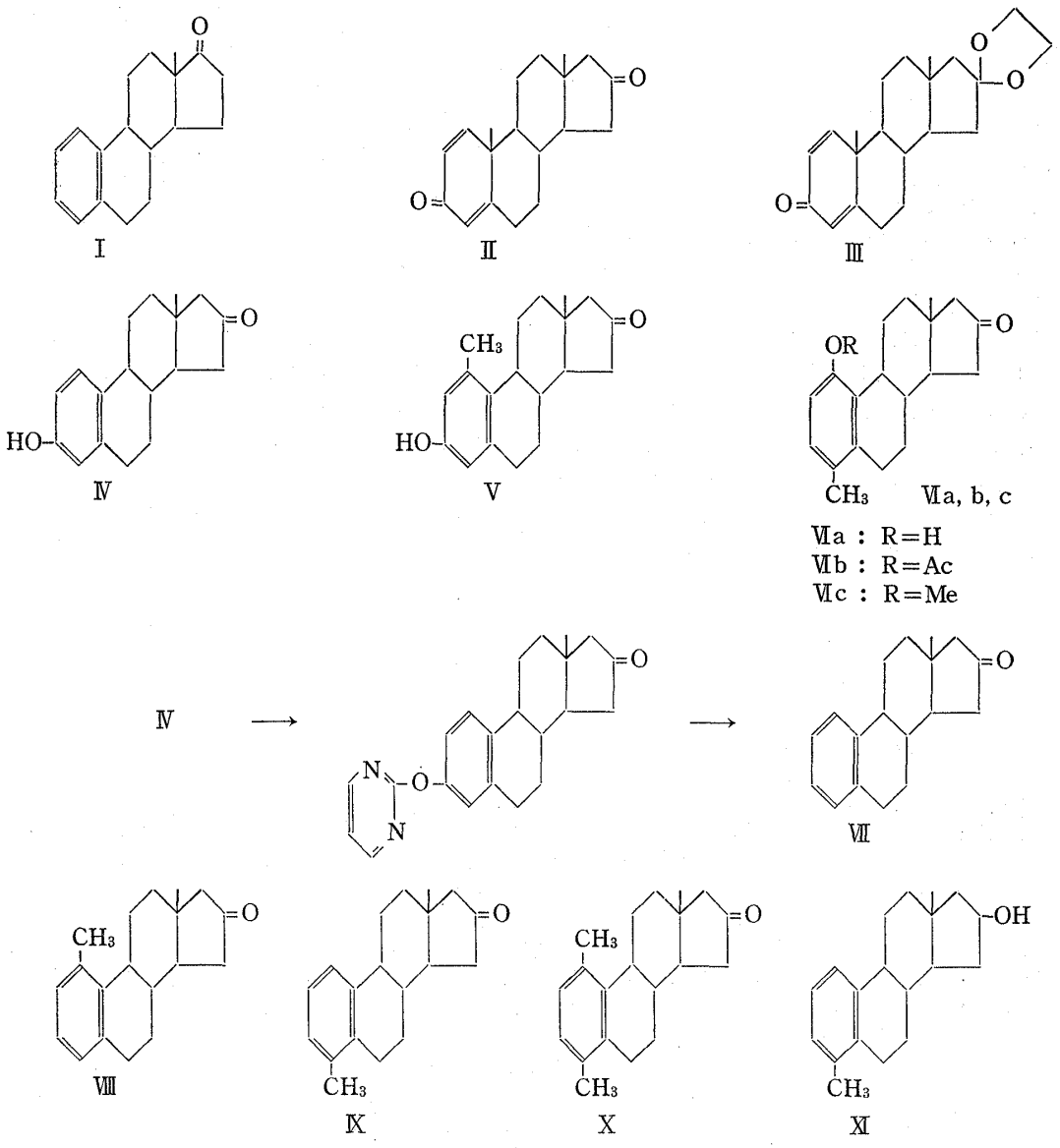

medium. The acetate (VIb) and methyl ether (VIc) were synthesised with the object of comparing their pharmacological effects with those of the phenol (VIa).

A-ring benzene derivatives were derived by the following two methods: the dienol-benzene rearrangement and the removal of the hydroxy group of the phenol derivative. Recently, Sawa, *et al.*[10] in our laboratory have developed a new method, by which the phenolic hydroxy group is reductively removed *via* its pyridyl or pyrimidyl ether to give the benzene derivative.

Estra-1,3,5(10)-trien-16-one (VII) was synthesised through the pyrimidyl ether of IV by this method. When 3-hydroxyestra-1,3,5(10)-trien-16-one (IV) was treated with 2-bromopyrimidine, anhydrous potassium carbonate, and cupric oxide in pyridine under reflux for 5 hr, it gave the pyrimidyl ether, mp 185—187°, in 79% yield. On hydrogenation with 20% palladised charcoal in ethanol at 60°, the pyrimidyl ether was reduced to give a 98% yield of estra-1,3,5(10)-trien-16-one (VII), mp 156°, shown to be identical with an authentic sample[11] by mixed melting point determination and infrared (IR) and ultraviolet (UV) spectra. This compound (VII) was also synthesised from IV by Newman's procedure,[12] that is, by dimethyl-

10) Y.K. Sawa, R. Maeda, and J. Irisawa, personal communication.
11) K. Sakakibara, Japan Patent 14377 (1966).
12) M.S. Newman and H.A. Karnes, *J. Org. Chem.*, **31**, 3980 (1966).

thiocarbamoyl ether formation followed by pyrolysis, hydrolysis, and reduction with Raney nickel.

1-Methylestra-1,3,5(10)-trien-16-one (VIII), mp 176°, was obtained from V through its pyrimidyl ether, mp 169°, under the conditions used for VII.

4-Methylestra-1,3,5(10)-trien-16-one (IX) was obtained as crystals, mp 193° from VIa by the pyrimidyl ether method or by the thiocarbamoyl method.[12] Moreover, lithium aluminium hydride reduction of II, followed by the dienol-benzene rearrangement with acetic acid, gave 4-methylestra-1,3,5(10)-trien-16-ol (XI), mp 128—130°, which was oxidised with chromium trioxide to give IX.

1,4-Dimethylestra-1,3,5(10)-trien-16-one (X) was obtained from the ketal (III) under the conditions used for 17-keto steroids.[13] Compound (III) was treated with methyl magnesium bromide in ether and the reaction mixture was worked up with aqueous hydrochloric acid. Deketalisation of the reaction product gave X, mp 176—177°, in 47% overall yield.

The pharmacological activities of these synthesised compounds were investigated by the Miyake group in our laboratory. All of these compounds lacked estrogenic effect and their lipid-shifting activities were weak. These results will be reported in detail by T. Miyake and his co-workers.

Experimental[14]

Ethylene Ketal[3] (III) of Androsta-1,4-diene-3,16-dione (II)——A solution of I (3.033 g) and toluene-*p*-sulphonic acid (30 mg) in 2-methyl-2-ethyl-1,3-dioxolane[15] (100 ml) was distilled at 105—115° to give a distillate (*ca.* 90 ml). To this distillation residue (*ca.* 10 ml) was added 2-methyl-2-ethyl-1,3-dioxolane (90 ml) and the mixture was distilled at the same way. This operation was carried out three times during 4.5 hr. The reaction residue was diluted with ether (100 ml), washed with 5% KOH and water, dried (Na_2SO_4), and evaporated to leave a residue (4.08 g). The residue was dissolved in light petroleum and chromatographed on alumina (Wöelm) to give a ethylene ketal (III) (2.62 g), which was crystallised from ether–CH_2Cl_2 as colourless prisms (2.16 g, 61.6% yield), mp 121—122°. *Anal.* Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.97; H, 8.60. IR ν_{max} cm^{-1}: 1664, 1630, 1603. UV λ_{max} mμ (ε): 245.5 (15300).

3-Hydroxyestra-1,3,5(10)-trien-16-one (IV)[3]——By Dryden's method,[16] compound (II) (2.06 g) was converted into IV (1.22 g, 71.9% yield), colourless needles, mp 246° (from acetone–MeOH).

3-Hydroxy-1-methylestra-1,3,5(10)-trien-16-one (V) and 1-Hydroxy-4-methylestra-1,3,5(10)-trien-16-one (VIa)——A solution of II (1.93 g) in 47% hydrobromic acid (30 ml) was left for 16 hr at room temperature and then heated at 55—65° for 7 hr, during which time green powder (1.66 g) was separated from the solution. The filtrate was further heated at 60—65° for 8 hr to give the green precipitate (200 mg). The combined precipitate, *Rf* 0.60 and 0.50 (solvent system: ethyl acetate:benzene=1:4), was heated under reflux in 5% NaOH (150 ml) for 3 hr and extracted with chloroform. The chloroform extract was washed with water, dried (Na_2SO_4), and evaporated to leave VIa (1.09 g, 56.7% yield), which was crystallised from MeOH–$CHCl_3$ as colourless prisms, mp 297°, *Rf* 0.60, $[\alpha]_D^{21}$ $-5.4\pm2°$ (c=0.147 in $CHCl_3$:MeOH=1:1). *Anal.* Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 79.79; H, 8.49. IR ν_{max} cm^{-1}: 3380, 1725, 1590, 852, 807. UV λ_{max} mμ (ε): 285 (2300). NMR (C_5D_5N) τ: 9.08 (CH_3), 7.82 (CH_3). The alkaline layer was acidified with 10% HCl, extracted with chloroform, washed with water, dried (Na_2SO_4), and evaporated to leave V (840 mg, 43.6% yield), which was crystallised from MeOH–$CHCl_3$ as colourless needles, mp 265°, *Rf* 0.50, $[\alpha]_D^{21}$ $-27.3\pm1.4°$ (c=0.487). *Anal.* Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.09; H, 8.52. IR ν_{max} cm^{-1}: 3250, 1722, 1615, 1591, 854, 720. UV λ_{max} mμ (ε): 282.5 (1680), 287.5 (1700). NMR τ: 9.05 (CH_3), 7.68 (CH_3).

1-Hydroxy-4-methylestra-1,3,5(10)-trien-16-one (VIa)——a) To a solution of II (2.965 g) in acetic anhydride (70 ml) was added 5% $ZnCl_2$–AcOH (6 ml) and left overnight at room temperature under nitrogen. The reaction mixture was poured into ice-water (300 ml) with stirring and filtered to separate a precipitate,

13) L.J. Chinn, *J. Org. Chem.*, **27**, 2703 (1962).
14) Nuclear magnetic resonance (NMR) spectra were taken for solutions in deuteriochloroform with a Varian A-60 spectrometer. Unless otherwise stated, UV, IR, and optical rotations were taken in 95% EtOH, Nujol mull, and $CHCl_3$, respectively. Melting points were measured with Kofler hot-stage apparatus and are uncorrected.
15) H.J. Dauben, Jr., B. Löken, and H.J. Ringold, *J. Am. Chem. Soc.*, **76**, 1359 (1954).
16) H.L. Dryden, Jr., G.M. Webber, and J.J. Wieczorek, *J. Am. Chem. Soc.*, **86**, 742 (1964).

which was dissolved in ether, washed with 10% NaOH, and water, dried (Na_2SO_4), and evaporated to leave VIb (3.35 g 98.4% yield) as colourless needles (from acetone), mp 169—170°, $[\alpha]_D^{23}$ +20.2±0.6° (c=1.050). *Anal.* Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.43; H, 8.01. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3003, 2983, 1745, 1596, 1588, 1225, 1033.

A solution of VIb (2.39 g) in 10% KOH–MeOH (100 ml) was heated under reflux for 3 hr and then acidified with 10% HCl. This was extracted with $CHCl_3$, washed with water, dried (Na_2SO_4), and evaporated to leave VIa (2.02 g, 97.2% yield), mp 297°.

b) A mixture of II (2.0 g) and Zn-dust (30 mesh) (32 g) in pyridine (5 ml) was heated under reflux for 40 hr and then filtered. The filtrate was diluted with water and extracted with ethyl acetate. The extract was washed with 1% HCl, 1% $NaHCO_3$, and water, dried (Na_2SO_4), and evaporated to leave a residue. The residue was crystallised from MeOH–$CHCl_3$ (1:1) to give VIa, mp 297° (400 mg).

1-Methoxy-4-methylestra-1,3,5(10)-trien-16-one (VIc)——To a boiling solution of VIa (1.094 g) and NaOH (3 g) in EtOH (36 ml) and water (10 ml) was added dimethyl sulfate (2 ml) in every 30 min for 4 hr, during which time the solution was kept in alkali. The solution was diluted with water and extracted with ethyl acetate. The extract was washed with water, dried (Na_2SO_4), and evaporated, leaving a crystalline residue (VIc) (1.15 g, 100% yield), which was recrystallised from acetone as colourless needles, mp 190—192°, $[\alpha]_D^{24}$ +34.7±3.3° (c=0.219). *Anal.* Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.50; H, 8.72. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1587, 1075. NMR τ: 9.08 (CH_3), 7.83 (CH_3), 6.23 (CH_3O).

Estra-1,3,5(10)-trien-16-one (VII)——a) A mixture of IV (1.106 g), 2-bromopyrimidine (686 mg), K_2CO_3 (848 mg), and CuO (138 mg) in pyrimidine (10 ml) was heated with stirring in an oil bath (bath temperature: 150°) for 5 hr, and then diluted with benzene (100 ml). After filtration, the filtrate was evaporated to leave a residue. The residue was dissolved in $CHCl_3$, treated with charcoal, and evaporated, leaving a crystalline residue (1.39 g). The residue was dissolved in petroleum ether (100 ml) and chromatographed on Al_2O_3 (Wöelm, containing 6% of water) (30 g) to give a pyrimidyl ether (1.13 g, 79.4% yield) as colourless neeldes (from MeOH), mp 185—187°. $[\alpha]_D^{23}$ −87.2±2.8° (c=0.460). *Anal.* Calcd. for $C_{22}H_{24}O_2N_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 75.79; H, 6.58; N, 8.29. IR ν_{max} cm^{-1}: 3141, 3081, 1740, 1580, 1572, 941, 891, 873, 831. UV λ_{max} mμ (ε): 265 (4750). NMR τ: 9.07 (CH_3), 2.55—3.13 (4H), 1.42—1.48 (2H).

A solution of the pyrimidyl ether (773 mg) in EtOH (80 ml) was hydrogenated with 20% palladised charcoal (900 mg) at 60°. The catalyst was filtered off, and the filtrate was evaporated to leave a crystalline residue (769 mg). The residue was dissolved in $CHCl_3$, washed with water, dried (Na_2SO_4), and evaporated, leaving VII (554 mg 98.2% yield) as colourless needles (from MeOH–acetone), mp 156°, $[\alpha]_D^{24}$ −117.4±2.2° (c=0.695). *Anal.* Calcd. for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 85.01; H, 8.77. IR ν_{max} cm^{-1}: 3060, 1740, 1575, 1570, 1565, 1494, 752, 743. UV ν_{max} mμ (ε): 266.5 (935), 273.7 (960). NMR τ: 9.08 (CH_3), 2.65—2.98 (4H). This compound was shown to be identical with an authentic sample[11] by mixed mp, IR and UV.

b) To a solution of IV (98 mg) in dimethylformamide (2 ml) was added NaH (40 mg) with stirring at room temperature. Dimethylthiocarbamoyl chloride (133 mg) was added to this suspension of Na-salt of IV and heated at 80° with stirring for 2 hr. The reaction mixture was poured into water to separate a precipitate, which was gathered, washed with water, and dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with 5% KOH and water, dried (Na_2SO_4), and evaporated, leaving a powder (105 mg). The residue was crystallised from MeOH–$CHCl_3$ to give a dimethylthiocarbamoyl ether (73 mg, 56.3% yield) as colourless prisms, mp 251—252°. *Anal.* Calcd. for $C_{21}H_{27}O_2NS$: C, 70.55; H, 7.61; N, 3.92; S, 8.97. Found; C, 70.37; H, 7.43; N, 3.65; S, 8.99. IR ν_{max} cm^{-1}: 1738, 1611, 1586, 1292, 1222.

The thiocarbamoyl ether (69 mg) was heated at 290—300° for 10 min and then dissolved in $CHCl_3$. The solvent was evaporated to leave a yellow crystalline residue (50 mg), which was recrystallised from MeOH–$CHCl_3$ to give a pyrolysis product (48 mg, 69.6% yield) as pale-yellow plates, mp 185°. *Anal.* Calcd. for $C_{21}H_{27}O_2NS$: C, 70.55; H, 7.61; N, 3.92; S, 8.97. Found: C, 70.36; H, 7.64; N, 3.96; S, 9.09. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1660, 1100.

A solution of the pyrolysis product (111 mg) in 10% NaOH–MeOH (5 ml) was heated under reflux for 2 hr, and then acidified with 10% HCl to give a precipitate, which was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with water, dried (Na_2SO_4), and evaporated, leaving an oily residue (103 mg). This was purified by preparative thin-layer chlomatography (TLC) (solvent system: ethyl acetate: benzene=1:9) to give a thiol (57 mg, 64.1% yield) as yellow prisms, mp 140—146° (from MeOH–ether), *Rf* 0.61. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1741, 1598, 1165, 1115.

A mixture of the thiol (47 mg) and Raney Ni (1 ml) in EtOH (5 ml) was heated under reflux for 2.5 hr. The catalyst was filtered off, and the filtrate was evaporated to leave an oily residue (35 mg), which was purified by preparative TLC to give VII (16 mg, 38.4% yield) as colourless prisms, mp 156°, *Rf* 0.71.

1-Methylestra-1,3,5(10)-trien-16-one (VIII)——Compound (VIII) was obtained from V through its pyrimidyl ether under the conditions used for VII. A mixture of V (304 mg), 2-bromopyrimidine (179 mg), K_2CO_3 (228 mg), and CuO (41 mg) in pyridine (5 ml) was heated at 150° for 5 hr to give a pyrimidyl ether (338 mg, 87.2% yield) as colourless needles (from MeOH–ether), mp 169°, $[\alpha]_D^{26}$ −10.0±0.7° (c=0.717). *Anal.* Calcd. for $C_{23}H_{26}O_2N_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 76.0; H, 6.89; N, 7.84. IR ν_{max} cm^{-1}:

3075, 3006, 1736, 1607, 1576, 1568, 1000, 827. UV λ_{max} mμ (ε): 263.5 (4330). NMR τ: 9.03 (CH_3), 7.62 (CH_3), 3.19 (2H, singlet), 2.97 (1H, triplet, J=5.2 cps), 1.45 (2H, doublet, J=5.2 cps).

A solution of the pyrimidyl ether (314 mg) was hydrogenated with 20% palladised charcoal to give VIII (234 mg, 100% yield) as colourless prisms (from MeOH–acetone). mp 176°, $[\alpha]_D^{26}$ −26.6±0.9° (c=0.710). *Anal.* Calcd. for $C_{19}H_{24}O$: C, 85.02; H, 9.01. Found: C, 84.68; H, 9.37. IR ν_{max} cm^{-1}: 3060, 3006, 1740, 1580, 850, 775, 764, 740. UV λ_{max} mμ (ε): 267 (230). NMR τ: 9.03 (CH_3), 7.63 (CH_3), 3.03 (3H, singlet).

4-Methylestra-1,3,5(10)trien-16-one (IX)——Compound (IX) was obtained from VIa by the pyrimidyl ether method under the conditions used for VII. A pyrimidly ether of VIa was obtained in 77.8% yield as colourless needles (from ether–MeOH), mp 188°, $[\alpha]_D^{21}$ +3.8±1.0° (c=0.452). *Anal.* Calcd. for $C_{23}H_{26}O_2N_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 76.22; H, 7.32; N, 7.53. IR ν_{max} cm^{-1}: 3068, 3038, 1742, 1590, 1580, 1571, 1313, 877, 817, 805. UV λ_{max} mμ (ε): 263.5 (4110). NMR τ: 9.08 (CH_3), 7.77 (CH_3), 2.82—3.32 (3H), 1.40—1.47 (2H). Compound (IX) was obtained in 83.1% yield as colourless needles (from MeOH), mp 193°, $[\alpha]_D^{21}$ −119.0±4.0° (c=0.39). IR ν_{max} cm^{-1}: 3063, 1738, 1585, 780, 745. UV λ_{max} mμ (ε): 264 (240). NMR τ: 9.08 (CH_3), 7.78 (CH_3), 2.77—3.07 (3H).

4-Methylestra-1,3,5(10)-trien-16-ol (XI)——A solution of II (2.0 g) in dry tetrahydrofuran (20 ml) was added dropwise to a solution of $LiAlH_4$ (3.0 g) in dry ether (150 ml) at room temperature for 1 hr and then heated under reflux for 40 min. Acetone (20 ml) and then water (10 ml) was added to this mixture with ice-cooling. This was extracted with ethyl acetate, and the extract was washed with water, dried (Na_2SO_4), and evaporated, leaving an oily residue (2.01 g). The residue was dissolved in acetic acid (20 ml) and water (2 ml) and heated under reflux for 10 min. The solution was extracted with ethyl acetate, washed with 10% Na_2CO_3 and water, dried (Na_2SO_4), and evaporated, leaving an oily residue (1.9 g). The residue was chromatographed on Al_2O_3 to give an acetate of XI, colourless needles, mp 162° (0.367 g), $[\alpha]_D^{21}$ +53.8±5.1° (c=0.173) (*Anal.* Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.45; H, 8.97) and XI (0.166 g), colourless prisms, mp 128—130°, $[\alpha]_D^{22}$ +53.7±2.2° (c=0.31), IR ν_{max}^{KBr} cm^{-1}: 3292, 3282, 784, 740 (*Anal.* Calcd. for $C_{19}H_{26}O$: C, 84.39; H, 9.69. Found: C, 83.54; H, 9.63).

Oxidation of XI——A solution of XI (100 mg) in acetone (5 ml) was oxidised with Jones reagent (0.13 ml) at room temperature for 10 min. The reaction product (47 mg), mp 193° was shown to be identical with IX.

1,4-Dimethylestra-1,3,5(10)-trien-16-one (X)——A solution of III (1.813 g) in dry ether (50 ml) was added dropwise to a boiling Grignard regent prepared from Mg (367 mg) and methylbromide (1 ml) in dry ether (10 ml) with stirring for 20 min, and this mixture was heated under reflux for 2 hr with stirring. To this was added water (2 ml) in an ice-bath, and the mixture was acidified with 1.7N HCl with stirring and left for 30 min. The ether layer was washed with 5% $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated, leaving an oily residue (1.767 g). The residue was dissolved in 80% acetic acid (50 ml) and left overnight at room temperatire. The solution was poured onto ice-water and extracted with ether. The extract was washed with 5% KOH and water, dried (Na_2SO_4), and evaporated, leaving a crystalline residue (1.44 g). The residue was dissolved in petroleum ether (100 ml) and chromatographed on Al_2O_3 (75 g) to give X (742 mg, 47.6% yield) as colourless needles (from ether), mp 176—177°, $[\alpha]_D^{21}$ −31.5±1.6° (c=0.451). *Anal.* Calcd. for $C_{20}H_{26}O$: C, 85.05; H, 9.28. Found: C, 85.07; H, 9.26. IR ν_{max} cm^{-1}: 1742, 1620, 1594, 854, 811, 772. UV λ_{max} mμ (ε): 271 (310). NMR τ: 9.05 (CH_3), 7.82 (CH_3), 7.67 (CH_3), 3.10 (2H).