Pentacyclic Steroids. 3. Synthesis of 4,6α-Ethanoestradiol, 4,6α-Ethanoestrone, and 17α-Ethynyl-4,6α-ethanoestradiol

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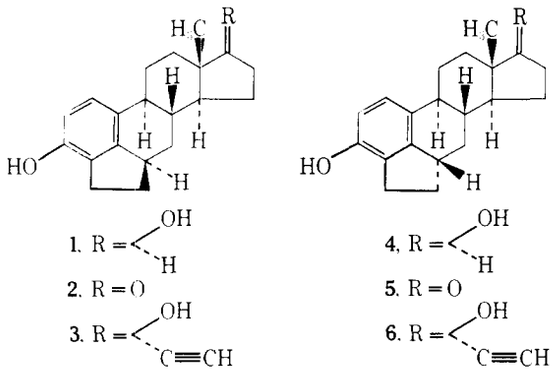
Syntheses of 4,6α-ethanoestradiol (**4**), 4,6α-ethanoestrone (**5**), and 17α-ethynyl-4,6α-ethanoestradiol (**6**) are described. Estrone was converted into 17β-acetoxy-3-methoxy-1,3,5(10)-estratriene-6α-acetic acid (**13**) in several steps. Cyclization of the acid chloride of **13** with aluminum chloride afforded 17β-acetoxy-3-hydroxy-4,6α-(1′-oxoethano)-1,3,5(10)-estratriene (**14**) in 94% yield. Clemmensen reduction of **14** provided a mixture of **4** and **15**, which upon base hydrolysis gave 4,6α-ethanoestradiol (**4**). The latter compound was converted into 4,6α-ethanoestrone (**5**) and 17α-ethynyl-4,6α-ethanoestradiol (**6**).

Recently we reported[1] the synthesis of a novel series of pentacyclic steroids, namely 4,6β-ethanoestradiol (**1**), 4,6β-ethanoestrone (**2**) and 17α-ethynyl-4,6β-ethanoestradiol (**3**). Detailed X-ray crystallographic studies[2] on the 17-*p*-bromobenzoate of **1** have shown that fusion of the ethano bridge across C-4 and C-6 from the β face in the steroidal skeleton forces the B ring to assume a highly distorted conformation. Thus presence of the fifth ring in **1** and **2** causes greatly enhanced bowing of the molecules toward the β face, when compared to the natural analogues estradiol (**8**) and estrone (**7**). This unusual strain on B-ring conformation can be released, at least to some extent, by reversal of the stereochemistry at C-6. Since the synthesis and biological profile of 4,6α-ethanosteroids are unknown in the literature,[3] it was of interest to prepare a series of such compounds. In this paper,

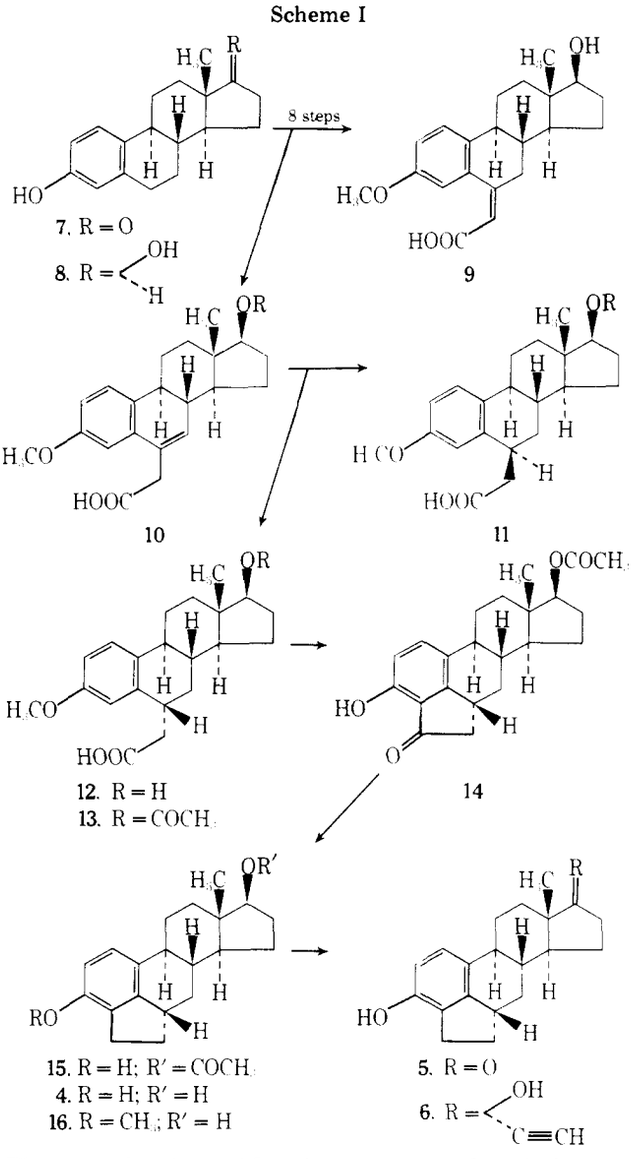


we report the synthesis of 4,6α-ethanoestradiol (**4**), 4,6α-ethanoestrone (**5**), and 17α-ethynyl-4,6α-ethanoestradiol (**6**).

The starting material was estrone (**7**), which was converted into a mixture of the intermediate acids **9** (minor product, 15%), and **10** (major product, 85%), in eight steps, as described earlier[1] (Scheme I). Hydrogenation of this mixture in the presence of 10% Pd/C gave primarily (>95%) the 6α-H isomer **11** (mp 186 °C). We have now found that reduction with lithium in liquid ammonia,[4] on the other hand, furnished a mixture of **11** and **12** in almost equal quantities. The compounds were separated by fractional crystallization and the purified acid **12** (mp 215–216 °C) was next converted into the acetate **13**. Cyclization of **13** with an excess of anhydrous $AlCl_3$ provided **14** in 94% yield. It is interesting to note that in spite of the stereochemical differences, ring closures of both **13** and its corresponding 6α-H isomer[1] take place with similar ease. The methoxy group was cleaved in the process.

Clemmensen reduction of **14** yielded a mixture of **15** and **4**, which, upon base hydrolysis and subsequent acidification, gave 4,6α-ethanoestradiol (**4**). Methylation of **4** formed **16**, whereas oxidation with CrO_3 yielded 4,6α-ethanoestrone (**5**). The latter, upon treatment with lithium acetylide–ethylenediamine complex, led to 17α-ethynyl-4,6α-ethanoestradiol (**6**).

Scheme I



The stereochemistry of C-17 in **6** was assigned on the basis of literature precedent.[1,5,6]

It is interesting to note that in the NMR spectra, absorption due to C–CH_3 signals in the 4,6α-ethanosteroids occurs at a lower field when compared to the corresponding signals in 4,6β-ethanosteroids. Thus the C–CH_3 signal in **4** shows up at δ 0.80, whereas in **1**, it appears at δ 0.74. Similar shifts are observed with **6** (0.93) and **3** (δ 0.80), **14** (δ 0.90) and its 4,6β-ethano isomer[1] (δ 0.78), and **16** (δ 0.80) and the corresponding 4,6β-ethano isomer[1] (δ 0.70).

The observed shift can be explained by the presence of the

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highly strained B ring in the β series which results in an enhanced bowing of the molecule toward the β face. This distorted conformation is shown by X-ray studies of 17-*p*-bromobenzoate of 4,6β-ethanoestradiol.[1,2] The shielding effect of the aromatic ring on the C–CH_3 group at C-18 could therefore be more pronounced in this series than the corresponding 4,6α-ethano isomers, resulting in the observed chemical shifts.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU 6L and a CEC 110 mass spectrometer. Proton nuclear magnetic resonance spectra (NMR) were recorded on a Varian T-60 spectrometer, using tetramethylsilane as the internal standard. Thin-layer chromatography (TLC) was performed on precoated TLC plates (silica gel 60 F254, EM reagents). Microanalyses were carried out by Spang Microanalytical Laboratories, Eagle Harbor, Mich.

A mixture of the acids **9** (15%) and **10** (85%) was prepared in several steps, from estrone, as described earlier.[1]

17β-Hydroxy-3-methoxy-1,3,5(10)-estratriene-6β-acetic Acid (11) and 17β-Hydroxy-3-methoxy-1,3,5(10)-estratriene-6α-acetic Acid (12). Lithium (0.063 g) was added to distilled liquid NH_3 (150 mL) with stirring to give a solution colored intensely blue. A solution of the acids **9** and **10** (1.026 g) in THF (30 mL) was then added, followed by another 0.063 g of lithium. After 25 min the blue color was discharged by addition of NH_4Cl (1 g), and the NH_3 was evaporated. The reaction mixture was diluted with water (100 mL) and THF was evaporated under reduced pressure. It was then acidified with 1 N HCl and extracted with EtOAc (3 × 50 mL). The EtOAc extract was washed with water, dried (Na_2SO_4), and concentrated to furnish **11** and **12** (1.1 g). NMR ($CDCl_3$) showed it to be a mixture of **11** and **12** in almost equal amounts [δ 0.80 (3 H, CCH_3 in **11**) and 0.73 (3 H, CCH_3 in **12**)]. Fractional crystallization from a mixture of $CHCl_3$–CH_3OH–petroleum ether (40–60 °C) afforded pure 17β-hydroxy-3-methoxy-1,3,5(10)-estratriene-6α-acetic acid (**12**) (0.506 g, 49%), mp 210–211 °C. The mother liquor on concentration yielded 17β-hydroxy-3-methoxy-1,3,5(10)-estratriene-6β-acetic acid (**11**) (0.5 g, 48.5%), mp 186 °C. An analytical sample of **12** was obtained by recrystallization (two more times) from $CHCl_3$–CH_3OH–petroleum ether: mp 215–216 °C; NMR ($CDCl_3$) δ 0.73 (3 H, CCH_3), 3.70 (3 H, OCH_3), 6.63 and 7.12 (2 H, ArH); MS *m/e* 344 (M^+). Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.10; H, 8.10.

17β-Acetoxy-3-methoxy-1,3,5(10)-estratriene-6α-acetic Acid (13). A solution of the acid **12** (1.2 g) in pyridine (6 mL) and Ac_2O (4.5 mL) was kept at room temperature for 48 h. After addition of water, the mixture was acidified with 1 N HCl and extracted with Et_2O (3 × 30 mL). The organic layer was washed with water, dried (Na_2SO_4), and filtered. Removal of the solvent provided 17β-acetoxy-3-methoxy-1,3,5(10)-estratriene-6α-acetic acid (**13**) (1.3 g, 97%). Recrystallization from CH_3OH–$CHCl_3$ provided pure acetate: mp 158–159 °C; NMR ($CDCl_3$) δ 0.80 (3 H, CCH_3), 3.80 (OCH_3), 6.77 and 7.24 (2 H, ArH); IR (Nujol) 1726 (acetate C=O) and 1698 cm^{-1} (COOH); MS 386 (M^+). Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.47; H, 7.82. Found: C, 71.09; H, 7.84.

17β-Acetoxy-3-hydroxy-4,6α-(1′-oxoethano)-1,3,5(10)-estratriene (14). A solution of the acid **13** (0.3 g), $SOCl_2$ (0.5 mL), and pyridine (3 drops) in CH_2Cl_2 (5 mL) was stirred at room temperature for 3 h. The solvent was removed by distillation at reduced pressure and the last traces of $SOCl_2$ were removed by codistillation three times with 10-mL portions of CH_2Cl_2. The resulting acid chloride IR (neat) 1800 (COCl) and 1732 cm^{-1} (acetate > C=O) was dissolved in CH_2Cl_2 (6 mL) and the solution was added dropwise over a period of 5 min to a stirred and cooled (0–2 °C) suspension of anhydrous $AlCl_3$ (0.475 g) in CH_2Cl_2 (8 mL). The mixture was stirred at ice-bath temperature for 2 h and kept at room temperature for 15 h. After treatment with ice water (30 mL) and concentrated HCl (0.5 mL), the mixture was extracted with Et_2O (2 × 30 mL). The organic layer was washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo to give 0.258 g (94%) of the crude **14**. TLC using $CHCl_3$–petroleum ether (40–60 °C) (ratio 3:1) as the solvent showed a single spot. The product was recrystallized from a mixture of CH_2Cl_2, Et_2O, and petroleum ether to give pure 17β-acetoxy-3-hydroxy-4,6α-(1′-oxoethano)-1,3,5(10)-estratriene (**14**): mp 250–251 °C; NMR ($CDCl_3$) δ 0.90 (3 H, CCH_3), 2.07 (acetate CH_3), 6.77 and 7.37 (2 H, ArH); MS 354 (M^+); IR (Nujol) 1730 (acetate > C=O) and 1700 cm^{-1} (five-member conjugated >C=O). Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.69; H, 7.27.

4,6α-Ethanoestradiol (4). A mixture of mossy Zn (3 g) and 5% $HgCl_2$ solution (6 mL) was kept for 1 h with occasional shaking and the aqueous layer was then decanted. The resulting amalgamated Zn was covered with concentrated HCl (10 mL) and water (10 mL). After addition of **14** (0.2 g) and toluene (2 mL) the mixture was refluxed under stirring for 1 h. More concentrated HCl (10 mL) was added and the heating continued for another 2 h. The mixture was cooled and extracted with Et_2O (3 × 25 ml) and then with EtOAc (3 × 25 mL). The organic layers were washed with water, combined, dried over $MgSO_4$, and filtered. Removal of the solvent provided a mixture of **4** and **15**. This was refluxed for 2 h with a solution of KOH (0.14 g) in 4.5 mL of CH_3OH and 0.5 mL of water. CH_3OH was removed and the residue was treated with water. The solution was acidified and worked up to give 0.12 g (71%) of **4**. It was recrystallized from a mixture of Et_2O–CH_2Cl_2–CH_3OH–petroleum ether to afford 4,6α-ethanoestradiol (**4**) as colorless needles: mp 258–259 °C; NMR ($CDCl_3$) δ 0.80 (3 H, CCH_3), 6.57 and 6.93 (2 H, ArH); Ms 298 (M^+); IR (Nujol) 3350 cm^{-1} (broad, OH). Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.50; H, 8.78. Found: C, 80.42; H, 8.79.

4,6α-Ethanoestradiol 3-Methyl Ether (16). Dimethyl sulfate (1.2 mL) was added dropwise during 30 min to a solution of 4,6α-ethanestradiol (**1**) (0.15 g) in CH_3OH (5 mL), acetone (5 mL), and 1 N KOH (10 mL). The mixture was stirred for 3 h at room temperature and left overnight. The product was concentrated in vacuo and the residual mixture was extracted with Et_2O (3 × 25 mL) and EtOAc (3 × 20 mL). The organic solutions were washed with water, combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residual solid (120 mg, 76%) was recrystallized from a mixture of Et_2O and petroleum ether to furnish pure 4,6α-ethanoestradiol 3-methyl ether (**16**): mp 192–193 °C; NMR ($CDCl_3$) δ 0.80 (3 H, CCH_3), 3.81 (3 H, OCH_3), 6.67 and 7.07 (2 H, ArH); MS 312 (M^+). Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.72; H, 9.03. Found: C, 80.61; H, 9.18.

4,6α-Ethanoestrone (5). Jones reagent[7] (0.35 mL) was added dropwise to a stirred solution of 4,6α-ethanoestradiol (**4**) (0.2 g) in acetone (25 mL) at 15–20 °C. After 10 min, the reaction mixture was treated with water (100 mL) and the product was extracted with Et_2O (3 × 50 mL). The Et_2O solution was washed with water, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue, upon treatment with a mixture of Et_2O–petroleum ether, gave 4,6α-ethanoestrone (**5**) (135 mg, 68%) as an oily solid, which showed a single spot on TLC: MS 296 (M^+); IR (Nujol) 3400 (broad, OH) and 1723 cm^{-1} (C=O).

17α-Ethynyl-4,6α-ethanoestradiol (6). Acetylene gas was bubbled into a solution of 4,6α-ethanoestrone (**5**) (0.15 g) in dimethyl sulfoxide (5 mL) under N_2 for 5 min. Lithium acetylide–ethylenediamine complex[5,6] (0.3 g) was added to the mixture and the acetylene gas was passed for another 3 h. The product was allowed to stand overnight at room temperature and then decomposed with a saturated solution of NH_4Cl. The reaction mixture was next extracted with EtOAc (3 × 40 mL) and Et_2O (3 × 25 mL). The organic layers were combined, washed with water, dried over Na_2SO_4, and filtered. Removal of the solvent in vacuo provided crude **6** (150 mg, 92%). The material was taken up in $CHCl_3$ and passed through a short column of silica gel (4 g) to give pure 17α-ethynyl-4,6α-ethanoestradiol (**6**) as a foamy solid: NMR ($CDCl_3$) δ 0.93 (3 H, CCH_3), 6.63 and 7.0 (2 H, ArH); MS 322 (M^+). Anal. Calcd for $C_{22}H_{26}O_2$: C, 81.95; H, 8.13. Found: C, 81.69; H, 8.13.

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Registry No.—**1**, 62842-06-2; **4**, 67938-58-3; **5**, 67938-59-4; **6**, 67938-60-7; **9**, 62842-14-2; **10**, 62842-12-0; **11**, 62842-15-3; **12**, 67938-61-8; **13**, 67938-62-9; **13** acid chloride, 67938-66-3; **14**, 67938-63-0; **15**, 67938-64-1; **16**, 67938-65-2; acetylene, 74-86-2.

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Reduction of Aryl Diethyl Phosphates with Titanium Metal: A Method for Deoxygenation of Phenols

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An exceedingly simple method for the deoxygenation of phenols by reduction of the corresponding aryl diethyl phosphates with freshly prepared, highly activated titanium metal in tetrahydrofuran is presented.

The deoxygenation of phenols is often times an important and necessary synthetic objective. This goal can be achieved by catalytic hydrogenation as well as dissolving metal reduction methods. Among the catalytic hydrogenation techniques are the reduction of tosylate esters,[1,2] mesylate esters,[3] potassium arylsulfonates,[4] phenyl ethers,[5] methyl ethers,[6] 1-phenyl-5-tetrazolyl ethers,[7] *O*-arylisoureas,[8] and phenylurethanes.[9] The use of dissolving metal methods includes alkali metal in liquid ammonia reduction of mesylate esters;[10] 2,4-diaminophenyl ethers;[11] and diethyl phosphate esters.[10,12] By far the best of the dissolving metal reductions is the latter in which aryl diethyl phosphate esters are reduced with lithium metal in liquid ammonia. The esters are easily formed [$HPO(OEt)_2$, CCl_4, Et_3N or NaH, THF, $ClPO(OEt)_2$] in high yields (70 to 100%). Reported reductions of the corresponding aryl diethyl phosphates with lithium, sodium, or potassium metal in liquid ammonia proceeds in 2 to 96% yield. This method was found to be compatible with isolated carbon–carbon double bonds (alkenes).

We recently reported a new method for the reduction of enol phosphates to alkenes in high yields with titanium metal.[13] We now wish to report herein an alternative procedure for reducing aryl diethyl phosphate esters to aromatic hydrocarbons in high yield under aprotic conditions utilizing freshly prepared titanium metal.[14]

Highly activated titanium metal can be freshly prepared from anhydrous titanium(III) chloride by reduction with either magnesium[15] or potassium[16] metals in anhydrous tetrahydrofuran. The optimum stoichiometry for this reaction in Figure 1 utilizes 3 equiv of aryl diethyl phosphate (prepared by treatment of 3 equiv of the phenol with 3.3 equiv of sodium hydride in anhydrous tetrahydrofuran in the presence of 3 equiv of diethyl phosphorochloridate) with 2 equiv of freshly prepared, highly activated titanium metal in tetrahydrofuran. Titanium metal is prepared by treatment of 2 equiv of anhydrous titanium(III) chloride with 6 to 6.6 equiv of potassium metal. The reduction reaction is allowed to reflux for 6 to 16 h, then quenched with absolute methanol at 5 °C, filtered through a column of silica gel:celite (1:4, respectively), concentrated in vacuo, and either distilled or crystallized to afford the respective aromatic hydrocarbon in high yield.

Table I lists the starting phenols, yields of the aryl diethyl phosphates, yields of the aromatic hydrocarbon products, and the time for each of the reductions. This new reduction method is exceedingly simple and it appears to be quite general for phenols with isolated ester functional groups, ethers, alcohols, and alkenes present in the structure. Reduction of the diethyl phosphate ester derived from methyl podocarpate with titanium metal in refluxing tetrahydrofuran for 17 h affords desoxymethyl podocarpate in 80% yield with no observed reduction of the ester moiety. Similarly, reduction of estradiol 3-(diethyl phosphate) produces estra-1,3,5(10)-trien-17β-ol in 86% yield. Styrene double bonds, aryl aldehydes, aryl ketones, aryl esters, and aryl chlorides were found not to be compatible with this new reduction technique.

Reduction of the diethyl phosphate ester derived from carvacrol with titanium metal in refluxing tetrahydrofuran for 8 to 16 h followed by quenching with deuterium oxide does not incorporate deuterium. Reduction of the diethyl phosphate ester derived from eugenol under similar conditions followed by quenching with methanol at 5 °C produces the expected product 3-(3-methoxyphenyl)propene (B) in only 4.7% yield along with alkylated product 3-(3-methoxyphenyl)-1-pentene (A) in 74% yield. Reduction of eugenol diethyl phosphate under identical conditions to the latter experiment in the presence of 1 equiv of 100% ethanol gives compounds A, B, C, and D in a ratio of 5:88:2:5 in 82% combined yield. This series of experiments indicates that the reduction is probably producing a carbanionic species (aryl anion) which in the absence of a proton source (ROH or H_2O) most likely cleaves tetrahydrofuran over a period of 6 to 16 h at reflux. Eugenol diethyl phosphate is reduced in the presence of a proton source (EtOH) to afford the expected product B in 72% yield;

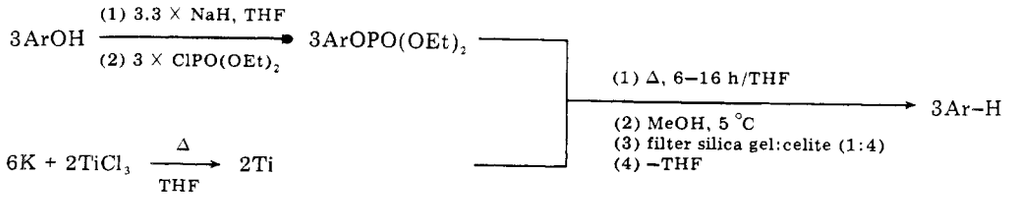

Figure 1.

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