cold ethereal solution containing diazomethane (0.250 g, 5.9 mmol), and was left overnight in the refrigerator. On evaporation of solvent the enol ether **7** was obtained in almost quantitative yield: mp 178 °C (from chloroform/petroleum ether); ν ($CHCl_3$) 1675, 1640, 1275–1200, 1075–1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.84 (s, 6 H), 3.75 (s, 6 H), 3.5 (2 H), 2.6–2.9 (4 H); ^{13}C NMR ($CDCl_3$) 37.9 (t, single-frequency off-resonance decoupling, C-4, 8), 39.8 (d, C-1, 5), 50.8 (q, CO_2CH_3), 57.7 (q, CH_3O-C-3.7), 106.1 (s, C-2, 6), 165.6 (s), 169.7 (s), (C-3, 7 and CO_2CH_3).

Partial Decarbomethoxylation of β-Keto Ester 3 to the Monoester 4. A mixture of β-keto ester **3** (1 g, 3.9 mmol) and sodium methoxide (2.12 g, 39 mmol) in 60 mL of Me_2SO containing 10 mol % methanol was stirred at 70–80 °C for 36 h. The reaction mixture was worked up as before; the residue showed two spots on TLC; both components were isolated by preparative TLC. The major compound was found to be unreacted starting material. The other component, isolated in about 1% yield (0.007 g), mp 84 °C (from ethanol), was identified as ester **4**: ν ($CHCl_3$) 1755, 1730, 1660, 1630 cm^{-1}; ^1H NMR ($CDCl_4$) δ 3.8 (3 H), 3.5 (2 H), 2.09–3.01 (6 H); M^+ *m/e* 196.

Decarbomethoxylation of Ester 3 to the Diketone 9. The ester **3** (0.5 g, 1.96 mmol) was refluxed with 6 N HCl (10 mL) for 3.5 h. The reaction mixture was cooled, and ice-cold water was added. Extraction with methylene chloride, washing with brine solution, drying (Na_2SO_4), and evaporation gave a residue which was crystallized from methanol, mp 84–85 °C. The compound was found identical with the authentic sample of **9** by mixture melting point, co-TLC, superimposable infrared, NMR, and mass spectra.

Enol Ether 8 of β-Keto Ester 1. Ester **1** (0.5 g, 1.35 mmol) was added to an ice-cold ethereal solution containing diazomethane (0.250 g, 5.9 mmol); the solution was left overnight in the refrigerator. On usual workup the enol ether **8** was obtained; it was crystallized from chloroform/petroleum ether in 90% yield (0.48 g): mp 135 °C; ν ($CHCl_3$) 1740, 1685, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.86 (6 H), 3.57 (6 H), 3.50 (6 H), 3.90 (2 H), 3.60 (2 H); ^{13}C NMR 49.0 (d, C-1, 5), 51.4 (q, C-2, 6 CO_2CH_3), 52.8 (q, C-4, 8, CO_2CH_3), 58.9 (d, C-4, 8), 59.0 (q, C-3, 7 OCH_3), 108.5 (s, C-2, 6), 164.5, 165.5 (s, C-3, 7/C-2, 6 CO_2CH_3), 171.9 (s, C-4, 8 CO_2CH_3); M^+ *m/e* 398. Anal. Calcd for $C_{18}H_{22}O_{10}$: C, 54.27; H, 5.57. Found: C, 54.46; H, 5.53.

Acknowledgments. We are indebted to Dr. Lin Tsai for valuable discussions, and to Mr. William R. Landis and Noel F. Whittaker for mass spectra.

Registry No.—**1**, 58648-36-5; **2**, 62708-46-7; **3**, 62708-47-8; **4**, 62708-48-9; **7**, 62708-49-0; **8**, 62708-50-3; **9**, 51716-63-3; dimethyl β-ketoglutarate, 1830-54-2; glyoxal, 107-22-2.

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

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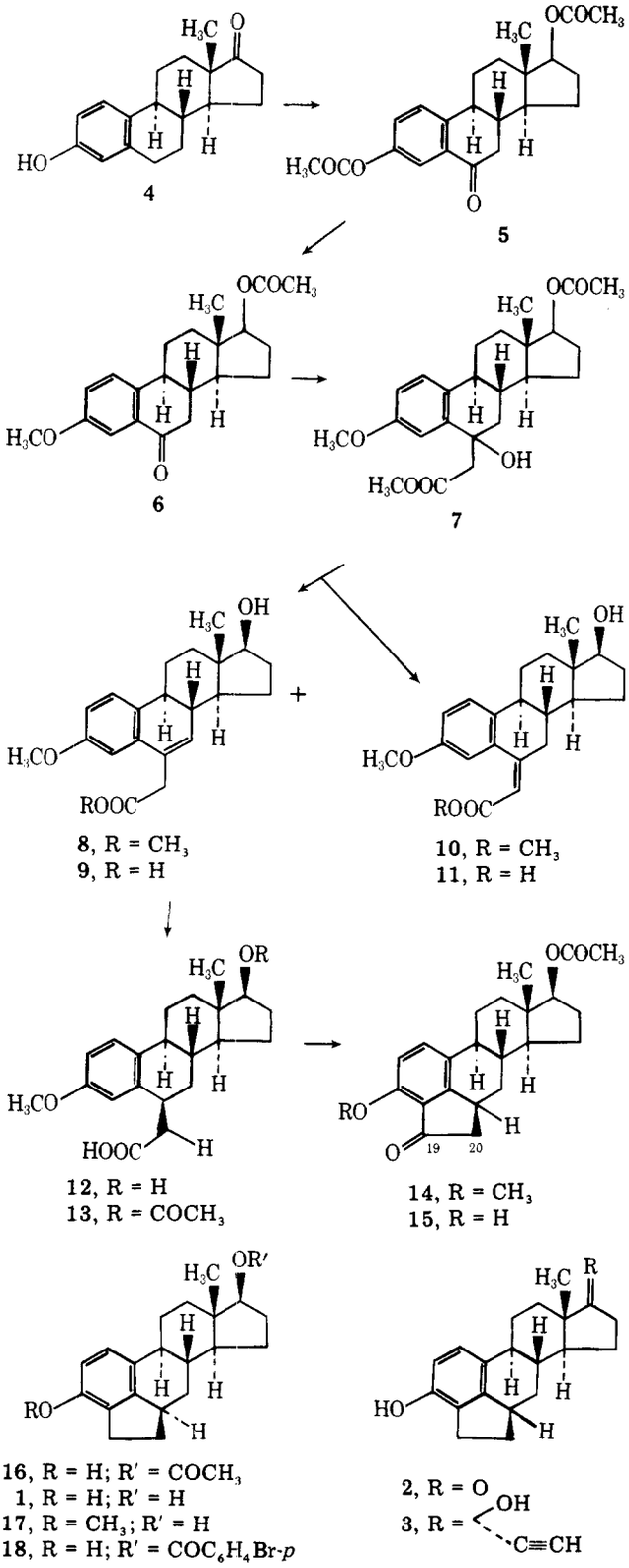
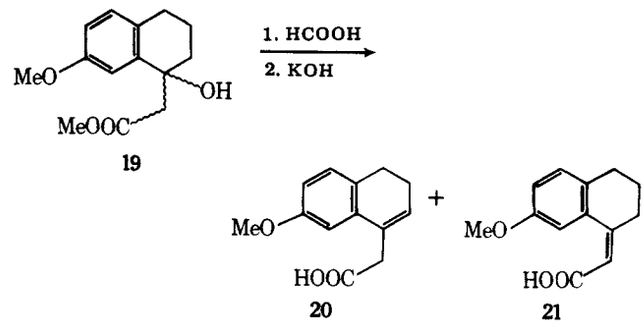
Synthesis of a new series of pentacyclic steroids, 4,6β-ethanoestradiol (**1**), 4,6β-ethanoestrone (**2**), and 17α-ethynyl-4,6β-ethanoestradiol (**3**), is described. Estrone is converted into the key intermediate 17β-acetoxy-3-methoxy-1,3,5(10)-estratriene-6β-acetic acid (**13**) in 11 steps. Friedel–Crafts cyclization of the acid chloride of **13** with aluminum chloride provides compounds **14** and **15**. Further structural modifications lead to **1**, **2**, and **3**. The absolute configuration of the *p*-bromobenzoate derivative of **1** has been confirmed by x-ray crystallography. Fusion of the ethano bridge at positions C-4 and C-6 from the β face leads to a unique class of steroids in which the B ring assumes a highly distorted conformation.

Substitution of the steroidal skeleton at C-6 has led to a number of important oral contraceptives.[1,2] Examples include dimethisterone, Provera (17α-acetoxy-6α-methylpregn-4-ene-3,20-dione), and megesterol acetate. Activity of such compounds has been explained on the assumption that the presence of alkyl substitution at C-6 prevents metabolic hydroxylation at this position. The syntheses of steroidal compounds with an ethano bridge across C-4 and C-6 are of special interest, since significant changes in the stereochemistry of steroidal skeleton can be effected with such substitutions. Studies with Dreiding models show that fusion of an ethano bridge at positions C-4 and C-6, from the β face, in the estrone molecule leads to a unique class of steroids in which the B ring assumes a highly distorted conformation. Little is known in the literature[3] about the formation and biological activities of steroids containing such a distorted B ring. We report here the synthesis of three such compounds, 4,6β-ethanoestradiol (**1**), 4,6β-ethanoestrone (**2**), and 17α-ethynyl-4,6β-ethanoestradiol (**3**). Further modifications could lead to a new class of steroids, whose biological profile remains to be examined.

The starting material was estrone (**4**), which was converted into **5** in three steps (Scheme I).[4] Hydrolysis, methylation, and acetylation[5] led to compound **6**. Reformatsky reaction upon **6** provided **7**, which on dehydration with formic acid gave a mixture of the esters **8** and **10**. Hydrolysis of this product with potassium hydroxide led to the unsaturated acids **9** and **11**. NMR spectra of the esters **8** and **10** (δ 5.98, endo olefinic H,

Scheme I





and 6.36, exo olefinic H, ratio 85:15) and of the acids **9** (δ 6.0 ppm, olefinic H) and **11** indicated that the endo isomers **8** and **9** were the major products in these reactions. This was also confirmed from studies[6] on the conversion of the model compound **19** into a mixture of **20** and **21**. Once again, the endo acid **20** was the predominant product (NMR δ 6.07, endo olefinic H, and 6.33, exo olefinic H, ratio 90:10).

Without separation, the mixture of **9** and **11** was hydrogenated, using 10% Pd/C as the catalyst. The product was primarily (>95% by NMR) the desired 6α-H acid **12**. The stereochemistry of **12** was assigned on the basis of its mode of formation (hydrogenation from α face) and from well-established precedence in literature.[7-9] Previously, it has been shown that hydrogenation of 6-dehydro-6-methylestrone leads to 6β-methylestrone.[9]

Attempts to cyclize compound **12** with anhydrous HF led to a complex mixture. Compound **12** was acetylated to **13**, cyclization of which with HF was also unsuccessful. Treatment of the acid chloride of **13** with 2–2.5 mol of anhydrous $AlCl_3$, however, yielded the desired ketone **14** in excellent yield. When more than 3 mol of anhydrous $AlCl_3$ was used, the product was the demethylated compound **15**.

It was interesting to note that in thin layer chromatography (silica gel, C_6H_6–CH_3OH, 85:15) the phenolic ketone **15** had a higher R_f value than the methoxy ketone **14**. This could be due to the hydrogen bonding between the five-member ketone and the hydroxyl group at position 3. Also, the cyclization of **13** into **15** was very facile and gave a remarkably high yield (86%). Clemmensen reduction and subsequent base hydrolysis proceeded smoothly to give the 4,6β-ethanoestradiol (**1**). Methylation of **1** led to **17** whereas oxidation with CrO_3 yielded estrone analogue **2**. The latter, upon treatment with lithium acetylide–ethylenediamine complex, provided 17α-ethynyl-4,6β-ethanoestradiol (**3**). The stereochemistry at C-17 in **3** was assigned on the basis of literature precedence.[10,11]

In order to define unambiguously the configuration at C(6) in 4,6β-ethanoestradiol (**1**), and to determine the conformation of the distorted B ring and its influence on the overall conformation of the molecule, the structure of 17p-bromobenzoate derivative **18** was examined by x-ray crystallography.[12] Single crystals of **18** were grown by evaporation of a cyclohexane–benzene solution. The crystal data follow: a = 13.417 (2), b = 23.404 (2), c = 7.333 (1) Å, space group $P2_12_12_1$. The structure was solved by conventional heavy-atom techniques and refined by full matrix least squares with hydrogen atoms placed at their geometrically expected positions and included in the structure-factor calculations for the final refinement. The final reliability index (R) was 9.9% for the 1361 observable spectra.

The α configuration of the hydrogen substituent at C-6 was unambiguously defined as illustrated in Figure 1. The B ring conformation in **18** was found to be highly distorted. From a

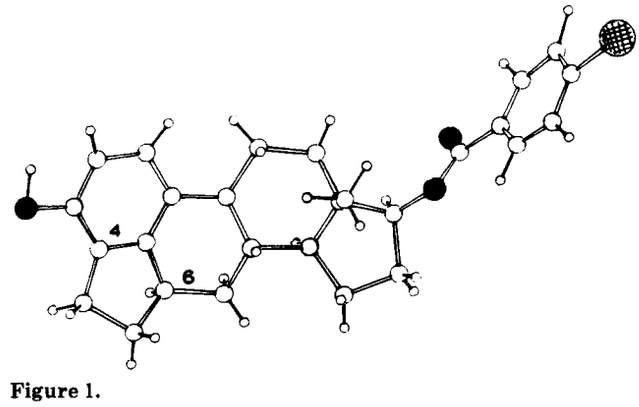


Figure 1.

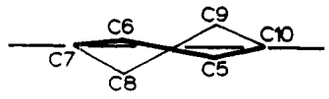


Figure 2.

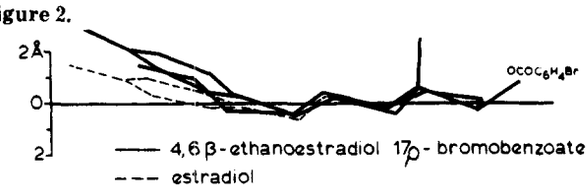


Figure 3.

projection along a line joining the midpoints of the C(5)–C(6) and C(8)–C(9) bonds (Figures 2), it is clear that atoms C(5) and C(6) are displaced from the horizontal plane far less than are atoms C(8) and C(9). If atoms C(7), C(6), C(5), and C(10) were coplanar, the ring would have a half-chair conformation. If, on the other hand, the C(5) and C(6) atoms were displaced to the same degree that the C(8) and C(9) atoms are, the ring would have a twist conformation.[13] There is no example in the literature of a steroid with a B ring so distorted. Its presence in the steroid results in a greatly enhanced bowing of the molecule toward the β face, as is illustrated in Figure 3, where the structure is superimposed upon that of estradiol.[14]

The results on the biological activities of **1, 2, and 3** will be published elsewhere.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer infrared spectrophotometer 700. 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, Ann Arbor, Mich.

17β-Acetoxy-3-methoxy-6-oxo-1,3,5(10)-estratriene (6). Following the procedure described in the literature,[4,5] estrone (**4**) was converted into 3,17β-diacetoxy-6-oxo-1,3,5(10) estratriene (**5**): mp 173–175 °C (lit.[4,5] mp 173.5–175 °C); IR 1765 (phenolic acetate >C=O), 1730 cm^{-1} (alcoholic acetate >C=O); NMR ($CDCl_3$) δ 0.83 (3 H, CCH_3), 2.05 [3 H, $OC(=O)CH_3$ at 17], and 2.28 [3 H, $OC(=O)CH_3$ at 3].

The 6-oxoacetate **5** (2 g) was hydrolyzed by methanolic potassium hydroxide solution to afford 1.5 g (97%) of 3,17β-dihydroxy-6-oxo-1,3,5(10)estratriene: mp 280 °C (lit.[4] mp 280–282 °C); IR 3525 (alcoholic OH), 3225 (phenolic OH), and 1670 cm^{-1} (six-member conjugated >C=O).

Following the procedure described by Kundu,[5] 0.75 g of 3,17β-dihydroxy-6-oxo-1,3,5(10)estratriene was converted to 0.73 g (91%) of 17β-hydroxy-3-methoxy-6-oxo-1,3,5(10)-estratriene: mp 80–82 °C (solidified and remelted at 130–132 °C) (lit.[5] mp 82–84 °C, solidified and remelted at 130–132 °C); IR 3470 (17β-OH), 1675 cm^{-1} (six-member conjugated >C=O); NMR ($CDCl_3$) δ 0.78 (3 H, CCH_3) and 3.83 (3 H, OCH_3).

Following literature procedure,[5] 17β-hydroxy-3-methoxy-6-oxo-1,3,5(10)-estratriene (1.3 g) was converted to 1.45 g (99%) of **6**: mp 167–169 °C (lit.[5] mp 168–169 °C); IR 1730 (acetate >C=O), 1680 cm^{-1} (six-member conjugated >C=O); NMR ($CDCl_3$) δ 0.83 (3 H, CCH_3), 2.05 [3 H, $OC(=O)CH_3$], and 3.83 (3 H, OCH_3).

17β-Acetoxy-6ζ-hydroxy-3-methoxy-1,3,5(10)-estratriene-6ζ-acetic Acid Methyl Ester (7). From 1.37 g of 3-methoxy-6-oxoestradiol 17β-acetate (**6**), 1.6 g of zinc, and 1.3 g of methyl bromoacetate in 40 ml of ether–benzene (1:1), there was obtained 1.6 g (96%) of the hydroxy ester **7**: IR 3520 (OH), 1740 (ester >C=O), and 1730 cm^{-1} (acetate >C=O); NMR ($CDCl_3$) δ 0.85 (3 H, CCH_3), 2.05 [3 H, $OC(=O)CH_3$], 3.75 [3 H, $-C(=O)OCH_3$], 3.8 (3 H, OCH_3), 6.8 and 7.2 (3 H, ArH).

17β-Hydroxy-3-methoxy-1,3,5(10),6-estratetraene-6-acetic Acid (9) and Compound 11. A solution of the hydroxy ester **7** (1.6 g, 3.9 mmol) and 97% formic acid (4 mL) was heated under reflux for 50 min. The reaction mixture was evaporated under reduced pressure to afford the unsaturated esters (**8** and **10**) as an oil (1.5 g, 98%), which showed a single spot on TLC: IR 1735 (ester >C=O) and 1725 cm^{-1} (acetate >C=O); NMR ($CDCl_3$) δ 0.85 (3 H, CCH_3), 2.07 [3 H, $OC(=O)CH_3$], 3.45 [2 H, $CH_2C(=O)OCH_3$], 3.7 [3 H, $OC(=O)CH_3$], 3.85 (3 H, OCH_3), 5.98 (endocyclic olefinic H), and 6.36 (exocyclic olefinic H) (ratio endo:exo 85:15), 6.8 and 7.16 (3 H, ArH). The acetate was hydrolyzed by stirring at room temperature for 48 h with a solution of potassium hydroxide (1 g) in methanol (18 mL) and water (2 mL). The crude acid (mixture of **9** and **11**) was crystallized from a mixture of ether, methylene chloride, and petroleum ether (bp 30–60 °C) to furnish the unsaturated acid **9** (1.10 g, 80%): mp 128–130 °C dec; IR 3440 (OH) and 1710 cm^{-1} (acid >C=O); NMR (CD_3OD) δ 0.75 (3 H, CCH_3), 3.8 (3 H, OCH_3), 6.0 (1 H, olefinic), 6.8 and 7.1 (3 H, ArH); MS *m/e* 342 (M^+, 68%), 298 (99%), 282 (67%), 171 (77%). Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.64; H, 7.65. Found: C, 73.52; H, 7.58.

17β-Hydroxy-3-methoxy-1,3,5(10)-estratriene-6β-acetic Acid (12). A solution of **9** and **11** (0.4 g, 1.2 mmol) in ethyl acetate (8 mL) and methanol (2 mL) was hydrogenated with 10% Pd/C (0.06 g) at room temperature. The calculated amount of hydrogen was absorbed during 2 h. The reaction mixture was filtered and the solvent was evaporated to afford 0.395 g (98%) of the crystalline reduced acid **12**. Recrystallization from a mixture of chloroform and petroleum ether afforded needles: mp 186 °C; IR 3450 (OH) and 1715 cm^{-1} (acid >C=O); NMR (CD_3OD) δ 0.8 (3 H, CCH_3), 3.75 (3 H, OCH_3), 6.7 and 7.2 (3 H, ArH); MS *m/e* 344 (M^+, 100%), 326 (3%), 298 (9%), 284 (29%), 258 (32%), 171 (31%). Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.18; H, 8.15.

17β-Acetoxy-3-methoxy-1,3,5(10)-estratriene-6β-acetic Acid (13). A solution of the acid **12** (0.316 g) in pyridine (1.5 mL) and acetic anhydride (1 mL) was kept at room temperature for 24 h. It was then decomposed with water and was made acidic with hydrochloric acid. The product was extracted with ether to afford 0.35 g (99%) of the acetate **13**. Recrystallization from chloroform–ether–methanol gave analytical sample: mp 185–186 °C; IR 1730 (acetate >C=O) and 1715 cm^{-1} (acid >C=O); NMR ($CDCl_3$) δ 0.85 (3 H, CH_3), 2.1 [3 H, $OC(=O)CH_3$], 3.8 (3 H, OCH_3), 6.8 and 7.3 (3 H, ArH). Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.47; H, 7.82. Found: C, 71.28; H, 7.93.

17β-Acetoxy-3-methoxy-19-oxo-4,6β-ethano-1,3,5(10)-estratriene (14) and 17β-Acetoxy-19-oxo-4,6β-ethano-1,3,5(10)-estratrien-3-ol (15). A solution of the acid **13** (1.2 g, 3.2 mmol), thionyl chloride (2 mL), and pyridine (8 drops) in methylene chloride (20 mL) was stirred at room temperature for 3 h. The solvent was removed by distillation at reduced pressure, and the last traces of thionyl chloride were eliminated by codistillation three times with 20-mL portions of methylene chloride. A solution of the acid chloride in methylene chloride (20 mL) was added dropwise over a period of 10 min to a stirred and cooled (ice bath) suspension of anhydrous aluminum chloride (1.8 g, 14.2 mmol) in methylene chloride (40 mL). After stirring for 3 h in the cold, the reaction mixture was kept at room temperature for 16 h. After treatment with ice–water (40 mL) and concentrated hydrochloric acid (2 mL), the mixture was extracted with ether (3 × 50 mL). The organic layer was separated and washed with water, 5% Na_2CO_3 solution, and finally with water. Evaporation of the solvent afforded 1.1 g of a crude product. TLC showed that the mixture was mainly the phenolic ketone **15**, contaminated with a small amount of methoxy ketone **14**. Chromatography on silica gel (33 g) with ethyl acetate–benzene (5:95) as eluate separated 0.95 g (86%) of the phenolic ketone **15**. This was recrystallized from methylene chloride–petroleum ether to furnish **15**: mp 208–209 °C; IR 3310 (OH), 1730 (acetate >C=O), and 1690 cm^{-1} (five-member conjugated and hydrogen-bonded >C=O); NMR ($CDCl_3$) δ 0.78 (3 H, CCH_3), 2.05 [3 H, $OC(=O)CH_3$], 6.7 and 7.25 (2 H, ArH), 7.0 (1 H, phenolic OH); MS *m/e* 354 (M^+, 99.9%). Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.30; H, 7.30.

In another experiment, with a smaller proportion of $AlCl_3$, the acid **13** (0.3 g, 0.8 mmol) was converted to its acid chloride as above. The crude acid chloride in methylene chloride (6 mL) was added to a solution of anhydrous aluminum chloride (0.27 g, 2 mmol) in methylene chloride (8 mL). The reaction mixture was stirred for 3 h at 5 °C and 14 h at 25 °C. Workup and recrystallization from methylene chloride–petroleum ether (bp 30–60 °C) furnished compound **14** (0.24 g, 84%): mp 249 °C; IR 1730 (acetate >C=O), 1710 cm^{-1} (five-member conjugated >C=O); NMR ($CDCl_3$) δ 0.80 (3 H, CCH_3), 2.06 [3 H, $OC(=O)CH_3$], 3.97 (3 H, $-OCH_3$), 6.80 and 7.4 (2 H, ArH); MS *m/e* 368 (M^+). Anal. Calcd for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 74.70; H, 7.54.

4,6β-Ethanoestradiol (1). A mixture of mossy zinc (6 g) and 5% $HgCl_2$ solution (12 mL) was kept at room temperature for 1 h with occasional shaking and the aqueous layer was then decanted. The amalgamated Zn was covered with concentrated HCl (30 mL) and H_2O (20 mL), and the ketone **15** (0.8 g) and toluene (7 mL) were added. The mixture was heated under reflux for 2.5 h, cooled, and

worked up to give 0.69 g of a crude mixture of **16** and **1**. This was hydrolyzed by refluxing for 2 h with a solution of 0.5 g of KOH in CH_3OH (10 mL). Methanol was removed and the residue was diluted with H_2O. The clear alkaline solution was acidified and worked up to furnish 0.575 g of the crude diol **1**. It was crystallized from ether–petroleum ether to afford 0.51 g (76%) of **1**: mp 206–207 °C; IR 3350 cm^{-1} (broad OH); NMR ($CDCl_3$) δ 0.74 (3 H, CCH_3), 6.65 and 7.02 (2 H, ArH); MS *m/e* 298 (M^+, 99%). Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.50; H, 8.78. Found: C, 80.50; H, 8.76.

A bis-*p*-bromobenzoate was obtained by treatment of **1** with *p*-bromobenzoyl chloride and pyridine at room temperature. Selective hydrolysis[12] of the phenolic ester with sodium carbonate solution at room temperature provided compound **18**, mp 258–260 °C. Anal. Calcd for $C_{27}H_{29}O_3Br$: C, 67.4; H, 6.1; Br, 16.6. Found: C, 67.14; H, 6.08; Br, Br, 16.61.

4,6β-Ethanoestradiol 3-Methyl Ether (17). To a solution of **1** (0.075 g) in methanol (2 mL) and 1 N KOH (5 mL), dimethyl sulfate (0.7 mL) was added dropwise. The mixture was stirred for 4 h at room temperature and left overnight. The separated solid was collected by filtration and dried to yield 0.0555 g (69.4%) of the methylated product **17**. Recrystallization from methanol–chloroform–ether yielded a semisolid: NMR ($CDCl_3$) δ 0.70 (3 H, CCH_3), 3.84 (3 H, OCH_3), 6.83 and 7.05 (2 H, ArH); MS *m/e* 312 (M^+). Anal. Calcd for $C_{21}H_{28}O_2 \cdot 2CH_3OH$: C, 73.37; H, 9.64. Found: C, 73.46; H, 9.34.

4,6β-Ethanoestrone (2). Jones reagent[15] (0.15 mL) was added to a solution of 4,6β-ethanoestradiol **1** (0.08 g) in acetone (20 mL) cooled to 5 °C and the mixture was stirred for 10 min. The reaction mixture was diluted with water and extracted with ether to afford the ketone **2** (0.06 g, 75%) which on recrystallization from ether–petroleum ether gave needles: mp 220–222 °C; IR 3370 (phenolic OH), 1730 cm^{-1} (five-member C=O); MS *m/e* 296 (M^+). Anal. Calcd for $C_{20}H_{24}O_2 \cdot \frac{1}{2}H_2O$: C, 78.65; H, 7.89. Found: C, 78.47; H. 7.60.

17α-Ethynyl-4,6β-ethanoestradiol (3). Acetylene gas was bubbled into a solution of compound **2** (0.175 g) in dimethyl sulfoxide (6 mL) under N_2 for 10 min. Lithium acetylide–ethylenediamine complex[10,11] (0.3 g) was then added and the acetylene was continued for another 3 h. After the reaction mixture had stood overnight at room temperature, it was decomposed with a saturated solution of ammonium chloride. The reaction mixture was extracted with ethyl acetate. The solid left after removal of the solvent was purified by preparative thin layer chromatography (silica gel, $CH_3OH/CHCl_3$, 20:80) to give 0.13 g (68.4%) of **3**. Recrystallization from a mixture of chloroform, ether, and petroleum ether afforded a material: mp 162–164 °C; IR 3400 and 3325 cm^{-1}; NMR ($CDCl_3$) δ 0.80 (3 H, CH_3), 2.63 (1 H, $-C\equiv CH$), 6.7 and 6.88 (2 H, ArH); MS *m/e* 322 (M^+). Anal. Calcd for $C_{22}H_{26}O_2$: C, 81.95; H, 8.13. Found: C, 81.74; H, 8.12.

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Registry No.—**1**, 62842-06-2; **1** bis-*p*-bromobenzoate, 62842-07-3; **2**, 62842-08-4; **3**, 62842-09-5; **5**, 3434-45-5; **6**, 20823-31-8; **7**, 62842-10-8; **8**, 62842-11-9; **9**, 62842-12-0; **10**, 62842-13-1; **11**, 62842-14-2; **12**, 62842-15-3; **13**, 62842-16-4; **13** acid chloride, 62842-17-5; **14**, 62842-18-6; **15**, 62842-19-7; **16**, 62842-20-0; **17**, 62842-21-1; **18**, 62230-95-9; 3,17β-dihydroxy-6-oxo-1,3,5(10)estratriene, 571-92-6;17β-hydroxy-3-methoxy-6-oxo-1,3,5(10)-estratriene, 50731-96-9.

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Notes

A Convenient Synthesis of (Chloromethyl)thio Aromatics and (Chloromethyl)thio Heteroaromatics

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(Chloromethyl)thio aromatics, and methods for their preparation, have been previously described in the literature. German Patent 845 511 describes the preparation of (chloromethyl)thio aromatics by treating 1 mol of aromatic thiol with at least 1 mol of formaldehyde in the presence of hydrogen chloride:

$$ArSH + CH_2{=}O \xrightarrow[HCl]{} ArSCH_2Cl \quad (1)$$

Dolman et al.[1] described the reaction of 1 mol of an aromatic thiol with 1 mol of formaldehyde in the presence of a catalytic amount of sodium methoxide to give the corresponding (hydroxymethyl)thio aromatic which was subsequently treated with 1.1 mol of thionyl chloride to afford the corresponding (chloromethyl)thio aromatic:

$$ArSH + CH_2{=}O \xrightarrow[NaOCH_3]{} ArSCH_2OH \xrightarrow{SOCl_2} ArSCH_2Cl \quad (2)$$

Senning and Lawesson[2] described the preparation of 1-[(chloromethyl)thio]-2,3,4,5,6-pentachlorobenzene by the chlorination of 1-(methylthio)-2,3,4,5,6-pentachlorobenzene with chlorine in refluxing carbon tetrachloride.

More recently, several examples of the preparation of (chloromethyl)thio heteroaromatics from the corresponding thiol and bromochloromethane have been described. In 1967, Pashkurov and Reznik[3] reported that the reaction of the so-