to yield 2.17 g (95%) of **4d** (A and B), mp 228–245°. When the thiolactone **4d** was chromatographed on silica gel using a 1:1 mixture of $CHCl_3$–petroleum ether (bp 30–60°) for elution, followed by recrystallization of the main fraction from MeOH, an analytical sample was obtained: mp 247–254°; $[\alpha]^{23}D$ −70.23; λ_{max}^{EtOH} 325 mμ (log ε 4.20); $\nu_{max}^{CHCl_3}$ (cm^{-1}) 3610 (OH), 1673 (conjugated C=C); nmr, Table I. *Anal.* ($C_{23}H_{30}O_2S$), C, H.

17ξ-Hydroxy-17-(5-methoxy-2-thienyl)androst-4-en-3-one (6).—In a three-necked flask under N_2, 1 g (0.0025 mole) of diol **2d** in 25 ml of PhH was added, and the mixture was brought to reflux temperature while stirring. To the refluxing mixture 1.00 g of dry, recrystallized Al(O-*i*-Pr)$_3$ and 6 ml of Me_2CO (dried over $MgSO_4$) were added; the mixture was then refluxed with stirring for 19 hr. At the end of the reflux period enough PhH was added to bring the total volume to 100 ml; the solution was then washed with eight 30-ml portions of a 15% solution of potassium sodium tartrate followed by four 30-ml portions of H_2O, and finally concentrated to give a crystalline product (square plates) which was recrystallized (PhH) to yield 0.616 g (61%) of **6**, mp 87–98°. Further recrystallization (PhH) gave an analytical sample: mp 95–101°; $[\alpha]^{23}D$ −46.22; λ_{max}^{EtOH} 251 mμ (log ε 4.30); $\nu_{max}^{CHCl_3}$ 3610 (OH), 1660 (conjugated C=O), 1208 and 1234 cm^{-1} (2-methoxythienyl). *Anal.* ($C_{24}H_{32}O_3S$) C, H.

γ-Mercapto-3-oxoandrost-4-ene-Δ$^{17,\gamma}$-crotonic Acid γ-Lactone (5).—When 875 mg of thiolactone **4d** was treated with Al(O-*i*-Pr)$_3$ and Me_2CO following the procedure described above, 560 mg of cream-colored solid was obtained which upon recrystallization (Me_2CO) gave 392 mg (45%) of thiolactone **5**, mp 215–225°. Further recrystallization (Me_2CO) gave the analytical sample: mp 234–236°; $[\alpha]^{23}D$ −54.64; λ_{max}^{EtOH} 239 mμ (log ε 4.29) and 328 mμ (log ε 4.15); $\nu_{max}^{CHCl_3}$ (cm^{-1}) 1673 (overlapping conjugated C=O groups); nmr, Table I. *Anal.* ($C_{23}H_{28}O_2S$) C, H.

Steroidal Cyclic Ethers

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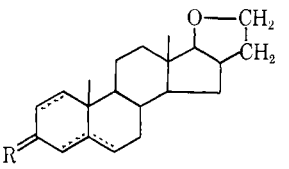
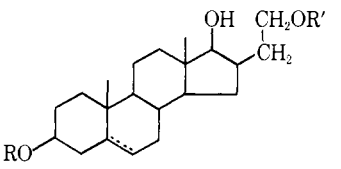
Several tetrahydrofuran derivatives of the androstane and estrane series were prepared by $NaBH_4$–BF_3 etherate reduction of the corresponding 17β-hydroxy-16β-acetic acid γ-lactones or by cyclization of the appropriate 16β-(2-hydroxyethyl)-17β-hydroxy steroids. The cyclic ethers were tested for estrogenic, antiestrogenic, antigonadotropic, and androgenic activities. Two of the estrane derivatives exhibited weak estrogenic properties while the remaining compounds were biologically inactive.

The observed antiestrogenic activites of a cyclic ether derivative of 19-nortestosterone, 4′,5′-dihydrospiro[estr-4-ene-17,2′(3′H)-furan]-3-one,[1] and a number of closely related compounds,[2] as well as the reported effectiveness of some of these substances as aldosterone antagonists,[3] suggested a study of the biological properties of a series of androstanes and estranes having a tetrahydrofuran structure fused to the D ring. The preparation of these compounds from a number of lactones or their precursors in the androstane[4] and estrane[5] series is reported.

$NaBH_4$–BF_3 etherate reduction[6] of 3β,17β-dihydroxy-5α-androstane-16β-acetic acid γ-lactone (**1**)[4] yielded 17β,2′-epoxy-16β-ethyl-5α-androstan-3β-ol (**2a**) in 34% yield together with a 46% yield of 16β-(2-hydroxyethyl)-5α-androstane-3β,17β-diol (**3a**). The major reduction product **3a** was allowed to react with *p*-toluenesulfonyl chloride in pyridine to give a mixture containing the mono- and the di-*p*-toluenesulfonates **3b** and **3c**. Treatment of the crude *p*-toluenesulfonate mixture with KO-*t*-Bu in *t*-BuOH essentially following the cyclization procedure of Brown,[2] led to the formation of the 3β-hydroxy ether **2a** and the *p*-toluenesulfonate **2b**. The latter (**2b**) was cleaved to **2a** with sodium in liquid ammonia–ammonium chloride.[7]





2a, R =  ; 5α-H

b, R =  ; 5α-H

4, R = O; 5α—H

5, R = O; Δ^{1,4}

8a, R =  ; Δ^5

b, R =  ; Δ^5

10, R = O; Δ^4

3a, R = R′ = H; 5α-H

b, R = H; R′ = Ts; 5α-H

c, R = R′ = Ts; 5α-H

7a, R = R′ = H; Δ^5

b, R = H; R′ = Ts; Δ^5

c, R = R′ = Ts; Δ^5

Ts = *p*-$CH_3C_6H_4SO_2$

Oxidation of **2a** in a two-phase system[8] led to the isolation of the ketone **4**, which upon dibromination followed by the elimination of the elements of HBr[9] gave the 1,4-dien-3-one **5**.

No pure reduction product could be isolated after $NaBH_4$–BF_3 etherate reduction of 3β,17β-dihydroxyandrost-5-ene-16β-acetic acid γ-lactone.[4] The desired 17β,2′-epoxy-16β-ethylandrost-5-en-3β-ol (**8a**) was obtained in the following manner. $LiAlH_4$ reduction of 3β,17β-diacetoxyandrost-5-ene-16β-acetic (**6**)[4] yielded the previously reported 16β-(2-hydroxyethyl)androst-5-ene-3β,17β-diol (**7a**).[10] The triol **7a**

(1) G. Bialy, A. P. Merrill, and G. Pincus, *Endocrinology*, **79**, 125 (1966).

(2) E. A. Brown, *J. Med. Chem.*, **10**, 546 (1967); U. S. Patent 3,297,686 (1967).

(3) G. E. Arth, H. Schwam, L. H. Sarett, and M. Glitzer, *J. Med. Chem.*, **6**, 617 (1963); S. H. Pines, R. A. Firestone, L. Re, M. A. Kozlowski, and M. Sletzinger, *Steroids*, **8**, 877 (1966); S. H. Pines, U. S. Patent 3,303,205 (1967).

(4) P. Kurath and W. Cole, *J. Org. Chem.*, **26**, 1939 (1961).

(5) P. Kurath and W. Cole, *ibid.*, **26**, 4592 (1961).

(6) G. R. Pettit and D. M. Piatak, *ibid.*, **27**, 2127 (1962); *cf.* G. R. Pettit, B. Green, T. R. Kasturi, and U. R. Ghatak, *Tetrahedron*, **18**, 953 (1962), and references to earlier work given in these two papers.

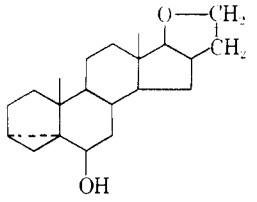
(7) D. B. Denney and B. Goldstein, *J. Org. Chem.*, **21**, 479 (1956); *J. Am. Chem. Soc.*, **79**, 4948 (1957).

(8) W. F. Bruce, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 139.

(9) R. Joly, J. Warnant, G. Nominé, and D. Bertin, *Bull. Soc. Chim. France*, 366 (1958); P. Wieland, K. Heusler, and A. Wettstein, *Helv. Chim. Acta*, **43**, 523 (1960).

(10) Ö. K. J. Kovács, A. F. Aboulezz, and B. Matkovics, *Acta Chim. Acad. Sci. Hung.*, **48**, 241 (1966).

was converted to the *p*-toluenesulfonate mixture containing **7b** and **7c** which, upon treatment with KO-*t*-Bu,[2] gave rise to a mixture of the cyclic ethers **8a** and **8b**. The hydroxy ether **8a** was isolated in pure form after column chromatography of the mixture on alumina; a second product isolated and characterized was shown to be the *i*-steroid **9** which was formed from **8b** by an *i*-steroid rearrangement[11] during chromatography of



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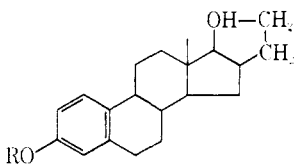
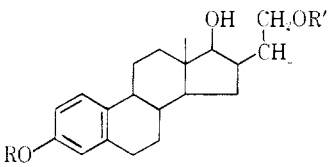
the original mixture.[12] Buffered hydrolysis of the early fractions obtained from the above chromatogram gave additional amounts of the *i*-steroid **9**. Oxidation of the alcohol **8a** with Jones reagent[13] gave rise to the α,β-unsaturated ketone **10**.

The reduction of 3,17β-dihydroxyestra-1,3,5(10)-triene-16β-acetic acid γ-lactone (**11a**)[5] with $NaBH_4$–BF_3 etherate[6] furnished the cyclic ether analog of estradiol **12a** and 16β-(2-hydroxyethyl)estra-1,3,5(10)-triene-3,17β-diol (**13a**). A similar reaction of 17β-hydroxy-3-methoxyestra-1,3,5(10)-trien-16β-acetic acid γ-lactone (**11b**)[5] led to the formation of **12b** and **13b** in 30 and 49% yields, respectively. Conversion of 16β-(2-hydroxyethyl)-3-methoxyestra-1,3,5(10)-trien-17β-ol (**13b**) to the *p*-toluenesulfonate **13c**, followed by treatment of the latter with KO-*t*-Bu,[2] gave rise to the cyclic ether **12b** in 85% yield. Birch reduction[14]

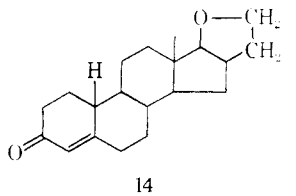


12a. R = H
b. R = CH_3



13a. R = R′ = H
b. R = CH_3; R′ = H
c. R = CH_3; R′ = *p*-$CH_3C_6H_4SO_2$

of **12b** under the conditions of Wilds and Nelson[15] followed by acid hydrolysis of the crude dienol ether intermediate led to the isolation of the 19-nortestosterone analog **14**.



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Biological Results.—The biological activity of the cyclic ethers was studied in laboratory animals using several established bioassays. The estrogenicity of the compounds was measured after subcutaneous administration to immature female mice as described by Dorfman[16] employing changes in the uterine weight as an end point. Only the estrane derivatives **12a** and **12b** showed weak uterotropic activities amounting to 0.005 and 0.002% of estrone, respectively.

Rat parabionts, a castrated male and an intact female, served for the evaluation of antigonadotropic and androgenic activities. The method described by Bunster and Meyer[17] with the following modifications was employed. No litter mates were used, skin incisions were joined with the aid of 11-mm surgical wound clips, and the abdominal area was banded with adhesive tape after the operation. The subcutaneous injections of the compounds to be evaluated were continued for 7 days and the animals were sacrified 24 hr after the last injection. Only **12a** showed statistically significant ($p = 0.05$) gonadotropin inhibition which was probably due to its estrogenicity. A slight increase in the seminal vesicle weight after the administration of **12a** likewise reflected the estrogenic activity of the substance.

The antiestrogenic activity of the compounds was evaluated after subcutaneous administration to immature female mice following the protocol of Edgren and Calhoun.[18] None of the cyclic ethers prepared showed any antiestrogenic activity.

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus. Optical rotations were measured with a Hilger and Watts polarimeter; ir spectra of all new compounds were obtained with a Perkin-Elmer Model 421 grating spectrophotometer in $CHCl_3$ solutions unless stated otherwise; the ν_{max} values are reported only where they contributed substantially to identify the product. The uv spectra of the unsaturated ketones, measured in MeOH solutions, were consistent with the structural assignments. The nmr spectra were recorded with a Varian A-60 nmr spectrometer at 60 MHz; 5–10% solutions in $CDCl_3$ were employed using TMS as an internal reference. Chemical shifts are reported in Hz from TMS (0 Hz) in the direction of decreasing field. Where analyses are indicated by symbols of the elements, analytical results were within ±0.3% of the theoretical values.

$NaBH_4$–BF_3 Etherate Reduction of 3β,17β-Dihydroxy-5α-androstane-16β-acetic Acid γ-Lactone (1).—A solution of 6.58 g of the lactone **1**[4] and 111.20 g of BF_3·Et_2O in 230 ml of THF was added dropwise to an ice-cooled suspension of 2.10 g of $NaBH_4$ in 115 ml of diglyme with stirring under N_2 over a period of 50 min.[6] The reaction mixture was stirred with cooling for 1 hr and then heated under reflux for 40 min. After cooling and careful addition of 150 ml of 2 *N* HCl and 800 ml of H_2O, the slurry was extracted in sequence with two 2000-ml portions of Et_2O and then with 1000 ml of the same solvent. The organic extracts were washed (2 *N* HCl, H_2O, saturated $NaHCO_3$, and to neutrality with H_2O). The insoluble interphase (triol **3a**) was carried into the aqueous extracts, collected on a filter, washed (H_2O), dried, and worked up as indicated below.

The Et_2O extracts were dried ($MgSO_4$), filtered, and evaporated to leave a 3.14 g of a solid residue. This material was purified by chromatography on 320 g of silica gel. From the C_6H_6–EtOAc (4:1 and 1:1) eluates a total of 2.26 g of residue was obtained after evaporation of the solvent. Recrystallization (Me_2CO) gave a first crop of 2.00 g of **17β,2′-epoxy-16β-ethyl-5α-androstan-3β-ol** (**2a**), mp 203–205°. Concentration of the mother liquors led to the isolation of a second crop of 0.13 g, mp 202–203°; the yield of **2a** was 34%. A portion of the first crop

(11) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp 314–320.

(12) R. S. Ludwiczak, T. Kubala, and I. Zyczyńska, *Rocz. Chem.*, **42**, 85 (1968); Dr. J. Tadanier of these laboratories informed us of a similar observation.

(13) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(14) A. J. Birch, *Quart. Rev.* (London), **4**, 69 (1950).

(15) A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5366 (1953).

(16) R. I. Dorfman, *Methods Hormone Res.*, **2**, 713 (1962).

(17) E. Bunster and R. K. Meyer, *Anat. Record*, **57**, 339 (1933).

(18) R. A. Edgren and D. W. Calhoun, *Proc. Soc. Exptl. Biol. Med.*, **94**, 537 (1957).

was recrystallized for analysis: mp 203–204°, $[\alpha]^{26}D$ +40° (*c* 1.07). *Anal.* ($C_{21}H_{34}O_2$) C, H.

The later EtOAc–MeOH (4:1 and 1:1) eluates of the above chromatogram contained 0.64 g of substance. This material was found to be identical with the above insoluble interphase product. The two crops were combined and recrystallized from MeOH to yield 3.08 g (46%) of **16β-(2-hydroxyethyl)-5α-androstane-3β,17β-diol** (**3a**), mp 263–265°. A sample of this material was recrystallized from MeOH for analysis: mp 271–272°, $[\alpha]^{26}D$ +2° (*c* 0.41, pyridine). *Anal.* ($C_{21}H_{36}O_3$) C, H.

Cyclization of 3a.—A mixture of 3.01 g of the triol **3a**, 3.06 g of *p*-toluenesulfonyl chloride, and 30 ml of pyridine was allowed to stand at room temperature overnight. It appears that not all of the triol **3a** had dissolved and thus 20 ml of pyridine was added. The mixture was warmed on the steam bath for 1 hr and then most of the pyridine was evaporated under reduced pressure. The residue was dissolved in 500 ml of CH_2Cl_2, the solution was washed with 100 ml of 10% aqueous AcOH, and the layers were separated. The aqueous phase was extracted twice with CH_2Cl_2 and discarded. The organic extracts were washed (H_2O), dried ($MgSO_4$), filtered, combined, and evaporated to leave 3.88 g of a mixture containing **3b** and **3c**. This material was treated with a solution of *t*-BuOK in *t*-BuOH (prepared from 220 ml of *t*-BuOH by dissolving 0.85 g of K) at room temperature overnight.[2] The reaction mixture was diluted with 500 ml of H_2O and the resulting slurry was extracted with Et_2O. The extract was washed (H_2O), dried ($MgSO_4$), filtered, combined, and evaporated to dryness under reduced pressure. The crude cyclization product (3.73 g) was purified by chromatography on 115 g of alumina, grade III. The residues resulting from the evaporation of the petroleum ether (bp 60–68°)–C_6H_6 (4:1 and 1:1) eluates were combined and recrystallized from Me_2CO–*n*-C_7H_{16} to furnish a first crop of 1.99 g of **17β,2′-epoxy-16β-ethyl-5α-androstan-3β-ol *p*-toluenesulfonate** (**2b**), mp 123–124°; a second crop amounted to 0.33 g, mp 117–119°. An analytical sample had the following physical constants: mp 123–124°, $[\alpha]^{26}D$ +10° (*c* 1.21). *Anal.* ($C_{28}H_{40}O_4S$) C, H.

Further eluates of the above chromatogram with C_6H_6 and C_6H_6–EtOAc (4:1) yielded, after evaporation of the solvent and recrystallization of the residue from Me_2CO, 0.46 g of the cyclic ether **2a**, mp 202–204°. The identity of this product with the above-prepared reference sample of **2a** was determined by mixture melting point determination and comparison of the ir spectra. A second crop of 0.10 g, mp 197–199°, was obtained.

Na–Liquid NH_3 Cleavage of 2b.—A solution of 1.42 g of the ester **2b** in 100 ml of anhydrous Et_2O was added dropwise to a solution of 0.67 g of Na in 100 ml of liquid NH_3 over a period of 30 min. About 15 min after the addition was completed the solution turned orange, and 3.30 g of NH_4Cl was added to discharge the orange color.[7] This was followed by the addition of 25 ml of H_2O and the NH_3 was allowed to evaporate. The slurry was diluted with 200 ml of H_2O and 500 ml of Et_2O, the layers were separated, and the aqueous phase was extracted twice more with Et_2O. The organic extract was washed (H_2O), dried, filtered, and evaporated to leave a residue of 0.96 g of reaction product. Chromatographic purification and recrystallization (Me_2CO) gave 0.65 g of the hydroxy ether **2a**, mp 201–203°; a second crop amounted to 0.11 g, mp 190–195°. A portion of the first crop was recrystallized for analysis: mp 203–205°, $[\alpha]^{25}D$ +39° (*c* 1.10). *Anal.* ($C_{21}H_{34}O_2$) C, H.

17β,2′-Epoxy-16β-ethyl-5α-androstan-3-one (**4**).—A solution of 5.47 g of **2a** in 320 ml of C_6H_6 was added to a solution of 8.75 g of $Na_2Cr_2O_7 \cdot 2H_2O$ in 43 ml of H_2O, 13.5 ml of concentrated H_2SO_4, and 8 ml of AcOH with vigorous stirring and cooling according to the oxidation procedure of Bruce.[8] Stirring at room temperature was continued for 22 hr under N_2. The above reaction mixture was diluted with 400 ml of C_6H_6, and the dark acid layer was separated and extracted with two 600-ml portions of C_6H_6. The C_6H_6 extracts were washed (H_2O, saturated $NaHCO_3$ solution, H_2O to neutrality). The C_6H_6 extracts were dried, filtered, combined, and evaporated to leave 5.10 g of a crystalline residue which was further purified by chromatography on silica gel and recrystallization from Me_2CO–*n*-C_7H_{16} to yield a first crop of 4.17 g of **4**, mp 155–156°; a second crop amounted to 0.22 g, mp 149–152°. An analytical sample was prepared from a portion of the first crop: mp 155–156°, $[\alpha]^{25}D$ +58° (*c* 1.10). *Anal.* ($C_{21}H_{32}O_2$) C, H.

17β,2′-Epoxy-16β-ethylandrosta-1,4-dien-3-one (**5**).—To a solution of 1.92 g of the ketone **4** in 30 ml of AcOH and 3.03 g of a 30% HBr solution in AcOH there was added 2.10 g of Br_2 in 8 ml of AcOH with stirring at room temperature over a period of 5 min, and stirring was continued for 15 min. The reaction mixture was diluted with 250 ml of H_2O and extracted with 400 ml of C_6H_6. The aqueous phase was separated and extracted with two 200-ml portions of C_6H_6. The organic extracts were washed to neutrality with H_2O, dried, combined, and evaporated under reduced pressure at 60° to yield a residue of 3.01 g of the partly crystalline dibromo ketone. The latter was dissolved in 45 ml of DMF and added to a stirred suspension of 3.02 g of LiBr and 3.03 g of Li_2CO_3 in 25 ml of DMF at 95°, under N_2, and the mixture was stirred for 18 hr at 90–100°.[9] The solution was allowed to cool and was diluted with 500 ml of Et_2O and 300 ml of H_2O. The layers were separated and the aqueous phase was extracted twice with 200 ml of Et_2O. The Et_2O extracts were washed (H_2O), dried, filtered, and evaporated to leave 1.93 g of partially crystalline reaction product which was further purified by chromatography on alumina and recrystallization from Me_2CO–*n*-C_7H_{16} to give 1.18 g of the desired 1,4-dien-3-one **5**, mp 141–143°; a second crop amounted to 0.14 g, mp 128–132°. For analysis a sample was sublimed at 160° under high vacuum and recrystallized: mp 144–145°, $[\alpha]^{25}D$ +37° (*c* 1.00). *Anal.* ($C_{21}H_{28}O_2$) C, H.

16β-(2-Hydroxyethyl)androst-5-ene-3β,17β-diol (**7a**).—A solution of 14.55 g of 3β,17β-diacetoxyandrost-5-ene-16β-acetic acid (**6**)[4] in 250 ml of THF was added dropwise to a stirred and cooled suspension of 4.68 g of $LiAlH_4$ in 300 ml of THF under N_2 over a period of 45 min. Stirring and cooling was continued for 1 hr, and the mixture was stirred at room temperature for 2.5 hr before warming to a gentle reflux for 15 min. The reaction mixture was cooled again by immersion into an ice bath. The careful addition of 40 ml of moist Et_2O was followed by the addition of 40 ml of H_2O, 700 ml of 2 *N* H_2SO_4, and 2000 ml of H_2O. The precipitate was collected on a filter, washed to neutrality with H_2O, and dried under reduced pressure at 60°. Recrystallization (EtOH) gave a first crop of 9.47 g of the triol **7a**, mp 268–270°, a second crop of 0.69 g, mp 262–264°, and a third crop of 0.20 g, mp 259–263°. A sample of the first crop of the triol **7a** was recrystallized for analysis: mp 269–270°, $[\alpha]^{25}D$ −40° (*c* 0.41, pyridine),[19] ν_{max}^{Nujol} 3497 and 3240 cm^{-1}. *Anal.* ($C_{21}H_{34}O_3$) C, H.

Cyclization of 16β-(2-Hydroxyethyl)androst-5-ene-3β,17β-diol (**7a**).—A mixture of 6.00 g of the triol **7a**, 5.17 g of *p*-toluenesulfonyl chloride and 100 ml of pyridine was allowed to stand at room temperature overnight. The reaction mixture furnished, after a work-up as described for the saturated compound **3a**, 7.26 g of the crude mixture of **7b** and **7c**. The *p*-toluenesulfonates were allowed to react in a solution of *t*-BuOH containing *t*-BuOK (prepared from 420 ml of *t*-BuOH by dissolving 1.62 g of K) at room temperature for 40 hr.[2] The reaction mixture was worked up as in the case of **3b** and **3c**, to leave 7.01 g of crude reaction product which was purified by chromatography on 230 g of alumina, grade III.

The late petroleum ether–C_6H_6 (4:1) and the early petroleum ether–C_6H_6 (1:1) eluates contained 1.23 g of an oil. This material and 1.12 g of AcOK, dissolved in 85 ml of Me_2CO and 36 ml of H_2O, was warmed on the steam bath to a gentle reflux for 24 hr. Removal of most of the solvent under reduced pressure, extraction of the resulting slurry with Et_2O, washing, drying, and evaporation of the organic solution led to the isolation of 1.09 g of crude product. This was purified by chromatography and recrystallization to yield 0.28 g of **17β,2′-epoxy-16β-ethyl-3α,5α-cycloandrostan-6β-ol** (**9**), mp 155–157°, which was found to be identical with the material characterized below.

The later eluates with petroleum ether–C_6H_6 (1:1) upon evaporation of the solvent, furnished crystalline residues amounting to 0.64 g. Several recrystallizations of this product (Me_2CO–*n*-C_7H_{16}) gave 0.15 g of the *i*-steroid **9**, mp 156–158°. A second crop of 0.30 g of compound, mp 147–150°, was obtained after concentrating the mother liquors. An analytical sample had the following physical constants: mp 156–158°; $[\alpha]^{26}D$ +61° (*c* 1.01); $\nu_{max}^{CDCl_3}$ 3601, 3055 cm^{-1};[20] nmr, multiplet between 220 and 250 Hz (ether, 3 H), triplet centered at 196 Hz ($J_{AX} \simeq$

(19) Kovács, *et al.*,[10] reported mp 270°, $[\alpha]^{20}D$ −7.5° (pyridine). A part of the above sample of **7a** was converted to the triacetate, mp 131–132°, $[\alpha]^{25}D$ −34° (*c* 1.06), ν_{max} 1720 cm^{-1}. *Anal.* ($C_{27}H_{40}O_6$) C, H. Kovács, *et al.*,[10] reported for the triacetate mp 133–134°, $[\alpha]^{20}D$ −37.5°. No explanation can be offered for the difference in the observed optical rotation of the triol **7a**.

(20) A. R. H. Cole, *J. Chem. Soc.*, 3807, 3810 (1954).

$J_{BX} \simeq 2.5$ Hz) (6α-H),[21] singlets at 64.5 (10-Me) and 48 Hz (13-Me), complex absorption between 0 and 50 Hz (cyclopropyl H).[21] *Anal.* ($C_{21}H_{32}O_2$) C, H.

The C_6H_6–EtOAc (9:1) eluates gave, after evaporation of the solvent, a total of 3.28 g of crystalline residue which upon recrystallization (Me_2CO) yielded a first crop of 2.47 g of **17β,2′-epoxy-16β-ethylandrost-5-en-3β-ol (8a)**, mp 181–183°. Concentration of the mother liquors led to the isolation of a second crop of 0.49 g, mp 175–179°. An analytical sample had mp 184–186°; $[\alpha]^{25}D$ −30° (*c* 1.01); nmr, broad absorption at 324 Hz (vinyl H),[22] multiplet between 220 and 250 Hz (ether, 3 H), partially overlapping broad absorption centered at 210 Hz (3α-axial H),[22] singlets at 62 (10-Me)[22] and 47 Hz (13-Me). *Anal.* ($C_{21}H_{32}O_2$) C, H.

17β,2′-Epoxy-16β-ethylandrost-4-en-3-one (10).—To a cold (5°) solution of 1.11 g of the hydroxy ether **8a** in 200 ml of Me_2CO was added while swirling 1.75 ml of CrO_3 reagent[13] under N_2. After 10 min the reaction mixture was diluted with 750 ml of H_2O, and the precipitate was collected on a filter, washed with several small amounts of H_2O, and dried at 60° under reduced pressure. The compound was dissolved in 40 ml of MeOH containing 4 drops of a 10% aqueous KOH solution and warmed on the steam bath for 5 min. The KOH was neutralized with AcOH, the solution was diluted with 100 ml of H_2O, and most of the MeOH was removed under reduced pressure on the steam bath. The aqueous suspension was cooled and extracted with Et_2O. The extract was washed (2 *N* HCl, H_2O), dried ($MgSO_4$), filtered, and evaporated to leave 0.76 g of crystalline oxidation product which was purified by chromatography on 30 g of alumina, grade III. The residues from the eluates with petroleum ether–C_6H_6 (4:1 and 1:1) gave after recrystallization from Me_2CO–*n*-C_7H_{16} a first crop of 0.56 g of **10**, mp 172–173°; a second crop amounted to 0.06 g, mp 168–170°. A part of the first crop was recrystallized for analysis: mp 173–174°, $[\alpha]^{20}D$ +125° (*c* 0.98). *Anal.* ($C_{21}H_{30}O_2$) C, H.

$NaBH_4$–BF_3 Etherate Reduction of 3,17β-Dihydroxyestra-1,3,5(10)-triene-16β-acetic Acid γ-Lactone (11a).—A solution of 3.12 g of the lactone **11a**[5] and 52.79 g of freshly distilled BF_3·Et_2O in 155 ml of THF was added to a well-stirred suspension of 0.96 g of $NaBH_4$ in 60 ml of diglyme with cooling under N_2.[6] The reaction mixture was processed as in the reduction experiments described above in the androstane series. The Et_2O extracts contained 2.87 g of crude reduction product. Material which was neither soluble in Et_2O nor in the H_2O layer was collected on a filter, washed (H_2O), and dried at 60° under reduced pressure. The product (0.76 g) was recrystallized (Me_2CO) to give 0.26 g of the triol **13a**, mp 247–248°, identical with the sample characterized below.

The residue from the Et_2O extracts, 2.87 g, was purified by chromatography on 280 g of silica gel. The C_6H_6–EtOAc (1:1) eluates yielded a crystalline residue of 1.12 g after evaporation of the solvent. Several recrystallizations of this material (Me_2CO) led to the isolation of 0.39 g of **17β,2′-epoxy-16β-ethylestra-1,3,5(10)-trien-3-ol (12a)**, mp 269–270°; a second crop of 0.38 g melted at 267–268°. The above first crop was given for analysis: $[\alpha]^{25}D$ +114° (*c* 1.02). *Anal.* ($C_{20}H_{28}O_2$) C, H.

Evaporation of the EtOAc–MeOH (9:1 and 4:1) eluates left a residue of 1.50 g of solid which was recrystallized (Me_2CO). A first crop of **16β-(2-hydroxyethyl)estra-1,3,5(10)-triene-3,17β-diol (13a)**, 0.23 g, melted at 245–246°; second crop, 0.46 g, mp 244–246°. The first crop was found to be analytically pure: $[\alpha]^{25}D$ +49° (*c* 0.62, pyridine). *Anal.* ($C_{20}H_{28}O_3$) C, H.

$NaBH_4$–BF_3 Etherate Reduction of 17β-Hydroxy-3-methoxyestra-1,3,5(10)-triene-16β-acetic Acid γ-Lactone (11b).—A solution containing 6.34 g of the lactone **11b**[5] and 84.21 g of freshly distilled BF_3·Et_2O in 230 ml of THF was added dropwise to an ice-cooled and stirred mixture of 1.56 g of $NaBH_4$ in 95 ml of diglyme under N_2 over a period of 45 min.[6] The reaction mixture was processed and worked up as in the case of the corresponding reductions discussed above to yield 8.85 g of crude reaction product which was purified by chromatography on 700 g of silica gel. Evaporation of the C_6H_6–EtOAc (9:1) eluates left a residue of 2.24 g of substance which was recrystallized from *n*-C_7H_{16} to yield a first crop of 1.52 g of **17β,2′-epoxy-16β-ethyl-3-methoxyestra-1,3,5(10)-triene (12b)**, mp 127–128°; a second crop amounted to 0.31 g, mp 126–127° (yield 30%). A part of the first crop was recrystallized for analysis, mp 127.5–128.5°, $[\alpha]^{25}D$ +113° (*c* 1.12). *Anal.* ($C_{21}H_{32}O_2$) C, H.

Recrystallization of the residues from the later eluates with EtOAc–MeOH (9:1, 4:1, and 1:1) from Me_2CO gave 3.16 g of **16β-(2-hydroxyethyl)-2-methoxyestra-1,3,5(10)-trien-17β-ol (13b)**, mp 203–205° (yield 49%). A sample was recrystallized for analysis: mp 210–211°, $[\alpha]^{25}D$ +47° (*c* 0.52, pyridine). *Anal.* ($C_{21}H_{30}O_3$) C, H.

Cyclization of 13b.—A solution of the triol **13b** (3.06 g), 2.72 g of *p*-toluenesulfonyl chloride, and 30 ml of pyridine was allowed to stand at room temperature for 24 hr. The crude *p*-toluenesulfonate **13c**, 3.07 g, was warmed on the steam bath in a solution of *t*-BuOH containing *t*-BuOK (prepared from 160 ml of *t*-BuOH and 0.62 g of K) for 2 hr; the reaction mixture was then allowed to stand at room temperature overnight. The mixture was diluted with 1000 ml of Et_2O and 250 ml of H_2O. The H_2O layer was separated and extracted with two additional portions of Et_2O. The organic extracts were washed (H_2O, saturated NaCl), dried, filtered, combined, and evaporated to leave 2.90 g of crude cyclization product. The compound was further purified by chromatography on 125 g of alumina, grade III, and the residues from the petroleum ether–C_6H_6 1:1 and 1:1) eluates (2.76 g) were recrystallized from *n*-C_7H_{16} to yield a first crop of 2.36 g of **12b**, mp 127.5–128.5°; second crop, 0.11 g, mp 126–128° (yield 85%). An analytical sample was prepared from the first crop: mp 127–128°; $[\alpha]^{25}D$ +112° (*c* 1.11); nmr, 451 (s), 409 (d), 401 Hz (s) (aromatic H), multiplets between 220 and 250 (cyclic ether, 3 H), 229 (OCH_3) and 47 Hz (13-Me). *Anal.* ($C_{21}H_{28}O_2$) C, H.

17β,2′-Epoxy-16β-ethylestr-4-en-3-one (14).—To a solution of 1.51 g of the methoxy ether **12b** in 120 ml of Et_2O cooled in Dry Ice–Me_2CO there was added about 300 ml of liquid NH_3. This was followed by the addition of 1.40 g of Li wire in small pieces over a period of 15 min, and 12 min later the careful addition of 50 ml of EtOH was initiated.[15] Most of the NH_3 was allowed to evaporate and 125 ml of H_2O was added carefully, and this was followed by 200 ml of Et_2O. The layers were then separated and the H_2O phase was extracted with two 250-ml portions of Et_2O. The organic extracts were washed to neutrality (H_2O), dried ($MgSO_4$), filtered, combined, and evaporated to leave 1.52 g of crystalline reaction product. This material was dissolved in 100 ml of MeOH and 42 ml of 3 *N* HCl and warmed to a gentle reflux for 30 min. The reaction mixture was allowed to cool, diluted with 200 ml of H_2O, and extracted with 500 ml of Et_2O. The H_2O phase was separated and extracted twice more. The organic extracts were washed (saturated $NaHCO_3$, H_2O to neutrality), dried, filtered, and evaporated to leave 1.51 g of a crystalline residue which was further purified by chromatography on 45 g of alumina, grade III. From the early eluates with petroleum ether–C_6H_6 (9:1) a residue of 0.36 g was obtained. Recrystallization of this substance from *n*-C_7H_{16} led to the recovery of 0.27 g of the starting material **12b**. The later petroleum ether–C_6H_6 eluates (9:1, 4:1, and 1:1) and the C_6H_6 eluates contained 1.10 g of the Birch reduction product **14**. The compound was recrystallized (Me_2CO *n*-C_7H_{16}) to yield 0.75 g of substance, mp 149–150°; second crop, 0.10 g, mp 135–140°. A sample of the first crop was recrystallized for analysis: mp 150–151°, $[\alpha]^{25}D$ +79° (*c* 1.01). *Anal.* ($C_{20}H_{28}O_2$) C, H.

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