5.6 at 300 v for 22 hr also showed only one spot (developed with Pauly reagent). For analysis a sample was dried over P_2O_5 at 100° *in vacuo*; a loss in weight of approximately 10% was observed.

Anal. Calcd for $C_{45}H_{70}N_{12}O_{12}S_2$: C, 52.2; H, 6.82; N, 16.2. Found: C, 51.9; H, 6.87; N, 15.9.

Acknowledgments.—We wish to thank Mrs. Frances Richman and Miss Margitta Wahrenburg for the bioassays under the direction of Dr. W. Y. Chan. We also wish to thank Mr. Joseph Albert for the elemental microanalyses.

The Synthesis, Stereochemistry, and Biology of 16-Hetero and 17-Oxa-D-homo Steroids[1]

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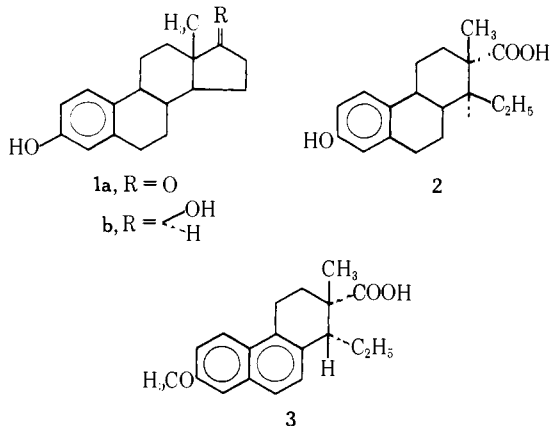
The synthesis, stereochemistry, and biological activities of 16-oxa, 16-aza-, and 17-oxa-D-homo steroids and related seco steroids derived from estrone 3-methyl ether, (±)-13-ethyl-3-methoxygona-1,3,5(10)-trien-17-one, and 14-isoequilenin are presented.

Stamler, Marmiston, Oliver, and others[2] have presented evidence that estrogens play a significant role in human female resistance toward atherosclerosis by virtue of their ability to alter serum lipid concentrations. However, the effect of estrogens on secondary sex characteristics is an obvious deterrent to any therapeutical value they may have in man. At our laboratories, there has been a consistent effort to obtain a substance which might mimic estrone (**1a**) or 17β-estradiol (**1b**) in its ability to alter blood fat patterns in animals without affecting the reproductive organs. A program which began with the investigation of new ring-D seco steroids related to some estrogenolic acids,[3-5] an example of which is doisynolic acid (**8**), led to the synthesis of 16-oxaestra-1,3,5(10)-triene-3,17-diol 3-methyl ether (**14b**), a substance which, in the rat, has significant effects on blood lipids and which is devoid of estrogenic effects at screening levels.[6] The synthesis and stereochemistry of **14b** and related seco and hetero steroids are described presently.



Synthesis and Stereochemistry.—The synthesis began with the ozonolysis of the enol acetate **4a** followed by hydrolysis to the aldehyde acid **5a** (Scheme I). The next synthetic step, the internal enol esterification between the reactive alkyl aldehyde and carboxyl groups, was without precedent and required study. Typical conditions[7] which have been used for the conversion of γ- and δ-ketocarboxylic acids to enol lactones or aldehydes to enol acetates gave only polymer or a low yield of the acetoxy lactone **11a**. Treatment of **5a** in methanol with *p*-toluenesulfonic acid led to the methoxy lactone **11b**.[8] However, rapid, azeotropic distillation of water from a dilute solution of **5a** in toluene containing *p*-toluenesulfonic acid gave a good yield of the enol lactone **6a**. Ozonolysis of the enol lactone **6a** followed by hydrolysis yielded **7a**. Reduction of the aldehyde acids **5a** and **7a** with sodium borohydride followed by acidification produced the six-membered ring lactone **9a** and the hydroxy acid **8a**, respectively. Azeotropic distillation of water from a toluene solution of **8a** containing a catalytic amount of *p*-toluenesulfonic acid yielded the lactone **9b**. Cleavage of the methyl ethers **9a** and **9b** with potassium hydroxide in ethanol[9] at 200° followed by treatment with strong acid gave the phenolic derivatives 17-oxa-D-homoestrone (**9d**) and 16-oxaestrone (**9e**), respectively. The lactones **9a** and **9b**, when reduced with lithium aluminum hydride, yielded the diols **12a** and **12b**, respectively, and, when reduced with diisobutylaluminum hydride[10] in toluene at −60°, yielded the hemiacetals **14a** and **14b**, respectively (Scheme II). When each was dissolved in methanol containing strong acid, a corresponding mixture of methyl ethers was obtained which was

(1) Presented in part at the 2nd International Congress on Hormonal Steroids, Milan, Italy, May 1966; J. S. Baran, *Excerpta Med.*, **111**, 387 (1966).

(2) For leading references see J. Stamler in "Atherosclerosis and Its Origin," M. Sandler and G. H. Bourne, Ed., Academic Press Inc., New York, N. Y., 1963, p 231.

(3) The related estrogenolic acid, 7-methylbisdehydrodoisynolic acid[4] (**3**), is a potent estrogen in the mouse and a weak estrogen in man.[5] It was reasoned that steroids related to **2** and **3** might still have pronounced effects on the lipid metabolism in man without estrogenic effects especially if they affected the lipid metabolism of animals with little or no effects on the reproductive organs.

(4) K. Miescher, *Chem. Rev.*, **43**, 367 (1948).

(5) K. Miescher, *Recent Progr. Hormone Res.*, **3**, 47 (1948); P. M. F. Bishop, G. C. Kennedy, and G. Wynn-Williams, *Lancet*, **255**, 764 (1948).

(6) R. E. Ranney and J. S. Baran, *Federation Proc.*, **25**, 387 (1966).

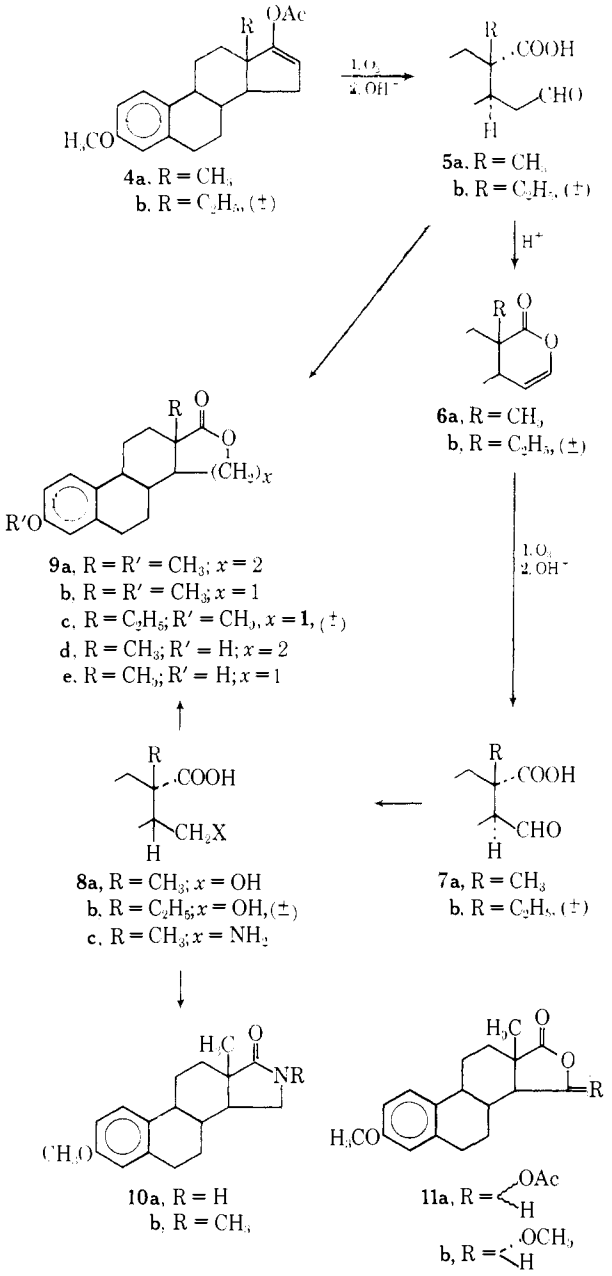
(7) See preparation of **6a** in the Experimental Section.

(8) The assignment of configuration to the C-16 hydrogen is based on its nmr spectrum. The half-line width for the C-16 hydrogen is about 5 cps which would be associated with a coupling of an equatorial C-16 hydrogen atom with the C-15 hydrogen atoms; see N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 51.

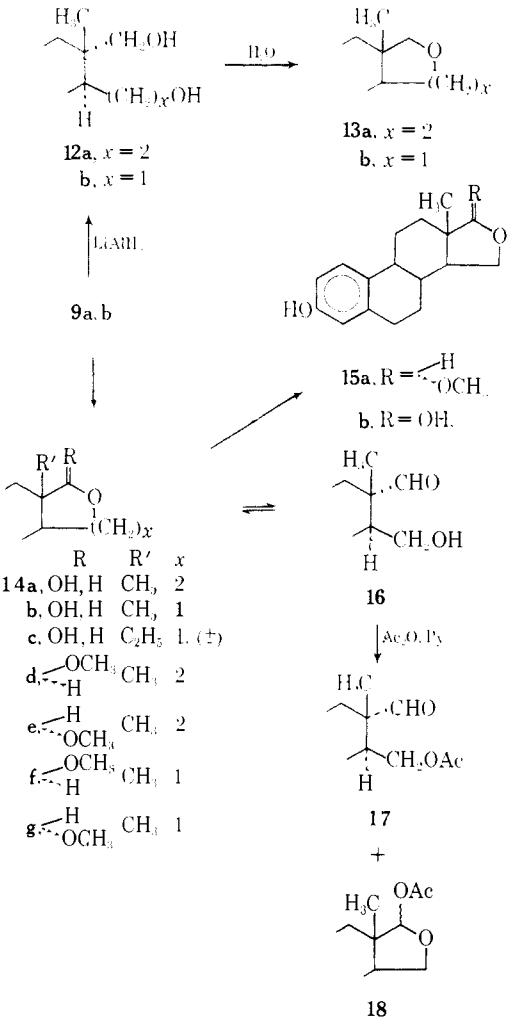
(9) G. P. Mueller and R. May, *J. Am. Chem. Soc.*, **71**, 3313 (1949).

(10) (a) J. Schmidtlin and A. Wettstein, *Angew. Chem. Intern. Ed. Engl.*, **3**, 240 (1964); (b) J. S. Baran, *J. Org. Chem.*, **30**, 3564 (1965).

SCHEME I



SCHEME II



separated by chromatography on basic alumina into the 17-oxa-D-homo-17a-ol 17a-methyl ethers **14d** and **14e** and 16-oxa-17-ol 17-methyl ethers **14f** and **14g**, respectively. When **14g** was cleaved with potassium hydroxide in ethanol at 220° to **15a** and the product was hydrolyzed, **15b** was obtained.

The assignment of configuration to the methyl ethers derived from **14a** and **14b** is based on estimates of their molecular rotations according to the methods of Whiffen[11] and Brewster[12] using the experimental values 249 for **13a** and 128 for **13b**. The ethers **13a** and **13b** were obtained by dehydration of the diols **12a** and **12b**, respectively. Hence, for the six-membered ring hemiacetal methyl ethers, the observed MD values of +342 and of −33° must correspond to the calculated values for isomers **14d** (calcd MD +354°) and **14e** (calcd MD −6°), respectively. Likewise, for the five-membered ring hemiacetal methyl ethers the observed MD values of +241 and of −102° must correspond to the 16-oxa-17β-methoxy derivative **14f** (calcd MD 317°) and 16-oxa-17α-methoxy derivative **14g** (calcd MD −61°), respectively.[13]

Recently, Listowsky, *et al.*,[14] have studied optical rotatory dispersion (ord) curves of aldopyranoses to 185 mμ and have formulated rules similar to the octant rule for ketones which predict the stereochemistry of anomeric aldopyranoses and their ethers from trends in their ord curves. Although no ord curves of aldofuranoses are known, if the analysis of these authors for aldopyranoses is applied to the anomeric 16-oxa-17-methoxy ethers, negative trends should be observed for the ord curves of the 17α-methoxy isomer and positive trends for the 17β isomer.[15] Since **14g** is preponderant in an equilibrium mixture of ethers and readily available by crystallization, it was converted to **20a** by the sequence **14g** → **19a** → **20a**. The methyl ether **19a** could be hydrolyzed to **19b** in aqueous tetrahydrofuran with strong acid. The 16-oxaestrane analog **20b** was similarly obtained from **13b** *via* **19c**. Figure 1 de-

(11) D. H. Whiffen, *Chem. Ind.* (London), 964 (1956).

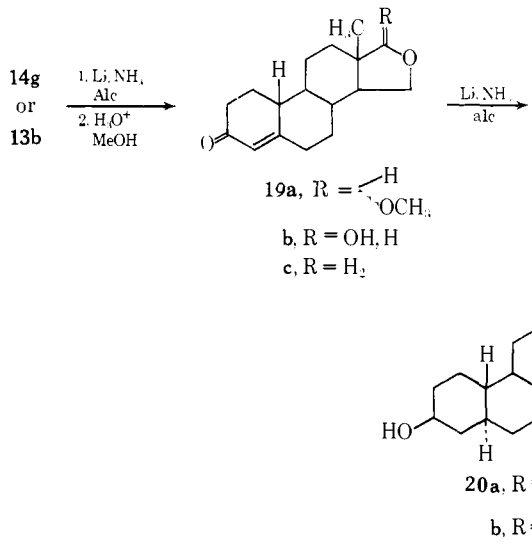
(12) J. H. Brewster, *J. Am. Chem. Soc.*, **81**, 5475, 5483 (1959).

(13) In estimating the molecular rotations of the 16-oxa steroids, calculations were based on an average of the contributions to two ring D conformations used by Brewster in predicting the rotatory effects of substituents in ring D of steroids.[12] Thus, the calculated values for **14f** and **14g** differ from the MD of **13b** by [+0.8*C*(OH) − 105] or +189° and [−0.8*C*(OH) + 105] or −189°, respectively.

(14) I. Listowsky, G. Avigad, and S. Englard, *J. Am. Chem. Soc.*, **87**, 1765 (1965).

(15) Note that Brewster's treatment when applied to the anomers **14f** and **14g** relative to **13b** also predicts the same trends.

picts the expected strong negative trend to 200 mμ for the ord curve of the 17α-methoxy isomer **20a** relative to unsubstituted derivative **20b**. It is evident from inspection of the curves in Figure 2 for **14f** and **14g** to 280 mμ that they follow trends predicted for each isomer. The weak rising curve for the hemiacetal in solution can be best explained by contributions largely from the 17α-ol in equilibrium with the hydroxyaldehyde form.[16]



Lemieux, *et al.*,[17] has shown that in the nmr spectra of anomeric aldopyranoses the axial hydrogen at the glycosidic carbon atom absorbs at a higher field than the equatorial counterpart. The fact that the C-17a axial hydrogen (230 cps) in the nmr spectrum of **14d** absorbs at higher field than its less shielded counterpart, the C-17a equatorial hydrogen (246 cps) in **14e**, is consistent with the assignment of the configurations of these epimers by rotation studies. It is interesting that in the nmr spectra of the furanoses exemplified by the anomers **14f** and **14g** the C-17α hydrogen (270 cps) absorbs at higher field than its counterpart, the C-17β hydrogen (275 cps).

Measurement of the relative contribution of C-13 methyl absorption in the nmr spectra of mixtures of epimers equilibrated with strong acid indicated that the ratio of **14d** to **14e** was about 1:2 and in **14a** the ratio of the 17aβ- to 17aα-hydroxy epimer was about 2:1. The product of the reduction of lactone **9a** with diisobutylaluminum hydride mutarotates in strong acid solution from 53 to 81°. This observation indicates that relatively more 17aα-hydroxy isomer is present in the reduction product than at equilibrium.

Physical and chemical evidence for the crystalline five-membered ring hemiacetal **14b** indicates that in the crystalline form it is present only as the hemiacetal; in solution the hemiacetal **14b** exists predominantly as the 17α-ol in equilibrium with about 5–10% of the hydroxyaldehyde form **16**.[16] Reaction of the hemiacetal **14b** with acetic anhydride in pyridine gave a mixture of acetates in which was present about 82% of the ace-

(16) Using the data in Figure 2 and the ord curve to 280 mμ of **17**, solutions to simultaneous equations for the percentage of each component that contributes to the ord curve of **14b** show that the per cent of the 17α-ol, 17β-ol, and hydroxy aldehyde form in solution are about 60, 30, and 10, respectively.

(17) R. V. Lemieux, R. K. Knullnig, H. J. Bernstein, and W. A. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958).

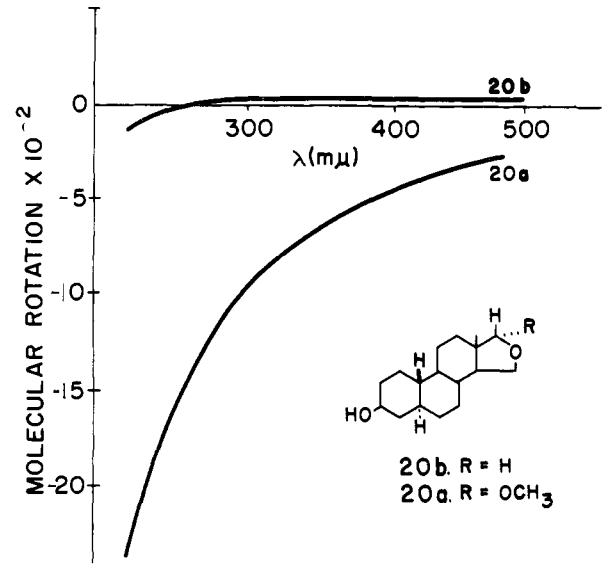


Figure 1.—Optical rotatory dispersion curves of **20a** and **20b** in methanol at 25°.

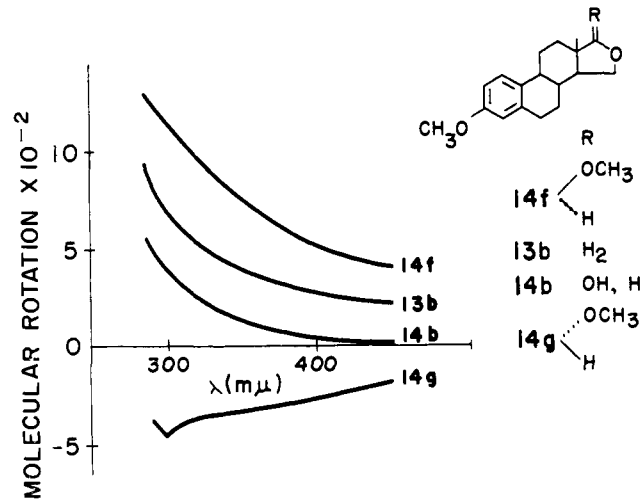
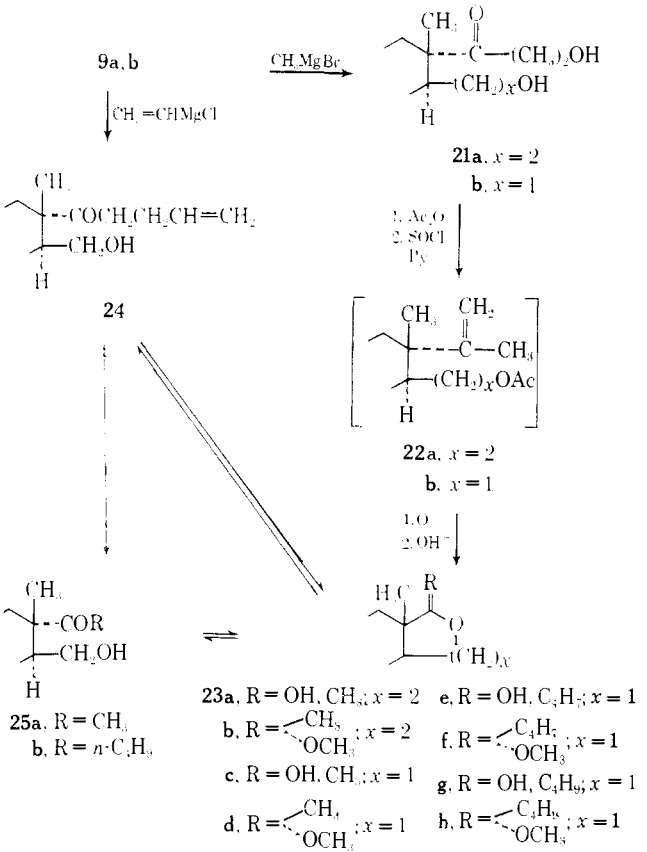


Figure 2.—Optical rotatory dispersion curves of **13b**, **14b**, **14f**, and **14g** in dioxane at 25°.

tate of the hydroxyaldehyde form **17** and 16% of the hemiacetal acetate **18**.

Strain is evident in the five-membered ring hemiacetal **14b** from its ability to exist and react in the hydroxyaldehyde form. As the reactivity of the carbonyl group at C-1 in **25** decreases, the effect of ring strain becomes more pronounced. Thus, the closely related carbonyl homologs **23c**, **23e**, and **23g** are in the ketonic form (in solution only) to the extent of about 67, 88, and 90%, respectively, whereas the relatively strain-free 17-oxa-D-homo derivative **23a** is in only the hemiacetal form. The compounds under discussion were prepared by the synthetic path outlined in Scheme III. Thus, the lactones **9a** and **9b**, when treated with methylmagnesium bromide in ether in equivalent or excess amounts, yielded the diols **21a** and **21b**, respectively, which after acylation and dehydration with thionyl chloride and pyridine yielded crude **22a** and **22b**, respectively. The mixture of **22a** and **22b** was subjected without purification to ozonolysis followed by hydrolysis to give **23a** and **23c**, respectively. Attempts to obtain a vinyl ketone by addition of vinylmagnesium

SCHEME III



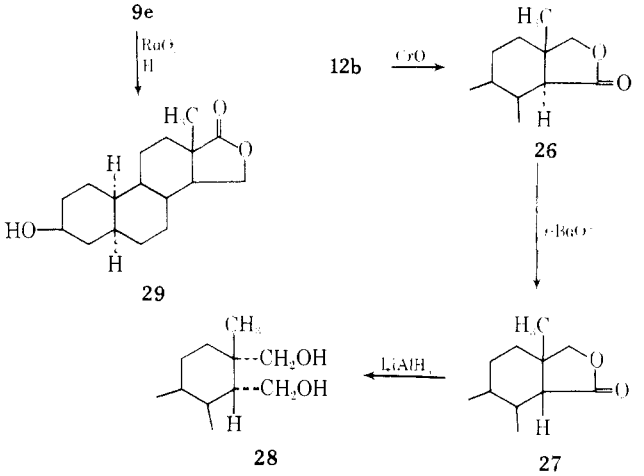
chloride to the lactone **9b** gave only **24**, the product of conjugate addition of vinylmagnesium chloride to the intermediate vinyl ketone. Reduction of the unsaturated ketone **24** with hydrogen in the presence of palladium on charcoal gave **25b**. When the hemiacetals or ketones **23a**, **23c**, **23e**, and **23g** were dissolved in methanol containing *p*-toluenesulfonic acid, the corresponding methyl ethers **23b**, **23d**, **23f**, and **23h** were obtained. The negative rotations and singlets for three protons of the C-13 methyl group about 58 cps in their nmr spectra provide evidence that they most likely possess the 17α-methoxy configuration (*vide supra*), the bulkier alkyl group being in the C-17 equatorial configuration.

The reluctance with which the lactone **9b** is formed and the ability of the hemiacetal **14b** to exist in the hydroxyaldehyde form provide indirect evidence for the C-D-*trans* ring junction in these compounds derived from **7a**. Although conversion of **6a** to **7a** was expected to proceed without isomerization of the equatorial aldehyde group at C-14, confirmatory evidence for this supposition was accumulated by the following experiments. Oxidation of the diol **12b** with chromic acid proceeded at the least hindered carbon atom to yield the lactone **26**. If **26** possesses the C-D-*trans* stereochemistry, it would be expected to epimerize to the more stable *cis* isomer.[18] When **26** was refluxed with potassium *t*-butoxide in *t*-butyl alcohol, the expected isomerization to **27** occurred in high yield. Reduction of the *cis*-lactone **27** with lithium aluminum hydride afforded **28** (Scheme IV).

Spectral evidence for the C-D-*trans* ring junction in 16-oxaestrone methyl ether (**9b**) was provided by the

(18) A. R. Van Horn and C. Djerassi, *J. Am. Chem. Soc.*, **89**, 951 (1967).

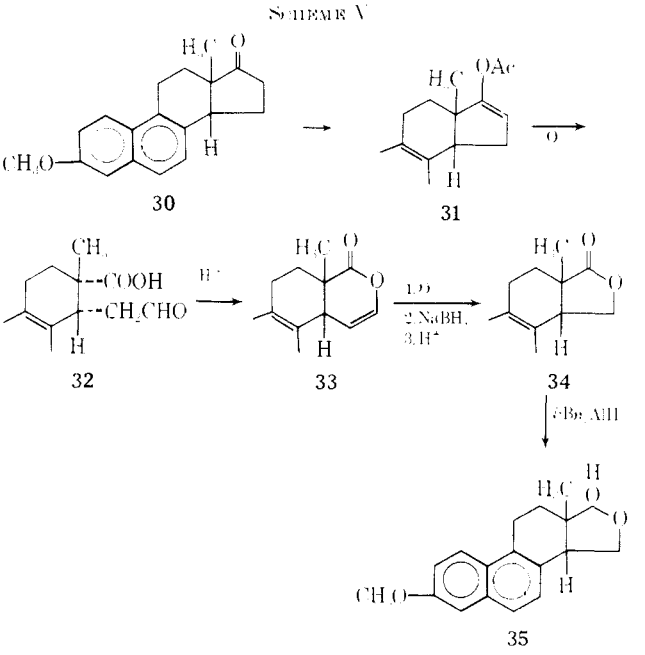
SCHEME IV



reduction of **9e** to the hexahydro derivative[19] **29** and determination of its ord curve. The positive Cotton effect exhibited by the lactone **29** in Figure 3 is in agreement with the prediction of the lactone-sector rule.[20]

The synthesis of the 16-oxa analogs derived from ±-13-ethyl-3-methoxygona-1,3,5(10)-trien-17-one and 14-isoequilenin (**30**) followed paths described for the synthesis of **14b**. Thus, **14c** was obtained from **4b** *via* the sequence formulated in Schemes I and II, whereas **35** was obtained in like manner *via* the sequence of reactions formulated in Scheme V. In Scheme V, the

SCHEME V



C-D-*cis* ring junction is assumed to remain intact. Indirect evidence which supports this conclusion is (1) the instant formation of the lactone **34** upon acidification of the salt of the hydoxy acid, and (2) the existence of **35** only in the hemiacetal form which contrasts with observations obtained with **14b** and **14c**. Dreiding models indicate that in the steroid nucleus when the A and B rings are aromatic, a great deal of strain exists

(19) The reduction of **29** is assumed to proceed *cis* from the α face; see R. E. Counsell, *Tetrahedron*, **15**, 202 (1961).

(20) J. P. Jenning, W. Klyne, and P. M. Scopes, *J. Chem. Soc.*, 7211 (1965).

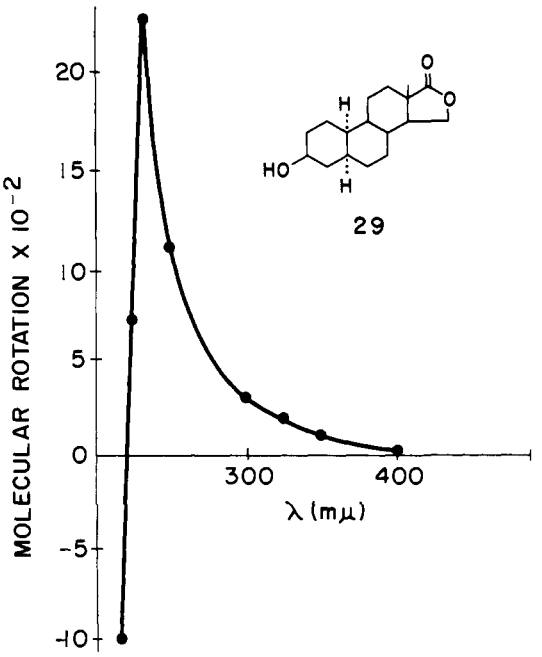


Figure 3.—Optical rotatory dispersion curve of **29** in methanol at 25°.

in the *trans*-fused C–D ring. Evidence for this conclusion was obtained when, in contrast to **30**, equilenin 3-methyl ether failed to form a 17-enol acetate when refluxed with isopropenyl acetate in the presence of strong acid.

16-Azaestrone 3-methyl ether (**10a**) was prepared by reductive amination of the aldehyde acid **7a** with Raney nickel and ammonia to the amino acid **8c** followed by heating of the amino acid at its melting point. Alkylation of the potassium salt of **10a** with methyl iodide gave the N-methyl lactam **10b**. Conversion of the amino acid **8c** with nitrous acid to the lactone **9b** establishes that the stereochemistry at C-14 remains unchanged in the transformation of **7a** to **8c**.

Biology.—Compounds were tested orally for their ability to lower serum cholesterol levels in adult male rats treated with propylthiouracil.[21] Compounds which exhibited hypocholesterolemic activity were tested for their estrogenic activity by injection using estrone as a standard in the mouse uterine growth assay.[22]

The compounds which exhibited activity at a dose less than 5 mg/kg in the hypocholesterolemic assay are listed below with the dosage required for hypocholesterolemic activity and per cent estrogenic activity of estrone in parentheses: **5a** (2 mg/kg, 0.06%), **7a** (0.2, 3), **8a** (1, 0.01), **14b** (MED, 0.4, <0.01), **15b** (1, <0.01), **32** (<1, 0.4), **10a** (2, <0.01).

The compounds which exhibited hypocholesterolemic activity at 10 mg/kg are listed below with their per cent estrogenic activity of estrone in parentheses: **9b** (<0.01%), **9d** (<0.01%), **12b** (0.03%), **13a**, **14a** (<0.01%), **17** (<0.01%), **9e** (<0.01%).

Compounds **8a**, **9b**, and **14b** showed no activity in the rat vaginal-smear assay[23] at 1 mg, whereas **10a** showed 0.25% the activity of estrone.

(21) R. E. Counsell, P. D. Klimstra, R. E. Ranney, and D. L. Cook, *J. Med. Pharm. Chem.*, **5**, 720 (1962).

(22) R. A. Edgren, *Proc. Soc. Exptl. Biol. Med.*, **92**, 569 (1956).

(23) J. D. Biggers and P. J. Claringbold, *J. Endocrinol.*, **11**, 277 (1954).

Compounds **19a** and **19b** exhibited no anti-desoxycorticosterone acetate, anabolic, androgenic, progesteronelike, or antiestrogenic activity.

Experimental Section[24]

(±)-17-Acetoxy-13-ethyl-3-methoxygona-1,3,5(10)-triene (4b).—When 11 g of (±)-13-ethyl-3-methoxygona-1,3,5(10)-trien-17-one[25] was substituted for estrone 3-methyl ether in the preparation of **4a**, the crude product which was obtained was purified by column chromatography on 750 g of silica gel in benzene. Elution of the column with 2% EtOAc in benzene yielded 2.3 g of crude **4b**, mp 126–136°. Crystallization from MeOH gave pure **4b**, mp 135–136°, λ_{max} 5.67 μ.

Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.67; H, 8.36.

***trans*-2-Carboxy-1-formylmethyl-2-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-7-ol 7-Methyl Ether (5a).**—A solution of 104 g of 17-acetoxy-3-methoxyestra-1,3,5(10),16-tetraene[26] in 600 ml of CH_2Cl_2 was placed in a 3-l. three-necked flask equipped with a stirrer. While the flask was cooled in a Dry Ice–2-propanol bath, ozone, which was generated at 110 v and a flow rate of 0.08 ft³/min, was passed through the stirred solution. After the absorption of ozone, as measured by an ozone meter, rose to a constant rate in about 2.75 hr, the solution was flushed with oxygen, then nitrogen. The flask was then equipped with a water-cooled condenser, and while stirring vigorously 110 g of powdered Zn and 300 ml of HOAc were added. After 5 min, the cooling bath was removed and replaced with a water bath which was heated slowly. When the temperature of the bath rose to about 32°, a vigorous exothermic reaction ensued. After the initial, exothermic reaction subsided, the mixture was heated at 90° for 25 min, cooled to 20°, and diluted with 800 ml of $CHCl_3$. The filtrate was washed with three 2-l. portions of H_2O and once with 5% aqueous $NaHCO_3$, dried ($MgSO_4$), and distilled to dryness *in vacuo*. The residue in 300 ml of pyridine and 150 ml of H_2O was heated on the steam bath in an atmosphere of nitrogen and slowly diluted with 1200 ml of 10% aqueous K_2CO_3. The solution was heated on the steam bath for another 25 min, and about 800 g of ice was added. The solution was washed with three 950-ml portions of CH_2Cl_2–Et_2O (18:3) and added with vigorous stirring to 205 ml of concentrated HCl and 300 g of ice. The oily precipitate gradually solidified into granular crystals which were collected by filtration, washed with water, and dried *in vacuo*. The crude product (80 g, mp 154–157°) was recrystallized from ether and petroleum ether to give pure **5a**: mp 156–158°; $[\alpha]_D$ +79°; λ_{max} 3.66, 5.79, and 5.88 μ.

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.12, H, 7.65. Found: C, 71.85; H, 7.57.

3-Methoxy-17-oxa-D-homoestra-1,3,5(10),15-tetraen-17a-one (6a).—A mixture of 6 g of *p*-toluenesulfonic acid hydrate and 4.5 l. of toluene was distilled until the water was removed. As the toluene was distilled, 20 g of **5a** in 500 ml of toluene was added over 1.5 hr; 2.5 l. of toluene was collected over 1 hr. The volume of the reaction solution was maintained at 4.5 l. by addition of dry toluene. The solution was concentrated *in vacuo* without external heating until it became cool. It was washed with 1 l. of aqueous $NaHCO_3$, dried ($MgSO_4$), and distilled to dryness. The residue (17.0 g) yielded, upon trituration in ether, 10.0 g of crude product, mp 140–144°. Several crystallizations from acetone gave pure **6a**: mp 158°; $[\alpha]_D$ −109°; λ_{max} 5.63 (s), 6.02 (w), and 6.18 (s) μ.

Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.31; H, 7.78.

When catalysts such as H_2SO_4, AcONa–Ac_2O, and AcCl were used, a very low yield of **6a** or polymeric material was obtained. When **5a** was refluxed with isopropenyl acetate in the presence

(24) The author wishes to thank Dr. R. T. Dillon and staff for the analyses, spectra, and rotations, and Dr. E. G. Daskakis and staff for the chromatography reported. The infrared spectra and rotations in a 1% solution at 25° were determined in $CHCl_3$, unless otherwise specified. The nmr spectra were determined in $CDCl_3$ on a Varian Model A-60 spectrometer at 60 Mc, with tetramethylsilane as an internal standard. Melting points are corrected. Davison silica gel, 60–200 mesh, was used for column chromatography and silica gel G (Merck AG) was used for thin layer chromatography.

(25) H. Smith, *et al.*, *Experientia*, **19**, 394 (1963).

(26) W. S. Johnson and W. F. Johns, *J. Am. Chem. Soc.*, **79**, 2007 (1957).

of *p*-toluenesulfonic acid, the crude product which was obtained in 30% yield after chromatography on Fluorosil melted at 150–161° and was different from **6a**. Its infrared spectrum (λ_{max} 5.68 μ) indicated that it was probably the acetoxy lactone **11a**.

***trans*-2-Carboxy-1-formyl-2-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-7-ol 7-Methyl Ether (7a).**—Ozonolysis of 6.0 g of **6a** according to the procedure outlined above for the preparation of **5a** yielded 5.4 g of aldehyde acid, mp 175–180°, which upon crystallization from ether and petroleum ether (bp 60–68°) gave 4.2 g of product, mp 187–198°. Recrystallization from ether (charcoal) gave **7a**, mp 190–191°, $[\alpha]D$ +88°.

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.53; H, 7.28.

***trans*-2-Carboxy-1-hydroxymethyl-2-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-7-ol 7-Methyl Ether (8a).**—To a solution of 4.0 g of $NaBH_4$ in 100 ml of EtOH was added gradually (stirring) 4.2 g of **7a**, mp 187–189°. After 10 min, the solid which precipitated was dissolved by the addition of 200 ml of H_2O. The solution was stirred for 30 min, diluted with 600 ml of H_2O, and acidified to pH 2 with dilute HCl. The precipitate was collected, washed with water, and dried at 60° *in vacuo*. The crude product (4 g), mp 156–160° dec, was recrystallized from acetone and petroleum ether: mp 163–165° dec, $[\alpha]D$ +63.5°.

Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.02; H, 7.95. Found: C, 70.67; H, 7.67.

3-Methoxy-17-oxa-D-homoestra-1,3,5(10)-trien-17a-one (9a).—When 5.0 g of **5a** was reduced with 5.0 g of $NaBH_4$ according to the procedure outlined for the preparation of **8a**, 3.75 g of the crude lactone, mp 160–163°, was obtained. Crystallization from MeOH gave pure **9a**, mp 167–168°, $[\alpha]D$ +86.5°.

Anal. Calcd for $C_{19}H_{24}O_4$: C, 75.97; H, 8.05. Found: C, 75.64; H, 7.84.

3-Methoxy-16-oxaestra-1,3,5(10)-trien-17-one (9b).—A mixture of 1.0 g of **8a**, 100 mg of *p*-toluenesulfonic acid, and 400 ml of benzene was distilled until 100 ml of distillate was collected. The solution was cooled, washed with aqueous $NaHCO_3$, and distilled to dryness. The crystalline residue (980 mg) melted at 163–165°. Crystallization from acetone gave pure **9b**, mp 170–171°, $[\alpha]D$ +66°.

Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.27; H, 7.75.

(±)-13-Ethyl-3-methoxy-16-oxagona-1,3,5(10)-trien-17-one (9c).—When 2.5 g of **4b** was substituted for **4a** in the preparation of **5a**, the crude crystalline aldehyde acid **5b** (λ_{max} 3.66, 5.78, 5.87, and 6.21 μ) was obtained. The crude **5b**, substituted for **5a** in the procedure for the preparation of **6a**, gave 850 mg of enol lactone **6b**, mp 118–120°, λ_{max} 5.70 μ. When the crude **6b** was ozonized according to the procedure for the preparation of **7a** and the product **7b** was treated according to the procedures described for the preparation of **8a** and **9a**, respectively, a crude lactone was obtained which when recrystallized from MeOH gave 350 mg of **9c**, mp 136–137°. Crystallization from MeOH gave pure **9c**, mp 147–149°, λ_{max} 5.62 μ.

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.97; H, 8.05. Found: C, 75.87; H, 8.20.

3-Hydroxy-17-oxa-D-homoestra-1,3,5(10)-trien-17a-one (9d).—A solution of 3.0 g of **9a** and 14.0 g of KOH in 80 ml of 95% EtOH was placed in a steel bomb equipped with a Teflon liner and a stirring bar and was heated in a Parr bomb at 200–220° for 24 hr with stirring. The mixture was acidified with 4 *M* HCl, concentrated by distillation, cooled to 5°, and stirred for 30 min. The precipitate was collected, washed with water, and dried *in vacuo* at 80°. It was recrystallized from acetone to give 2.0 g, mp 279–280°, $[\alpha]D$ +85° (pyridine).

Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.85; H, 7.79.

3-Hydroxy-16-oxaestra-1,3,5(10)-trien-17-one (9e).—When 1.5 g of **9b** was treated with 7.0 g of KOH and 40 ml of 95% EtOH according to the procedure outlined for the preparation of **10a**, 1.4 g of **9e**, mp 260–270°, was obtained. Crystallization from acetone gave pure **9e**, mp 282–284°, $[\alpha]D$ +59.5° (pyridine).

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 75.31; H, 7.59.

Alternatively, 6 ml of Ac_2O was added dropwise with stirring to 21 ml of concentrated HI. While the solution was refluxed, 3.0 g of **9b** was added over 1 min. The mixture was stirred at reflux for 5 min, cooled rapidly to 20°, and poured with stirring into ice–water. The precipitate was washed with water and dried *in vacuo* at 80°. The crude product (2.8 g), mp 277–284°, was recrystallized from acetone to give 750 mg of pure **9e**, mp 282–284°.

3,16α-Dimethoxy-17-oxa-D-homoestra-1,3,5(10)-trien-17a-one (11b). To a solution of 1.0 g of **5a** in 3 ml of MeOH was added 25 mg of *p*-toluenesulfonic acid hydrate. After several minutes the precipitate which appeared was collected by filtration, washed with cold MeOH and then ether, and dried. The crude product (600 mg) melted at 144–160°. Crystallization (CH_2Cl_2 and MeOH) gave pure **11b**: mp 169–171°; $[\alpha]D$ +161°; nmr peaks at 73 (C-13 methyl), 212 (C-16β methoxy), 225 (C-3 methoxy), 317 (triplet, half-line width 5 cps) (C-16α hydrogen) cps.

Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.70; H, 7.95. Found: C, 72.76; H, 8.07.

***trans*-1-(2-Hydroxy)ethyl-2-hydroxymethyl-2-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-7-ol 7-Methyl Ether (12a).**—A mixture of 5.0 g of **9a**, 1.0 g of $LiAlH_4$, and 175 ml of tetrahydrofuran (THF) was stirred at room temperature for 1 hr and diluted with 200 ml of ether. Then, 1 ml of H_2O, 0.75 ml of 20% aqueous NaOH, and 3.6 ml of H_2O was added dropwise and cautiously with vigorous stirring for 1 hr. The mixture was filtered, and the filtrate was distilled to dryness. Crystallization of the crude product gave 4.0 g of pure diol, mp 147°, $[\alpha]D$ +104°.

Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.96; H, 9.27. Found: C, 75.19; H, 9.30.

***trans*-1,2-Bishydroxymethyl-2-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-7-ol 7-Methyl Ether (12b).**—When 5.0 g of **9b** was reduced with $LiAlH_4$ according to the procedure described for the preparation of **12a**, 4.0 g of pure diol, mp 147°, $[\alpha]D$ +17°, was obtained.

Anal. Calcd for $C_{18}H_{28}O_3$: C, 74.44; H, 9.03. Found: C, 74.73; H, 9.27.

3-Methoxy-17-oxa-D-homoestra-1,3,5(10)-triene (13a). A solution of 800 mg of **12a**, 400 mg of *p*-toluenesulfonic acid hydrate, and 600 ml of benzene was distilled slowly over 2.5 hr, while 300 ml of benzene was collected. The solution was cooled, washed with aqueous $NaHCO_3$, and distilled to dryness. The residue was purified by column chromatography on 48 g of silica gel in benzene. Elution of the column with benzene–EtOAc (98:2) yielded 547 mg of **13a**. Recrystallization from Et_2O–MeOH gave pure **13a**, mp 95°, $[\alpha]D$ +102°, nmr peak at 62 cps.

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.57; H, 9.08.

3-Methoxy-16-oxaestra-1,3,5(10)-triene (13b). A mixture of 350 mg of **12b** and 220 mg of methanesulfonyl anhydride in 2 ml of pyridine was stirred at room temperature for 16 hr, diluted with water, and extracted with CH_2Cl_2. The organic solution was washed with 100 ml of 0.5 *M* HCl, then with H_2O and aqueous $NaHCO_3$, dried ($MgSO_4$), and distilled to dryness. The residue was purified by column chromatography on 20 g of silica gel in benzene. Elution with benzene–EtOAc (99:2) gave 258 mg of crude product. Recrystallization (Et_2O–MeOH) gave **13b**, mp 106–107°, $[\alpha]D$ +47.5°, nmr peak at 53.5 (3 H, C-13 methyl) cps.

Anal. Calcd for $C_{18}H_{26}O_2$: C, 79.37; H, 8.88. Found: C, 79.15; H, 9.01.

3-Methoxy-17-oxa-D-homoestra-1,3,5(10)-trien-17a-ol (14a).—To 1.8 g of **9a** in 90 ml of toluene cooled in a Dry Ice–2-propanol bath (under nitrogen) was added dropwise with stirring a solution of 25% diisobutylaluminum hydride in toluene. The solution was stirred for 1 hr and poured with vigorous stirring into a mixture of 100 g of ice, 100 ml of H_2O, and 50 ml of HOAc. After the ice melted, the organic layer was separated, washed twice with H_2O and then with aqueous $NaHCO_3$, dried ($MgSO_4$), and distilled to dryness *in vacuo*. The crude, crystalline product weighed 1.6 g. A thin layer chromatogram eluted with 15% EtOAc in benzene indicated that only the hemiacetal was present. The crude product had $[\alpha]D$ +53° (dioxane–H_2O 4:1) and $[\alpha]D$ −81° (dioxane–H_2O 4:1, HCl added). Crystallization from Et_2O and hexane after equilibration with stong acid gave a sample: mp 145°; $[\alpha]D$ +70°; nmr peaks at 57 and 61.5 (C-13 methyls in ratio of about 2:1, respectively), 227 (C-3 methoxy), 259.5 and 281 (C-17aα and -β hydrogens, respectively) cps; λ_{max} 2.74, 2.95 μ (hydroxyl) and no carbonyl absorption bands.

Anal. Calcd for $C_{19}H_{28}O_3$: C, 75.46; H, 8.67. Found: C, 75.33; H, 8.57.

3-Methoxy-16-oxaestra-1,3,5(10)-trien-17-ol (14b). Using a solution of 7.2 g of **9b** in 400 ml of toluene and 35 ml of 25% diisobutylaluminum hydride in toluene and following the pro-

cedure described for the preparation of **14a**, 7.0 g of crystalline product, mp 127–133°, was obtained. Crystallization from acetone and hexane gave **14b**: mp 139°; $[\alpha]D$ +10.5°; $[\alpha]D$ +13.5° (dioxane–H_2O 4:1); λ_{max} 2.73, 2.94 (hydroxyl), and 5.79 μ (weak, aldehyde); λ_{max}^{KBr} 2.97, 3.05 μ (hydroxyl) and no carbonyl absorption; nmr peaks at 55 (C-18 methyl), 68 (very weak, C-18 methyl), 226.5 (C-3 methoxy), 300.5 and 303.5 (C-17β hydrogen) cps. The rotation was unchanged over 1 hr after 1 drop of concentrated HCl was added to the solution of the lactol in aqueous dioxane.

Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 75.23; H, 8.32.

(±)-13-Ethyl-16-oxagona-1,3,5(10)-trien-17-ol (14c).—When 1.0 g of **9c** was reduced according to the procedure for the preparation of **14b**, 800 mg of **14c** was obtained. Crystallization from acetone–hexane gave pure **14c**: mp 174–176°; λ_{max} 2.78, 2.95, 5.85 μ (weak); λ_{max}^{KBr} 2.98, 3.08 μ; nmr peaks at 58 (triplet, C-18 methyl), 312.5 and 313.5 (doublet, C-17 hydrogen) cps.

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.39; H, 8.64.

3,17aβ-Dimethoxy-17-oxa-D-homoestra-1,3,5(10)-triene (14d) and 3,17aα-Dimethoxy-17-oxa-D-homoestra-1,3,5(10)-triene (14e).—A solution of 4.25 g of **14a**, mp 135–141°, and 100 mg of *p*-toluenesulfonic acid hydrate in 100 ml of MeOH was concentrated by distillation to about 30 ml, then cooled. The crystalline product was collected by filtration, washed with cold MeOH, and dried. It weighed 3.7 g, mp 103–104°. The nmr spectrum in $CDCl_3$ exhibited peaks at 61.5 and 56 cps indicating the presence of isomers at C-17a in the ratio of about 2:1. Separation of the 17aα- and -β-methoxy isomers was accomplished by column chromatography of 3.7 g of the mixture in benzene solution on 430 g of Woelm basic alumina (activity 1). Development of the column was followed by nmr spectroscopy. Elution of the column with benzene yielded the 17aα-methoxy isomer (mp 87–88°) and then a mixture of isomers, which was chromatographed again to yield additional 17aα-methoxy isomer and 600 mg of the 17aα-methoxy isomer (mp 168–169°). Crystallization of each crude fraction from methanol containing a trace of pyridine gave analytical samples of **14e**: mp 93–94°; $[\alpha]D$ −10.5°; nmr peaks at 61.5 (C-13 methyl), 204 (C-17aα methoxy), 224.5 (C-3 methoxy), 246 (C-17aβ hydrogen) cps; and **14d**: mp 174–175°; $[\alpha]D$ +108.5°; nmr peaks at 56 (C-13 methyl), 208.5 (C-17aβ methoxy), 224.5 (C-3 methoxy), 230 (C-17aα hydrogen) cps.

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.90; H, 8.92. Found for **14d**: C, 75.90; H, 9.13. Found for **15b**: C, 75.78; H, 8.80.

3,17β-Dimethoxy-16-oxaestra-1,3,5(10)-triene (14f) and 3,17α-Dimethoxy-16-oxestra-1,3,5(10)-triene (14g).—A solution of 3.0 g of **14b** and 20 mg of *p*-toluenesulfonic acid hydrate in 150 ml of MeOH was concentrated by distillation to 30 ml in 15 min and cooled. The crystalline precipitated was collected, washed with MeOH, and dried. The crude product (1.5 g, mp 98–102°) was recrystallized from CH_2Cl_2 and MeOH to give **14g**: mp 108–109°; $[\alpha]D$ −34°; nmr peaks at 55 (C-13 methyl), 203.5 (C-17α methoxy), 227 (C-3 methoxy), 270 (C-17β hydrogen) cps.

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.79; H, 8.87.

A 500-mg sample of the mother liquors containing the 17α- and 17β-methoxy isomers was separated by preparative thin layer chromatgraphy using 8 × 8 in. plates coated with 200 μ of aluminum oxide G (Brinkmann) and developing the plates with benzene. The plates were spotted with phosphomolybdic acid in EtOH to identify the desirable fraction. The slower moving alumina fraction was collected and extracted with 200 ml of benzene–EtOAc (19:1) for 30 min at room temperature. The organic extract, when distilled to dryness, yielded 45 mg of crude product. Crystallization from ether and hexane gave pure **14f**: mp 142–144°; $[\alpha]D$ +79.5°; nmr peaks at 54.5 (C-13 methyl), 210 (C-17β methoxy), 226 (C-3 methoxy), 275 (C-17α hydrogen) cps.

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.09; H, 8.54.

When 3 mg of **14f** was heated for several minutes in MeOH containing 1 mg of *p*-toluenesulfonic acid, a thin layer chromatogram of the product indicated that an equilibrium mixture of **14f** and **14g** was obtained.

17α-Methoxy-16-oxaestra-1,3,5(10)-trien-3-ol (15a).—A mixture of 0.3 g of **14g**, 9 g of KOH, and 50 ml of 95% EtOH was placed in a Teflon liner in a hydrogenation bomb equipped with a stirring bar and was heated with stirring at 225° for 24 hr. The reaction mixture was distilled to dryness *in vacuo*. The residue was dissolved in 50 ml of H_2O. The solution was acidified to pH 5 with HOAc and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O and aqueous $NaHCO_3$, dried ($MgSO_4$), and distilled to dryness. The product was recrystallized twice from ether–hexane to yield 1.7 g of **15a**: mp 146–146.5°; λ_{max} 2.73, 2.98 μ.

Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.93; H, 8.29.

16-Oxaestra-1,3,5(10)-triene-3,17-diol (15b).—A solution of 2.0 g of **15a** in 40 ml of 1 *M* HCl and 300 ml of THF was distilled slowly over 35 min until 100 ml of distillate was collected. The solution was neutralized with aqueous $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ extract was separated, dried ($MgSO_4$), and distilled to dryness. The product was recrystallized from ether and $CHCl_3$ to give 500 mg of pure material: mp 165–168°; $[\alpha]D$ +8.5° (dioxane); λ_{max}^{KBr} 3.00 (broad), 5.79 (weak), 6.18 μ; nmr (deuterioacetone) peaks at 53 and 65 (C-13 methyl; ratio about 4:1, respectively), 565 (0.2 H, aldehyde) cps.

Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.48; H, 8.08.

***trans*-1-Acetoxymethyl-2-formyl-2-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-7-ol 7-Methyl Ether (17).**—A solution of 1.7 g of **14b**, 8 ml of pyridine, and 4 ml of Ac_2O was kept at 100° for 2 hr, cooled, and slowly diluted with ice and H_2O. Trituration of the oil which precipitated yielded crystals which were collected by filtration and dried. The crude product, a mixture of **17** and **18**, weighed 1.6 g and had nmr peaks at 58 and 65 (0.16 H and 0.82 H, respectively, C-13 methyl), 118 and 125 (acetate), 354 (0.18 H, C-17 hydrogen, **16c**) cps. Recrystallization of the mixture from acetone–hexane–ether gave 1.0 g of pure **18**: mp 117°; $[\alpha]D$ +77.5°; nmr peaks at 65 (C-13 methyl), 114 (acetate), 226 (C-3 methoxy), 223–268 (multiplet, 2 H methyleneoxy), 564 (1 H, aldehyde) cps.

Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.44; H, 7.86.

17α-Methoxy-16-oxaestr-4-en-3-one (19a).—To a solution of 15 ml of *t*-butyl alcohol, 100 ml of THF, and 300 ml of redistilled NH_3 was added with stirring a solution of 10 g of **14g** in 700 ml of tetrahydrofuran followed by sufficient Li (about 1 g) to keep the solution blue for 1 hr. Methanol was added to destroy excess Li, and the solution was distilled to dryness. The residue was warmed on a steam bath with 200 ml of MeOH–4 *M* HCl (95:5) for 30 min in a nitrogen atmosphere, carefully neutralized with aqueous $NaHCO_3$, and concentrated by distillation. The product was collected by filtration, dried, and recrystallized twice from acetone–hexane to yield 3.5 g of **19a**: mp 154–156°; $[\alpha]D$ −54°; λ_{max} 239 mμ (ϵ 16,700); nmr peaks at 57 (C-13 methyl), 202 (C-17α methoxy), 270 (C-17β hydrogen) cps.

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.54; H, 9.26.

17-Hydroxy-16-oxaestr-4-en-3-one (19b).—A solution of 2.5 g of crude **19a**, 150 ml of THF, and 50 ml of 0.5 *M* HCl was concentrated by slow distillation to 100 ml over 45 min, cooled, neutralized with aqueous $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ was dried ($MgSO_4$) and distilled to dryness. The residue was purified by column chromatography on 100 g of silica gel in benzene. Elution of the column with benzene–EtOAc (5:1) gave 1.3 g of crude **19b**. Crystallization from ether gave an analytical sample: mp 124–126°; $[\alpha]D$ −35.0°; λ_{max} 2.78, 2.95, 5.80 (weak), 5.97 μ.

Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.94; H, 8.78.

16-Oxaestr-4-en-3-one (19c).—Compound **13b** (1.2 g) was substituted for **14g** in the procedure described for the preparation of **19a**. When the solution of the conjugated ketone in MeOH and HCl was neutralized with bicarbonate, a crystalline precipitate was obtained, collected by filtration, and dried *in vacuo*. Crystallization of the product (1.0 g) gave 800 mg of pure **19c**, mp 121–125°, λ_{max} 238.5 mμ (ϵ 16,200).

Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.24; H, 9.21.

17α-Methoxy-16-oxa-5α-estran-3β-ol (20a).—To a solution of 20 ml of *t*-butyl alcohol, 70 ml of THF, and 200 ml of redistilled NH_3 was added with stirring a solution of 3.5 g of **19a** in 50 ml of THF followed by sufficient Li wire to keep the solution blue for 1 hr. The excess Li was destroyed with MeOH, and the mixture was slowly distilled to dryness. The residue was extracted with $CHCl_3$ and H_2O. The organic layer was separated, dried ($MgSO_4$), and distilled to dryness. The residue was purified by column chromatography on 150 g of alumina. Elution with

benzene–EtOAc (19:1) yielded 700 mg of crude product, mp 130–135°. Crystallization from acetone–hexane gave **20a**: mp 142–143°; $[\alpha]D$ −76.5°; λ_{max} 2.76, 2.90 μ (hydroxyl); nmr peaks at 53 (C-13 methyl), 266 (C-17β hydrogen) cps.

Anal. Calcd for $C_{18}H_{36}O_3$: C, 73.43; H, 10.27. Found: C, 73.72; H, 10.24.

16-Oxa-5α-estran-3β-ol (20b).—When 350 mg of **19c** was substituted for **19a** in the procedure for the preparation of **20a**, 300 mg of crude alcohol, mp 150–152°, was obtained. Crystallization from acetone–hexane gave **20b**, mp 155–158°, λ_{max} 2.87 μ.

Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.06; H, 10.58.

***trans*-1-(2-Hydroxy)ethyl-2-(1-hydroxy-1-methyl)ethyl-2-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-7-ol 7-Methyl Ether (21a).**—When 4.0 g of **9a** was treated with methylmagnesium bromide according to the procedure described for the preparation of **21b**, 4.3 g of **21a** was obtained. Recrystallization from ether gave pure **21a**, mp 128–129°.

Anal. Calcd for $C_{20}H_{32}O_3$: C, 75.86; H, 9.70. Found: H, 76.02; H, 9.79.

***trans*-1-Hydroxymethyl-2-(1-hydroxy-1-methyl)ethyl-2-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-7-ol 7-Methyl Ether (21b).**—A solution of 2.1 g of **9b**, 20 ml of 3 *M* methylmagnesium bromide in ether, and 100 ml of THF was stirred at 25° for 3 hr and poured carefully with stirring into 250 ml of saturated aqueous NH_4Cl. The separated, aqueous layer was washed with three 75-ml portions of CH_2Cl_2. The combined organic extract was washed with saturated aqueous NH_4Cl, dried ($MgSO_4$), and distilled to dryness. The residue, when triturated in ether, yielded 1.5 g of diol, mp 163–165°. Crystallization from ether gave **21b**, mp 166–169°, $[\alpha]D$ −0°.

Anal. Calcd for $C_{20}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.62; H, 9.48.

3-Methoxy-17aβ-methyl-17-oxa-D-homoestran-1,3,5(10)-17aα-ol (23a).—When 4.1 g of **21a** was acylated, then dehydrated according to the procedure described for the preparation of **22b**, 3.7 g of crude **22a** (λ_{max} 5.78, 6.11, 6.19 μ) was obtained. It was ozonized and hydrolyzed according to the procedure described for the preparation of **23c** to yield 3.3 g of **23a** as amorphous product. The crude product was purified by column chromatography on silica gel (250 g) in benzene. Elution of the column with 10 and 20% EtOAc in benzene gave 1.7 g of crystalline product: λ_{max} 2.78, 2.90 μ. Recrystallization from ether–hexane gave **23a**: mp 105–106°; $[\alpha]D$ +7°; nmr peaks at 62 (C-13 methyl), 79 (C-17 methyl) cps.

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.56; H, 8.80.

3,17aα-Dimethoxy-17β-methyl-17-oxa-D-homoestra-1,3,5(10)-triene (23b).—When a solution of 1.7 g of **23a** in 20 ml of MeOH was warmed for 10 min, concentrated, and cooled, the crystalline product which appeared was collected and dried; yield 650 mg, mp 100–105°. Recrystallization from MeOH–CH_2Cl_2 gave **23b**: mp 118–120°; $[\alpha]D$ −14.5°; nmr peaks at 62 (C-13 methyl), 71 (C-17β methyl), 195 (C-17α methoxy) cps.

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.05; H, 9.18.

3-Methoxy-17-methyl-16-oxaestra-1,3,5(10)-trien-17-ol (23c) or *trans*-2-Acetyl-1-hydroxymethyl-2-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-7-ol 7-Methyl Ether (25a).—A solution of 3.5 g of **21b** in 10 ml of pyridine and 5 ml of Ac_2O was left at room temperature for 20 hr, then diluted with 200 ml of H_2O, and extracted with $CHCl_3$. The $CHCl_3$ was washed successively with excess 1 *N* HCl, H_2O, and aqueous $NaHCO_3$, dried ($MgSO_4$), and distilled to dryness. The crude monoacetate (λ_{max} 2.73, 2.85, 5.77 μ, 3.3 g, was dissolved in 15 ml of pyridine. To the resulting solution was added with stirring at −15°, 2.0 g of $SOCl_2$ in 10 ml of pyridine. After 5 min, the solution was diluted with 200 ml of $CHCl_3$. The $CHCl_3$, washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and distilled to dryness *in vacuo*, yielded 3.2 g of **20b** (λ_{max} 5.77, 6.10, 6.21, 6.35 μ) which was used without further purification. Ozone, which was generated in a Welsbach ozone generator set at 80 v and a flow rate of 0.04 ft^3/min, was passed through a solution of 3.2 g of crude **20b** in 70 ml of CH_2Cl_2, cooled in a Dry Ice–2-propanol bath for 15 min. The solution was flushed with nitrogen, then stirred at reflux for 5 min with 2 g of Zn and 8 ml of HOAc. The mixture was diluted with $CHCl_3$, and the filtrate was washed with H_2O then aqueous $NaHCO_3$, dried ($MgSO_4$), and distilled to dryness. The residue (2.1 g; λ_{max} 5.78, 5.90 μ) was warmed in H_2O–MeOH containing 3 g of KOH for 5 min under nitrogen. The solution was acidified with aqueous HCl and extracted with $CHCl_3$. The $CHCl_3$ was washed with $NaHCO_3$, dried ($MgSO_4$), and distilled to dryness. The residue, 2.9 g, was dissolved in benzene and purified by column chromatography on 150 g of silica gel. Elution with benzene–EtOAc (9:1) yielded 350 mg of **23c (25a)**, mp 118–125°. Crystallization from acetone and petroleum ether gave an analytical sample: mp 122–123°; $[\alpha]D$ +45°; λ_{max} 2.78, 2.90, 5.91, 6.21 μ; nmr peaks at 52 and 72 (C-13 methyl, ratio ~1:2, respectively), 85 (C-17 methyl, weak), 133 (methylcarbonyl), 226 (C-3 methoxy) cps.

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.33; H, 8.75.

3,17α-Dimethoxy-17-methyl-16-oxaestra-1,3,5(10)-triene (23d).—A mixture of 1.9 g of **23c** and 25 mg of *p*-toluenesulfonic acid hydrate in 25 ml of CH_2Cl_2 and 20 ml of MeOH was concentrated by slow distillation. The crystalline precipitate was collected and recrystallized twice from CH_2Cl_2–MeOH containing a trace of *p*-toluenesulfonic acid to give 1.55 g of product, mp 165–170°. Another crystallization (charcoal) gave **23d**: mp 163–166°; $[\alpha]D$ −28°; nmr peaks at 52 (C-13 methyl), 77 (C-17 methyl), 197 (C-17 methoxy) cps.

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.16; H, 9.02.

3-Methoxy-17β-(3-butenyl)-16-oxaestra-1,3,5(10)-trien-17α-ol (23e) or *trans*-2-(3-Butenyl)carbonyl-1-hydroxymethyl-2-methyl-1,2,3,4,4a,10,10a-octahydrophenanthren-7-ol 7-Methyl Ether (24).—A solution of 3.0 g of **9b**, 50 ml of 3 *M* vinylmagnesium chloride in THF (M and T Corp.), and 50 ml of THF was stirred (nitrogen atmosphere) for 3 hr and poured gradually with stirring into a mixture of 100 ml of H_2O and 600 g of ice. Acidification with 25 ml of HOAc gave, by filtration and drying *in vacuo*, 3.8 g of product which was purified by column chromatography on 240 g of silica gel in benzene. Elution of the column with benzene–EtOAc (19:1) yielded about 2.5 g product, mp 106–109°. Recrystallization from ether–acetone gave an analytical sample: mp 108–110°; $[\alpha]D$ +113°; λ_{max} 2.74, 5.88, 6.08 μ; λ_{max}^{KBr} 2.96, 6.08, 6.23, 6.33 μ; nmr peaks at 54 (~0.12 H, C-13 methyl), 63 (~0.88 H, C-13 methyl), 295–315 (multiplet, 3 H, vinyl hydrogens) cps.

Anal. Calcd for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.17, 77.02; H, 8.78, 9.06.

3,17α-Dimethoxy-17β-(3-butenyl)-16-oxaestra-1,3,5(10)-triene (23f).—When 50 mg of **24** was methylated according to the procedure described for the preparation of **23d**, it yielded 45 mg of **23f**: mp 108–110°; $[\alpha]D$ −15°; nmr peaks at 55.5 (C-13 methyl), 195 (C-17α methoxy), 293–311 (multiplet, 3 H, vinyl hydrogens) cps.

Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.40; H, 8.82.

3-Methoxy-17-(3-butyl)-16-oxaestra-1,3,5(10)-trien-17-ol (23g) or *trans*-2-(3-*n*-Butyl)carbonyl-1-hydroxymethyl-2-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-7-ol 7-Methyl Ether (25b).—A mixture of 300 mg of **24**, 100 mg of 5% Pd–$CaCO_3$, and 40 ml of EtOAc absorbed 1 equiv of hydrogen in 45 min. The mixture was filtered, and the filtrate was distilled to dryness. The product (275 mg, mp 100–102°) when recrystallized from acetone–hexane melted at 106–108°; $[\alpha]D$ +40°; λ_{max} 2.77, 5.88 μ; λ_{max}^{KBr} 2.96 μ, no carbonyl; nmr peaks at 54 and 72 (~0.1 H and 0.9 H, respectively) cps.

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.69; H, 9.33.

3,17α-Dimethoxy-17β-(*n*-butyl)-16-oxaestra-1,3,5(10)-triene (23h).—When 75 mg of **23g** was methylated according to the procedure described for the preparation of **23d**, 50 mg of product, mp 125–126°, was obtained. Recrystallization from CH_2Cl_2–MeOH gave **23h**: mp 126–127°; $[\alpha]D$ −14.5°; nmr peaks at 55 (C-13 methyl), 195 (C-17α methoxy) cps.

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.32; H, 9.76.

3-Methoxy-16-oxaestra-1,3,5(10)-trien-15-one (26).—A hot solution of 290 mg of **12b** in 25 ml of acetone was cooled, and 0.6 ml of 8 *N* aqueous chromic acid–H_2SO_4 was added with stirring. After 5 min, the mixture was diluted with 0.5 ml of 2-propanol, then with H_2O until a crystalline precipitate appeared. The product (225 mg, mp 137–138°) recrystallized from MeOH gave **26**, mp 148–149°, $[\alpha]D$ +25.5°, λ_{max}^{KBr} 5.64 μ.

Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.20; H, 7.97.

3-Methoxy-16-oxa-14β-estra-1,3,5(10)-trien-15-one (27).—A mixture of 200 mg of **26**, 200 mg of potassium *t*-butoxide, and 20 ml of *t*-butyl alcohol was stirred at reflux (nitrogen atmosphere), cooled, and acidified with 2 ml of 4 *M* HCl. The solution was evaporated to dryness, and the residue was triturated with H_2O, collected by filtration, and dried. The product (195 mg) melted at 148–154°. A mixture melting point with **26** was 116–124°. Recrystallization from CH_2Cl_2–MeOH, gave **27**, mp 161°, $[\alpha]D$ +200°, λ_{max} 5.67 μ.

cis-**1,2-Bishydroxymethyl-2-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-7-ol 7-Methyl Ether (28).**—When 750 mg of **27** was reduced according to the procedure described for the preparation of the diol **12a** and the crude product was triturated in acetone–ether, 710 mg of **28**, mp 178–180°, was obtained; after recrystallization from acetone, mp 180–181°, $[\alpha]D$ +140°. A mixture melting point with **12b** was 130–133°.

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.28; H, 8.87.

3β-Hydroxy-16-oxa-5α,10α-estran-17-one (29).—A mixture of 450 mg of **9e**, 500 mg of ruthenium oxide catalyst, and 50 ml of dioxane was shaken with hydrogen at 1040 psi (maximum) at 104° for 7 hr and cooled. The mixture was filtered, and the filtrate was distilled to dryness *in vacuo*. The residue was purified by column chromatography on 61 g of silica gel in benzene. Elution with benzene–EtOAc (19:1) gave 232 mg of product. Crystallization from acetone–hexane gave an analytical sample, 80 mg, mp 204–205°, λ_{max} 5.64 μ.

Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.62; H, 9.47. Found: C, 73.34; H, 9.41.

17-Acetoxy-3-methoxy-14β-estra-1,3,5(10),6,8,16-hexaene (31).—A solution of 15 g of 14-isoequilenin 3-methyl ether,[27] 800 ml of isopropenyl acetate, and 4 g of *p*-toluenesulfonic acid was distilled for 6 hr (400 ml of distillate). After 4 days at 25°, it was concentrated to about 30 ml and diluted with ether. The ether was washed with aqueous $NaHCO_3$, dried ($MgSO_4$), and distilled to dryness. The residue was dissolved in 500 ml of cyclohexane and filtered through 300 g of Fluorosil (60–100 mesh). The Fluorosil was washed with 1.2 l. of cyclohexane. The cyclohexane was distilled to dryness. The residue, triturated with MeOH, yielded a first crop of enol acetate (6 g, mp 85–87°). Two recrystallizations from MeOH–CH_2Cl_2 gave **31**, mp 92–93°, $[\alpha]D$ +229°.

Anal. Calcd for $C_{21}H_{22}O_3$: C, 78.23; H, 6.88. Found: C, 78.29; H, 6.84.

cis-**2-Carboxy-1-formylmethyl-2-methyl-1,2,3,4-tetrahydrophenanthren-7-ol 7-Methyl Ether (32).**—When 3.2 g of **31** was ozonized according to the procedure for the preparation of **5a**, 2.5 g of crude aldehyde acid, mp 169–171°, was obtained. Crystallization from acetone gave **32**: mp 173–174°; $[\alpha]D$ −7° (dioxane); λ_{max}^{KBr} 2.88, 3.03, 5.76, 5.85, 6.21 μ.

Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 72.81; H, 6.57.

3-Methoxy-17-oxa-D-homo-14β-estra-1,3,5(10),6,8,15-hexaen-17a-one (33).—When 8.2 g of **32** was substituted for **5a** in the preparation of **6a**, a crystalline product was obtained which was purified by column chromatography on 650 g of silica gel in benzene. Elution of the column with benzene–EtOAc (98:2) gave 7 g of enol lactone, mp 184–189°; from acetone–hexane, mp 184–187°, $[\alpha]D$ +344°.

Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.35; H, 5.96.

3-Methoxy-16-oxa-14β-estra-1,3,5(10),6,8-pentaen-17-one (34).—When the enol lactone **33** was substituted for **6a** in the preparation of **7a** and **9a**, 900 mg of **34**, mp 184–186°, was obtained. Crystallization of the crude product from acetone–hexane gave **34**, mp 184–186°, $[\alpha]D$ +228°, λ_{max} 5.67 μ.

Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.29; H, 6.34.

3-Methoxy-16-oxa-14β-estra-1,3,5(10),6,8-pentaen-17-ol (35).—When 1.1 g of **34** was substituted for **9b** in the preparation of **14b**, and the product was recrystallized from acetone–hexane, 590 mg of **35** was obtained: mp 183–185°; $[\alpha]D$ +106.5°; λ_{max} 2.78, 2.95 μ (hydroxyl); nmr peak at 69 (3 H, C-13 methyl).

Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.79; H, 6.92.

trans-**1-Aminomethyl-2-carboxy-2-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-7-ol 7-Methyl Ether (8c) and 3-Methoxy-16-azaestra-1,3,5(10)-trien-17-one (10a).**[28]—A mixture of 10 g of **7a**, 3 teaspoonsful of Raney nickel (W-2), 325 ml of concentrated NH_4OH, and 650 ml of MeOH was shaken at 860 psi (maximum) (72°) for 8 hr in a 2-l. Parr bomb, cooled, and filtered. The filtrate was concentrated by distillation. The amino acid **8c**, which was collected by filtration and dried, weighed 7.5 g and melted at 140–144° (gas evolution). A solution of 7.5 g of **8c** in 400 ml of xylene was concentrated by distillation over 45 min; 200 ml of xylene was collected. The solution was then distilled to dryness. The residue, triturated in acetone, yielded 3.25 g of product, mp 190–200°. Crystallization from acetone gave **10a**: mp 210–212°; $[\alpha]D$ +70.5°; λ_{max} 2.91, 3.10, 5.88, μ.

Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91. Found: C, 76.09; H, 8.20; N, 4.91.

Hydrochloride of 8c.—A solution of 300 mg of **10a** and 10 ml of concentrated HCl was refluxed for 1 hr and cooled. The crystalline precipitate which was collected by filtration and washed with water weighed 100 mg, mp 208–210°. Trituration in acetone gave an analytical sample, mp 212–214°.

Anal. Calcd for $C_{18}H_{26}ClNO_3$: C, 63.61; H, 7.71; Cl, 10.43; N, 4.12. Found: C, 63.59; H, 7.83; Cl, 10.67; N, 4.38.

N-Methyl-3-methoxy-16-azaestra-1,3,5(10)-trien-17-one (10b).—A solution of 400 mg of **10a**, 100 mg of NaH in mineral oil (55%), and 200 ml of dry toluene was refluxed for 45 min. Then 10 ml of MeI was added. The mixture was refluxed for 30 min, cooled, washed with H_2O, dried ($MgSO_4$), and distilled to dryness. Trituration in ether yielded 320 mg of **10b**, mp 165–170°; from acetone–hexane, mp 174–176°, $[\alpha]D$ +46.5°, λ_{max} 5.88 μ.

Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.3; H, 8.43; N, 4.68. Found: C, 76.11; H, 8.48; N, 4.60.

Conversion of 8c to 9b with Nitrous Acid.—To 400 mg of **10a** in 10 ml of H_2O–HOAc (1:1) was added gradually with stirring at 25° 400 mg of $NaNO_2$. After 15 min, the solution was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ was washed with H_2O, dried ($MgSO_4$), and distilled to dryness. The residue was refluxed with 10 mg of *p*-toluenesulfonic acid in 200 ml of benzene. The benzene was concentrated to 100 ml by distillation, washed with aqueous $NaHCO_3$, dried ($MgSO_4$), and distilled to dryness. The residue, when triturated in MeOH, yielded 30 mg of crystalline product whose mixture melting point with **9b** and infrared spectrum (KBr disk) was indistinguishable from those of **9b**.

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