The Stereospecific D-Homoannulation of 17-Hydroxy-3-methoxyestra-1,3,5(10)-triene-17α-carboxaldehyde

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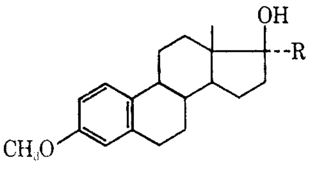
Received April 29, 1969

17-Hydroxy-3-methoxyestra-1,3,5(10)-triene-17α-carboxaldehyde (2), prepared by ozonolysis of 3-methoxy-19-nor-17α-pregna-1,3,5(10),20-tetraen-17-ol (1), rearranged exclusively into 17aβ-hydroxy-3-methoxy-D-homoestra-1,3,5(10)-trien-17-one (6) on silica gel, with boron trifluoride, and thermally. The less strict steric requirements of 2 did not alter its course of rearrangement from that of the 17-hydroxy-17α-pregnan-20-ones. Aldol 2 was characterized by reduction to diol 3, which formed monoacetate ester 4 and acetonide 5. Ketol 6 was characterized by acetylation to acetate ester 7, by reduction to diols 8 and 11, and by oxidation to 17-hydroxy-3-methoxy-D-homoestra-1,3,5(10),16-tetraen-17a-one (14). Diol 8 formed diacetate ester 9 and acetonide 10 and diol 11 formed diacetate ester 12 and acetonide 13. Structures and configurations were confirmed by infrared, ultraviolet, and proton magnetic resonance spectroscopy.

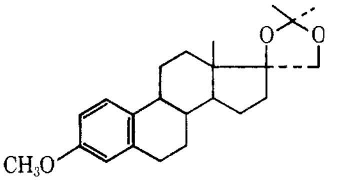
One of the most interesting aspects of the D-homoannulation of 17-hydroxypregnan-20-ones is the dependence of the selectivity of bond migration on the configuration at C-17 in the starting material.[1] The following arguments have been advanced to explain this selectivity in the Lewis acid catalyzed rearrangements. Bonding between the two oxygen atoms and the metal atom (and presumably the hydrogen atom in the thermal rearrangement) forces the oxygen atoms into a *cis* relationship.[2] This constraint and the consequent planarity of the metal atom, the two oxygen atoms, and the two carbon atoms bearing them determine the conformation of the transition state for rearrangement, which is assumed to approximate that of the product.[3,4] Thus, rearrangement of a 17-hydroxy-17α-pregnan-20-one with migration of C-16 would produce a boat-form D ring having a prow–stern interaction of H and CH_3, although rearrangement with migration of C-13 would produce a chair-form D ring having a relatively stable 1,3-diaxial interaction of the same H and CH_3. In practice the rearrangement of 17-hydroxy-17α-pregnan-20-ones has afforded only the products of C-13 migration.

This paper reports the preparation of 17-hydroxy-3-methoxyestra-1,3,5(10)-triene-17α-carboxaldehyde (2) and its stereospecific rearrangement into 17aβ-hydroxy-3-methoxy-D-homoestra-1,3,5(10)-trien-17-one (6) with silica gel, boron trifluoride, and heat. It also reports several chemical transformations of 2 and 6 which clarified their structures.

Ozonolysis of 3-methoxy-19-nor-17α-pregna-1,3,5(10),20-tetraen-17-ol (1) in methylene dichloride and pyridine at −70° produced **2**.[5] Although it could not be completely purified, its structure followed unequivocally from the following observations. Recrystallization of crude **2** from cyclohexane provided material which contained about 80% **2** as shown by thin layer chromatography and proton magnetic resonance spectroscopy. The latter showed the aldehydic proton resonance at 9.82 ppm and angular methyl group proton resonance at 0.97 ppm. Its infrared spectrum showed hydroxyl and carbonyl group absorption. The remaining 20% of the sample was mostly **6** plus a small amount of **1**.



1, R = CHCH$_2$
2, R = CHO
3, R = CH$_2$OH
4, R = CH$_2$OCOCH$_3$



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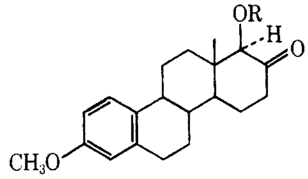
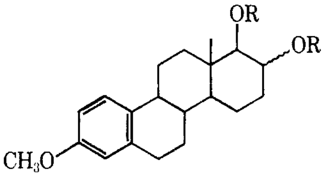


6, R = H
7, R = COCH$_3$



8, 17β, R = H
9, 17β, R = COCH$_3$
10, 17β, R+R = C(CH$_3$)$_2$
11, 17α, R = H
12, 17α, R = COCH$_3$
13, 17α, R+R = C(CH$_3$)$_2$

Reduction of crude **2** with lithium aluminum hydride afforded 17-hydroxy-3-methoxyestra-1,3,5(10)-triene-17α-methanol (3) in 59% yield based on **1**.[6] Sodium periodate oxidized **3** quantitatively to estrone methyl ether, showing that the five-membered D ring of **2** was still intact. Diol **3** was further characterized as its monoacetate ester **4**, which formed with acetic anhydride and pyridine at 25°, and as its acetonide **5**. The structures of **3**, **4**, and **5** were confirmed by their infrared and proton magnetic resonance spectra.[7] All three

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(1) N. L. Wendler in "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, New York, N. Y., 1964, part II, pp 1114–1121.

(2) R. B. Turner, *J. Amer. Chem. Soc.*, **75**, 3484 (1953).

(3) I. Elphimoff-Felkin, *Bull. Soc. Chim. Fr.*, 1845 (1956).

(4) N. L. Wendler, D. Taub, and R. Firestone, *Experientia*, **15**, 237 (1959).

(5) This is a more direct route to 17-hydroxy steroid 17α-carboxaldehydes, which have also been prepared in two steps by osmium tetroxide oxidation of the corresponding 17-vinyl steroid 17β-ol followed by periodic acid cleavage of the resulting triol [D. A. Prins and T. Reichstein, *Helv. Chim. Acta*, **24**, 945 (1941)].

(6) 17-Hydroxy steroid 17-methanols have also been prepared by sodium hydroxide catalyzed hydrolysis of the corresponding 17-methylene steroid epoxides [D. Bertin and L. Nedelec, *Bull. Soc. Chim. Fr.*, 2140 (1964)] and by lithium aluminum hydride reduction of the correponding methyl 17-hydroxy steroid 17-carboxylate [A. Schubert and S. Schwarz, *Experientia*, **21**, 499 (1965)].

(7) The proton magnetic resonance spectra of **4** and **5** showed anomalous singlets at 1.27 ppm, equivalent to about one proton, not exchangeable with deuterium oxide, and not present in the samples of **2** and **3** from which **4** and **5** were derived. This signal was not due to acetonitrile of crystallization as shown by determining the spectra with added acetonitrile nor was it due to 3-methoxy-17-methylestra-1,3,5(10)-trien-17β-ol [**D**, C. Djerassi, L. Miramontes, G. Rosenkranz, and F. Sondheimer, *J. Amer. Chem. Soc.*, **76**, 4092 (1954)], which might have formed by overreduction of **2**. While a sample of **D** showed the 1.27-ppm singlet, its absence in **4** and **5** was definitely proven by thin layer chromatography.

compounds showed nonequivalence of the side-chain methylene group protons,[8] which had coupling constants of 11, 11.5, and 8.5 cps, respectively.

Attempted purification of **2** by elution chromatography on silica gel produced **6** and no trace of **2**.[9] Boron trifluoride etherate in acetonitrile completely rearranged **2** into **6** in less than 10 min at 25°. Compound **2** was observed to melt at about 110°, then resolidify. The product of this thermal reaction was also shown to be **6**. That **6** was the exclusive product of rearrangement was established by several criteria in each of the three cases.

In the rearrangement of **2** on silica gel and in the thermal rearrangement, 91 and 100%, respectively, of the starting **1** were accounted for as **6** and as unchanged **1**.

The residue from the recrystallization filtrate of **6**, obtained by boron trifluoride rearrangement of **2**, was acetylated and chromatographed by elution on silica gel. Besides **7**, the acetate ester of **6**, small amounts of an unidentified oil and of estrone methyl ether were obtained. Since no unchanged **1** was isolated, as would have been expected, it seems reasonable to assume that the oil arose by dehydration of **1** by boron trifluoride. This was confirmed by its spectral properties, which denied the presence of hydroxyl or carbonyl groups. Since it lacked these groups, it could not have arisen from D-homoannulation of **2**. The origin of the estrone methyl ether is not understood. A total of 89% of the starting **1** was thus accounted for as **6**, **7**, the oil, or estrone methyl ether in this rearrangement.

The infrared and proton magnetic resonance spectral properties of **6** and **7** were consistent with their structural formulations. Both were distinguished as 17a-oxy-17-ones and not as the isomeric 17-oxy-17a-ones by their C-17a proton magnetic resonance signals, which were sharp singlets at 3.83 and 5.00 ppm, respectively. By inference from the theory, rearrangement of **2**, therefore, took place with C-13 migration, producing a 17aβ-OH in **6**. This inference of a 17aβ-OH configuration in **6** and a 17aβ-$OCOCH_3$ configuration in **7** is based on the assumption that no equilibration of the ketol isomers and no epimerization at C-17a occurred under the conditions of the rearrangement and of the acetylation.

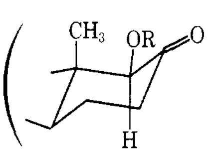
Confirmation of the formulations of **6** and **7** was afforded by the results of the lithium aluminum hydride reduction of **6**, which produced 3-methoxy-D-homoestra-1,3,5(10)-triene-17β,17aβ-diol (**8**) in 65% yield (estimated total yield, 79%) and 3-methoxy-D-homestra-1,3,5(10)-triene-17α,17aβ-diol (**11**) in 1% yield (estimated total yield, 6%). The sodium–isopropyl alcohol reduction of **6** was tried as a means of obtaining a better yield of **11** for characterization. It produced **11** in 34% yield and **8** (contaminated by a small amount of a supposed third diol) in 25% yield.[10]

Ketol **6** was further characterized by air oxidation in *t*-butyl alcoholic potassium *t*-butoxide at room temperature[11] which afforded 17-hydroxy-3-methoxy-D-homoestra-1,3,5(10),16-tetraen-17a-one (**14**). The infrared and ultraviolet[12] spectral properties of **14** were consistent with its formulation.

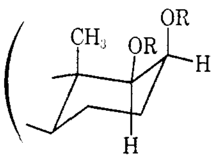
The proton magnetic resonance spectra of **8** and its diacetate ester **9** and acetonide **10** and **11** and its diacetate ester **12** and acetonide **13** served to establish their configurations at C-17 and C-17a and, thereby, the configurations of **6** and **7** at C-17a. It is implicit in these assignments that no isomerization or epimerization of **6** occurred under the conditions of the lithium aluminum hydride reduction or the work-ups. Table I gives the pertinent chemical shifts and coupling constants.

TABLE I

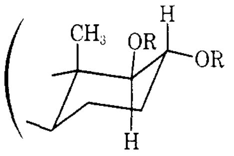
CHEMICAL SHIFTS AND COUPLING CONSTANTS



6,7



8, 9, 10



11, 12, 13

Compound	δ (17)[a]	δ (17a)[a]	δ (18)[a]	J (17–17a)[b]
6		3.83	0.68	
7		5.00	0.85	
8			1.02	
9	5.33	4.92	1.05	3.5
10	4.20	3.67	0.95	6
11			0.85	
12	4.92	4.75	0.93	10
13	3.7	3.02	0.88	10

[a] Parts per million relative to tetramethylsilane. [b] Cycles per second.

The broadness of the signals of the C-17 protons of **8**, **9**, **10**, and **13** due to their coupling with the C-16 protons easily distinguished them from the signals of the C-17a protons, which coupled only with the C-17 protons. Values of *J* (17–17a) were taken from the signals of the C-17a protons and agreed with the values expected for equatorial–axial splitting (**9** and **10**) and for axial–axial splitting (**12** and **13**).[13] A Dreiding model of **10** with ring D in the chair conformation indicated unfavorable crowding of the C-18 angular methyl group and the β-methyl group of the acetonide ring. This interaction was relieved with ring D in the boat or twist conformation and may be reflected in the relative *J* (17–17a) values of **9** and **10**.

2β-Hydroxy and 2β-acetoxy groups of ring A of the 5α-androstanes have a significant deshielding effect on

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[8] R. C. Cookson, T. A. Crabb, J. J. Frankel, and J. Hudec, *Tetrahedron, Suppl.*, **7**, 335 (1966).

[9] Bertin and Nedelec (ref 6) observed the D-homoannulation of 17-hydroxy-3-oxoandrost-4-ene-17α-carboxaldehyde in attempting to purify it by chromatography on Florisil. They did not elucidate the structure of their D-homoketol.

[10] Interestingly the sodium–isopropyl alcohol "reduction" of **6** also produced a small amount of enolone **14**, probably by air oxidation of **6** in the basic medium after the sodium had been exhausted. Although the reaction was conducted under nitrogen pressure, exclusion of oxygen was evidently incomplete.

[11] These conditions provide an additional and particularly gentle method for this type of oxidation (P. J. Neustaedter in "Steroid Reactions," C. Djerassi, Ed., Holden-Day, Inc., San Francisco, Calif., 1963, pp 131–133).

[12] Presumably the reported λ_{max} 267 mμ (ε 16,200) for 3α,17-dihydroxy-5β-D-homoandrost-16-ene-11,17a-dione [N. L. Wendler, D. Taub, and R. P. Graber, *Tetrahedron*, **7**, 173 (1959)] should be λ_{max} 267 mμ (ε 6200).

[13] N. S. Bhacca and D. H. Williams, "Applications of Nmr Spectroscopy in Organic Chemistry. Illustrations from the Steroid Field," Holden-Day, Inc., San Francisco, Calif., 1964, pp 77–85.

TABLE II

RELATIVE CHEMICAL SHIFTS OF C-18 PROTONS

Compounds	Calcd Δδ (C-18)[a,b]	Found Δδ (C-18)[a]
8–6	0.275	0.34
9–7	0.175	0.20
11–6	0.035	0.17
12–7	0.03[c]	0.07

[a] Parts per million relative to tetramethylsilane. [b] The C-17a substituent was neglected in calculating the Δδ (C-18) values. [c] Estimated.

the chemical shift of the C-19 protons relative to 2α-hydroxy and 2α-acetoxy groups.[14,15] Since ring D and C-18 of **6-13** have a mirror image relationship with ring A and C-19 of the 5α-androstanes, the δ (C-18) values of Table I may be compared with the calculated C-19 values from the Zürcher,[14] and Cohen and Rock[15] data. This is shown in Table II, which at least qualitatively reflects the expected relationship of the δ (C-18) values, thereby also confirming the configurational assignments.

Returning in conclusion to consideration of the theory of the rearrangement it may be seen that the steric advantage of a prow–stern interaction of H and H, over a prow–stern interaction of H and CH_3, was not great enough to divert the course of the rearrangement. The preference of the chair transition state over the boat transition state prevailed.

Experimental Section

General.—Reagent grade solvents were used for reactions unless otherwise noted. Melting points were taken in capillaries and are corrected. Silica gel for column chromatography was supplied by the Davison Chemical Co. Thin and thick layer chromatographic plates were coated with silica gel supplied by Merck A. G. (GF_{254}). The spots were brought out on the thin layer plates by spraying with 20% ethanolic sulfuric acid, then heating on a hot plate. Infrared spectra were determined on 0.75% potassium bromide pellets on a Perkin Model 21 spectrophotometer. Ultraviolet spectra were recorded on a Cary Model 11 spectrophotometer on 95% ethanol solutions. Proton magnetic resonance spectra were determined with tetramethylsilane as an internal reference on a Varian Model A-60 spectrometer. Optical rotations were determined on 1% chloroform solutions.

17-Hydroxy-3-methoxyestra-1,3,5(10)-triene-17α-carboxaldehyde (2).—A stream of ozone (0.12 mol) was bubbled through a stirred solution of 3-methoxy-19-nor-17α-pregna-1,3,5(10),20-tetraen-17-ol[16] (**1**, mp 107–109°, 25.00 g, 0.0800 mol) in methylene dichloride (40 ml) and pyridine (5 ml), cooled by means of a Dry Ice–acetone bath (−70°). The mixture, which contained a white precipitate, was flushed for about 10 min with oxygen. Triethylamine (5 ml) was added and the cooling bath was removed. After 1 hr the red solution, the temperature of which had risen to 25°, was washed with 2 *N* hydrochloric acid (800 ml) and then with 2.5% sodium bicarbonate solution (800 ml). It was dried over sodium sulfate and concentrated on the steam bath under water aspirator vacuum to a yellow oil (this preparation is subsequently referred to as "crude **2**"), which was diluted to 100.0 ml with acetonitrile. One-fourth (25.0 ml) of the solution was reconcentrated and the residue was recrystallized twice from acetone–hexane: ivory microcrystals; 2.79 g; 44.6% yield; mp *ca.* 110° with gradual resolidification and remelting at 179–183°; tlc R_F 0.25 with trailing which would obscure **6**; ir 2.88 (—OH) and 5.88 μ (—CH=O); pmr (20% $CDCl_3$) 9.82 ppm (s, 1, —CH=O), 0.97 ppm (s, about 2.4 $-\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$ of **2**), and 0.70 ppm (s, about 0.6, $-\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$ of **6**); $[\alpha]^{25}\mathrm{D}$ +57.1°. The presence of about 20% **6** in this preparation of **2** was thus indicated. Assuming 80% **2** and 20% **6** in the mixture the rotation of pure **2** would be +69°.

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.47; H, 8.58.

17-Hydroxy-3-methoxyestra-1,3,5(10)-triene-17α-methanol (3).—A solution of crude **2** (prepared from 15.62 g, 0.0500 mol, of **1** and 0.075 mol of ozone) in tetrahydrofuran (Du Pont drum quality, 150 ml) was added during 20 min to a solution of lithium aluminum hydride (3.79 g, 0.100 mol) in tetrahydrofuran (150 ml) held under nitrogen. The mixture was heated for 1.0 hr under reflux. Water (7.6 ml) was added dropwise with stirring and the mixture was filtered with suction through kieselguhr. Concentration of the cloudy solution at 40–50° under water aspirator vacuum gave a yellow oil. A solution of the yellow oil in chloroform (about 30 ml) was washed with 2 *N* hydrochloric acid (100 ml), then with 2.5% sodium bicarbonate solution (100 ml), dried over sodium sulfate, filtered, and concentrated to a yellow oil, which solidified. The solid was recrystallized twice from acetonitrile: colorless needles; 9.27 g; 58.7% yield based on **1**; mp 168–174° with an allotropic change in the middle of the range; $[\alpha]^{25}\mathrm{D}$ +45°; pmr [15% $DCON(CD_3)_2$ with added D_2O] AB quartet centered at 3.58 ppm (2, δ 11 cps, *J* = 11 cps, $-CH_2O-$) and 0.90 ppm (s, 3, $-\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.20; H, 9.01.

Oxidation of 3 by Sodium Periodate.—Solid sodium metaperiodate (0.32 g, 1.5 mmol) was added in portions during 10 min with stirring to a solution of **2** (0.32 g, 1.0 mmol) in dioxane (21 ml) and water (4 ml). The mixture was stirred for 3 hr at 25°, then diluted with water (about 130 ml). The resulting solid was collected, washed with water, and dried: 0.29 g; 100% yield; mp 168–171°. It was identified as estrone methyl ether (3-methoxyestra-1,3,5(10)-trien-17-one) by mixture melting point and tlc comparisons.

17-Hydroxy-3-methoxyestra-1,3,5(10)-triene-17α-methanol 20-Acetate (4).—A solution of **3** (1.00 g, 3.16 mmol) in pyridine (10 ml) and acetic anhydride (10 ml) was let stand for 5 hr at 25°, then diluted with water (about 200 ml). The resulting white solid was collected and dried: 1.13 g; 96.6% yield; mp 92–94°. Recrystallization from acetonitrile gave 0.54 g (46% yield) of colorless prisms of unchanged melting point: $[\alpha]^{25}\mathrm{D}$ +29.7°; ir 2.85 (—OH) and 5.80 (shoulder at 5.77) and 8.0–8.1 μ (—O-$COCH_3$); pmr (20% $CDCl_3$ with added D_2O) AB quartet centered at 4.17 (2, δ 8.5 cps, *J* = 11.5 cps, $-CH_2O-$), 2.08 (s, 3, $-OCOCH_3$), 1.27 (∼1, ?), and 0.93 ppm (s, 3, $-\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$).

17-Hydroxy-3-methoxyestra-1,3,5(10)-triene-17α-methanol Cyclic 17,20-Acetone Acetal (5).—A mixture of **3** (3.16 g, 0.0100 mol), *p*-toluenesulfonic acid monohydrate (0.02 g, 0.0001 mol), and acetone (60 ml) was stirred for 2 hr at 25°. The steroid dissolved as the reaction proceeded. Water (about 600 ml) and 5% sodium bicarbonate solution (10 ml) were added. The resulting white solid (3.54 g, 99.3% yield, mp 96–97°) was recrystallized from acetonitrile: colorless prisms; 2.78 g; 77.9% yield; mp 97–98°; $[\alpha]^{25}\mathrm{D}$ +27.0°; pmr 4.17 (d, 1) and 3.60 (d, 1, δ 34 cps, *J* = 8.5 cps, $-CH_2O-$), 1.40 and 1.33 (singlets, 2 × 3, $\mathrm{CH_3}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$), 1.27 (s, ∼1 H, ?), and 0.86 ppm (s, 3, $-\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$).

17aβ-Hydroxy-3-methoxy-D-homoestra-1,3,5(10)-trien-17-one (6). A. With Silica Gel.—Crude **2** (prepared from 3.12 g, 0.0100 mol, of **1** and 0.011 mol of ozone) was chromatographed on a column of silica gel (100 g). Fractions of about 100 ml in volume were cut. The eluant was 80:20 pentane–ether. Fractions 7–20 (0.62 g, 20%) were mostly **1** and fractions 20–25 (0.59 g, 19% based on **1**) were mostly **6** with some **1** as shown by tlc. Fractions 21–45 (1.64 g, 52.2%) were mostly **6**. Two recrystallizations from acetonitrile gave pure **6** as colorless prisms: 1.20 g; 38.0% yield based on **1**; mp 183–185°; ir 2.92 (—OH) and 5.86 μ ($-\overset{|}{\underset{|}{\mathrm{C}}}=O$); pmr (20% $CDCl_3$ with added D_2O) 3.83 (s, 1, $-\mathrm{O}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{H}$) and 0.68 ppm (s, 3, $-\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$).

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(14) Reference 13, Chapter 2.

(15) A. I. Cohen and S. Rock, *Steroids*, **3**, 243 (1964).

(16) Compound **1** was prepared from 3-methoxy-19-nor-17α-pregna-1,3,5(10)-trien-20-yn-17-ol [G. D. Searle Co.] in yields of 75–85% by hydrogenation over palladium on strontium carbonate at 10–60 psig and 25° [F. B. Colton, U. S. Patent 2,666,769 (Jan 19, 1954)].

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.62; H, 8.39.

B. With Boron Trifluoride.—Boron trifluoride etherate (47%, 3.0 ml) was added to a solution of crude **2** in acetonitrile (three-fourths, 75.0 ml, of the solution described under the preparation of **2**). The reaction was shown by tlc to be complete after 10 min at 25°. After 30 min the solution was quenched in water (about 1 l.). The resulting solid (18.41 g) was recrystallized from acetonitrile: 14.27 g; 75.7% yield based on **1**; mp 172–180°. Recrystallization of part (3.00 g) of this material from ethyl acetate gave a different crystalline form (colorless needles) of **6**: 2.24 g; mp 183–185° with a phase change at about 175°; $[\alpha]^{25}\mathrm{D}$ +10.5°. Whereas the ir of the two forms were not identical as potassium bromide pellets, they were identical as chloroform solutions. The new form showed the correct elemental analysis.

Anal. Found: C, 76.54; H, 8.40.

C. With Heat.—The melting point conditions of **6** were simulated by heating 13.8 mg of **2** from 100 to 200° during 20 min. The residue was triturated with 1 drop of acetonitrile and dried, 13.9 mg, mp 174–180°. It was identical with the **6** obtained by method A by mixture melting point, ir, and tlc comparisons. The latter showed a small amount of **1** as the only impurity.

17aβ-Hydroxy-3-methoxy-D-homoestra-1,3,5(10)-trien-17-one Acetate (7).—A pyridine (15 ml) and acetic anhydride (15 ml) solution of the residues from the mother liquors from the preparation of **6** by method B was let stand for 17 hr at 25°. The solution was partitioned between chloroform (25 ml) and dilute hydrochloric acid (0.67 *N*, 300 ml). The chloroform layer was washed with 2.5% sodium bicarbonate solution, dried over sodium sulfate, filtered, concentrated, and chromatographed on silica gel (210 g). An unidentified colorless oil (0.64 g, 3.6% yield based on **1**) was eluted in fractions 1–11 (400 ml fractions) with 90:10 pentane–ether. Estrone methyl ether (0.70 g, 4.1% yield based on **1**) was eluted by 85:15 and 80:20 pentane–ether in fractions 12–25. Elution by 70:30 pentane–ether afforded **7** (2.12 g, 9.9% yield based on **1**, mp 194–202°) in fractions 36–45. Recrystallization from acetonitrile gave thin colorless prisms: 1.55 g (7.2% yield); mp 202–204°; $[\alpha]^{25}\mathrm{D}$ +22.7°; ir 5.72 and 8.1 ($-\mathrm{OCOCH_3}$) and 5.81 μ ($-\overset{|}{\mathrm{C}}{=}\mathrm{O}$); pmr (20% $\mathrm{CDCl_3}$) 5.00 (s, $-\mathrm{OCO}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{H}$) and 0.85 ppm (s, $-\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$).

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.19; H, 7.95.

3-Methoxy-D-homoestra-1,3,5(10)-triene-17β,17aβ-diol (8). A. From the Lithium Aluminum Hydride Reduction of 6.—A solution of **6** (6.29 g, 0.0200 mol) in tetrahydrofuran (65 ml) was added dropwise with stirring to a solution of lithium aluminum hydride (1.52 g, 0.0400 mol) in tetrahydrofuran (65 ml). After heating the mixture for 4 hr under reflux water (2.5 ml) was added. The mixture was filtered with suction through kieselguhr and the cloudy filtrate was concentrated at 40–50° under water aspirator vacuum to an oil. A chloroform solution (about 100 ml) of the oil was washed with 2 *N* hydrochloric acid (100 ml). The mixture was filtered through kieselguhr to remove insoluble aluminum salts. The chloroform layer was washed with 2.5% sodium bicarbonate solution (100 ml), dried over sodium sulfate, filtered, and concentrated with a large volume of ethyl acetate to about 100 ml. Dense colorless granules separated and two subsequent crops were collected; 4.88 g, 77.1% yield. Recrystallization of the granules from chloroform–ethyl acetate gave 3.96 g (64.7% yield) of **8**: mp 187–191°; $[\alpha]^{25}\mathrm{D}$ +82.3°; pmr (<10% $\mathrm{CDCl_3}$) 1.02 ppm (s, 3, $-\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.92; H, 8.74.

B. From the Sodium–Isopropyl Alcohol Reduction of 6.—In the chromatography of the sodium–isopropyl alcohol reduction product of **6** described below, **8** (1.57 g, 24.8% yield) was eluted by 40:60 pentane–ether in fractions 18–25. It was recrystallized from acetonitrile (1.50 g, 23.7% yield, mp 181–187°) and identified as being mostly **8** by tlc (R_F 0.25), mixture melting point, ir, and pmr comparisons. Its tlc spot had a slower running halo. Its pmr spectrum showed an additional weak $-\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$ singlet at 0.83 ppm. The halo and 0.83-ppm signal were supposed to be due to a third diol component.

3-Methoxy-D-homoestra-1,3,5(10)-triene-17β,17aβ-diol Diacetate (9).—One-fifth (4.95 g) of the crude **6**, obtained by ozonolysis of **1** (25.00 g, 0.0800 mol) followed by boron trifluoride rearrangement of the resulting crude **2**, was reduced by lithium aluminum hydride, all according to the procedures given. A solution of the crude **8** thus obtained in pyridine (25 ml) and acetic anhydride (25 ml) was let stand for 23 hr at 25°, then quenched in dilute hydrochloric acid. The resulting solid (5.66 g) was chromatographed on silica gel (160 g). The product (3.88 g, 60.6% yield from **1**) was eluted by 80:20 pentane–ether in fractions 16–29 (400-ml fractions) and was recrystallized from acetonitrile: colorless microscopic crystals; 3.19 g; 49.9% yield from **1**; mp 159–161°; $[\alpha]^{25}\mathrm{D}$ +44.9°; ir 5.77 and 8.0–8.1 μ ($-\mathrm{OCOCH_3}$); pmr (20% $\mathrm{CDCl_3}$) 5.33 (m, 1, $-\mathrm{OCO}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{H}$ at C-17), 4.92 (d, 1, J = 3.5 cps, $-\mathrm{OCO}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{H}$ at C-17a), 2.02 and 2.03 (singlets, 2 × 3, 2 × $-\mathrm{OCOCH_3}$), and 1.05 ppm (s, 3, $-\overset{|}{\underset{|}{\mathrm{C}}}-\mathrm{CH_3}$).

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 72.27; H, 8.16.

3-Methoxy-D-homoestra-1,3,5(10)-triene-17β-17aβ-diol Cyclic Acetone Acetal (10).—A solution of **8** (1.53 g, 4.83 mmol), *p*-toluenesulfonic acid monohydrate (0.05 g, 2.4 mmol), and acetone (45 ml) was stirred for 24 hr at 25°. 2,2-Dimethoxypropane (90%, 0.05 g, 4.8 mmol) was added and stirring was continued for 6 hr. The solid (1.65 g, 95.8% yield) obtained by quenching the reaction solution in dilute sodium bicarbonate was percolated through silica gel (100 g) with 80:20 pentane–ether. Fractions of about 200 ml were cut. The product (1.42 g, 82.3% yield, mp 141–143°) appeared in fractions 1–5 and was recrystallized from acetonitrile: colorless needles; 1.28 g; 74.3% yield; mp 143–144°, $[\alpha]^{25}\mathrm{D}$ −30.6°; pmr (20% $\mathrm{CDCl_3}$) 4.20 (m, 1, J = 6, 12 cps, $-\mathrm{O}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{H}$ at C-17), 3.67 (d, 1, J = 6 cps, $\mathrm{O}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{H}$ at C-17a), 1.50 and 1.35 (singlets, 2 × 3, $\mathrm{CH_3}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$), and 0.95 ppm (s, 3, $-\overset{|}{\underset{|}{\mathrm{C}}}-\mathrm{CH_3}$).

Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.15; H, 8.97.

3-Methoxy-D-homoestra-1,3,5(10)-triene-17α,17aβ-diol (11). A. From the Sodium–Isopropyl Alcohol Reduction of 6.—Freshly cut sodium (9.2 g, 0.40 g-atom) was added in small pieces in regular intervals during 2 hr to a refluxing solution of **6** (6.29 g, 0.0200 mol) in isopropyl alcohol (400 ml) held under nitrogen pressure. After being let cool the mixture was quenched in ice–water (2 l.) containing hydrochloric acid (0.48 mol). This mixture was extracted with chloroform. The chloroform extracts were washed with 5% sodium bicarbonate solution, dried over sodium sulfate, filtered, concentrated, and chromatographed on silica gel. Fractions of about 400 ml were cut. Following **8** (fractions 18–25) a mixture of **8** and **11** (0.76 g, 12% yield) was eluted by 40:60 pentane–ether in fractions 26–30. This was followed by nearly pure **11** (2.14 g, 33.8% yield) in fractions 31–47. Recrystallization from ethyl acetate gave colorless, microscopic crystals: 1.71 g; 27.0% yield; mp 165–166°; $[\alpha]^{25}\mathrm{D}$ + 67.0°.

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.25; H, 9.16.

B. From the Lithium Aluminum Hydride Reduction of 6.—A mixture of the residue (2.18 g) from the mother liquors of recrystallization of **8**, acetone (40 ml), and *p*-toluenesulfonic acid monohydrate (0.015 g, 0.075 mmol) was stirred at 25° for 46 hr. The resulting solution was partitioned between 2.5% sodium bicarbonate solution (200 ml) and chloroform (20 ml). The aqueous phase was further extracted with chloroform (three times with 5 ml). The combined chloroform extracts were dried over sodium sulfate, filtered, concentrated, and chromatographed on silica gel (100 g). Fractions of about 200 ml were cut. Elution by 90:10 pentane–ether gave **10** (0.91 g, mp 139–143°). Part (0.36 g, 1.0 mmol) of this material was hydrolyzed in acetic acid (9.0 ml)–water (1.0 ml) at 30° during 3 hr into **8**: 0.30 g; 95% yield; mp 178–189° undepressed on admixture with **8**; estimated by tlc to contain less than 10% **11**. A small (0.18 g, 2.9%) yield of mostly **8** with some **11** was eluted by 60:40 pentane–ether in fractions 46–53 followed by mostly **11** with some **8** (0.29 g, 4.7% yield), eluted by ether in fractions 54–65. Thus, estimating fractions 6–15 as representing 90% **8** and 10% **11**, fractions 46–53 as representing 100% **8**, and fractions 54–65 as representing 100% **11** the yields in this reduction were 79% **8** and 6% **11**. Two recrystallizations of the residue of fractions 54-65 from ethyl acetate gave **11**: 0.09 g; mp 163–165° undepressed on admixture with material prepared by method A; $[\alpha]^{25}\mathrm{D}$ +67.5°; pmr (saturated $CDCl_3$) 0.85 ppm (s, 3, $-\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$).

Anal. Found: C, 75.74; H, 8.84.

3-Methoxy-D-homoestra-1,3,5(10)-triene-17α,17aβ-diol Diacetate (12).—A solution of **11** (63.6 mg, 0.200 mmol), pyridine (1 ml), and acetic anhydride (1 ml) was let stand for 22 hr at 25°, then quenched in water. The resulting solid (76.2 mg, 94.8% yield, mp 177–181°) was recrystallized from acetonitrile: 52.5 mg; 65.5% yield; mp 183–184.5; $[\alpha]^{25}\mathrm{D}$ +15.1°; pmr (10% $CDCl_3$) 4.92 (m, 1, $-\mathrm{O}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{H}$ at C-17), 4.75 (d, 1, J = 10 cps, $-\mathrm{O}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{H}$ at C-17a), 1.97 and 2.03 (singlets, 2 × 3, 2 × $-\mathrm{OCOCH_3}$), and 0.93 ppm (s, 3, $-\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$).

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 72.05; H, 8.02.

3-Methoxy-D-homoestra-1,3,5(10)-triene-17α,17aβ-diol Cyclic Acetone Acetal (13).—A mixture of **11** (0.32 g, 1.0 mmol), 2,2-dimethoxypropane (0.21 g, 2.0 mmol), *p*-toluenesulfonic acid monohydrate (0.01 g, 0.05 mmol), and acetone (6.0 ml) was stirred at 25° for 24 hr. As at this time solid still remained suspended and some **11** remained unchanged as shown by tlc, tetrahydrofuran (6.0 ml) was added and stirring was continued for 24 hr more. Solid still remained and some **11** remained unchanged. Molecular sieves (Linde 4A, 1.0 g) were added and stirring was continued for 96 hr. An estimated 10% or less of **11** remained unchanged. Chloroform (about 6 ml) was added to dissolve the organic portion of the precipitate and the mixture was stirred with sodium bicarbonate (0.42 g, 5.0 mmol) for 2 hr. It was filtered with suction through kieselguhr. After being concentrated to about 5.0 ml the filtrate was streaked onto a 20 cm × 40 cm thick layer chromatographic plate, which was developed with chloroform. The product (0.33 g, 93% yield, mp 191–193°) was extracted from the band which appeared at R_F 0.20–0.49. It recrystallized from ethyl acetate as colorless plates: 0.28 g; 79% yield; mp 197–198°; $[\alpha]^{25}\mathrm{D}$ +80.9°; pmr (20% $CDCl_3$) about 3.7 (m, 1, $-\mathrm{O}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{H}$ at C-17), 3.02 (d, 1, J = 10 cps, $-\mathrm{O}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{H}$ at C-17a), 1.38 and 1.40 (singlets, 2 × 3, $\mathrm{CH_3}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$), and 0.88 ppm (s, 3, $-\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$).

Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.09; H, 8.99.

17-Hydroxy-3-methoxy-D-homoestra-1,3,5(10),16-tetraen-17a-one (14). A. From the Potassium *t*-Butoxide–Oxygen Oxidation of 6.—A solution of *t*-butyl alcohol (100 ml), potassium *t*-butoxide (4.49 g, 0.0400 mol), and one-fifth of the crude **6**, obtained from the ozonolysis of **1** (25.00 g, 0.0800 mol) followed by boron trifluoride rearrangement of the resulting crude **2**, was stirred for 4 hr at 25°. It was quenched in water (0.6 l.) containing hydrochloric acid (0.060 mol) and the quench was extracted with chloroform (once with 30 ml, twice with 10 ml). The combined chloroform extracts were washed with 2.5% sodium bicarbonate solution, dried over sodium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (160 g). Fractions of about 400 ml were cut. The product (1.94 g, 38.8% yield from **1**, mp 173–175°) was eluted in fractions 4–15 by 80:20 pentane–ether and crystallized from acetonitrile as colorless blades: 1.51 g; 30.2% yield from **1**; mp 176–177°; $[\alpha]^{25}\mathrm{D}$ +34.3°; ir 2.93 (—OH), 5.98 ($-\overset{|}{\mathrm{C}}{=}\mathrm{O}$), and 6.05 μ ($-\overset{|}{\mathrm{C}}{=}\overset{|}{\mathrm{C}}-$); uv λ_{max} 219 mμ (ε 9150), 269 (7750), and 286 (shoulder, 4150); pmr (~12% $CDCl_3$ with added D_2O) 1.10 ppm (s, 3, $-\overset{|}{\mathrm{C}}\mathrm{CH_3}$).

Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 77.18; H, 7.46.

B. From the Sodium-Isopropyl Alcohol "Reduction" of 6.—In the chromatography of the sodium–isopropyl alcohol reduction product of **6** crude **14** (1.09 g), admixed with several lesser unidentified components, was eluted by 60:40 pentane–ether in fractions 2–8. Two recrystallizations from acetonitrile gave **14** having mp 172–174°, identified by tlc, mixture melting point, and ir comparisons with **14** obtained by method A.

Registry No.—**2**, 21887-08-1; **3**, 21887-09-2; **4**, 21904-43-8; **5**, 21887-10-5; **6**, 21887-11-6; **7**, 21887-12-7; **8**, 21887-13-8; **9**, 21887-14-9; **10**, 21887-15-0; **11**, 21887-16-1; **12**, 21887-17-2; **13**, 21887-18-3; **14**, 21887-19-4.

Acknowledgment.—The author thanks the following members of the staff of the Sterling–Winthrop Research Institute for their contributions to this work: Dr. R. G. Christiansen for interest and encouragement, Mr. K. D. Fleischer and Mr. C. E. Joseph for microanalyses, Mrs. G. E. Barnett for rotations, Mrs. M. W. Becker and Mrs. E. G. Boll for spectral determinations, and Dr. R. K. Kullnig and Miss C. M. Martini for aid in interpreting the spectra.