STEROIDS CCLXXII[1]. BIOLOGICALLY-ACTIVE LABILE ETHERS III[2]. A NEW CLASS OF POTENT ESTROGENS.

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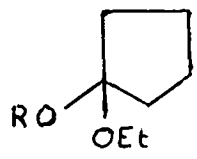
Possible structural modifications for increasing the sensitivity of steroid ethers are discussed. 3-Methoxyestra-1,3,5(10)-trien-17-one cyclic ethylene ketal and cyclic ethylene monothioketal suffer cleavage of the ketal ring on exposure to a combination of either lithium aluminum hydride and aluminum trichloride, or diborane and boron trifluoride. The resultant 17β-(2-hydroxyethyl) ether and thioether have been converted into a range of new estrane derivatives, several of which show pronounced estrogenic activity by the oral route of administration. Other 17-ketals also undergo cleavage to form 17β-ethers.

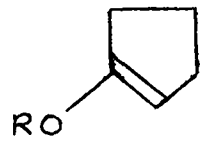
The chemical literature of the past two decades bears powerful testimony to the ingenuity of the organic chemists' endeavors to modify the steroid skeleton and thereby enhance biological activity[3]. From these efforts there have resulted estrogenic, progestational and corticoid agents of a potency vastly superior to their naturally-occurring analogs.

In the androstane and estrane series protection of sensitive alcoholic functions has normally been achieved

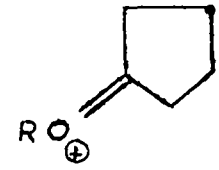
through their conversion to ester groups. However, Ercoli and his co-workers recently revealed useful biological activity for certain androstane ethers.[4] Of particular significance was the activity of these derivatives by oral administration whereas the corresponding esters have utility only by injection. The protecting groups employed by the Italian workers constituted either a ketal (A) or a vinyl ether (B). From a chemical standpoint these two ethers both readily give on protonation an intermediate charged oxonium ion (C) the formation of such a species being essential for easy hydrolysis and release of the free alcohol. There are clearly numerous variants of the ketal or acetal structural type which fulfill this structural requirement. In accord with expectations, synthesis of the chemically labile 17β-tetrahydropyranyl ethers (D) of both androstanes[5] and estrogens[2] led to new classes of orally-active labile ethers of marked biological potency. On chemical grounds it was expected that an E_1 or E_2 elimination of HX from a structure of type E [where X=a good leaving group, alone or after protonation] should lead to a labile vinyl ether. Lability of a different type is incorporated into the ether moiety F where proton abstraction adjacent to a carbonyl, nitrile, or similar function (C=X), can be followed by C-O bond rupture as indicated, leaving a 17β-oxanion. Prompted by the growing importance of orally-active estrogens in estrogen-progestin fertility control combinations we undertook the synthesis of com-



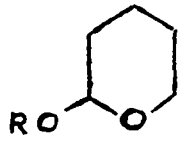
A



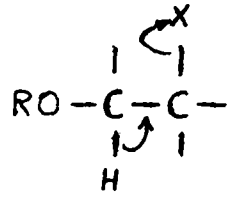
B



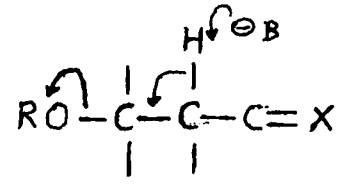
C



D



E



F

pounds containing structural features E and F. Our results are the subject of the present communication. Preliminary biological assays appear to vindicate the reasoning employed and a new class of estrogenic steroids 17β-ethers has been uncovered[6].

As starting material in a synthesis of retro(9β,10α)-steroids[7] we required an ample supply of 11α- or 11β-hydroxyestra-1,3,5(10)-triene derivatives. The earlier report of successful Brown hydration[8] of estra-1,3,5(10),9(11)-tetraene-3,17β-diol diacetate to yield the 11α-hydroxy derivative[9] led us to examine the hydration of the 17-cyclic ethylene ketal of 9(11)-dehydroestrone methyl ether (Ia)[10,11].

A crude mixture of estrone methyl ether and the 9,11-dehydro derivative[10] was converted to the mixed 17-cyclo-ethylene ketals, Ia and Ib. The mixture was subjected to the action of diborane gas, generated externally from boron

trifluoride and sodium borohydride, worked up by addition of alkaline hydrogen peroxide, and the crude reaction product chromatographed over alumina to yield a crystalline alcohol. However, the isolated product was not the expected 11α-alcohol Ic, but was the primary alcohol IIa resulting from cleavage of the cyclic ethylene ketal group in the precursor Ib. The structure followed from elemental analysis and from nuclear magnetic resonance (n.m.r.) spectral examination of sundry derivatives (vide infra).

Eliel and his co-workers have described numerous examples of ketal cleavage by double metal hydrides in combination with Lewis acids[12,13], and applications of this reagent mixture to the cleavage of monothio ketals and dithio ketals has also attracted attention.[14-16] It was apparent that, for the ketal under investigation, diborane-boron trifluoride was serving as a hitherto unrecognized alternative combination of reagents for the reductive opening of the cyclic ethylene ketal ring. A rapid rate of generation of diborane gas presumably sweeps into the reaction vessel sufficient boron trifluoride etherate to act as the necessary Lewis acid. If precautions are taken to exclude the boron trifluoride then no ketal cleavage takes place, and numerous examples are to be found in the literature where ketal protecting groups remain intact during hydroboration of a double bond.[17]

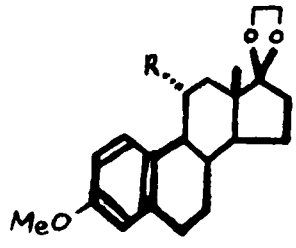
The availability of the 17β-(2-hydroxyethyl) ether IIa offered the chance to prepare a series of 17β-(2-substituted

ethyl) ethers of types E and F (vide supra). Besides obtaining a novel class of estrogenic compounds it was anticipated that subsequent reduction of ring A would lead to the corresponding 19-nortestosterone 17β-(2-substituted-ethyl) ethers which would constitute another new group of potentially interesting steroids. In practice it proved more convenient to prepare the 2-hydroxyethyl ether IIa from the ketal Ib by cleavage with lithium aluminum hydride-aluminum trichloride.[13]

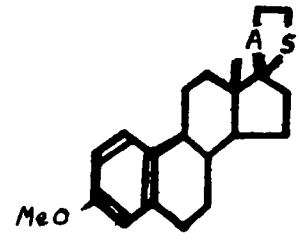
In the n.m.r. spectrum[18] the 2-hydroxyethyl ether (IIa) showed, besides the expected resonances for aromatic protons and the C-3 methoxyl (singlet at 224 c.p.s.), an unresolved pattern of peaks at 218 c.p.s., half-band width 5 c.p.s., equivalent to four protons. In the absence of nearby polar groups and double bonds a cyclic ethylene ketal usually gives rise to a four-proton 'singlet' resonance at ca. 232-238 c.p.s.[19], with half-band width of the order of 3 to 4 c.p.s. Apparently the couplings between the four methylene protons of the dioxalane ring are quite small so that the envelope of the resonance multiplet appears as a 'singlet', except with the most powerful instruments. Conversion of the alcohol IIa to the primary acetate IIb was accompanied by a clarification of the n.m.r. spectrum which revealed a two-proton 'triplet' resonance at 254 c.p.s., J, ca. 5 c.p.s., for the methylene bearing the acetate, and a second, partially-obscured 'triplet' at 225 c.p.s., J, ca. 5 c.p.s., for the adjacent methylene. Another, ill-resolved

triplet, J, ca. 8 c.p.s., assignable to the 17α-proton appeared at 206 c.p.s. The spectral pattern was thus indicative of the freely rotating side chain -CH.O.CH_2.CH_2.OAc. N.m.r. spectral data for further derivatives (see experimental section) were in complete agreement with this interpretation.

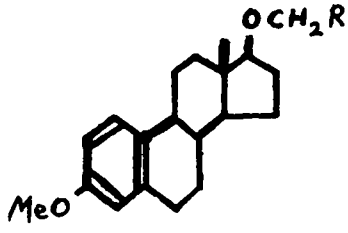
The alcohol IIa was converted to the tosylate IIc which with potassium cyanide and dimethylformamide readily underwent displacement by cyanide ion to afford the nitrile IId. Reaction of the tosylate with potassium chloride in dimethylformamide led however to estradiol 3-methyl ether proving thereby that the ketal cleavage reaction leads to the 17β-oriented 2-hydroxyethyl ether side chain.[20] The desired 17β-(2-chloroethyl) ether IIe was formed unexpectedly when the alcohol IIa was treated with an excess of tosyl chloride and pyridine during 60 hr. Apparently the initially-formed tosylate IIc undergoes a displacement reaction with chloride ion in pyridine. The mesylate IIf was prepared and gave the piperidine derivative IIg and iodo compound IIh by appropriate substitution reactions. The tetrahydropyranyl ether IIi was also prepared. When treated with 2-chloro-1,1,2-trifluorotriethylamine reagent[21] the alcohol IIa furnished the 17β-(2-fluoroethyl) ether IIj in addition to some estradiol 3-methyl ether. Chromic oxide and pyridine oxidation[22] of the alcohol IIa furnished the corresponding aldehyde IIk together with some of the acid III. The latter was readily obtained also by chromic acid oxidation[23] of IIa



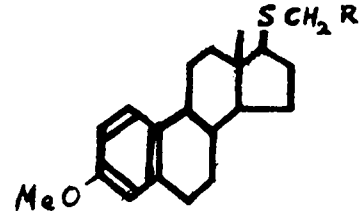
I. a) R = H; $\Delta^{9(11)}$
b) R = H
c) R = OH



III. A = O
V. A = S



II. a) R = CH_2OH
b) R = CH_2OAc
c) R = CH_2OTs
d) R = $CH_2C{\equiv}N$
e) R = CH_2Cl
f) R = CH_2OMs
g) R = CH_2N⟨⟩
h) R = CH_2I
i) R = CH_2-O-⟨O⟩
j) R = CH_2F
k) R = CHO
l) R = CO_2H
m) R = CO_2CH_3



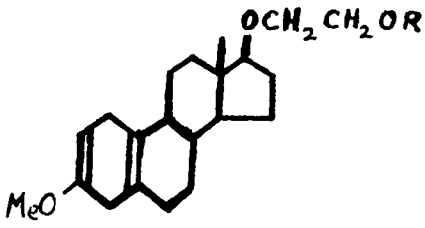
IV. a) R = CH_2OH
b) R = CH_2OAc
c) R = CH_2F
d) R = CH_2Cl
e) R = CH_2OTs
f) R = CH_2OMe
g) R = CH_3

Esterification then led to the methyl ester IIm. An analogous series of compounds was next obtained from the product, IVa, of reductive cleavage of estrone 3-methyl ether cyclic ethylene monothio ketal (III) with lithium aluminum hydride - aluminum trichloride. From the studies of Eliel and his co-workers it is known that the monothio ketals cleave to give exclusively the 2-hydroxyethyl thioether side chain with the thermodynamically more stable quasi-equatorial configuration predominating.[14] The alcohol IVa was readily converted to its acetate IVb and, by treatment with the 2-chloro-1,1,2-trifluorotriethylamine reagent,[21] to the 17β-(2-fluoroethyl) thioether IVc. Attempts to prepare the mesylate or tosylate esters led instead to the 2-chloroethyl thioether IVd. The tosylate ester IVe was eventually prepared by conversion of the alcohol IVa to the sodium alcoholate and addition of tosyl chloride. With methanolic hydrochloric acid the alcohol IVa furnished the 17β-(2-methoxyethyl) thioether IVf. Prolonged exposure of the monothio ketal III to lithium aluminum hydride in dioxan at reflux in the presence of a large excess of aluminum trichloride led to the ethyl thioether IVg, a reaction for which there is ample analogy.[12] The thioethyl group was readily identified from the n.m.r. spectrum of IVg which featured prominently a triplet, J, 7 c.p.s. and a quartet, J, 7 c.p.s., at 155.5 c.p.s. for the methyl and methylene protons respectively in an A_2X_3 system. Certain of the 17β-thioethers IV proved to be noticeably

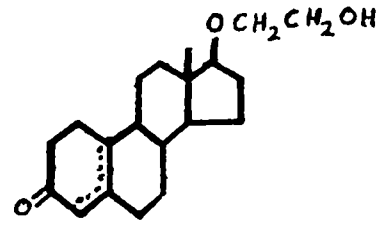
less stable than their 17β-oxygen ether counterparts II. Thus, the 2-tosyloxy ethyl thio derivative IVe decomposed slowly during attempted purification.

Estrone 3-methyl ether was reacted with ethane dithiol and boron trifluoride to afford the dithio ketal V. Several unsuccessful attempts were made to cleave this dithio ketal with lithium aluminum hydride and aluminum trichloride. Failure to do so is in accord with previous findings.[15]

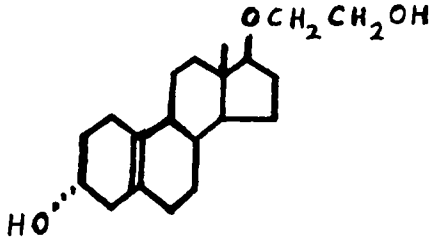
Reduction of the hydroxyethyl ether IIa with lithium in ammonia[24] led to the 1,4-dihydro derivative VIa, further characterized as the derived acetate VIb. Hydrolysis of the vinyl methyl ether function in the alcohol VIa with aqueous hydrochloric or oxalic acid led to the αβ-unsaturated 3-ketone VIIa and β,γ-unsaturated 3-ketone VIIb, respectively. The latter was reduced by borohydride to the 3α-alcohol VIII,[25] an ethanolic solution of which took up one mole of hydrogen in the presence of platinum catalyst giving 17β-(2-hydroxyethoxy)-5β,10β-estran-3α-ol (IXa). The corresponding diacetate IXb was prepared. Hydrogenation of the estr-5(10)-en-3-one derivative VIIb over ruthenium oxide at elevated temperature and pressure[26] resulted in the formation of IXa and the stereoisomeric 17β-(2-hydroxyethoxy)-5α,10α-estran-3β-ol (IXc). Assignment of stereochemistry in IXc is based on the observation of Counsell that the major product of such hydrogenations results from reduction from the α-face at the three centers, C-3, C-5 and C-10[27].



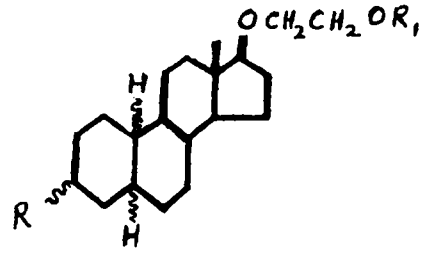
VI. a) R = H
b) R = Ac



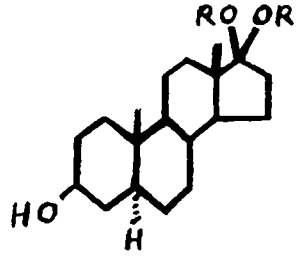
VII. a) Δ^4
b) $\Delta^{5(10)}$



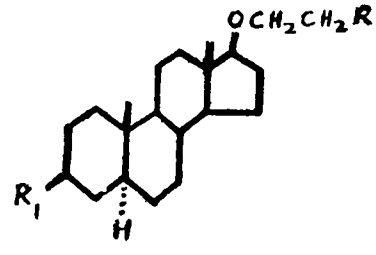
VIII.



IX. a) 5β,10β; R = 3αOH; R_1 = H
b) 5β,10β; R = 3αOAc; R_1 = Ac
c) 5α,10α; R = 3βOH; R_1 = H



X. a) RR_1 = $-CH_2-CH_2-$
b) R = R_1 = Et



XI. a) R = R_1 = OH
b) R = R_1 = OAc
c) R = H; R_1 = OH
d) R = H; R_1 = OAc

The finding (vide supra) that diborane-boron trifluoride may be used as an alternative to previously described double metal hydride - Lewis acid combinations[17] led us to examine the utility of this new reagent pair in the cleavage of other ketals. 3β-Hydroxy-5α-androstan-17-one cyclic ethylene ketal (Xa) was subjected to a fast stream of externally generated diborane and worked up with alkaline peroxide. Thereby was obtained the expected 17β-(2-hydroxyethoxy)-5α-androstan-3β-ol (XIa). This diol and the derived diacetate XIb proved to be identical with the analogous diol and diacetate derivative from cleavage of the same ketal with lithium aluminum hydride-aluminum trichloride. The diethyl ketal Xb also undergoes carbon-oxygen bond cleavage by lithium aluminum hydride - aluminum trichloride to afford 17β-ethoxy-5α-androstan-3β-ol (XIc), further characterized through the monoacetate XId. Assignment of the 17β-orientation to the ethoxy side chain is based on reaction mechanism studies[12] and on the results for the cyclic ethylene ketal (vide supra).

Biological Activities

The 17β-oxa and thia compounds (II and IV) have been assayed for estrogenicity by the procedures of Rubin et al.[28] Preliminary results show that the 2-chloroethoxy (IIe) and 2-fluoroethoxy (IIj) derivatives both have estrogenic potencies 4 times that of estrone (activity = 1.0) when administered orally By subcutaneous administration the respective activities are 0.5, and 0.05 times that of estrone. Other 2-substituted-ethyl ethers

(II) also showed appreciable oral activity but low potency by injection[29]. For the labile ethers a higher level of oral activity as against injection is maintained, similar to that noted earlier for tetrahydropyran-2-yl ethers.[2,5] The thia analogs showed lower activities.

EXPERIMENTAL[31]

17β-(2-Hydroxyethoxy)-3-methoxyestr-1,3,5(10)-triene (IIa). - (a) A solution of 38 g. of a mixture of estrone 3-methyl ether cyclic ethylene ketal (Ib) and the corresponding 9(11)-dehydro analog (Ia)[10] in 750 ml. of dry tetrahydrofuran was kept at ca. 50° and a stream of diborane (generated externally from 160 g. sodium borohydride in 600 ml. of tetrahydrofuran by dropwise addition of ethereal boron trifluoride) passed through during 1.5 hr. The mixture was then poured slowly into 3 l. of ice water. Methylene chloride extracts of the latter were washed with water, dried over sodium sulfate and evaporated to afford an oil. A solution of this oil in 180 ml. of tetrahydrofuran was cooled to -5°, and 60 ml. of 8% aqueous sodium hydroxide was added, followed by dropwise addition of 120 ml. of 10% aqueous hydrogen peroxide. After stirring the mixture for 1.5 hr. the whole was poured into water and extracted with methylene chloride. The washed (H_2O) and dried (Na_2SO_4) extracts on evaporation afforded a solid which was subjected to chromatography over 1.5 g. of alumina. Crystalline fractions which were eluted with benzene containing 1-2% chloroform totaled 13 g., m.p. 105-107°. Several crystallizations from acetone-hexane afforded an analytical sample of IIa, m.p. 109-110°; $[\alpha]_D$ + 69°; λmax 278-280 (log ε 3.32) and 286-288 mμ (log ε 3.27); νmax 3440, 1616, 1505, 1450, 1300 and 1230 cm^{-1}; n.m.r. 47.5 (s., 18-H), 224 (s., OMe), and 218 c.p.s. (m., $O-CH_2-CH_2-OH$ methylene protons).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15; O, 14.53. Found: C, 76.28; H, 9.20; O, 14.39.

(b) A solution of 30 g. of lithium aluminum hydride in 1.2 l. ether was added dropwise at 0°, with stirring, to an ethereal solution of aluminum trichloride (400 g. in 1.2 l.). The mixture was then allowed to stand for 1 hr. A solution of 70 g. of the ketal Ia in 300 ml. of anhydrous tetrahydrofuran was then added and the reaction mixture was stirred at room temperature for 18 hr. The excess of lithium aluminum hydride was destroyed by careful addition of ethyl acetate. A saturated aqueous sodium sulfate solution (50 ml.) was then added, and the inorganic material filtered off, and washed with ethyl acetate. The organic

solution was dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo* to afford 60 g. of an amorphous material. Crystallization from methylene chloride - hexane gave 37.5 g. of the 17β-(2-hydroxyethyl) ether, IIa, m.p. 104-106°. After chromatography of the mother liquors onto neutral alumina, an additional 14.6 g. of the ether IIa was obtained, m.p. 105-107°. This material was suitable for further reactions without purification.

Acetylation of the derived alcohol IIa with acetic anhydride-pyridine led to the corresponding primary acetate IIb. Crystallization from methanol-water gave the analytical sample, m.p. 72-73°; $[\alpha]_D$ + 60°; λmax 278-280 (log ε 3.31), and 287 mμ (log ε 3.26); νmax 1735 cm^{-1}; n.m.r. 48 (s., 18-H), 124-5 (s., OAc), 225 (s., OMe), 225 (t., J 5 c.p.s., CH_2-O-C_{17}), and 254 (t., J 5 c.p.s., CH_2OAc), and 206 c.p.s. (t., 17α-H).

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66; O, 17.18. Found: C, 74.15; H, 8.60; O, 17.15.

17β-(2-Hydroxyethoxy)-3-methoxyestr-1,3,5(10)-triene p-toluene sulfonate (IIc). - A mixture of 5 g. of the hydroxyethyl ether IIa and 10 g. of p-toluenesulfonyl chloride in 50 ml. of dry pyridine was stirred for 3 hr. at room temperature. The whole was then poured into water and the precipitate collected at the filter, washing well with 5% aqueous hydrochloric acid and water. Crystallization of the dried solids (6.6 g.) from methylene chloride - methanol furnished the analytical sample, m.p. 122-124°; $[\alpha]_D$ + 51°; λmax 224 (log ε 4.31), 274 (log ε 3.30) and 287 mμ (log ε 3.31); νmax 1612, 1601. 1578, 1177, 922, 908, 813, 755 and 660 cm^{-1}.

Anal. Calcd. for $C_{28}H_{36}O_5S$: C, 69.40; H, 7.49; O, 16.51; S, 6.61. Found: C, 69.75; H, 7.51; O, 16.38; S, 6.99.

17β-(2-Cyanoethoxy)-3-methoxyestra-1,3,5(10)-triene (IId).- A mixture of 11.85 g. of tosylate (IIc) and 11.85 g. of potassium cyanide was dissolved in 500 ml. of dimethylformamide and heated to 80° for 20 hr. The reaction mixture was then poured into water. The precipitate which formed was filtered off, washed with water and dried (8 g.). The crude material was chromatographed on 300 g. of neutral alumina to afford, by elution with 1:1 hexane - benzene, 5.72 g. of the derived nitrile (IId), m.p. 101-102°. Further crystallizations from methylene chloride - methanol gave the analytical sample, m.p. 101-102°; $[\alpha]_D$ + 64°; λ max 279 (log ε 3.27), and 287 mμ (log ε 3.22); νmax 2244, 1615, 1505, 1255, 810 and 777 cm^{-1}; n.m.r. 48 (s., 18-H), 226-5 (s., OMe), 222 (t., J 7 c.p.s., CH_2O) and 154 c.p.s. (t., J 7 c.p.s., CH_2CN).

Anal. Calcd. for $C_{22}H_{29}O_2N$: C, 77.84; H, 8.61; O, 9.42; N, 4.13. Found: C, 77.65; H, 8.42; O, 9.24; N, 4.32.

17β-(2-Chloroethoxy)-3-methoxyestra-1,3,5(10)-triene (IIe). - A mixture of 10 g. of the hydroxyethyl ether IIa in 100 ml. of pyridine with 20 g. of p-toluenesulfonyl chloride was kept at room temperature during 60 hr. and then poured into water. Ethyl acetate extracts of the aqueous mixture were washed repeatedly with dilute hydrochloric acid and with water to neutrality. Evaporation of the dried extracts gave 14 g. of an amorphous solid. The benzene soluble portion was subjected to chromatography over 600 g. of silica whereby was obtained 1.5 g. of the 2-chloroethyl ether IIe, m.p. 79-82°, showing a strongly positive Beilstein test. Recrystallization from methylene chloride - methanol afforded a pure sample, m.p. 80-81°; $[\alpha]_D$ + 50°; λmax 278 (log ε 3.28) and 288 mμ (log ε 3.23); νmax 1610, 1575, 1492, 1255, 813 and 780 cm^{-1}; n.m.r. 48 (s., 18-H), 225.5 (s., OMe), and 220-265 c.p.s. (m., CH_2O, CH_2Cl and 17α-H protons).

Anal. Calcd. for $C_{21}H_{29}O_2Cl$: C, 72.28; H, 8.38; O, 9.17; Cl, 10.17. Found: C, 72.25; H, 8.14; O, 9.08; Cl, 10.35.

Further elution of the column with more polar solvent mixtures gave 1.74 g. of the above tosylate ester IIc.

Attempted preparation of the chloroethyl ether IIe by a displacement reaction of 5 g. of the tosylate IIc with 5 g. of potassium chloride in 200 ml. of dimethylformamide, using the general reaction procedure outlined in the preparation of the cyanoethyl analog IId, led only to 2.9 g. of estradiol, indistinguishable by m.p., mixed m.p., i.r. and plate chromatography from an authentic sample.

17β-(2-Hydroxyethoxy)-3-methoxyestra-1,3,5(10)-triene methane sulfonate (IIf). - To a solution of 1 g. of alcohol (IIa) in 4 ml. of anhydrous pyridine, 0.36 ml. of freshly distilled mesyl chloride was added at 0°. The reaction mixture was left at room temperature for 1 hr. and then poured into water. The precipitate which formed was filtered off, washed with water and dried, affording 1.15 g. of the mesylate ester IIf, m.p. 126-128°. Recrystallization from methylene chloride - hexane provided the analytical sample: m.p. 128-130°; $[\alpha]_D$ + 43°; λmax 278 (log ε 3.32) and 286 mμ (log ε 3.27); νmax 1615, 1577, 1502, 1283, 1252, 1025, 970, 930, 870, 817, 773 and 740 cm^{-1}; n.m.r. 48.5 (s., 18-H), 226.5 (s., OMe), and 190-220 c.p.s. (m., H-C-O protons).

Anal. Calcd. for $C_{22}H_{32}O_5S$: C, 64.70; H, 7.90; O, 19.60; S, 7.80. Found: C, 64.53; H, 7.90; O, 19.32; S, 7.84.

3-Methoxy-17β-(2-piperidinoethoxy)estra-1,3,5(10)-triene (IIg). - A mixture of 2.76 g. of the mesylate IIf in 17.3 ml. of benzene and 13.3 ml. of piperidine was maintained at reflux for 20 hr. under anhydrous conditions. The reaction mixture was then poured into water and extracted with ethyl acetate. The organic layer was washed with water, dried (Na_2SO_4), filtered and evaporated to dryness to give a semi-crystalline residue which was chromatographed over 300 g. of silica to give 1.97 g. of the piperidyl derivative IIg. A recrystallized specimen showed m.p. 79-80°; $[\alpha]_D$ + 57°; λmax 278 (log ε 3.30) and 287 mμ (log ε 3.25); νmax 1612, 1585, 1505, 1240, 900, 867, 820, 787 and 766 cm^{-1}.

Anal. Calcd. for $C_{26}H_{39}O_2N$: C, 78.54; H, 9.89; O, 8.05; N, 3.52. Found: C, 78.11; H, 10.04; N, 3.56; O, 7.65.

17β-(2-Iodoethoxy)-3-methoxyestra-1,3,5(10)-triene (IIh). - A solution of 200 mg. of the mesylate IIf and 200 mg. of sodium iodide in 20 ml. of diglyme was heated under reflux for 2 hr. The reaction mixture was poured into water and extracted with ether, washing with water. Evaporation of the dried extracts yielded 150 mg. of amorphous material which was chromatographed on 20 g. of silica to give 100 mg. of the iodoethyl ether IIh, m.p. 57-60°, showing a positive Beilstein test. Recrystallization from ether-methanol gave a pure sample: m.p. 62-4°; $[\alpha]_D$ + 39°; λmax 278-280 (log ε 3.36) and 287 mμ (log ε 3.31); νmax 1607, 1585, 1505, 1240, 867, 816 and 785 cm^{-1}.

Anal. Calcd. for $C_{21}H_{29}O_2I$: C, 57.27; H, 6.64; O, 7.26; I, 28.82. Found: C, 58.03; H, 6.88; O, 7.28; I, 28.32.

3-Methoxy-17β-(2-[(tetrahydropyran-2-yl)oxy]ethoxy)estr-1,3,5(10)-triene (IIi). - One fifth of a solution of 500 mg. of the alcohol (IIa) in 25 ml. of benzene and 1 ml. of dihydropyran was distilled to eliminate moisture. After cooling, 20 mg. of p-toluene sulfonic acid was added and the reaction mixture was allowed to stand 90 hr. at room temperature. After addition of 5% aqueous bicarbonate solution and extraction with benzene, the organic fraction was dried over anhydrous sodium sulfate, filtered and evaporated to dryness *in vacuo*. The amorphous product was chromatographed on 20 g. of neutral alumina, affording 320 mg. of the tetrahydropyranyl ether (IIi), which could not be crystallized but appeared to be homogeneous by paper chromatography, $[\alpha]_D$ + 52°; λmax 278-280 mμ (log ε 3.22); νmax: no OH absorption, 1666 cm^{-1}; n.m.r. 48.5 (s., 18-H), 225.5 (s., OMe), 281 (m., O-CH-O), and 198-248 c.p.s. (m., other CH-O protons).

Anal. Calcd. for $C_{26}H_{38}O_4$: C, 75.32; H, 9.24; O, 15.44. Found: C, 75.37; H, 9.29; O, 15.56.

17β-(2-Fluoroethoxy)-3-methoxyestra-1,3,5(10)-triene (IIj). - A solution of 1 g. of the alcohol (IIa) in 12.5 ml. of methylene chloride was allowed to react at room temperature during 60 hr. with 853 mg. of 2-chloro-1,1,2-trifluorotriethylamine under anhydrous conditions. The solvent was then removed under high vacuum affording 1.5 g. of amorphous material. The latter was chromatographed on 240 g. of silica to give 470 mg. of the fluoroethyl ether IIj, m.p. 103-106°. Further elution of the column furnished 290 mg. of a substance identified as estradiol 3-methyl-ether by comparison with an authentic specimen. Recrystallization of the fluoroethyl ether from ether - methanol provided a pure sample of IIj, m.p. 105-106°; $[\alpha]_D$ + 53°; λmax 278-280 (log ε 3.32) and 287 mμ (log ε 3.27); νmax 1612, 1575, 1500, 1255, 1045, 875, 808 and 779 cm^{-1}; n.m.r. 48 (s., 18-H), 225 (s., OMe), ca. 210 (m., CH_2O), 244 and 295 (pair of t., J_{HH} ca. 5 c.p.s., J_{HF} 51 c.p.s., CH_2F).

Anal. Calcd. for $C_{21}H_{29}O_2F$: C, 75.86; H, 8.79; O, 9.62; F, 5.72. Found: C, 76.31; H, 8.72; O, 9.62; F, 5.77.

Chromic Oxide Oxidation of the Hydroxyethyl Ether IIa. To a solution of 1.2 g. of the alcohol IIa in 12 ml. of pyridine at 0°, 1.2 g. of chromic oxide was added and the reaction mixture was stirred 15 hr. at room temperature. The inorganic salts were then filtered off and washed with 100 ml. of ethyl acetate. The organic fraction was successively washed with 7% aqueous dilute hydrochloric solution until acid, with 10% aqueous sodium hydroxide solution in order to remove the acidic product IIl, and finally with water. Evaporation of the dried and filtered solution then afforded 1 g. of amorphous material. This product was chromatographed onto 40 g. of silica. Elution with benzene-ether (8:2) furnished 230 mg. of the aldehyde (IIk), m.p. 87-94°. Further elution of the column with benzene-ether (7:3) gave 410 mg. of the starting alcohol IIa. Recrystallization of the aldehyde IIk from methylene chloride-hexane provided the analytical sample: m.p. 123-125°; $[\alpha]_D$ + 52°; λmax 278 (log ε 3.22) and 287 mμ (log ε 3.11); νmax 1763, 1612, 1680, 1620, 1255, 1040, 815, 782 and 705 cm^{-1}.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59; O, 14.61. Found: 76.65; H, 8.52; O, 14.90.

The alkaline fraction was neutralized with 5% hydrochloric acid and then extracted with methylene chloride. The organic layer was then washed, dried, filtered and evaporated to dryness, affording 130 mg. of crude acid. Recrystallization from methylene chloride-hexane gave the pure acid IIl, m.p. 155-159°; $[\alpha]_D$ + 36°; λmax 274-276 (log ε 3.41) and 278 mμ (log ε 3.30); νmax 3600-2500, 1780,

1618, 1582, 1505, 1260, 1210, 1120, 1045, 875, 813, 780 and 682 cm^{-1}.

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 9.18; O, 18.58. Found: C, 72.69; H, 8.58; O, 18.70.

17β-(Carbomethoxy)-3-methoxyestra-1,3,5(10)-triene methyl ester (IIm). - A solution of 340 mg. of the acid II1 in 23 ml. methanol and 2 drops of concentrated sulfuric acid was heated under reflux for 1 hr. Water was then added and the solution extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated to dryness. The amorphous residual product (350 mg.) was chromatographed over 15 g. alumina to obtain 280 mg. of the ester IIm. Recrystallization from methylene chloride-hexane furnished a pure specimen, m.p. 75-77°; $[\alpha]_D$ + 40°; λmax 278 (log ε 3.35) and 287 mμ (log ε 3.29); νmax 1740, 1612, 1582, 1505, 1290, 1238, 1120, 1035, 857, 822 and 788 cm^{-1}.

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44; O, 17.85. Found: C, 73.42; H, 8.65; O, 18.13.

Chromic Acid Oxidation of the Hydroxyethyl ether IIa. A cooled solution of 1 g. of the hydroxyethyl ether IIa in 100 ml. of acetone was treated dropwise with chromic acid reagent[23] until an excess of the reagent was present. Dilution with 20 volumes of water followed by extraction with ethyl acetate afforded a solution from which the acidic product was extracted by dilute aqueous sodium hydroxide. Neutralization of the latter with dilute hydrochloric acid and extraction with methylene chloride gave, by evaporation of the dried extracts, the acid III, m.p. 151-155°. A recrystallized sample proved to be identical with the acid prepared by chromic oxide-pyridine oxidation of the hydroxyethyl ether IIa.

3-Methoxyestra-1,3,5(10)-trien-17-one cyclic ethylene monothioketal (III). - A solution of 16 g. of estrone methyl ether in 800 ml. of benzene was allowed to react with 16.6 ml. of β-mercaptoethanol in the presence of 800 mg. of p-toluenesulfonic acid at reflux temperature during 72 hr. in an apparatus equipped with a water separator. The reaction solution was then washed well with water, dried and evaporated. Crystallization of the solid residue from methylene chloride-methanol afforded 16.7 g. of the hemithioketal III, m.p. 95-103°. The analytical sample showed m.p. 106-107°; $[\alpha]_D$ - 12°; λmax 278-280 (log ε 3.29) and 287 mμ (log ε 3.25); νmax 1602, 1495, 1240, 1080, 1045, 910, 858 and 845 cm^{-1}; n.m.r. 51.5 (s., 18-H), 226 (s., OMe) and 225-263 c.p.s. (m., methylene protons of hemithioketal).

Anal. Calcd. for $C_{21}H_{28}O_2S$: C, 73.21; H, 8.19; O, 9.31; S, 9.29. Found: C, 73.49; H, 8.32; O, 9.32; S, 9.14.

17β-[(2-Hydroxyethyl)thio]-3-methoxyestra-1,3,5(10)-triene (IVa). - A solution of 8.2 g. of aluminum trichloride in 98.4 ml. of ether was cooled to 0-5° and 43.6 ml. of 0.36M ethereal lithium aluminum hydride was added, with stirring. Next, 17.36 g. of estrone 3-methyl ether 17-hemithioketal (III) dissolved in 550 ml. of ether was added and the resultant mixture was boiled under reflux during 5 hr. The excess of lithium aluminum hydride was destroyed carefully with aqueous sulfuric acid and the whole was then diluted with water to 2 l. Ethyl acetate extracts were washed with water until neutral, dried and evaporated. Chromatography of the residue over alumina gave 2.37 g. of starting hemithioketal, m.p. 103-107°, followed by 11.44 g. of the 2-hydroxyethyl thioether IVa, m.p. 68-70°. Recrystallization from methanol-methylene chloride furnished the pure sample, m.p. 73-75°; $[\alpha]_D$ + 42°; λmax 278 (log ε 3.35) and 288 mμ (log ε 3.29); νmax 3585, 1612, 1500, 1235, 1070 and 1035 cm^{-1}.

Anal. Calcd. for $C_{21}H_{30}O_2S$: C, 72.83; H, 8.67; O, 9.26; S, 9.24. Found: C, 73.07; H, 8.84; O, 9.01; S, 8.90.

17β-(Ethylthio)-3-methoxyestra-1,3,5(10)-triene (IVg). A solution of 1 g. of the hemithioketal III in 40 ml. of dioxan was added dropwise to a reducing solution prepared by slowly mixing 6.65 g. of aluminum chloride in 48 ml. of ether with 2 g. of lithium aluminum hydride in 48 ml. of ether. The mixture was then refluxed vigorously with expulsion of ether. After 12 hr. the reaction was worked up in the usual way (ethyl acetate addition and extraction) whereupon there was obtained a solid product. Chromatography over alumina supplied 520 mg. of the ethyl thioether (IVg), m.p. 72-87°. Recrystallization from hexane-ether gave an analytical sample, m.p. 95-97°; $[\alpha]_D$ + 50°; λmax 278 (log ε 3.36) and 287 mμ (log ε 3.29); νmax 2890, 1612, 1500, 1245, 1037, 910, 860, 847, 828 and 790 cm^{-1}; n.m.r. 47 (s., 18-H), 76 (t., J 7 c.p.s., CH_3 of EtS), 155.5 (q., J 7 c.p.s., CH_2 of EtS), and 226 c.p.s. (s., OMe).

Anal. Calcd. for $C_{21}H_{30}OS$: C, 76.32; H, 9.36; O, 4.62; S, 9.70. Found: C, 76.39; H, 9.22; O, 5.11; S, 9.78.

17-[(2-Hydroxyethyl)thio]-3-methoxyestra-1,3,5(10-triene acetate (IVb). Acetylation of the above alcohol IVa with acetic anhydride and pyridine at room temperature in the normal manner led to the corresponding acetate IVb, m.p. 39-43°. The analytical sample, prepared by the recrystallization from methylene chloride-methanol, showed

m.p. 43-44°; $[\alpha]_D$ + 31°; λmax 278 (log ε 3.33) and 288 mμ (log ε 3.28); νmax 1750, 1612, 1497 and 1240 cm^{-1}.

Anal. Calcd. for $C_{23}H_{32}O_3S$: C, 71.09; H, 8.30; O, 12.36; S, 8.25. Found: C, 71.12; H, 8.23; O, 12.14; S, 8.35.

17β-[(2-Fluoroethyl)thio]-3-methoxyestra-1,3,5(10)-triene (IVc). - A solution of 1 g. of the alcohol IVa in 12.5 ml. of methylene chloride was treated with 800 mg. (6 m.moles) of 2-chloro-1,1,2-trifluorotriethylamine reagent[21] and the reaction solution kept 16 hr. at room temperature. The solid which remained on evaporation of the reaction mixture was extracted with methylene chloride, washed with water, and recovered by evaporation of the solvent. Chromatography over alumina gave, by elution with 9:1 hexane-benzene, 240 mg. of the 2-fluoroethyl thioether IVc, m.p. 90-96°. Further crystallizations from ether-methanol gave the analytical sample, m.p. 94-96°; $[\alpha]_D$ + 42°; λmax 278 (log ε 3.32) and 287 mμ (log ε 3.27); νmax 1602, 1500, 1250, 1230, 1058 and 1032 cm^{-1}.

Anal. Calcd. for $C_{21}H_{29}OSF$: C, 72.36; H, 8.39; O, 4.10; S, 9.70; F, 5.45. Found: C, 72.36; H, 8.43; O, 4.02; S, 9.53; F. 5.66.

17β-[(2-Chloroethyl)thio]-3-methoxyestra-1,3,5(10)-triene (IVd). The 2-hydroxyethyl thioether IVa (500 mg.) in 2 ml. pyridine was treated with 0.18 ml. of methylene-sulfonyl chloride at room temperature. After 5 hr. the mixture was poured into water and the precipitate which separated was collected at the filter, washed with dilute hydrochloric acid and water, and crystallized from hexane-methylene chloride to yield 480 mg. of the 2-chloroethyl thioether IVd. Further crystallizations from the same solvent mixture led to the analytical sample, m.p. 73-74°; $[\alpha]_D$ + 22°; λmax 278 (log ε 3.35) and 287 mμ (log ε 3.29); νmax 1625, 1576, 1503, 1257, 1040 and 695 cm^{-1}.

Anal. Calcd. for $C_{21}H_{29}OSCl$: C, 69.08; H, 8.01; S, 8.78; Cl, 9.73. Found: C, 69.28; H, 8.04; S, 8.54; Cl, 9.79.

17β-[(2-Hydroxyethyl)thio]-3-methoxyestra-1,3,5(10)-triene p-toluenesulfonate (IVe). - A mixture of 1.6 g. of IVa in 160 ml. ethyl ether containing 11 mg. metallic sodium was stirred for 72 hr. Anhydrous ether (100 ml.) and 570 mg. of p-toluene sulfonyl chloride were then added and the reaction mixture was stirred for a further 6 hr. The precipitate which formed was filtered off and washed with ether, tetrahydrofuran and ethyl acetate. The organic solution was concentrated *in vacuo*, affording an amorphous material. Chromatography on 50 g. neutral alumina provided, by elution with hexane-benzene (8:2), 510 mg. of a semi-

crystalline compound. The latter was recrystallized from methylene chloride-hexane to afford the tosylate IVe, m.p. 130-137°; $[\alpha]_D$ + 64°; λmax 225 (log ε 4.29), 278 (3.53), and 286-287 mμ (3.44); νmax 2830, 1610 and 1510 cm^{-1}.

No satisfactory analysis could be obtained for this substance. Further elution of the chromatographic column with benzene furnished 500 mg. of starting material (IVa).

3-Methoxy-17β-[(2-Methoxyethyl)thio]estra-1,3,5(10)-triene (IVf). - A mixture of 300 mg. of the primary alcohol IVa in 300 ml. of methanol and 1 ml. of concentrated hydrochloric acid was kept at reflux during 72 hrs. after which the whole was poured into water and extracted with ethyl acetate. The extracts were washed to neutrality, dried, and evaporated to yield 175 mg. of the 2-methoxymethyl thioether IVf, m.p. 75-76°. An analytical sample, arrived at by recrystallization from methanol-ether, showed m.p. 77-78°; $[\alpha]_D$ + 38°; λmax 278-280 (log ε 3.27) and 287 mμ (log ε 3.23); νmax 2845, 1612 and 1580, 1500, 1258, 1115, 1055, 965, 870, 815, 805 and 785 cm^{-1}; n.m.r. 47 (s., 18-H), 203 (s., primary OMe), 227 (s., ring A OMe), 165 (t., J 7 c.p.s., SCH_2) and 214 c.p.s. (t., J 7 c.p.s., OCH_2).

Anal. Calcd. for $C_{22}H_{32}O_2S$: C, 73.28; H, 8.95; O, 8.88. Found: C, 73.47; H, 8.89; O, 9.35.

17β-(2-Hydroxyethoxy)-3-methoxyestra-2,5(10)-diene (VIa). - To a stirred solution of 7.5 g. of lithium in 600 ml. of ammonia was added, in small portions, 2 g. of the hydroxyethyl ether IIa. After 3.5 hr. had elapsed ethanol was added dropwise and the ammonia was then allowed to evaporate before addition of water and extraction with benzene. The organic extracts were washed repeatedly with water, dried, and evaporated to yield 1.47 g. of crystalline residue, m.p. 127-129°. This was recrystallized from acetone-hexane to obtain an analytically-pure specimen of the vinylic ether VIa, m.p. 136-137°; $[\alpha]_D$ + 109°; νmax 3400, 1666, 1225, 788, 760 and 700 cm^{-1}.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70; O, 14.44. Found: C, 76.41; H, 9.83; O, 13.97.

Mol. wgt. Calcd. 332. Found, by mass spectrometry, 332(32).

17β-(2-Hydroxyethoxy)-3-methoxyestra-2,5(10)-diene acetate (VIb). - Acetylation of 200 mg. of the vinyl ether VIa with 0.4 ml. of acetic anhydride in 1 ml. of pyridine at room temperature overnight gave, by the usual work-up procedure, 190 mg. of the corresponding primary acetate VIb. A pure sample resulted by recrystallization from aqueous methanol, m.p. 72-73°; $[\alpha]_D$ + 96°; νmax 1742, 1226, 1145, 1118, 1055, 948, 795, 756 and 705 cm^{-1}.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15; O, 17.09. Found: C, 73.71; H, 9.18; O, 17.38.

17β-(2-Hydroxyethoxy)estr-4-en-3-one (VIIa). - A mixture containing 200 mg. of the vinyl ether VIa, 8 ml. of methanol, 2 ml. of water, and 0.72 ml. of concentrated hydrochloric acid was maintained under reflux during 20 min., then poured into water. Ethyl acetate extracts were washed with aqueous sodium bicarbonate and with water, dried, and evaporated. Several crystallizations of the 150 mg. of solid residue from acetone-hexane gave the analytical sample, m.p. 115-116°; $[\alpha]_D$ + 52°; λmax 240 mμ (log ε 4.19); νmax 3440, 1668, 1624, 1135, 1095, 1080, 894, 884, 856, 763 and 703 cm^{-1}; n.m.r. 50 (s., 18-H), 349.5 (s., half-band width 4.5 c.p.s., 4-H) and ca. 217 c.p.s. (m., H-C-O-protons).

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50; O, 15.07. Found: C, 75.67; H, 9.61; O, 14.79.

17β-(2-Hydroxyethoxy)estr-5(10)-en-3-one (VIIb). - A solution of 1.35 g. of oxalic acid in 15 ml. of water was added dropwise to a stirred solution of 1 g. of the vinyl ether VIa in 45 ml. of methanol. After 3.5 hr. the whole was poured into 200 ml. of saturated sodium chloride solution and extracted with ethyl acetate. After being washed with aqueous sodium bicarbonate and with water, the extracts were dried and evaporated to yield a solid residue. Several crystallizations of the residue from acetone-hexane led to 590 mg. of 17β-(2-hydroxyethoxy)estr-5(10)-en-3-one, m.p. 91-92°; $[\alpha]_D$ + 172°; νmax 3480, 1712 and 1070 cm^{-1}.

17β-(2-Hydroxyethoxy)estr-5(10)-en-3α-ol (VIII). - The crude ketone obtained from oxalic acid hydrolysis of 1 g. of the methyl vinyl ether VIa was dissolved in 50 ml. of dry tetrahydrofuran and 1 g. of lithium tri-t-butoxy aluminum hydride was added. The whole was boiled under reflux during 15 min., then poured into water, extracted with ethyl acetate, and washed with water. Evaporation of the dried extracts furnished 700 mg. of the diol VIII, m.p. 140-143°. Four crystallizations from acetone gave the analytical sample, m.p. 148-149°; $[\alpha]_D$ + 142°; νmax 3270, 1450, 1350, 1335, 1140, 1112, 1100, 1075 and 1055 cm^{-1}.

Anal. Calcd. for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06; O, 14.98. Found: C, 75.16; H, 10.18; O, 14.94.

17β-(2-Hydroxyethoxy)-5β-estran-3α-ol (IXa). - A solution of 530 mg. of the unsaturated diol VIII in 10 ml. of acetic acid was shaken with hydrogen over Adam's catalyst prepared by prereduction of 300 mg. of platinum oxide in 7 ml. of acetic acid. The filtered solution was poured into water and extracted with methylene chloride, washing with aqueous sodium bicarbonate solution and with water. Evapora-

tion of the dried, washed extracts gave 360 mg. of crude product IXa, m.p. 90-107°. Recrystallization from acetone-hexane gave a pure sample of the diol IXa, m.p. 129-130°; $[\alpha]_D$ - 7°; νmax 3400, 3170 and 1065 cm^{-1}.

Anal. Calcd. for $C_{20}H_{34}O_3H_2O$: C, 70.54; H, 10.66; O, 18.80. Found: C, 70.89; H, 10.51; O, 18.76.

17β-(2-Hydroxyethoxy)-5β-estran-3α-ol diacetate (IXb). Acetylation of the above diol with acetic anhydride and pyridine at room temperature in the normal manner led to the corresponding diacetate IXb which, after several crystallizations from methanol-water, had m.p. 79-80°; $[\alpha]_D$ + 38°; νmax 1750, 1740 and 1245 cm^{-1}.

Anal.Calcd. for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42; O, 19.68. Found: C, 70.74; H, 9.68; O, 18.87.

Hydrogenation of 17β-(2-Hydroxyethoxy)estr-5(10)-en-3-one (VIIb ⟶ IXa + IXc). - A solution of 600 mg. of the unconjugated ketone VIIb in 50 ml. of ethanol was shaken with 60 mg. of ruthenium oxide catalyst and hydrogen at 120° and 2000 p.s.i. pressure during 7 hr. After filtration the solution was evaporated and the residual oil chromatographed over 70 g. of neutral alumina. Elution with 10:1 ether-chloroform gave first 270 mg. of 17β-(2-hydroxyethoxy)-5α,10α-estran-3β-ol (IXc). The analytical sample obtained by recrystallization from acetone-hexane showed m.p. 80-87°; $[\alpha]_D$ - 31°; νmax 3450, 3350-3100 and 1095 cm^{-1}.

Anal. Calcd. for $C_{20}H_{34}O_3H_2O$: C, 70.54; H, 10.66; O, 18.80. Found: C, 70.45; H, 10.48; O, 18.81.

Further elution with the same solvent mixture yielded 200 mg. of the isomeric 5β-estrane-3α,17β-diol 17β-(2-hydroxyethyl) ether IXa, m.p. 125-126°, raised to 127-128° by crystallization from acetone-hexane and undepressed on admixture with the sample prepared above.

Anal. Calcd. for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found, for a sample dried at 90° for 24 hr.: C, 74.91; H, 10,85.

17β-(2-Hydroxyethoxy)-5α-estran-3β-ol (XIa). - (a) A solution of 2 g. of 3β-hydroxy-5α-androstan-17-one cyclic ethylene ketal (Xa) in 45 ml. of tetrahydrofuran was subjected to a fast stream of externally-generated diborane gas during 2.5 hr., and then worked up as previously described. Thereby was obtained 1.92 g. of solid, m.p. 130-145°. Chromatography over 200 g. of alumina and elution with 1:1 benzene-chloroform yielded 520 mg. of unchanged ketal. Further elution with 1:4 benzene-chloroform furnished 1.03 g. of the 2-hydroxyethyl ether XIa which, after recrystallization from acetone-hexane, showed m.p.

160-161°; $[\alpha]_D$ + 41°; νmax 3280, 1143, 1110, 1085 and 1043 cm^{-1}.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78; O, 14.26. Found: C, 74.92; H, 10.80; O, 14.69.

(b) Reduction of 1 g. of the ketal Xa in 30 ml. of ether with 0.5 g. of lithium aluminum hydride and 4 g. of aluminum trichloride was carried out as described above for the ketal Ia. The crude solid product amounted to 1 g. and was recrystallized from acetone and ether-hexane to afford 800 mg. of a sample, m.p. 160-161°, undepressed on admixture with the specimen prepared by diborane reductive cleavage.

17β-(2-Hydroxyethoxy)-5α-estran-3β-ol diacetate (XIb). Acetylation of the above diol XIa with acetic anhydride and pyridine at room temperature in the normal manner led to the corresponding diacetate XIb. The pure specimen resulting from recrystallization from aqueous methanol had m.p. 80-81°; $[\alpha]_D$ + 13°; νmax 1742, 1245, 1146, 1112, 1058, and 1030 cm^{-1}; n.m.r. 45 (s., 18-H), 49.5 (s., 19-H), 120 and 123 (2s., two acetate methyls), 218 (t., J ca. 5 c.p.s. CH_2-O-C_{17}), 251 (t., J ca. 5 c.p.s., CH_2-OAc methylene), and 281 c.p.s., half-band width 23 c.p.s. (m., 3α-H).

Anal. Calcd. for $C_{25}H_{40}O_5$: C, 71.39; H, 9.59; O, 19.02. Found: C, 71.62; H, 9.04; O, 18.92.

17β-Ethoxy-5α-androstan-3β-ol (XIc). - A solution of 10 g. of 3β-hydroxy-5α-androstan-17-one in 200 ml. of absolute ethanol was treated with 10 ml. of ethyl orthoformate and 100 mg. of p-toluenesulfonic acid and the whole kept 69 hr. at room temperature. After neutralization of the acid with sodium ethoxide the solution was taken to dryness at the pump and 8.3 g. of the resultant diethyl ketal Xb was crystallized from aqueous methanol.

Dry ether (100 ml.) was slowly added to 10 g. of aluminum trichloride with cooling and the mixture kept ice-cold for 0.5 hr. before adding a filtered solution of 310 mg. of lithium hydride in 50 ml. of ether. A solution of 1 g. of the ketal Xb in 100 ml. of dry ether was added next, followed after a lapse of 2.5 hr. by dropwise addition of 100 ml. of 10% aqueous sulfuric acid. Ether extracts were washed with water, dried and evaporated. The resultant 920 mg. of solid was chromatographed over neutral alumina when 2:1 benzene-hexane eluted 530 mg. of 5α-androstane-3β,17β-diol 17β-ethyl ether (XIc). Four crystallizations from acetone-hexane gave the analytical sample, m.p. 155-156°; $[\alpha]_D$ + 11°; νmax 3540, 1090, 1080 and 1050 cm^{-1}; n.m.r. 44.5 (s., 18-H), 48.5 (s., 19-H), 69 (t., J 7 c.p.s. CH_3 of ethoxy), and 202 c.p.s. (q., J 7 c.p.s., CH_2 of ethoxy).

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32; O, 9.98. Found: C, 78.99; H, 11.50; O, 10.18.

17β-Ethoxy-5α-androstan-3β-ol acetate (XId). - Acetylation of the diol monoether XIc with acetic anhydride-pyridine at room temperature overnight gave the derived acetate XId. A sample crystallized three times from aqueous methanol showed m.p. 118-119°; $[\alpha]_D$ - 4°; νmax 1730 and 1265 cm^{-1}.

Anal. Calcd. for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57; O, 13.24. Found: C, 76.10; H, 10.64; O, 13.49.

3-Methoxyestra-1,3,5(10)-trien-17-one cyclic ethylene mercaptole (V). - To a solution of 15 g. estrone 3-methyl ether in 750 ml. acetic acid 15 ml. ethane dithiol and 15 ml. boron trifluoride were added. The reaction mixture was left at room temperature for 16 hr., under stirring. The precipitate, which formed, was filtered off and washed with 10% sodium hydroxide until neutral. The crude product was chromatographed on alumina, affording 10.8 g. of dithioketal V. Recrystallization from methylene chloride-methanol gave the analytical sample: m.p. 135-136°; $[\alpha]_D$ + 22°; λmax 279 (log ε 2.90), and 287 mμ (2.86); νmax 2832, 1607, 1501, 1448, 1425, 1380, 1318, 1290, 1270, 1245, 1230, 1035, 905, 835 and 785 cm^{-1}.

Anal. Calcd. for $C_{21}H_{28}OS_2$: C, 70.06; H, 7.84; O, 4.44; S, 17.81. Found: C, 70.35; H, 7.85; O, 4.59; S, 17.81.

All attempts to reduce this dithioketal V with lithium aluminum hydride-aluminum trichloride furnished unchanged dithioketal only.

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31. Except where stated otherwise rotations are for chloroform solutions, ultraviolet spectra are for ethanol solutions, and infrared spectra are for potassium bromide discs. Melting points were taken on the Fisher-Johns block and are uncorrected. Microanalyses are by either Mid-West Micro-Laboratories, Indianapolis 20,

Indiana, or by A. Bernhardt, Muhlheim (Ruhr), Germany. Alumina used for chromatography was neutralized by stirring with ethyl acetate and reactivated by heating at 120° for 72 hr. Unless stated otherwise the alumina had activity grade III, as defined by H. Brockmann and H. Schodder, Ber., 74, 73 (1941). In the presentation of n.m.r. data, s. = singlet, d. = doublet, t. = doublet, q. = quartet, and m. = multiplet.

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