solution of 0.330 g. (0.73 mmole) of 9α-fluoro-16α-methoxyhydrocortisone acetate (XXIX) and 0.175 g. (1.57 mmoles) of selenium dioxide in 18 ml. of *t*-butyl alcohol containing 0.055 ml. of pyridine was treated as described in the preparation of XXII. The crude material was chromatographed on silica gel. The solids eluted by benzene-ether (3:1) were combined and recrystallized from acetone-hexane to give 0.103 g. (32% yield) of crystals, m.p. 226–229° dec. An additional recrystallization gave the analytical specimen (40 mg.) as white crystals, m.p. 238–240° dec.; $[\alpha]_D$ + 70.5° (acetone); λ_{max} 240 mμ (ε 17,100); ν_{max} 3400, 1730, 1712, 1650, 1612, 1600, 1230, 1098 cm.$^{-1}$

Anal. Calcd. for $C_{24}H_{31}FO_7$: C, 63.98; H, 6.94; F, 4.22. Found: C, 64.50; H, 7.77; F, 4.63.

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Retropinacol Rearrangement of Estradiol 3-Methyl Ether

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Distillation of estradiol 3-methyl ether from boric acid gives preponderantly the olefin *2*. The by-products of this reaction have been isolated and characterized. Other methods of effecting the rearrangement are described.

Among the possible synthetic routes to 18-nor steroids is that utilizing retropinacolic elimination of the C-17 substituent of a suitable androstane or estrane. In this reaction migration of the angular methyl group to C-17 occurs, leaving, ideally, a double bond located between carbons 13 and 17 (such as olefin *2*). Such compounds are excellent starting materials for the preparation of hormonal analogs lacking a C-13 substituent.[1,2]

Among the first of a large number of such rearrangements in steroid literature is that contained in the structure elucidation of estradiol by Cohen, Cook, and Hewett[3]; methyl migration was observed both with estradiol 3-methyl ether and with 17α-methylestradiol 3-methyl ether upon treatment with Lewis acid catalysts. Later Miescher and Kagi[4] proved that treatment of 17α-hydroxyandrostanes with formic acid gave as a major product a $\Delta^{13(17)}$, 17-methyl steroid ("pseudoandrostene"), the rearrangement in this case being facilitated by the coplanarity of the four centers involved.[5] "Retro"-steroids, postulated to be Δ^{13},-17-methylandrostenes and -estratetraenes, were prepared in the same period by treatment of 17-chloroandrostanes (or -estratrienes) with base.[6] More recently the reaction of 17β-tosylates with various nucleophilic agents has been investigated; the products are in part the 13(17)-olefins.[2,7] Finally, both androstanes[8] and pregnanes[9] possessing a C-17–tertiary hydroxyl have been shown to undergo this rearrangement readily under acidic conditions.

The use of this reaction in the synthesis of 18-nor hormones was unattractive due to the difficulties in obtaining starting materials of the proper configuration and/or in the subsequent low yields of the desired isomer. These objections were removed by the discovery that estradiol 3-methyl ether on distillation from boric acid yields 65–70% of olefin *2*.[10] Ozonolysis of *2* to a diketone (*6*) (λ_{max} 5.83 μ) established the ditertiary nature of the double bond. Base treatment of this diketone led to a hydroxy ketone (*9*) (NMR showed only *O*-methyl, no C-methyl) which formed in turn an unsaturated ketone (*8*) whose ultraviolet absorption (λ_{max} 239 mμ) eliminates two (*3*, *10*) of the three possible ditertiary olefins not conjugated with the A-ring. Thus only structure *2* is consistent with the data.[11] Conclusive proof of the structure of this olefin was obtained by its conversion to 18-norestrone methyl ether.[1]

Accompanying olefin *2* were several products isolated by osmium tetroxide hydroxylation of the entire olefin mixture and subsequent chromatographic analysis. The glycols obtained were oxidized with periodate and the cleavage products were treated with base to complete the identifications. Additional quantities of these cleavage

(1) W. F. Johns, *J. Am. Chem. Soc.*, **80**, 6456 (1958).
(2) G. Stork, H. N. Khastgir, and A. J. Solo, *J. Am. Chem. Soc.*, **80**, 6457 (1958).
(3) A. Cohen, J. W. Cook, and C. L. Hewett, *J. Chem. Soc.*, 445 (1935).
(4) K. Miescher and H. Kagi, *Helv. Chim. Acta*, **32**, 761 (1949); **22**, 683 (1939).
(5) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).
(6) U. Westphal, Y.-L. Wang, and H. Hellmann, *Ber.*, **72**, 1233 (1939).
(7) O. S. Madaeva, *J. Gen. Chem. U.S.S.R.*, **25**, 1373 (1958), *Zhur. Obshchei Khim.*, **27**, 2573 (1957); F. Sondheimer, O. Mancera, M. Urquiza, and G. Rosenkranz, *J. Am. Chem. Soc.*, **77**, 4145 (1955); J. Elks and C. W. Shoppee, *J. Chem. Soc.*, 241 (1953).
(8) O. S. Madaeva, *J. Gen. Chem. U.S.S.R.*, **26**, 3267 (1956); N. L. Wendler, R. P. Graber, and G. G. Hazen, *Tetra.*, **3**, 144 (1958); V. Tortorella, G. Lucente, and A. Romeo, *Annal. Chim. (Rome)*, **50**, 1198 (1960).
(9) See, for example, H. L. Herzog *et al.*, *J. Am. Chem. Soc.*, **81**, 6478, 6483 (1960); J. E. Herz *et al.*, *J. Am. Chem. Soc.*, **78**, 4813 (1956); R. Hirschmann *et al.*, *J. Am. Chem. Soc.*, **78**, 4814 (1956).
(10) Dr. D. A. Tyner of these laboratories was the first to utilize these conditions and we wish to thank him for allowing us to identify and exploit the products.
(11) *Cf.* ref. 4 for a similar proof of structure.

products were obtainable by direct ozonolysis of crude *2* followed by chromatography.

The major component, the C-13–C-17 glycol (*5*) was cleaved to the known diketone *6*. None of the epimeric *cis* glycol was found. The stereospecificity of this hydroxylation is not easily predicted from inspection of the molecular model of this compound and configurational assignments are therefore tentative.

Among the minor constituents were a pair of glycols (*11*, *12*) found to be epimeric by virtue of their cleavage to the same diketone (*15*). The lack of aldehyde absorption in the infrared spectrum of *15* again shows the glycols and their parent olefin (*10a*) to be ditertiary. Since both olefins *2* and *10* have very nearly the same spatial orientation the major glycol (*11*) is assumed to have the same configuration as the sole glycol of olefin *2*. By ro-

tational comparison with its diastereomer (*12*) evidence can be adduced for the configurations of glycols *5*, *11*, and *12*.

Mild base treatment of diketone *15* afforded a hydroxycyclohexanone (*14*) (λ_{max} 2.85, 5.89 μ) and an unsaturated ketone (*13*) (λ_{max} 251 mμ, $[\alpha]_D$ −15°).[12] Further treatment of the unsaturated ketone (or the hydroxy ketone) with base yielded an isomeric unsaturated ketone (*17*) with a similar ultraviolet spectrum (λ_{max} 250 mμ, $[\alpha]_D$ +194°). None of the starting compound was detectable from this transformation indicating the extreme position of the reaction equilibrium. Catalytic reduction of either unsaturated ketone occurred readily, giving in each case a cyclohexanone (λ_{max} 5.85 μ). The spectral and analytical data of the six compounds stemming from the initial pair of glycols most rationally supports the 13(14) position of the double bond in the parent olefin (*10*).

The second unsaturated ketone (*17*) is most reasonably epimeric at the labilized C-8 position. The C-17-methyl group may have inverted also but the relatively minor alteration possible here (especially in view of the almost planar D-ring) seems insufficient to explain completely the strong change in rotation or in the secondary infrared maxima and the lack of significant change in the NMR spectrum. More pertinent is the well documented stability relationships of *cis*- and *trans*-hydrindanones, present here as the B and C rings. The closest analogy to this situation is in the B-norcholestanes, in which the greater stability of the *cis* fusion has been demonstrated.[13] Additional confirmatory data is supplied by systems containing a terminal five-membered ring.[14]

When another pair of glycols was isolated, it became clear that the parent olefins arose from a secondary protrotropic shift during the retropinacol rearrangement. The first of the pair (*20*) was cleaved to a monoketone (λ_{max} 5.78 μ) shown later to be identical in all respects to 18-nor-13α-estrone methyl ether (*21*).[1,15] The second glycol (*23*) was cleaved to a ketoaldehyde (*25*) (λ_{max} 3.66, 5.82 μ). The hydroxycyclohexanone (*26*) (λ_{max} 2.85, 5.86 μ), formed on mild base treatment, readily afforded an unsaturated ketone (*27*) (λ_{max} 225 mμ, λ_{max} 5.96 μ). Catalytic reduction gave the *d*-D-homonorsteroid *24* identical in the infrared to a sample of the authentic *dl*-material,[16] a comparison affording proof of the structures *22–27*.

Glycol *29* was isolated in small amounts as the only evidence of formation of the Δ^{12} steroid *28* in this rearrangement. The structure of this glycol was established only after additional material became available from an alternate reaction sequence (see below). The low yield of this olefin may be attributed to the thermodynamic control of the reaction products and the lower stability of the secondary-tertiary double bond as compared to the preponderant ditertiary olefins found.[17]

Accompanying the glycols was a crystalline olefin (*3*), shown to be inert to osmium tetroxide by a subsequent experiment. This lack of reactivity coupled with the ultraviolet (only anisole absorption) and NMR (no vinyl hydrogens) spectra point clearly to C-8(14) as the position of the unsaturation in this molecule.

In an attempt to obtain olefin intermediates unstable at the distillation temperatures (380–450°), the temperature of the boric acid rearrangement was decreased to a point (280°) at which the product was only partially formed. After one hour at this temperature, the product was isolated, hydroxylated, and chromatographed. Only a small amount of glycol *5* was obtained along with large amounts of conjugated olefins and starting material (*1a*). No other glycols were found nor was any C-17 borate ester detected. Attempts to convert the olefins formed at 280° to olefin *2* by heating with boric acid were unsuccessful. One explanation of this result is that the stable olefins *2* and *10a* are initially formed in something approximating an equilibrium mixture; on prolonged treatment partial isomerization to the more remote positions ($\Delta^{8(9)}$ or $\Delta^{8(14)}$) occurs.

The simplest mechanistic path for this rearrangement[18] to follow is *via* the carbonium ion *i*, formed by concerted elimination of a protonated hydroxyl or borate ester, and shift of the angular methyl group.[19] *cis*-Elimination by ester pyrolysis has been

(12) The corresponding D-homo unsaturated ketone (with a six-membered C-ring) has λ_{max} 248.5 mμ (log ϵ 4.12): W. S. Johnson, B. Bannister, and R. Pappo, *J. Am. Chem. Soc.*, 78, 6331 (1956).

(13) W. G. Dauben, G. A. Boswell, and G. H. Berezin, *J. Am. Chem. Soc.*, 81, 6082 (1959); W. G. Dauben, *Bull. soc. chim. France*, 1960, 1338.

(14) In the 18-nor steroids (ref. 1) the *cis* juncture again predominates (70% at equilibrium). For other examples see J. F. Biellmann, D. Francetic, and G. Ourisson, *Tetra. Letters*, 1960 (18), 4; ref. 13, and articles cited in these papers.

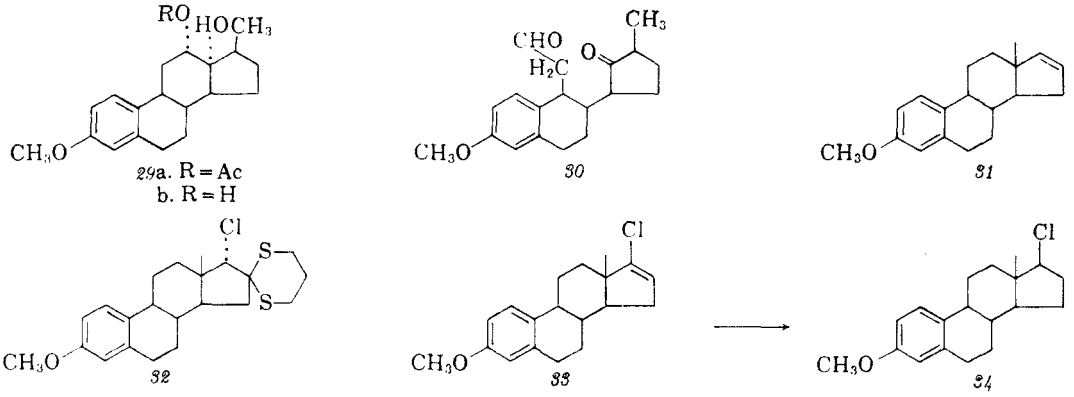
(15) That the C-13 hydrogen is alpha in compounds *3*, *19*, and *22* is strongly supported by this experiment, and also by consideration of hydrindanone stabilities.

(16) This sample was kindly supplied by Dr. J. A. Cella of these laboratories, prepared according to W. S. Johnson, D. K. Banerjee, W. P. Schneider, C. D. Gutsche, W. E. Shelberg, and L. J. Chinn, *J. Am. Chem. Soc.*, 74, 2832 (1952).

(17) For examples of polycyclic olefin stabilities see R. B. Turner, W. R. Meador, and R. E. Winkler, *J. Am. Chem. Soc.*, 79, 4122 (1957); W. G. Dauben, E. C. Martin, and G. J. Fonken, *J. Org. Chem.*, 23, 1205 (1958).

(18) For a comprehensive review of the mechanism and stereochemistry of this rearrangement see C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, p. 473, and G. W. Wheland, *Advanced Organic Chemistry*, J. Wiley and Sons, Inc., New York, N. Y., 1949, p. 451.

(19) The β-configuration of the C-17 methyl in olefins *3*, *10*, and *28* is derived by consideration of this mechanism; the methyl group has no opportunity to leave the β-face during the migration, at least in the direct reaction path.



proposed[20] for boric acid dehydrations as an alternate mechanism which would lead to the unrearranged olefin *31*. Although it is possible that olefin would protonate yielding ion *i* and then rearrange to *ii*, it would have to do so completely

i *ii*

since none of this product (*31*) was detected; this explanation seems unlikely and unnecessarily complex.[21]

Having readily isolated and identified derivatives of several estratetraenes, it was possible to confirm early structural assignments in this area. Phosphorus pentachloride and estradiol 3-methyl ether reacted to give the 17-chloro compound *4a*, $[\alpha]_D$ +15°. Rearrangement of this intermediate with sodium acetate at 120° gave an olefin mixture from which could be separated the crystalline olefin *10a*, identified by hydroxylation to the known 13,14-glycol *11*. Direct correlation of olefin *10a* to the compounds in the literature[6] was accomplished by methylation of Westphal's olefin *10c* (following his preparative route through compounds *1b*, *4b*, and *10b*), thus demonstrating his structural assignments to be correct.

The remaining components of the olefin mixture containing *10a*, as produced from pure chloride *4a*, were determined by hydroxylation and chromatography. The preponderant glycol found was the 13,17-diol *5*; also isolated were smaller amounts of glycol *11* and its diastereomer *12*. The remaining material was largely unchanged olefin from which was isolated the crystalline naphthalene *7* (λ_{max} 280 mμ, no vinyl protons in the NMR). Again no glycol from the Δ^{16}-olefin *31* was isolated.[22] From this analysis it appears that the "retroestratetraene"[6] is a minor component of the mixture produced.

Phosphorus pentachloride is normally expected to react with a secondary hydroxyl by inversion.[23] To eliminate the possibility of retention of configuration[24] in the displacement of the C-17 β-hydroxyl, an alternate route of synthesis of the chloride *4a* was sought. A direct method, by treating the thioketal *32* (formed from the corresponding ketone)[25] with deactivated Raney nickel, failed to produce a monochloro compound.

Indirect proof of the configuration of chloride *4a* was secured by preparation of the C-17 β-chloride. Treatment of estrone methyl ether with phosphorus pentachloride[26] yielded the vinyl chloride *33* which could be reduced to the new saturated chloride *34*. Configurational assignment is made on the basis of rotational data,[24] greater stability towards elimination than its axial isomer *4a* (as would be predicted from the four coplanar center rule)[5] and mode of preparation.

That zinc chloride at 180° is an efficient rearrangement catalyst for estradiol 3-methyl ether was shown by repeating the work of Cohen, Cook, and Hewett.[3] The olefinic mixture produced was treated with osmium tetroxide and was then chromatogrammed. No 13,17-glycol was obtained. The bulk of the material was a mixture of styrenes and more highly conjugated compounds, including the phenanthrene *16* described originally. The olefin *2* may be an intermediate in the formation of the products found and might be obtained in good yield from milder reaction conditions employing this catalyst. However, under these conditions it

(20) G. L. O'Connor and H. R. Nace, *J. Am. Chem. Soc.*, **77**, 1578 (1955). Also see J. Fajkos, *Coll. Czech. Comm. Chem.*, **20**, 312 (1955) for the pyrolysis of an androstan-17β-ol hexahydrobenzoate to the corresponding Δ^{16}-compound.

(21) See also C. H. De Puy and R. W. King, *Chem. Revs.*, **1960**, 431.

(22) It seems probable in view of this result that the olefin obtained from the analogous androstane would similarly give the $\Delta^{13(17)}$ olefin. *Cf.* M. Gut and M. Uskokovic, *J. Org. Chem.*, **24**, 673 (1959).

(23) R. J. Bridgewater and C. W. Shoppee, *J. Chem. Soc.*, 1709 (1953); C. W. Shoppee, *J. Chem. Soc.*, 1138 (1946).

(24) C. W. Shoppee, M. E. H. Howden, and R. Lack, *J. Chem. Soc.*, 4874 (1960).

(25) G. P. Mueller and W. F. Johns, *J. Org. Chem.*, **26**, 2403 (1961).

(26) See L. Mamlok and J. Jacques, *Bull. soc. chim. France*, **1960**, 484 for a similar reaction in the androstanes.

is an imperceptible portion of the product.[27] Similarly, treatment of estradiol 3-methyl ether with aluminum chloride under mild conditions followed by hydroxylation of the product yielded no glycol.

The Bamford-Stevens rearrangement[28] offered the possibility of an even more selective olefin preparation via a bulky cyclic intermediate. Base catalyzed decomposition of the *p*-tolylsulfonylhydrazone of estrone methyl ether yielded an olefinic mixture shown to consist of roughly equal amounts of olefins *2* and *10a* as determined by glycol analysis. Glycol *29* was also isolated for the first time; it formed a monoacetate on acetylation and a ketoaldehyde on cleavage. Mild or vigorous base treatment of the ketoaldehyde (*30*) led only to an amorphous hydroxy ketone. This data confirms the Δ^{12} C-17 methyl structure (*28*) as the parent olefin of these derivatives.

EXPERIMENTAL[29]

17β-Methyl-3-methoxy-18-norestra-1,3,5(10),13(17)-tetraene (2).[30] An intimate mixture of 100 g. of estradiol 3-methyl ether and 25.0 g. of boric acid was heated at 140° in a nitrogen atmosphere by means of a metal bath. After 20 min. a quantity of water containing boric acid was distilled by raising the temperature to 200°. The receiver was changed, the pressure was reduced to 10–25 mm. and the temperature was raised to the boiling point of the steroid (380–450°). The actual distillation occurred over a 10-min. period. This distillate consisted of 88 g. of a pale yellow, viscous oil, $[\alpha]_D$ +92°. Careful chromatography of 2.0 g. of this material on 400 g. of silica yielded only noncrystalline fractions from elution with 15% benzene–petroleum ether (b.p. 65–68°). The center fractions were essentially pure 18-nor-17β-methyl-3-methoxyestra-1,3,5(10),13(17)-tetraene (*2*); $[\alpha]_D$ +90°; $\lambda_{max}^{CHCl_3}$ 6.21, 6.34 μ; λ_{max} 277 (log ε 3.35), 286(3.31) mμ[31].

Anal. Calcd. for $C_{19}H_{24}O$: C, 85.02; H, 9.01. Found: C, 84.84; H, 9.02.

Estradiol 3-methyl ether (0.15 g.) was also eluted from the silica column with 2% ethyl acetate–benzene; it was identified by its infrared spectrum and melting point.

17β-Methyl-3-methoxy-18-norestra-1,3,5(10)-trien-13α,17α-diol (5). To a solution of 9.40 g. of the total crude tetraene *2* (as obtained above) in 150 ml. of ether was added 1.0 equivalents of osmium tetroxide (8.90 g.). The solution started to boil gently and a black precipitate formed immediately. The solution was stirred at room temperature overnight, and was then diluted with 400 ml. of ethanol and a solution of 10 g. of sodium sulfite in 200 ml. of water. The mixture was heated at reflux for 1 hr. and was filtered, using hot ethanol and hot benzene to wash the precipitate. The solution was then concentrated to a small volume under reduced pressure. The normal extraction and concentration procedure[32] yielded 6.40 g. of material. Crystallization from acetone gave 1.66 g. of the 13,17-diol *5*, m.p. 173–179°. Recrystallization from acetone gave the pure material as hard irregular prisms of an acetone solvate, m.p. 181–182°; $[\alpha]_D$ +117°; λ_{max} 2.82, 2.97 μ; 8.800 τ (C-17-CH_3).[33]

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.29; H, 9.12.

Chromatography of the mother liquors (5.0 g.) on 240 g. of silica yielded an additional 1.50 g. of crude glycol *5*, eluted with 10% ethyl acetate in benzene. Recrystallization from acetone–petroleum ether yielded 0.60 g. of the pure glycol, m.p. 173–178°, identical in the infrared to the material obtained by direct crystallization.

Eluted first (with benzene) from the silica column was 0.20 g. of crude *17β-methyl-3-methoxy-18-nor-13α-estra-1,3,5(10),8(14)-tetraene(3)* which on recrystallization from 2-propanol gave the analytical sample, m.p. 83–84°; $[\alpha]_D$ +135°; 6.258 (*O*-methyl), 9.700 and approximately 10.000 τ (C-17 CH_3).

Anal. Calcd. for $C_{19}H_{24}O$: C, 85.02; H, 9.01. Found: C, 84.82; H, 8.94.

Retreatment of this tetraene with excess osmium tetroxide in ether for 3 days at room temperature effected no change. Treatment with ozone at −70° until 1 mole of ozone had been taken up (determined by the ozone concentration of the effluent gases) afforded only noncrystalline materials which lacked the normal aromatic spectrum.

Elution of the chromatographic column with 5% ethyl acetate in benzene gave 0.15 g. of crystalline residue which upon recrystallization from acetone–petroleum ether and treatment with charcoal yielded 40 mg. of *17β-methyl-3-methoxy-18-norestra-1,3,5(10)-trien-13α,14α-diol(11)*, m.p. 126–128°; $[\alpha]_D$ +83°; λ_{max} 2.83, 2.99 μ.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.69; H, 8.56.

Continuing the chromatogram with 15% ethyl acetate in benzene yielded 0.45 g. of crude diol which on recrystallization from acetone afforded 0.15 g. of the pure *17β-methyl-3-methoxy-18-nor-13α-estra-1,3,5(10)-trien-16α,17α-diol (23)*, m.p. 188–189°; $[\alpha]_D$ +92°; λ_{max} 2.85, 2.99 μ.

Anal. Found: C, 75.19; H, 8.91.

Ethyl acetate (20%) in benzene as eluant of the chromatographic column gave 0.20 g. of impure *20*. Recrystallization from acetone yielded *17β-methyl-3-methoxy-18-nor-13α-estra-1,3,5(10)-trien-17α,20-diol(20)*, m.p. 160–161°, $[\alpha]_D$ +129°; λ_{max} 2.85, 2.92 μ.

Anal. Found: C, 75.45; H, 8.79.

Attempts to hydroxylate olefin *2* with potassium permanganate in acetone, iodine and silver acetate in wet acetic acid, or with performic acid gave a variety of non-crystalline products which proved to contain little C-13–C-17 glycol.

1-(3-Oxobutyl)-7-methoxy-1,2,3,4,4aα,9,10,10aβ-octahydrophenanthren-2-one(6).[30] *A. Ozonolysis of the tetraene 2.* A solution of 86 g. of the tetraene *2* in 400 ml. of methylene chloride and 400 ml. of methanol at −70° was treated with a stream of oxygen containing 1 equivalent of ozone over a 5-hr. period. At the end of this time the effluent gas showed a sharp increase in concentration of ozone. Zinc dust (40 g.) and 40 ml. of acetic acid in 40 ml. of methylene chloride

(27) Steroid texts, L. F. Fieser and M. Fieser, *Steroids*, Reinhold Publishing Corporation, New York, N. Y., 1959, p. 456, and C. W. Shoppee, *Chemistry of Steroids*, Academic Press, Inc., New York, N. Y., 1958, p. 116, are somewhat misleading in their description of the original experiments, implying olefin *2* is isolable.

(28) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952); R. Hirschman, C. S. Snoddy, Jr., C. F. Hiskey, and N. L. Wendler, *J. Am. Chem. Soc.*, **76**, 4013 (1954).

(29) All melting points were taken on a Fisher-Johns melting point apparatus. Rotations were determined in chloroform solution (1%), ultraviolet spectra in methanol, and infrared spectra as potassium bromide disks unless otherwise stated.

(30) We wish to thank Mr. C. Jung for his assistance in carrying out large scale preparations.

(31) The maxima indicated here are characteristic of the anisole A-ring; further mention of them will be omitted.

(32) The usual isolation of the reaction product was accomplished by dilution of the reaction with water and extraction with benzene; the extract was washed with water and aqueous potassium bicarbonate, dried over anhydrous magnesium sulfate, and concentrated to dryness under reduced pressure.

(33) We wish to thank Dr. N. L. McNiven for the NMR spectra and his helpful comments on their interpretation. The spectra were determined in deuterochloroform.

were added to the stirred solution. The Dry Ice bath was removed and replaced by an ice bath. Decomposition of the ozonide seemed to occur near 0°, as evidenced by a sudden discontinuity in the temperature increase (to 5°). After 45 min. the solution was filtered and washed with water, and worked up in the normal manner.[32] The residue was crystallized from acetone–petroleum ether, yielding 49.0 g. (51%) of hard prisms, m.p. 118–119°; $[\alpha]_D$ +98°; λ_{max} 5.87 μ.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 76.14; H, 7.81.

An additional 3–8% of pure *6* could be obtained from chromatography of the mother liquors on silica, eluted by 10% ethyl acetate in benzene. The yield of this diketone on direct crystallization rose to 65% from smaller runs.

B. Periodate oxidation of the glycol 5. The diketone *6* was also obtained by treating the glycol *5* (0.10 g.) in 10 ml. of dioxane and 0.2 ml. of pyridine with 0.10 g. of periodic acid dihydrate in 1 ml. of water for 2 hr. at room temperature. Dilution with water and filtration furnished 90 mg. of *6*, m.p. 112–116°, identical in the infrared with the material obtained from the previous experiment.

8-Methoxy-2,3,4,4aα,4bβ,5,6,10bα,11,12-decahydrochrysen-2-one (*8*).[30] A solution of 54.90 g. of the diketone *6* in 2.2 l. of methanol and 350 ml. of 10% aqueous potassium hydroxide was heated in an atmosphere of nitrogen for 1 hr. The solution was cooled and diluted with 0.5 l. of water. The precipitate which formed was collected on a filter, washed with water and dried, yielding 42.20 g. of the unsaturated ketone *8*, m.p. 146–147°, and 7.30 g., m.p. 143–145°. Recrystallization from acetone–petroleum ether gave the analytical sample as flat plates, m.p 146–147°; $[\alpha]_D$ +85°: λ_{max} 5.97, 6.19 μ; λ_{max} 239 mμ(log ϵ 4.25).[34]

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.81; H, 7.86. Found: C, 80.57; H, 7.82.

8-Methoxy-12α-hydroxy-1,2,3,4,4aα,4bβ,5,6,10bα,11,12,-12aα-dodecahydrochrysen-2-one (*9*). The diketone *6* (4.0 g.) was slurried in 240 ml. of methanol containing 2 ml. of 10% aqueous potassium hydroxide. This was stirred vigorously at room temperature for 20 min., diluted with water and filtered, yielding 3.7 g. of crystals. Chromatography on 200 g. of silica yielded 3.0 g. of starting material. The remainder, eluted at 10% ethyl acetate–benzene, was largely the hydroxy ketone *9*, which on recrystallization from acetone–petroleum ether yielded the pure compound, m.p. 200–203°; $[\alpha]_D$ +27°; λ_{max} 2.92, 5.82 μ; 7.258 τ (*O*-methyl group; spectrum run in deuterated pyridine).

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.84; H, 7.95.

Treatment of this hydroxy ketone in refluxing methanol containing 5% aqueous potassium hydroxide gave a good yield of the unsaturated ketone *8*.

17β-Methyl-3-methoxy-13,14-seco-18-norestra-1,3,5(10)-trien-13,14-dione (*15*). A solution of the glycol *11* (35 mg.) in 5 ml. of methanol containing 0.4 ml. of pyridine was treated with 100 mg. of periodic acid dihydrate in 1 ml. of water at room temperature for 22 hr. (only starting material was isolated after 1 hr.). Dilution with water gave 30 mg. of the dione, m.p. 139–141° which was recrystallized from acetone–petroleum ether to give the analytical sample with the same melting point; λ_{max} 5.86, 5.90 μ.

Anal. Found: C, 76.07; H, 8.12.

An identical procedure on 50 mg. of the epimeric glycol *12* yielded, after 22 hr., 45 mg. of the diketone, m.p. 137–140°, with the correct infrared spectrum. Again, a 1-hr. reaction period returned mainly starting material.

Ozonolysis of the crude *2* yielded additional small amounts of the diketone *15* after chromatography, eluted at 2% ethyl acetate in benzene from a silica column.

2-Methyl-4aβ-hydroxy-8-methoxy-c-nor-1,2,3,4,4a,4bβ,5,6,10bα,11,11aα-undecahydrochrysen-1-one (*14*) and *2-methyl-8-methoxy-c-nor-1,2,3,4,4bβ,5,6,10bα,11-nonahydrochrysen-1-one* (*13*). A solution of 1.50 g. of the diketone *15* in 75 ml. of methanol containing 7.5 ml. of 1% aqueous potassium hydroxide was stirred at room temperature for 10 min. The solution was diluted with water and acidified with hydrochloric acid. The precipitate was collected on a filter, washed with water and dried, yielding 1.0 g. of crystals. Chromatography of this material on 40 g. of silica yielded, at 2% ethyl acetate in benzene, 0.45 g. of the pure unsaturated ketone *13*, m.p. 140–142° after recrystallization from acetone–petroleum ether; $[\alpha]_D$ −15°; λ_{max} 6.03, 6.19 μ; λ_{max} 251 mμ (log ϵ 4.10)[34]; 6.242(*O*-methyl), 8.792 and 8.892 τ (C-17 CH_3).

Anal. Calcd. for $C_{17}H_{22}O_2$: C, 80.81; H, 7.86. Found: C, 80.87; H, 7.92.

Eluted at 5% ethyl acetate in benzene was 0.44 g. of the hydroxy ketone *14*. By recrystallization from acetone–petroleum ether the pure sample, m.p. 117–119°, was obtained; $[\alpha]_D$ +61°; λ_{max} 2.85, 5.89 μ.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 76.13; H, 8.06.

2-Methyl-8-methoxy-c-nor-1,2,3,4,4a,4bα,5,6,10bα,11,11a-undecahydrochrysen-1-one (*18*). To a solution of 0.67 g. of of the unsaturated ketone *13* in 40 ml. of ethanol was added 100 mg. of 5% palladium-on-charcoal catalyst. The mixture absorbed 1 equivalent of hydrogen in 20 min. Concentration of the filtered solution yielded a semicrystalline residue which upon recrystallization from methanol gave 0.38 g. of rods, m.p. 89–93°; $[\alpha]_D$ +25°; λ_{max} 5.87 μ.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 80.24; H, 8.51. Found: C, 80.30; H, 8.53.

2-Methyl-8-methoxy-c-nor-1,2,3,4,4bα,5,6,10bα,11-nonahydrochrysen-1-one (*17*). A solution of 100 mg. of the unsaturated ketone *13* in 10 ml. of methanol containing 1 ml. of 5% aqueous potassium hydroxide was heated at reflux for 1 hr. in an atmosphere of nitrogen. The product was isolated by extraction,[32] yielding 99 mg. of semicrystalline material, $[\alpha]_D$ +194°, which on recrystallization from petroleum ether, yielded 60 mg. of the pure unsaturated ketone *17*, m.p. 93–95°, $[\alpha]_D$ +194°; λ_{max} 6.00, 6.10 μ; λ_{max} 250 mμ (log ϵ 4.08)[34]; 6.242 (O-methyl), 8.792 and 8.912 τ (C-17 CH_3).

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.81; H, 7.86. Found: C, 80.83; H, 7.96.

No trace of the starting material could be found in the mother liquors by direct or spectral examination, or by consideration of the rotation of the crude product.

This unsaturated ketone readily took up 1 equivalent of hydrogen when dissolved in ethanol containing 5% palladium-on-carbon catalyst. The noncrystalline product showed the typical cyclohexanone absorption at 5.85 μ.

1β-Acetaldehydo-2β-acetyl-7-methoxy-1,2,3,4,4aα,9,10,10aβ-octahydrophenanthrene (*25*). Treatment of 0.10 g. of the glycol *23* in 15 ml. of methanol containing 0.3 ml. of pyridine with 0.10 g. of periodic acid dihydrate in 1 ml. of water at room temperature for 1 hr. provided, by dilution with water and filtration, 80 mg. of crude *25*. Recrystallization from petroleum ether gave 70 mg. of pure ketoaldehyde, m.p. 92–93°; $[\alpha]_D$ + 62°; λ_{max} 3.66, 5.82 μ.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.73; H, 8.07.

8-Methoxy-3-hydroxy-1,2,3,4,4α,4bβ,5,6,10bα,11,12,12a-dodecahydrochrysen-1-one (*26*). A solution of 50 mg. of the ketoaldehyde *25* in 3 ml. of methanol containing 1 ml. of 1% aqueous potassium hydroxide was stirred at room temperature for 30 min. The solution was diluted with water and filtered. Recrystallization from acetone–petroleum ether gave the analytical sample, 45 mg., m.p. 175–182°; $[\alpha]_D$ +39°; λ_{max} 2.85, 5.86 μ.

Anal. Found: C, 75.75; H, 7.74.

(34) To cancel the effect of the aromatic A-ring on this spectrum, an equal concentration of estrone methyl ether was run in the reference cell of the spectrophotometer. This eliminates the shifted and enhanced maxima as well as peaks created only by the overlapping of the unsaturated ketone and anisole absorptions.

8-Methoxy-1,4,4aα,4bβ,5,6,10aα,11,12,12aβ-decahydrochrysen-1-one (27). A methanol solution (30 ml.) of 0.22 g. of the hydroxy ketone *26* and 6 ml. of 10% aqueous potassium hydroxide was heated to reflux under nitrogen for 1 hr. The solution was cooled and extracted,[32] yielding 0.22 g. of semicrystalline residue. This was chromatographed on 10 g. of silica. Elution with 2% ethyl acetate gave 160 mg. of crystals which were recrystallized from acetone–petroleum ether, affording 80 mg. of the pure unsaturated ketone *27*, m.p. 163–164°; $[\alpha]_D$ −8°; λ_{max} 5.96 μ; λ_{max} 225 mμ (log ε 4.22).[34]

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.81; H, 7.86. Found: C, 80.47; H, 7.65.

8-Methoxy-1,2,3,4,4aα,4bβ,5,6,10bα,11,12,12aβ-dodecahydrochrysen-1-one (24). A solution of 0.15 g. of the unsaturated ketone *27* in 70 ml. of ethanol containing 75 mg. of 5% palladium-on-charcoal and 0.05 ml. of 10% aqueous potassium hydroxide absorbed 1 equivalent of hydrogen in 5 min. The solution was filtered and concentrated *in vacuo*. The residue was filtered through 4 g. of silica in 5% ethyl acetate–benzene, giving 0.11 g. of product, crystallized from methanol to yield 80 mg. of pure *24* as granular crystals, m.p. 172–174°; $[\alpha]_D$ +46°; λ_{max} 5.86 μ.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 79.97; H, 8.35.

A chloroform spectrum of this material was identical to that of *dl-24* prepared by an independent route.[16]

18-Nor-13α-estrone-3-methyl ether (21). The glycol *20* (70 mg.) in 10 ml. of methanol and 0.2 ml. of pyridine was treated with 0.10 g. of para-periodic acid in 1 ml. of water at room temperature for 1 hr. Dilution with water gave 50 mg. of a crystalline product, m.p. 118–119°, isolated by filtration. Recrystallization from ether–petroleum ether gave the analytical sample, m.p. 121–122°; $[\alpha]_D$ −66°; λ_{max} 5.78 μ.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.14; H, 8.25.

This sample was identical in all respects to a sample synthesized by a different route.[1]

Boric acid-catalyzed rearrangement of estradiol 3-methyl ether at 280°. An intimate mixture of 15 g. of estradiol 3-methyl ether and 15 g. of boric acid was heated over a 15-min. period to 280°[35] and was maintained at that temperature for 1 hr. The mixture was then cooled and diluted with water. The usual work-up gave 13.8 g. of an oil, which was chromatographed on 500 g. of silica. Elution with 15% benzene in petroleum ether gave a total of 7.84 g. of oil, the latter portions of which crystallized in part giving, after recrystallization from *i*-propyl alcohol, 50 mg. of the naphthalene *7*, m.p. 78–81°; (described fully below). Further elution of the column provided 5.5 g. of crude estradiol 3-methyl ether (37%), identified by its infrared spectrum.

The olefin mixture (4.3 g., after chromatographic purification) in 700 ml. of ether was treated with 3.9 g. of osmium tetroxide for 65 hr. Following the work-up described for the preparation of glycol *5* there was obtained 4.60 g. of oil. This was chromatographed on 200 g. of silica. Elution with benzene gave 0.80 g. of oily mixture; $[\alpha]_D$ +21; λ_{max} 228 (log ε 4.56), 264 (3.77), 321, 336 mμ; λ_{max} 6.13, 6.22 μ.

The only crystalline component was eluted with 5% ethyl acetate in benzene. This gave 1.42 g. of crude glycol *5*, which on recrystallization from acetone–petroleum ether gave 0.78 g. of crystals, m.p. 173–180°, identical in the infrared with an authentic sample.

Treatment of the total noncrystalline glycol fractions with periodic acid followed by chromatography gave only noncrystalline mixtures containing ketone but no discernible aldehyde absorption in the infrared.

17α-Chloro-3-methoxyestra-1,3,5(10)-triene(4a). A solution of 28.4 g. of estradiol 3-methyl ether in 0.8 l. of carbon tetrachloride at 5° was treated with 22 g. of phosphorus pentachloride. After 2 hr. of vigorous stirring, the solution was treated with an excess of aqueous potassium bicarbonate, and then was worked up in the usual manner.[32] The residue was chromatographed quickly on 0.8 kg. of silica, the product being eluted with 5% benzene in petroleum ether. Recrystallization of this material yielded 9.5 g. of the chloride *4a*, m.p. 103–106°. Recrystallization of a portion yielded the analytical sample, m.p. 107–108°; $[\alpha]_D$ +15°; 5.837 and 5.937(17β-H), 6.242 (*O*-methyl), 9.195 τ (C-18 CH_3).

Anal. Calcd. for $C_{19}H_{25}ClO$: C, 74.85; H, 8.27. Found: C, 74.83; H, 8.23.

Attempts were made to invert this chloride by use of both lithium chloride in refluxing tetrahydrofuran (4 days) or tetraethylammonium chloride in refluxing chloroform (24 hr.). In neither case was there evidence of formation of the higher melting β-isomer, although in the former the recovery of starting material was only 70%.

17β-Methyl-3-methoxy-18-norestra-1,3,5(10),13-tetraene (10a).[3] To a solution of 3.5 g. of the chloride *4a* in 150 ml. of diethylene glycol was added 2 g. of sodium acetate and 1 g. of potassium iodide dissolved in 50 ml. of water. The reaction was heated at reflux with stirring for 20 hr., was cooled, and was extracted with benzene in the usual way.[32] The residue, 2.78 g., gave 0.80 g. of crystals, m.p. 78–88° from propanol, and was recrystallized to give 0.40 g. of the pure olefin *10a*, m.p. 107–109°; $[\alpha]_D$ −38°.

Anal. Calcd. for $C_{19}H_{24}O$: C, 85.02; H, 9.01. Found: C, 85.18; H, 9.04.

Varying the amounts of potassium iodide used or running the reaction in ethanol at 125° had little effect on the yields of olefins *2* and *10*.

The same olefin (10a) could be obtained from methylation of the phenol *10c*, described by Westphal and prepared by his procedure: 0.30 g. of *10c*, m.p. 156–159°, was slurried with 4 g. of potassium carbonate in 50 ml. of ethanol and 10 ml. of methyl iodide. The mixture was heated at reflux and stirred for 3 hr., cooled and diluted with water yielding 0.24 g. of crystals, m.p. 80–90°. Recrystallization from methanol yielded 110 mg. of the olefin *10a* described above, identical by the normal comparisons of physical properties.

Hydroxylation of the retroestratetraene mixture. Estradiol methyl ether (50 g.) and 50 g. of calcium carbonate in 0.5 l. of chloroform were treated with 46 g. of phosphorus pentachloride at 5–10°. After 1 hr. excess cold aqueous sodium bicarbonate was added, and the chloroform solution was separated, and washed successively with dilute hydrochloric acid, water, and aqueous sodium bicarbonate. The chloroform solution was dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure yielding 54 g. of amorphous product, the crude chloride *4a*. A solution of 150 g. of this material in 1 l. of 80% aqueous ethanol containing 8 g. of sodium acetate and 0.2 g. of potassium iodide was heated at 125° in a 2-l. Parr bomb. The solution was then concentrated to a small volume and the product isolated by extraction.[32] The residue (12.0 g.) was chromatographed quickly over 250 g. of silica gel, 11.1 g. of an oily substance being obtained with benzene.

A portion (4.2 g.) of this purified olefin mixture was treated in 200 ml. of ether with 4.0 g. of osmium tetroxide. After 16 hr. the reaction mixture was poured into a solution of 0.6 g. of lithium aluminum hydride dissolved in 100 ml. of ether. The reaction mixture was heated at reflux for 2 hr., cooled, and treated cautiously with water and then dilute hydrochloric acid. The product, extracted with benzene in the usual way, was chromatographed on 400 g. of silica. Elution with 2% ethyl acetate in benzene gave 0.60 g. of an oil which on crystallization and recrystallization from 2-propanol and then from petroleum ether gave 0.12 g. of *17β-methyl-3-methoxy-18-nor-estra-1,3,5(10),6,8,13-hexaene (7)*, m.p. 84–85°; $[\alpha]_D$ −1°; λ_{max} 280 mμ (log ε 3.41); 6.192 (*O*-methyl), 8.642 and 8.750 τ (C-17 CH_3).

Anal. Calcd. for $C_{19}H_{20}O$: C, 86.32; H, 7.63. Found: C, 86.14; H, 7.84.

The same compound was isolated in small yield from both the low temperature boric acid treatment (280°) and from

(35) Similar treatment at 230° for 20 min. effected no change.

direct chromatography of the crude chloro compound (before base treatment).

Elution of the column with 5% ethyl acetate in benzene gave 0.83 g. of crystals which on recrystallization from acetone–petroleum ether gave 0.62 g. of the pure glycol *11* (m.p. 126–128°), identity confirmed by comparison of the infrared spectra.

Elution with 10% ethyl acetate in benzene yielded a crystalline material (0.18 g.) which on recrystallization from acetone–petroleum ether afforded 0.12 g. of *17β-methyl-3-methoxy-18-norestra-1,3,5(10)-trien-13β,14β-diol* (*12*), m.p. 136–138°; $[\alpha]_D$ +153°; λ_{max} 3.00 μ (the infrared in potassium bromide or chloroform was distinctly different from that of the glycol *11*).

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.29; H, 8.65.

The same glycol (*12*) was also obtained by hydroxylation of the pure olefin *10a* in approximately the same ratio to its epimer (*11*) as found here.

Further elution of the column with 10% ethyl acetate in benzene yielded 1.5 g. of crude crystalline material which was recrystallized to yield 1.05 g. of the 13,17-glycol *5*, identical in the infrared to an authentic sample.

Ozonolysis of the retroestratetraene mixture. The chloride *4a* (9.2 g., m.p. 103–106°) was rearranged in 245 ml. of 80% aqueous ethanol containing 1.25 g. of sodium acetate and 60 mg. of potassium iodide at 125° for 12 hr. Isolation of the product as described above gave a total of 1.2 g. of the olefin *10a*, m.p. 92–100°. The mother liquors (5.8 g.) in 150 ml. of methylene chloride and 50 ml. of methanol were treated with 1 equivalent of ozone at −70°. The solution was then treated with 10 g. of zinc dust and 10 ml. of acetic acid. After stirring at 0° for 30 min., the solution was filtered, washed with water and dilute potassium bicarbonate, dried over magnesium sulfate, and concentrated to dryness, yielding 6.03 g. of oil.

Chromatography of this material gave first, 0.40 g. of oil, λ_{max} 281 (log ε 2.78) mμ. Elution with 3% ethyl acetate in benzene gave, after recrystallization from acetone–petroleum ether, 1.10 g. of the pure 13,14-dione (*15*) m.p. 136–139°, identical in the infrared to an authentic sample. Elution of the column with 5% ethyl acetate in benzene yielded, after recrystallization from acetone–petroleum ether, 1.95 g. of the 13,17-diketone (*6*) m.p. 117–119°, showing no difference in the infrared from the known compound.

3-Methoxy-17α-chloroestra-1,3,5(10)-trien-16-one propylene thioketal (*32*). A solution of 0.18 g. of 3-methoxy-17α-chloroestra-1,3,5(10)-trien-16-one[25] in 0.5 ml. of propanedithiol and 0.5 ml. of redistilled boron trifluoride etherate was allowed to stand at room temperature for 25 min. The solution was diluted with methanol and then water. It was extracted with benzene, the benzene solution washed twice with 2% aqueous potassium hydroxide, dried and concentrated *in vacuo* yielding 0.25 g. of an oil (no carbonyl absorption in the infrared). The material was adsorbed on 4 g. of silica. The fractions eluted with 60% benzene in petroleum ether were recrystallized from acetone–petroleum ether and from methylene chloride–methanol yielding 125 mg. of the pure thioketal *32*, m.p. 151–153°.

Anal. Calcd. for $C_{22}H_{29}ClOS_2$: C, 64.60; H, 7.15. Found: C, 64.84; H, 7.37.

Raney nickel reduction of the thioketal 32. Raney nickel catalyst (W-5) was deactivated by refluxing for 30 min. in 1:1 ethanol-acetone. To one-half teaspoon of this catalyst in 30 ml. of ethanol was added 0.12 g. of the thioketal *32*. The solution was stirred at room temperature for 2 hr., filtered and concentrated to dryness. The residue was chromatogrammed on 4 g. of silica gel. Elution with 15% benzene–petroleum ether gave 25 mg. of residue which on recrystallization from 2-propanol gave 12 mg. of crystalline material, m.p. 68–71°, identical in the infrared to an authentic sample of 3-methoxyestra-1,3,5(10),16-tetraene (*31*).

Further elution of the column with 70% benzene in petroleum ether yielded 30 mg. of crystalline material which was recrystallized from methylene chloride–methanol to yield crystals, m.p. 147–149°, identical in the infrared to starting material.

A third substance, eluted with 5% ethyl acetate in benzene, exhibited a strong carbonyl absorption in the infrared (5.78 μ). Comparison of the spectrum to that of several related carbonyl compounds failed to afford a proof of structure. No further work was done with this noncrystalline material.

3-Methoxy-17-chloroestra-1,3,5(10),16-tetraene (*33*). To 500 ml. of chloroform were added 50 g. of estrone methyl ether and 60 g. of phosphorus pentachloride. The solution was heated at reflux for 90 min., was cooled and was poured onto 0.5 kg. of ice. Excess aqueous potassium hydroxide was added and the product was isolated in the normal fashion, yielding 60 g. of an oil. The product was chromatographed on 800 g. of alumina (Merck). Elution with 10% benzene in petroleum ether yielded 24 g. of product, which on recrystallization from petroleum ether yielded 10.4 g. of the pure chloride *33*, m.p. 114–115°; $[\alpha]_D$ +97°.

Anal. Calcd. for $C_{19}H_{23}ClO$: C, 75.35; H, 7.65. Found: C, 75.05; H, 7.37.

Elution of the column with polar solvents led first to noncrystalline mixtures, from which could be obtained additional chloride *33*, by treatment in refluxing collidine (1 hr.) and repeated chromatography. There was also obtained 12.4 g. of starting material, m.p. 165–170°.

From rechromatography of the collidine-treated mother liquors (8.4 g.) on silica (650 g.) there was obtained by ether recrystallization of material eluted with 15% benzene–petroleum ether 0.28 g. of a new compound, m.p. 163–167°; $[\alpha]_D$ + 50°; λ_{max} 267 (log ε 3.30), 276(3.36), 286(3.19) mμ; 2.792, 2.917, 3.183, 3.333 (the two aromatic hydrogens), 4.367 (C-16 H), 6.133 (*O*-methyl), 9.125 τ (C-13 CH_3). This compound is most probably the 4-chloro derivative of *33:* 3-methoxy-4,17-dichlorestra-1,3,5(10),16-tetraene.

Anal. Calcd. for $C_{19}H_{22}Cl_2O$: C, 67.66; H, 6.56. Found: C, 67.80; H, 6.24.

3-Methoxy-17β-chloroestra-1,3,5(10)-triene (*34*). A solution of 1.43 g. of the chloride *33* in 15 ml. of dioxane and 20 ml. of ethanol containing 150 mg. of 5% palladium-on-charcoal was treated with hydrogen. The calculated amount of gas was absorbed within 30 min. and the reduction was interrupted. The solution was filtered and concentrated to dryness under reduced pressure. The residue was recrystallized from methylene chloride–methanol yielding 0.73 g. of the saturated chloride *34*, m.p. 136–148°. Further recrystallization from this solvent pair and from acetone–petroleum ether gave 0.46 g. of the pure compound, m.p. 168–169°; $\alpha]_D$ +91°; 6.233 (*O*-methyl), 9.153 τ (C-18 CH_3). (The C-17 α-H peak is masked by the *O*-methyl absorption.)

Anal. Calcd. for $C_{19}H_{25}ClO$: C, 74.85; H, 8.27; Cl, 11.63. Found: C, 74.72; H, 7.93; Cl, 11.82.

Treatment of 0.15 g. of the chloride *34* in 45 ml. of 80% aqueous ethanol at 125° for 12 hr. or in 20 ml. of diethylene glycol containing 0.20 g. of potassium iodide and 0.40 g. of sodium acetate in 6 ml. of water at reflux for 18 hr. returned nearly quantitative yields of starting material.

Zinc chloride treatment of estradiol 3-methyl ether. A mixture of 21 g. of estradiol 3-methyl ether and 42 g. of zinc chloride was heated under nitrogen at 180° for 30 min. The normal isolation[32] gave 20.05 g. of pale yellow oil. A portion (9.7 g.) of this material was chromatographed on 970 g. of silica. Elution with 20% benzene in petroleum ether gave 7.80 g. of oil, the earliest fractions exhibiting a maximum at 227 mμ (log ε 4.08); $[\alpha]_D$ +15°. The latter fractions were rich in the phenanthrene *25*. Crystallization of several of these latter fractions readily yielded 0.21 g. of pure *25*, m.p. 149–151°, possessing the expected strong absorption in the ultraviolet. Elution with 30% benzene in petroleum ether yielded semicrystalline mixtures (0.62 g.) of additional substances with multiple intense maxima in the ultraviolet.

Analysis of 4.3 g. of the zinc chloride olefin mixture was accomplished by treatment with 3.9 g. of osmium tetroxide

in 200 ml. of ether for 18 hr. The sodium sulfite decomposition of the osmate ester was used (as described above) yielding 4.2 g. of a mobile oil. This was chromatographed on 200 g. of silica. Elution with 30% benzene in petroleum ether gave 3.53 g. of an oil, essentially the same as the starting product by comparison of ultraviolet and infrared spectra. Further elution with benzene–ethyl acetate mixtures, expected to elute the known glycols provided only small amounts of noncrystalline oils.

Aluminum chloride treatment of estradiol 3-methyl ether. A solution of 7.0 g. of estradiol 3-methyl ether and 8.0 g. of aluminum chloride in 250 ml. of chlorobenzene was allowed to stand at room temperature for 20 hr. The product was isolated in the usual manner and was then analyzed with the osmium tetroxide procedure as described above. Again no crystalline glycols or starting material could be obtained even after chromatography. The bulk of the product was highly conjugated and/or inert to hydroxylation.

Bamford-Stevens rearrangement of estrone methyl ether. A slurry of 11.0 g. of estrone methyl ether and 9.0 g. of *p*-tolylsulfonylhydrazide in 600 ml. of ethanol and 4 ml. of concd. hydrochloric acid was heated at reflux for 30 min. The condenser was removed and the solution was concentrated to half volume, cooled, and diluted with water. The product was collected on a filter and then recrystallized from ethanol yielding 13.5 g. of *estrone 3-methyl ether p-tolylsulfonylhydrazone*, m.p. 201–203°; $[\alpha]_D$ +59°; λ_{max} 3.09, 6.02 μ.

Anal. Calcd. for $C_{26}H_{32}N_2O_3S$: C, 68.99; H, 7.17. Found: C, 68.97; H, 7.17.

Sodium metal (6 g.) was added to 250 ml. of ethylene glycol and the solution was stirred and warmed gently until the sodium dissolved (after an initial induction period, solution occurred with great vigor). The hydrazone (13.0 g.) was added and the stirred solution was heated at 130–170° for 45 min. A gentle evolution of gas began at 130° and continued for 30 min. The solution was then cooled, diluted with water, and filtered. The oily precipitate was dissolved in benzene, washed twice with water, dried, and concentrated to dryness, yielding 8.5 g. of oil. From 2-propanol there was obtained 1.60 g. of crystals in two crops. Recrystallization from methylene chloride–methanol gave 1.10 g. of pure olefin *10a*, m.p. 109–110°, identical in the infrared to that of the known compound.

The mother liquors of this reaction (6.8 g.) were treated with osmium tetroxide (6.6 g.) for 18 hr. and then worked up with sodium sulfite as described for earlier hydroxylations. The product was chromatographed on 700 g. of silica. Eluted with 100% benzene was 0.15 g. of material, which was recrystallized from 2-propanol to yield 60 mg. of the olefin *3*, m.p. 73–76° (identical infrared spectra).

Eluted with 8% ethyl acetate in benzene was 2.5 g. of an oil containing a small amount of crystalline material. Acetylation and rechromatography of this material gave 0.40 g. of the pure 13α,14α-diol *11*; the remainder, eluted in a separate band, failed to crystallize; lithium aluminum hydride treatment of this material (to remove the acetate grouping) followed by another chromatogram failed to yield any crystalline material.

Elution of the column with 10% ethyl acetate in benzene yielded first 0.12 g. of the β-glycol *12*, m.p. 133–136°. Continued elution with the same solvents provided 3.9 g. of a crystalline mixture from which could be obtained directly 1.6 g. of crystalline 13,17-diol *5*, m.p. 176–180° (identity confirmed by infrared). The remainder of the material was acetylated with pyridine–acetic anhydride and rechromatographed. Besides an additional 0.38 g. of the 13,17-diol there was obtained 0.80 g. of a new compound by elution of the silica column with 5% ethyl acetate in benzene. Recrystallization from acetone–petroleum ether afforded 0.40 g. of pure *17β-methyl-3-methoxy-18-norestra-1,3,5(10)-trien-12α,13α-diol 12-monoacetate* (*29a*), m.p. 138–140°; $[\alpha]_D$ +136°; λ_{max} 2.85, 5.82 μ.

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.01; H, 8.03.

Elution of the column with 20% ethyl acetate in benzene gave, after recrystallization from acetone–petroleum ether, 50 mg. of a crystalline compound, m.p. 146–148°, identical in all respects to the 17,20-diol *20*.

17β-Methyl-3-methoxy-18-norestra-1,3,5(10)-trien-12α,13α-diol (*29b*). A solution of 0.37 g. of the diol monoacetate *29a* in 15 ml. of methanol containing 5 ml. of 10% aqueous potassium hydroxide was heated at reflux for 1 hr. The solution was cooled and diluted with water; the resulting precipitate was collected on a filter, yielding 0.35 g. of material, m.p. 158–160°. Recrystallization from acetone–petroleum ether afforded 0.34 g. of the pure diol *29b* m.p. 161–163°, $[\alpha]_D$ +104°; λ_{max} 2.85, 2.99 μ.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 75.46; H, 8.67. Found: C, 75.58; H, 8.58.

17β-Methyl-3-methoxy-12,13-seco-18-norestra-1,3,5(10)-trien-12,13-dione (*30*). The diol *29b* (0.15 g.) in 5 ml. of methanol was treated with 0.6 ml. of pyridine and a solution of 0.15 g. of paraperiodic acid in 2 ml. of water. After 30 min. the solution was diluted with water and the product isolated by extraction with benzene. The resulting oil was chromatographed on 4 g. of silica gel, the product being eluted at 2% ethyl acetate in benzene. Attempts to crystallize the material failed; however, the infrared spectrum (λ_{max} 3.62, 5.77 μ) and elemental analysis agree with the assigned structure.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 76.05; H, 8.16.

Treatment of this ketoaldehyde with potassium hydroxide in refluxing methanol yielded an amorphous hydroxy ketone, λ_{max} 2.74, 5.78 μ.

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