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# The Conformation of Ring A in 5(10),9(11)-Estradienes[1]

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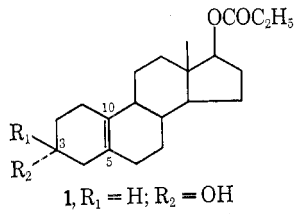
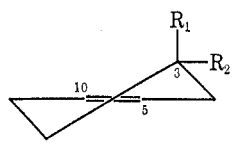
Reduction of 17β-hydroxyestra-5(10),9(11)-dien-3-one acetate (**6**) by lithium tri-*t*-butoxyaluminum hydride occurred with only a low degree of stereoselectivity. The major and minor products were shown to be the 3α and 3β alcohols **8** and **9** *via* a study of their respective osmylation products. These results, along with nmr spectral data, suggest that conformational preference in this system is weak but in favor of form **3** for ring A. These conclusions are compared with predictions based on molecular models.

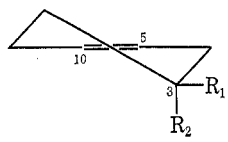
It has previously been established[2] that the 5(10)-estrenes **1** and **2** adopt ring A form **3** preferentially over the alternative half-chair[3] conformation **4**. We have



**1**, $R_1 = H; R_2 = OH$
**2**, $R_1 = OH; R_2 = H$

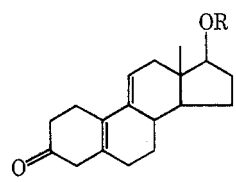


**3**

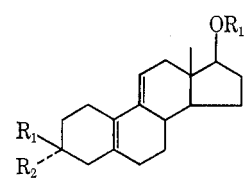


**4**

attempted to explain this unusual type of conformational preference on the basis of nonbonded repulsions between the C-1 and C-11 hydrogen substituents. From molecular models it appears that such interactions are not serious in conformation **3** but are severe in **4**. Preference for conformation **3** also accounts for the stereoselective formation of the equatorial 3α alcohol **1** (**3**, $R_1 = H; R_2 = OH$) by hydride reduction of the corresponding 3 ketone.[4] This type of conformational preference is not exhibited by all 5(10)-unsaturated steroids.[5] Our general aim is to understand the manner in which structural features elsewhere in the molecule determine the conformational status of ring A. In this connection we were particularly interested in a report by Brown and Bernstein[6] that the 5(10),9(11)-estradien-3-one **5** on reduction by sodium borohydride gives the corresponding 3β alcohol **7**, mp 164–167°, in 60% yield after two recrystallizations. Although firm evidence for assignment of the C-3 configuration was not given, we were nonetheless intrigued by the stereoselectivity of the reduction, which should betoken a considerable degree of conformational integrity for ring A. We therefore undertook a more detailed study of ring A chemistry in the 5(10),9(11)-estradiene system. Our first objective was to perform the hydride reduction of a 17 ester of ketone **5** in order to facilitate the detection and separation of epimeric 3-alcohol products.[7]



**5**, R = H
**6**, R = OAc



**7**, $R_1 = R_3 = H; R_2 = OH$
**8**, $R_1 = OAc; R_2 = H; R_3 = OH$
**9**, $R_1 = OAc; R_2 = OH; R_3 = H$
**10**, $R_1 = OAc; R_2 = H; R_3 = OAc$
**11**, $R_1 = OAc; R_2 = OAc; R_3 = H$

The unsaturated keto ester **6** was prepared in four steps from 17β-hydroxyestra-5(10)-en-3-one acetate following the procedures of Brown and Bernstein[8] and

(1) We gratefully acknowledge support of this work by the National Institutes of Health, U. S. Public Health Service, under Grant AM09279. We are also indebted to Dr. H. Herzog and the Schering Corporation for generous gifts of steroid starting materials.

(2) S. G. Levine, N. H. Eudy, and C. F. Lefler, *J. Org. Chem.*, **31**, 3995 (1966).

(3) The current status of conformational analysis of cyclohexene derivatives is described in E. Eliel, N. L. Allinger, S. J. Angyl, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York, N. Y., 1965, pp 109–111.

(4) O. R. Vail and D. M. S. Wheeler, *J. Org. Chem.*, **27**, 3803 (1962); O. H. Wheeler and J. L. Mateos, *Can. J. Chem.*, **36**, 1431 (1958).

(5) S. G. Levine and A. C. Ghosh, *Tetrahedron Lett.*, 39 (1969).

(6) J. J. Brown and S. Bernstein, U. S. Patent 3,143,557 (1964); *Chem. Abstr.*, **61**, 10746 (1964).

(7) After this work was in progress, a later paper by the Lederle group appeared in which the 3-ketone reduction product, mp 164–167°, was considered to be a mixture of epimers which resisted extensive effort at separation: M. Heller, R. H. Lenhard, and S. Bernstein, *Steroids*, **10**, 21 (1967).

(8) J. J. Brown and S. Bernstein, *ibid.*, **1**, 113 (1963).

of Perelman and coworkers.[9] This product could not be crystallized but was found to be essentially pure by thin layer chromatography (tlc) and gave appropriate ir, nmr, and uv spectra. Reduction of the carbonyl group in **6** was performed with lithium tri-*t*-butoxyaluminum hydride in tetrahydrofuran at −70°, since these reaction conditions had earlier[2] given rise to stereoselective reduction in the 5(10)-monoolefin series. The oily reduction product displayed spectral characteristics expected for the 3 alcohol(s) derived from **6**. Examination of this product by tlc revealed two components which were extremely close in mobility. We have designated the more polar constituent as alcohol A and the less polar constituent as alcohol B; the former appeared to be present in larger amount. A small sample of this mixture, on saponification, was converted nearly quantitatively into a crystalline product, mp 164–168°, in agreement with the melting point previously reported for the "$\beta$ alcohol" produced by sodium borohydride reduction of ketone **5**. The components of this mixture could not be distinguished by tlc. The remaining sample of hydride reduction products was largely resolved into its components by column chromatography on alumina. This provided 3 alcohol A, mp 148–149.5°, $[\alpha]D$ +217°, $R_f$ 0.33 (three elutions with $CHCl_3$),[10] and 3 alcohol B, mp 88–91°, $[\alpha]D$ +103°, $R_f$ 0.40 (three elutions with $CHCl_3$). Both compounds gave elemental analyses in agreement with their formulation as 5(10),9(11)-estradiene-3,17$\beta$-diol monoacetates. We have estimated that alcohols A and B are produced in *ca.* 65:35 ratio based on our chromatography results as well as optical-rotation data. Reduction of the 3 ketone is, therefore, less stereoselective than in the 5(10)-monounsaturated system.[2] We nonetheless undertook to determine the C-3 configurations of alcohols A and B.

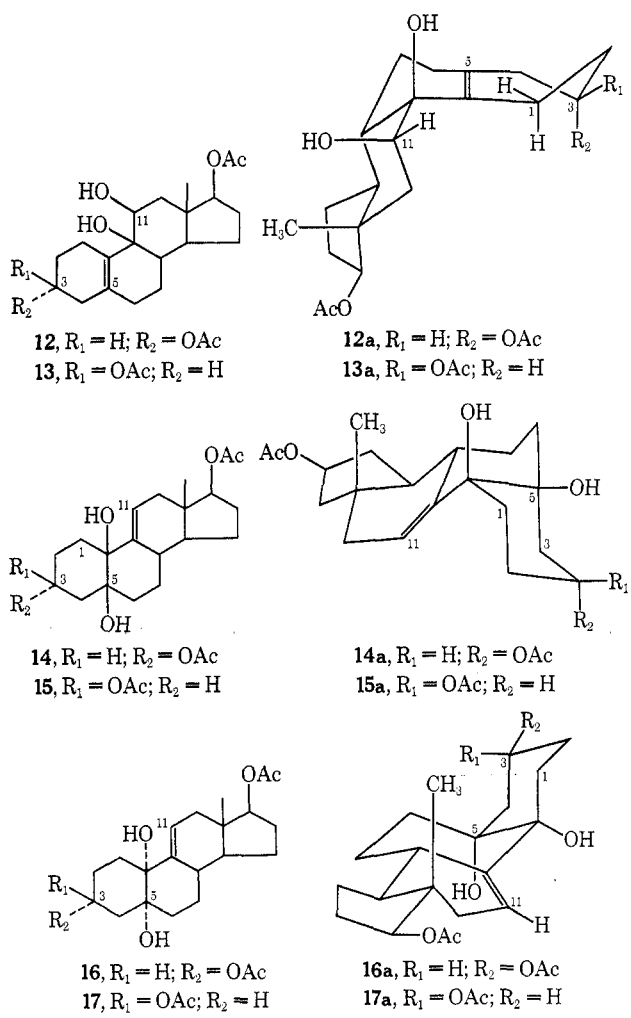
We have, in past work,[11] identified the C-3 configurations of certain 5(10)-unsaturated steroids by taking advantage of the known stereoselectivity[12] of electrophilic addition to give 5$\alpha$,10$\beta$ adducts. The resulting A/B-*trans* products are conformationally fixed and therefore amenable to nmr analysis in which the C-3 configuration is deduced from the C-3 proton resonance characteristics. This simple approach was, however, not successful with the epimeric 3 alcohols A and B, since treatment of either substance with bromine (or chlorine) led to a complex mixture of intractable products.

Seeking a milder addition reagent for the preparation of conformationally fixed derivatives of A and B, we studied the reaction of these dienes with osmium tetroxide with the hope of preparing 5,10-*cis*-diol adducts. This approach had been successful in our original work with 5(10)-monounsaturated steroids,[2] and it proved applicable to the present diene systems as well.

The 3 acetate derived from alcohol A was treated with slightly over 1 molar equiv of osmium tetroxide; decomposition of the resulting osmate esters with hydrogen sulfide gave a mixture of three products which were distinguishable by tlc but had very similar mobilities. This mixture was largely resolved into its components by a combination of column chromatography on alumina (continuous solvent gradient) and preparative tlc on silica gel. The three products were isomeric and gave elemental analyses in agreement with the molecular formula $C_{22}N_{32}O_6$ expected for a diol adduct. These compounds have been designated as diols $A_1$, $A_2$, and $A_3$ in their order of increasing mobility. We shall show that they may be allotted the 3$\alpha$-acetate structures **12**, **14**, and **16**, thereby establishing the 3$\alpha$-OH configuration for alcohol A.

Diols $A_2$ and $A_3$ appeared to be 5,10 ditertiary alcohols, since (a) the nmr and ir spectra of both compounds (Table I) showed the presence of a vinyl hydrogen, and (b) in neither case was a carbinol proton visible in the spectrum. A further spectral feature noted for both compounds was the presence of a broad ($W_{1/2} \cong 15$ cps)[2,13] signal in the $\delta$ 5 region appropriate for an axial C-3 proton of the type –CHOAc. This observation has structural significance, since examination of molecular models (see **14a** and **16a**, Chart I)

CHART I




reveals that a C-3 axial substituent must possess the $\beta$ configuration in *either* of the A/B-*cis*-$\Delta^{9(11)}$-estrene systems. Diols $A_2$ and $A_3$ are thus identified as

(9) M. Perelman, E. Farkas, E. J. Fornefeld, R. J. Kraay, and R. T. Rapala, *J. Amer. Chem. Soc.*, **82**, 2402 (1960).

(10) Solvent was allowed to evaporate from the plate at room temperature between the second and third runs.

(11) S. G. Levine, D. M. Feigh, and N. H. Eudy, *Tetrahedron Lett.*, 4615 (1967).

(12) A. D. Cross, E. Denot, R. Acevedo, R. Urquiza, and A. Bowers, *J. Org. Chem.*, **29**, 2195 (1964).

(13) A. Hassner and C. Heathcock, *ibid.*, **29**, 1350 (1964).

TABLE I

NUCLEAR MAGNETIC RESONANCE DATA

| Compd | Structure | H-3 Configuration | H-3 Orientation | H-3 δ, ppm | H-3 $W_{1/2}$, cps | H-11 δ, ppm | $CH_3$-18 δ, ppm |
|---|---|---|---|---|---|---|---|
| A (3-OH)[a] | **8** | β | | 3.87 | 18 | 5.46 | 0.80 |
| B (3-OH)[a] | **9** | α | | 3.98 | 15 | 5.46 | 0.80 |
| A | **10** | β | | 4.95[b] | 18 | 5.53 | 0.80 |
| B | **11** | α | | 5.03 | 15 | 5.52 | 0.82 |
| $A_1$ | **12, 12a** | β | Equatorial | 5.08 | 8 | 4.11[c] | 1.15 |
| $A_2$ | **14, 14a** | β | Axial | 5.15 | 18 | 5.75 | 0.77 |
| $A_3$ | **16, 16a** | β | Axial | 4.85 | 15 | 5.95 | 0.75 |
| $B_1$ | **13, 13a** | α | Axial | 4.80 | 21 | 4.17[c] | 1.08 |
| $B_2$ | **15, 15a** | α | Equatorial | 5.12 | 8 | 5.78 | 0.84 |
| $B_3$ | **17, 17a** | α | Equatorial | 5.14 | 7 | 5.96 | 0.80 |

[a] All other entries refer to the 3-acetate derivatives. [b] The high-field end of this absorption is obscured by overlap with the H-17α signal which is centered at δ 4.74. [c] Apparent triplet with 3-cps spacing.

3α acetates, thereby establishing that alcohol A, the major hydride reduction product from ketone **6**, is a 3α alcohol.

Stereochemical assignments for diols $A_2$ and $A_3$ were completed by deduction of the respective C-5,C-10 configurations from a comparison of their nmr spectra. The 3β-proton signal of diol $A_2$ appearing at δ 5.15 is deshielded by *ca.* 0.3 ppm with respect to the corresponding signal from diol $A_3$. This observation is easily accounted for by assigning to $A_2$ the 5β,10β-dihydroxy-3α-acetate structure **14**. The 3β proton and 5β hydroxyl are then placed in a 1,3-*syn*, axial relationship (**14a**) in which such deshielding is commonly observed.[2,14] Diol $A_3$ must, therefore, be assigned the 5α,10α-dihydroxy-3α-acetate structure **16** (and **16a**). Also in accord with these assignments is the location of the C-11 vinyl proton signal of **16**, which appears 0.2 ppm downfield from the corresponding signal in the 5β,10β-diol **14**. Comparison of perspective views **16a** and **14a** reveals that in the former case the 10α-OH group is in position to cause deshielding of the vinyl proton.[15]

Diol $A_1$ was easily recognized as a 9,11 adduct, since (a) evidence for a C-11 vinyl hydrogen was lacking in its ir and nmr spectra, and (b) the nmr spectrum included an apparent triplet at δ 4.11, appropriate for a C-11 carbinol proton coupled to the two C-12 methylene hydrogens. This proton would form the X portion of an ABX system, and, since the triplet spacing is close to 3 cps, $J_{AX} + J_{BX}$ must equal *ca.* 6 cps. Since there cannot be a large coupling constant between the C-11 carbinol proton and a C-12 proton, it follows that the C-11 proton is equatorial and the C-11 hydroxyl is axial. The molecular geometry (**12a**) then requires an 11β configuration for the alcohol substituent. This conclusion finds clear verification in the low-field position of the C-18 angular methyl singlet, which appears at δ 1.15, reflecting the deshielding influence[16] of the 1,3-*syn*, axial hydroxyl group at C-11. Diol $A_1$ is thus assigned structure **12** (**12a**).

The above configurational assignments were verified through a parallel sequence of experiments which started with alcohol B and provided complementary results. The 3 acetate derived from alcohol B was treated with osmium tetroxide and the products were separated by chromatography on alumina. Three diols were obtained, all isomeric with those described above. These were designated as diols $B_1$, $B_2$, and $B_3$, and are assigned structures **13**, **15**, and **17**. Diols $B_2$ and $B_3$ were recognized as 5,10-diols based on the pertinent nmr parameters (Table I). By inference from our results in the A series, these are 3β-acetate derivatives and must be assigned structures **15** and **17**, respectively, or vice versa. In agreement, the 3α-proton resonance appeared in both cases as a relatively narrow signal ($W_{1/2}$ = 7–8 cps) diagnostic for an equatorial hydrogen substituent as required by **15a** and **17a**. Allotment of the 5β,10β-diol structure **15** to isomer $B_2$ follows from its infrared spectral characteristics. Whereas the other five osmium tetroxide products each displayed a single composite band at 1732–1734 $cm^{-1}$ for the 3- and 17-ester functions, diol $B_2$ exhibited well-resolved bands at 1733 and 1745 $cm^{-1}$. The high-frequency band is accounted for by hydrogen bonding to the ether oxygen of the axial 3β-acetate substituent.[17] The required proximate hydroxyl group is provided by structure **15** (**15a**) for isomer $B_2$ in which a 5β-OH group is located 1,3-*syn*, axial to the 3β-ester function.

The second 5,10 adduct, diol $B_3$, is consequently assigned the 5α,10α-diol structure **17** (**17a**).

Diol $B_1$ exhibited nmr signals characteristic of a 9,11 adduct and is assigned the 3β-acetoxy-9β,11β-diol structure **13** (**13a**) on grounds analogous with those given for the 3α-acetoxy-9β,11β-diol **3** (**3a**).

The experiments described to this point constitute abundant proof that the major and minor hydride reduction products (alcohols A and B) from dienone **2** are the 3α and 3β alcohols **8** and **9**, respectively. These products are formed in a ratio of *ca.* 65:35 in favor of the α alcohol; hence the reduction can be thought of as only slightly stereoselective. This implies that ring A of 5(10),9(11)-estradienes is not subject to appreciable conformational control. In agreement, the high values of $W_{1/2}$ (Table I) for alcohols **8** and **9** signify that they exist predominantly as the equatorial alcohols **8a** (OH-3α, H-3β) and **9a** (H-3α, OH-3β), respectively. The higher value of $W_{1/2}$ for epimer **8** indicates a higher degree of ring A conformational homogeneity and

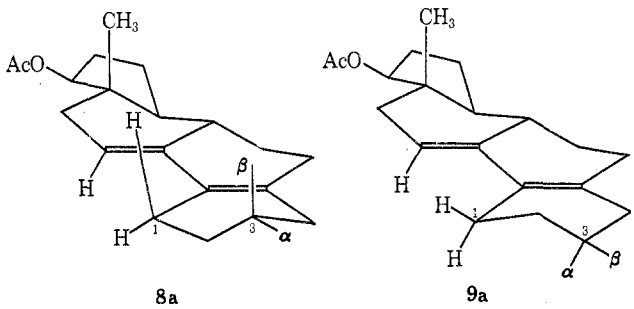
(14) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, Chapter 8.

(15) M. Tomoeda, M. Inuzuka, T. Furuta, and T. Takahashi, *Tetrahedron Lett.*, 1233 (1964).

(16) Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T., Okamoto, and K. Tsuda *Chem. Pharm. Bull.* (Tokyo), **10**, 338 (1962).

(17) F. Dalton, J. I. McDougall, and G. D. Meakins, *J. Chem. Soc.*, 4068 (1963); H. B. Henbest and B. J. Lovell, *ibid.*, 1965 (1957).

hence a greater inherent stability of the half-chair ring-A conformation in **8a** compared with the one seen in **9a**.




**8a** **9a**

We were very interested to find pronounced conformational preference in ring A of the $\Delta^{5(10)}$-9$\beta$,11$\beta$-diol system. The 3$\alpha$- and 3$\beta$-acetoxy epimers **12** and **13** show $W_{1/2}$ values for the C-3 protons of 8 and 21 cps, respectively. These values are appropriate for equatorial and axial protons, respectively, indicating that ring A exists preferentially as shown in **12a** and **13a**. This half-chair ring A conformation is opposite that found[2] in the normal (9$\alpha$) series.

These results, in combination with those described earlier, demonstrate that the nature of conformational preference in ring A of 5(10)-unsaturated steroids is a sensitive function of the structure of the molecule as a whole. We have attempted to rationalize this relationship by comparing our results with predictions from molecular models. In doing so we have considered only nonbonded interactions, since the alternative ring A conformers would necessarily be identical in bond angle strain and torsional strain.

For the $\Delta^{5(10)}$,9$\beta$,11$\beta$-diol system **12a** (**13a**), Dreiding models of the two half-chair ring A conformers disclosed significant nonbonded H–H repulsions in each case. Interaction energies were evaluated[18] from the internuclear distances and summed for each of the alternative ring A conformations. The predicted stability advantage was 1.11 kcal/mol in favor of conformation **12a** (**13a**), in general agreement with our above conclusions based on nmr data.

For the 5(10),9(11)-estradiene system, similar computations led to the prediction of a small preference, 0.26 kcal/mol, in favor of conformation **9a**. We consider this estimate to be erroneous, however, in view of the experimental results cited above as indicating some preference for conformation **8a**. A likely cause of this discrepancy is that our energy assessments were based on standard carbon angles, whereas it is now known[20] that the preferred C–C–C angle is nearer to 111–112°. This error in the molecular models would significantly influence the positions of interacting hydrogen substituents and hence our evaluation of conformational preference in ring A. It may be that only in cases of strong conformational preference[21] can the result be reliably predicted from a conventional molecular model. It is evident that a more accurate approach than the present one is needed for a clear understanding of conformational preference effects in 5(10)-unsaturated steroids.

In conclusion, we would like to refer again to the stereochemistry of osmium tetroxide attack on the 9(11) double bond of estra-5(10),9(11)-dienes **10** and **11**. The exclusive formation of 9$\beta$,11$\beta$ adducts is surprising, since it appears from models that the $\beta$ side is the more hindered. By comparison, addition reactions (epoxidation[22] and hydroboration[23]) to the double bond of $\Delta^{9(11)}$-estrone derivatives occur primarily from the $\alpha$ side. This aspect of estra-5(10),9(11)-diene chemistry will be investigated further.

## Experimental Section

Nmr spectra were measured at 100 Mcps on a Varian HA-100 spectrometer. Optical rotations were taken as 1% solutions in chloroform at 25°. Melting points were determined with a Kofler micro melting point apparatus and are uncorrected. Analytical tlc plate coatings were 0.25 mm thick and were prepared using Brinkmann silica gel G. Preparative tlc plates measured 20 × 20 or 40 × 20 cm and were coated to a thickness of 1.0 mm with silica gel H. The developed preparative plates were freed of solvent and lightly sprayed with water. In most cases this allowed delineation of product zones which appeared opaque (white) on a translucent background. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

**17$\beta$-Hydroxyestra-5(10),9(11)-dien-3-one Acetate (6).**—A solution of pyridinium bromide perbromide (8.55 g) and 17$\beta$-hydroxy-5(10)-estren-3-one acetate (7.7 g) in pyridine (154 ml) was left at 25° for 16 hr. The reaction solution was then added slowly with stirring to cold 20% sulfuric acid. The resulting mixture was extracted with benzene, washed to neutrality with water, dried ($MgSO_4$), and freed of solvent at reduced pressure, leaving an oil (7.1 g): uv max ($CH_3OH$) 302 m$\mu$ ($\epsilon$ 22,900); (isooctane) 285 m$\mu$ ($\epsilon$ 19,000); ir ($CS_2$) 1740 (ester C=O) and 1665 cm$^{-1}$ (conjugated C=O), as expected for 17$\beta$-hydroxyestra-4,9-dien-3-one acetate. All of this product was added to a solution of acetyl chloride (3.60 ml) and methyl orthoformate (7.1 ml) in methanol (710 ml). The reaction mixture was stirred for 5 min at 25° and then mixed with an excess of saturated aqueous $NaHCO_3$. Organic solvents were removed at reduced pressure and the product was extracted into ether, dried ($MgSO_4$), and concentrated, leaving 3,3-dimethoxyestra-5(10),9(11)-dien-17-ol acetate (7.5 g) as an oil: uv max ($CH_3OH$) 234.5 m$\mu$ ($\epsilon$ 21,900) and 241.5 (21,500); (isooctane) 235 m$\mu$ ($\epsilon$ 18,300) and 242 (19,500); ir ($CS_2$) 1735 cm$^{-1}$ (ester C=O); nmr ($CDCl_3$) $\delta$ 5.45 (m, 1, H-11) and 3.18 (br s, 6, $OCH_3$). A solution of the entire product in acetone (226 ml) was stirred with 8% aqueous $H_2SO_4$ (5.66 ml) for 5 min at 26°. The reaction solution was then mixed with 800 ml of ice–water containing suspended celite. The precipitated product, mixed with Celite, was collected by suction filtration, extracted into benzene, washed with water, dried, and freed of solvent, leaving 6.4 g of amorphous product: uv max ($CH_3OH$) 240 m$\mu$ ($\epsilon$ 17,300); (isooctane) 241 m$\mu$ ($\epsilon$ 18,300); ir ($CS_2$) 3030 (H-11), 1733 (ester C=O), and 1720 cm$^{-1}$ (ketone C=O); nmr ($CDCl_3$) $\delta$ 5.53 (m, 1, H-11) in agreement with its formulation as 17$\beta$-hydroxyestra-5(10),9(11)-dien-3-one acetate. This product was homogeneous by tlc but could not be crystallized; it appeared to be very unstable toward autoxidation[24] and was ordinarily prepared just prior to its reduction.

**Estra-5(10),9(11)-diene-3$\alpha$,17$\beta$-diol 17-Acetate (8) and Extra-5(10),9(11)-diene-3$\beta$,17$\beta$-diol 17-Acetate (9).**—A solution of ketone **6** (1.70 g) in tetrahydrofuran (8.5 ml) was slowly added with stirring to a cold (−70°) solution of lithium tri-*t*-butoxyaluminum hydride (6.8 g) in the same solvent (95 ml). After 2.5 hr the reaction mixture was placed in storage at 2° for 16 hr. The solution was then poured into 300 ml of ice–water containing

(18) Following Hendrickson,[19] we calculated hydrogen–hydrogen repulsion energies, $E_{HH}$ from measured internuclear distances, $r$, using the relationship $E_{HH} = 2300\epsilon^{-3.6r} - 49.2/r^6$.

(19) J. B. Hendrickson, *J. Amer. Chem. Soc.*, **89**, 7036 (1967).

(20) R. A. Wohl, *Chimia*, 219 (1964).

(21) Our calculations on the normal 5(10)-estrene system (as **1**) led to the prediction that conformer **3** is more stable than **4** by 1.4 kcal/mol, in agreement with experiment.

(22) K. Tsuda, S. Nozoe, and Y. Okada, *Chem. Pharm. Bull.* (Tokyo), **11**, 1022 (1963).

(23) P. Turnbull, K. Syhora, and J. Fried, *J. Amer. Chem. Soc.*, **88**, 4764 (1966).

(24) This difficulty appears to be general for $\Delta^{5(10),9(11)}$-3 ketones and has been noted even for crystalline derivatives. See ref 8, footnote 3.

10.8 ml of acetic acid. After removal of organic solvent at reduced pressure, the reaction products were extracted into benzene, washed with water, dried, and concentrated, leaving 1.68 g of residue. By tlc, this product was shown to consist primarily of two components, which were present in unequal amount and very close in mobility, $R_f$ (three elutions with $CHCl_3$) 0.33 (major) and 0.40 (minor). A sample (0.1 g) of this product was set aside and the remainder (1.58 g) was subjected to chromatographic separation.

The above mixture was loaded onto a chromatographic column (2.3-cm diameter) packed with alumina activity III (145 g) in 24% carbon tetrachloride–hexane. Elution was performed by a continuous, linear solvent gradient from a 15:20:65% benzene–carbon tetrachloride–hexane mixture to 100% benzene (1600 ml total), then with pure benzene (3500 ml), and finally with 10% ether in benzene. The earliest eluates provided 0.33 g of pure (tlc) 3β alcohol **9**, which crystallized from cold ether as fine needles: mp 88–90°; $[\alpha]^{27}D$ +103°; uv max (isooctane) 235 mμ (ε 20,000), 242 (21,000), and 250 (infl, 13,000); ir ($CS_2$) 3610 (OH), 3030 (H-11), and 1735 $cm^{-1}$ (ester C=O); nmr ($CDCl_3$) δ 5.46 (m, 1, H-11), 4.71 (t, 1, H-17α), 3.98 (m, 1, H-3α), 2.06 (s, 3,$OCOCH_3$), and 9.80 (s, 3, $CCH_3$).

*Anal.* Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.93. Found: C, 75.72; H, 8.94.

Treatment of the 3β alcohol **9** with acetic anhydride in pyridine at room temperature produced the 3β,17β diacetate **11**: mp 107–109°; $[\alpha]D$ +84.0°; ir ($CS_2$) 1735 $cm^{-1}$ (ester C=O); nmr ($CDCl_3$) δ 5.52 (m, 1, H-11), 5.03 (m, 1, H-3α), 4.72 (t, 1, H-17α), 2.04 (s, 3, $OCOCH_3$), 2.02 (s, 3, $OCOCH_3$), and 0.82 (s, 3, $CCH_3$).

*Anal.* Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 74.01; H, 8.53.

Continued elution provided a series of mixture fractions (0.147 g total) which were assayed by tlc both individually and after combining; they were found to contain only alcohols **8** and **9** and in approximately equal amount.

Subsequent benzene eluants provided 0.651 g of pure (tlc) 3α alcohol **8**, which crystallized from cold ether as needles: mp 148–149.5°; $[\alpha]D$ +217°; uv max (isooctane) 235 mμ (ε 20,000), 242 (21,000) and 250 (infl, 13,000); ir ($CS_2$) 3615 (OH), 3030 (H-11), and 1734 $cm^{-1}$ (ester C=O); nmr ($CDCl_3$) δ 5.46 (m, 1, H-11), 4.70 (t, 1, H-17α), 3.87 (m, 1, H-3β), 2.04 (s, 3, $OCOCH_3$), and 0.79 (s, 3, $CCH_3$).

*Anal.* Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.93. Found: C, 75.75; H, 8.78.

Treatment of the 3α alcohol **8** with acetic anhydride in pyridine at room temperature produced the 3α,17β diacetate **10**: mp 134–135.5°; $[\alpha]D$ +182°; ir ($CS_2$) 3030 (H-11) and 1732–1740 $cm^{-1}$ (ester C=O); nmr ($CDCl_3$) δ 5.53 (m, 1, H-11), 4.95 (m, 1, H-3β), 4.73 (t, 1, H-17α), and 2.02 (s, 3, $OCOCH_3$).

*Anal.* Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.92; H, 8.46.

**5(10)-Estrene-3α,9β,10β,17β-tetrol 3,17-Diacetate (12), 9(11)-estrene-3α,5β,10β-17β-tetrol 3,17-Diacetate (14), and 9(11)-estrene-3α,5α,10α,17β-tetrol 3,17-Diacetate (16).**—A solution of diene **10** (0.360 g) and osmium tetroxide (0.295 g) in benzene (6 ml) and pyridine (0.2 ml) was stored at 26° for 16 hr, cooled to 0°, and saturated with hydrogen sulfide. The black precipitate was collected on a celite pad and washed with ethyl acetate. The combined filtrates were washed thoroughly with water and freed of solvent, leaving 0.299 g of residue. Assay by tlc (two elutions with 30% acetone in carbon tetrachloride) revealed three components, **12**, **14**, and **16**, having $R_f$ values of 0.67, 0.74, and 0.82, respectively.

The total material was chromatographed on a column (2.3-cm diameter) packed with alumina activity III (140 g) in benzene. Elution was by continuous solvent gradient (linear) from benzene to 10% isopropyl alcohol in benzene (1400-ml total). The early eluates gave 0.070 g of pure (tlc) 5α,10α-diol **16**: mp 182.5–183.5° (from ether); ir ($CS_2$) 3540–3600 (OH) and 1732 $cm^{-1}$ (ester C=O); nmr ($CDCl_3$) δ 5.95 (m, 1, H-11), 4.85 (m, 1, H-3β), 4.70 (m, 1, H-17α), 2.02 (s, 3, $OCOCH_3$), 2.04 (s, 3, $OCOCH_3$), and 0.75 (s, 3, $CCH_3$).

*Anal.* Calcd for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 67.14; H, 8.27.

Later eluents from the chromatography column provided 0.035 g of the 5β,10β-diol **14**, slightly contaminated (tlc) with the β adduct **16**. One recrystallization from ether gave pure **14**: mp 181.0–182.5°; ir ($CS_2$) 3540–3600 (OH) and 1733 $cm^{-1}$ (ester C=O); nmr ($CDCl_3$) δ 5.75 (m, 1, H-11), 5.15 (m, 1, H-3β), 4.70 (m, 1, H-17α), 2.04 (s, 3, $OCOCH_3$), 2.00 (s, 3, $OCOCH_3$), and 0.77 (s, 1, $CCH_3$).

*Anal.* Calcd for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 67.03; H, 8.28.

Subsequent eluents furnished 0.150 g of a mixture of approximately equal amounts of **14** and **12**. Separation was accomplished by preparative tlc employing 30% acetone in carbon tetrachloride as eluent. This provided pure 9β,11β-diol adduct **12**: mp 131.5–133°; ir ($CS_2$) 3540–3600 (OH) and 1733 $cm^{-1}$ (ester C=O); nmr ($CDCl_3$) δ 5.08 (m, 1, H-3β), 4.72 (m, 1, H-17α), 4.11 (m, 1, H-11α), 208 (s, 6, $OCOCH_3$), and 1.15 (s, 3, $CCH_3$).

*Anal.* Calcd for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 67.12; H, 8.24.

**5(10)-Estrene-3β,9β,11β,17β-tetrol 3,17-Diacetate (13),5(10)-Estrene-3β,5β,10β,17β-tetrol 3,17-Diacetate (15), and 5(10)-Estrene-3β,5α,10α,17β-tetrol 3,17-Diacetate (17).**—A solution of diene **11** (0.129 g) and osmium tetroxide (0.110 g) in benzene (7 ml) was stored in the dark at 26° for 2 days. Work-up was performed as described above for the similar reaction with diene **10**. The total product mixture amounted to 0.131 g. Assay by tlc employed as eluent a solution of ethyl acetate (10%) and isopropanal (2.5%) in chloroform and revealed three components, **13**, **15**, and **17**, having $R_f$ values of 0.46, 0.55, and 0.41, respectively. Separation of these compounds by preparative tlc employed the same solvent system but two successive elutions. A 0.065-g sample of the mixture thus provided **13** (0.012 g), **15** (0.008 g), and **17** (0.019 g); additional quantities of these products were prepared in the same way and corresponding samples were pooled prior to recrystallization.

The 9β,11β-diol adduct **13** was recrystallized from $CH_3OH$: mp 184–194° (with evolution of gas); ($CS_2$) 3540–3600 (OH) and 1733 $cm^{-1}$ (ester C=O); nmr ($CDCl_3$) δ 4.80 (m, 1, H-3α), 4.72 (m, 1, H-17α), 4.17 (t, 1, H-11α), 2.02 (s, 6, $OCOCH_3$), and 1.08 (s, 1, $CCH_3$).

*Anal.* Calcd for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 67.26; H, 8.37.

The 5β,10β-diol adduct **15** was recrystallized from ether–hexane: mp 144.5–146°; ir ($CS_2$) 3560, 3520 (hydrogen-bonded OH), 3040 (H-11), 1745 (3-ester C=O, hydrogen bonded), and 1732 $cm^{-1}$ (17 ester); nmr ($CDCl_3$) δ 5.78 (m, 1, H-11), 5.12 (m, 1, H-3α), 4.70 (m, 1, H-17α), 2.06 (s, 3, $OCOCH_3$-17), 2.10 (s, 3, $OCOCH_3$-3), and 0.84 (s, 3, $CCH_3$).

*Anal.* Calcd for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 67.05; H, 8.31.

The 5α,10α-diol adduct **17** was recrystallized from aqueous methanol: mp 154–156°; ir ($CS_2$) 3550–3600 (OH), 3030 (H-11), and 1735 $cm^{-1}$ (ester C=O); nmr ($CDCl_3$) δ 5.96 (m, 1, H-11), 5.14 (m, 1, H-3), 4.70 (H-17), and 2.07 (br s, 6, 2 $OCOCH_3$).

*Anal.* Calcd for $C_{22}H_{32}O_6 \cdot {}^1/_2H_2O$: C, 65.80; H, 8.28. Found: C, 65.94; H, 8.31.

**Registry No.**—**6**, 22841-97-0; **8**, 22841-99-2; **9**, 22842-00-8; **10**, 22842-01-9; **11**, 22842-02-0; **12**, 22842-03-1; **13**, 22922-36-7; **14**, 22842-04-2; **15**, 22842-05-3; **16**, 22842-06-4; **17**, 22842-07-5; 3,3-dimethoxyestra-5(10),9(11)-dien-17β-ol acetate, 22841-98-1.