Anal. Calcd for $C_{16}H_{23}NO_8$: C, 53.77; H, 6.48; N, 3.92. Found: C, 53.50; H, 6.22; N, 4.07.

F. Derivatives of DL-(1,2,4/3,5)-5-Amino-1,2,3,4-cyclopentanetetrol (18, 27, and 28). Tetra-*O*-acetyl-DL-(1,2,4/3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (18). 1. From 6 or 5.—A mixture of 0.23 g (0.55 mmol) of 6 (or the molar equivalent of mesylate 5) and sodium acetate (0.1 g) was refluxed in water (10 ml) for 2 hr and evaporated. The residue was acetylated and the product was crystallized in ether to give 0.12 g (63%) of 18, mp 108–110°. Recrystallization from the same solvent raised the melting point to 111–112°. Mixture melting points with the pentaacetyl derivatives of configuration 1,2,3,5/4 (14, mp 123–124°), as well as 1,2,3,4/5 (15, mp 145–146°) and 1,4/2,3,5 (mp 148.5–149°) showed marked depression in each case; for nmr *cf.* Table I.

Anal. Calcd for $C_{15}H_{21}NO_9$: C, 50.11; H, 5.90; N, 3.90. Found: C, 50.53; H, 6.02; N, 3.84.

2. From 12 or 13.—A mixture of 0.85 g (1.41 mmol) of 13 (or the molar equivalent of 12), sodium acetate (0.3 g), and water (40 ml) was refluxed for 17 hr. Evaporation, acetylation, and work-up in the same manner as described under 1 afforded 0.44 g (67%) of 18, identical in all respects with the product described above.

DL-(1,2,4/3,5)-5-Acetamido-1,2,3,4-cyclopentanetetrol (27).—Compound 18 was de-O-acetylated with methanolic ammonia as described for 22 and the syrupy product obtained after evaporation was extracted with hot ethyl acetate. Only part of the residue which was insoluble in ethyl acetate, showing a single spot on tlc, could be induced to crystallization on trituration with 4:1 2-propanol–ethanol; 36 mg (43%) of colorless crystals, mp 142–144°, was obtained.

Anal. Calcd for $C_7H_{13}NO_5$: C, 43.83; H, 6.86; N, 7.28. Found: C, 44.31; H, 7.01; N, 7.38.

3,4-Di-*O*-acetyl-1,2-*O*-isopropylidene-DL-(1,2,4/3,5)-5-acetamido-1,2,3,4-cyclopentanetetrol (28).—Compound 27 (70 mg) was treated in *N,N*-dimethylformamide (3.5 ml) with 2,2-dimethoxypropane (0.20 ml) and *p*-toluenesulfonic acid (3 mg) for 3 hr at room temperature. Neutralization, acetylation, and work-up as described above for 26 gave a syrup which crystallized from ether: 50 mg (44%) of colorless crystals; mp 135–136°; nmr τ 8.71 and 8.43 [two s, 3 H, $C(CH_3)_2$], 8.01 (s, 3 H, HNAc), 7.94 and 7.92 (two s, 3 H, 2 OAc).

Anal. Calcd for $C_{14}H_{21}NO_7$: C, 53.32; H, 6.71; N, 4.44. Found: C, 53.37; H, 6.63; N, 4.45.

G. Tetra-*O*-acetyl-(1,2,3,4,5/0)-5-acetamido-1,2,3,4-cyclopentanetetrol (34).—A mixture (0.25 g) of the mono- and di-*O*-mesyl derivatives (31 and 32), as obtained on mesylation of 30 (*cf.* section C), was heated in water (10 ml) in the presence of sodium acetate (0.12 g) for 8 hr and subsequently evaporated. The residue was acetylated to give a syrupy mixture of 33 and 34, which was chromatographed on a silica gel column (Wakogel C-200, 30 g) in 5:1 benzene–ethanol. Fractions showing R_f 0.39 (tlc) were combined and evaporated to dryness. The residue was crystallized in ethanol to give 34 (17 mg, 6% from 30), mp 173–174°. The product was identified by a comparison of ir spectra and a mixture melting point determination with an authentic sample of 34, prepared by another route.[5]

H. Tetra-*O*-acetyl-DL-(1,2,4,5/3)-5-acetamido-1,2,3,4-cyclopentanetetrol (33).—Those fractions of the above column separation exhibiting a spot at R_f 0.41 (tlc) were pooled and evaporated to dryness. The residue was crystallized in ethyl acetate–petroleum ether to give 33 (60 mg, 22% from 30), mp 160–161°. Recrystallization from the same solvent yielded the analytically pure sample, mp 162–163.5°. Admixture with the 1,3,5/2,4 analog 17 (mp 161.5–162.5°) showed a distinct depression of the melting point.

Anal. Calcd for $C_{15}H_{21}NO_9$: C, 50.11; H, 5.90; N, 3.90. Found: C, 50.35; H, 5.80; N, 3.97.

Acknowledgments.—The authors wish to express their appreciation to the Japan Ministry of Education for supporting this investigation and the Japan Society for the Promotion of Science for granting a visiting professorship (to F. W. L.). We are also indebted to Professor H. Z. Sable for kindly performing the comparative measurements.

Registry No.—3, 41476-97-5; 4, 34081-56-6; 5, 41476-99-7; 6, 41477-00-3; 7, 41477-01-4; 8, 41477-02-5; 9, 41477-03-6; 10, 41477-04-7; 11, 41477-05-8; 12, 41477-06-9; 13, 41477-07-0; 14, 41477-08-1; 15, 41477-09-2; 16, 29799-76-6; 17, 41477-11-6; 18, 14086-55-6; 19, 41477-13-8; 20, 41477-14-9; 21, 41477-15-0; 22, 41477-16-1; 24, 41477-17-2; 25, 41477-18-3; 26, 41477-19-4; 27, 41477-20-7; 28, 16171-79-2; 29, 29799-77-7; 30, 41477-23-0; 33, 41477-24-1; 34, 34081-53-3; mesyl chloride, 124-63-0; tosyl chloride, 98-59-9; 2,2-dimethoxypropane, 77-76-9; *p*-toluenesulfonic acid, 104-15-4.

Synthesis of Some 17-Substituted 3,10-Ethano-5α-estranes[1]

FRANK M. HAUSER, ABRAHAM PHILIP, AND F. I. CARROLL*

Chemistry and Life Sciences Division, Research Triangle Institute, Research Triangle Park, North Carolina 27709

Received June 6, 1973

Several 17-substituted derivatives of 3-hydroxy-3,10-ethano-5α-estrane were prepared. The synthetic sequence centers about the transformation of dehydroisoandrosterone 3-acetate (4a) into a 19a-methylandrostane-3,17,19-trione (7e). Treatment of 7e with ethanolic potassium hydroxide effected an internal condensation of the 19a-methyl ketone with the 3-ketone moiety to give 3,10-[2′-oxoethano]-5α-estran-3-ol-17-one (9b). Selective reduction of 9b with lithium tri-*tert*-butoxyaluminum hydride afforded 3,10-[2′-oxoethano]-5α-estran-17-ol (9c). Wolff–Kishner reduction of 9c under forcing conditions gave 3,10-ethano-5α-estrane-3,17-diol (10a) which served as starting material for the synthesis of the 17-substituted 3,10-ethano-5α-estranes. The circular dichroism properties of the 3,10-[2′-oxoethano]-5α-estranes with various 17 substituents were studied. The sign of the Cotton effect can be explained if both the back and front octants are considered.

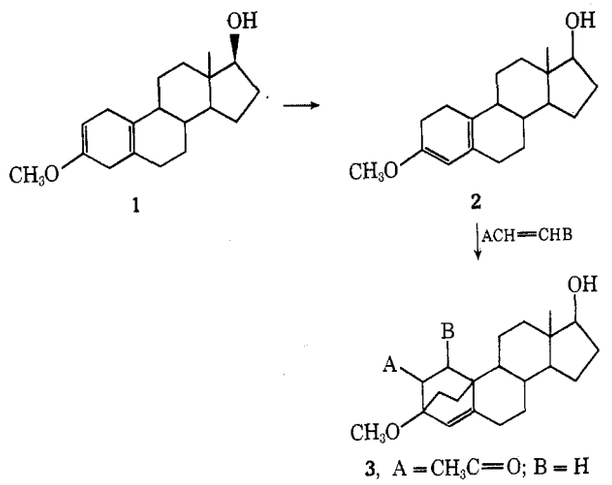
The literature contains but one report on the synthesis of 3,10-ethanoestranes, and this was by Birch and coworkers.[2] In order to more fully investigate the chemical and physical properties of these steroid derivatives, as well as to study their biological effects, we undertook the synthesis of the parent steroid and several 17-substituted derivatives. The Birch synthesis of 3,10-ethanoestranes, shown in Chart I, was accomplished by first isomerizing 1,4-dihydroestradiol 3-methyl ether (1) to a mixture of 1,4- and 1,2-dihydroestradiol 3-methyl ether (1 and 2), followed by a Diels–Alder reaction on the conjugated diene steroid 2 with methyl vinyl ketone to furnish the ethanoestrane adduct 3.[2]

Our initial synthetic efforts followed the precedent set down by Birch and coworkers.[2] We found that the isomerization of 1 to 2 using Triton B catalyst in dimethyl sulfoxide was superior to the method reported by Birch; however, we were unsuccessful in obtaining

(1) This investigation was supported by Contract NIH-71-2457 from the Contraceptive Development Branch Center for Population Research, National Institute of Child Health and Human Development, National Institutes of Health.

(2) A. J. Birch and B. McKague, *Aust. J. Chem.*, **23**, 341 (1970).

CHART I



3, A = $CH_3C{=}O$; B = H

Diels–Alder adducts from the diene mixture. Attempts to thermally isomerize 1,4-dihydroestradiol (**1**) to 1,2-dihydroestradiol (**2**) in a sealed tube in the presence of a dienophile as a trapping agent were also unsuccessful.

An alternate, although longer sequence, which started with dehydroisoandrosterone 3-acetate (**4a**) was devised. The sequence involved the conversion of **4a** to a 19a-methyl-3,19-diketo derivative which could be internally condensed to yield the desired A-ring bicyclo[2.2.2]octanone compound. Thus, dehydroisoandrosterone (**4a**) was converted into the known bromohydrin[3] **5** with *N*-bromoacetamide in aqueous dioxane and perchloric acid. Compound **5** was then photolyzed at reflux in benzene or carbon tetrachloride with iodine and lead tetraacetate to furnish the 6,19 ether **6a** in high yield.[4] For convenience as well as to include the possibility of manipulating various ketones later in the synthetic sequence, **6a** was converted to the ketal derivative **6b**. It was necessary to reacetylate after the ketalization, since the appearance of 3500 cm^{-1} hydroxy absorption in the infrared spectrum and only a weak singlet at 2.06 ppm in the pmr spectrum indicated that some of the 3 acetate was lost in the reaction. In our initial attempts to convert the 19,6 ether **6b** to the olefinic alcohol **4b** employing published procedures,[5] we noticed that the singlet at 2.00 ppm for the 3 acetate integrated for too few protons, indicating that formation of **4c** by cleavage of the 3 acetate was occurring. Alternatively, it was found that **6b** could be converted to **4b** in 82% yield by treating **6b** with either acid-washed zinc dust or zinc–copper couple[6] for 10 min in refluxing 2-propanol. Attempts to oxidize the 19 alcohol **4b** to the 19 aldehyde **4d** with chromium trioxide in pyridine gave poor yields. However, employing the Collins reagent,[7] which uses methylene chloride as the reaction solvent, we were able to consistently oxidize **4b** to pure aldehyde **4d** in high yield (70–80%). The pmr spectrum in chloroform-d_1 shows two absorptions at 9.60 and 9.61 ppm in a ratio of 1:2 for the aldehydic proton. This probably represents two geometric configurations of the 19 aldehyde.

Methyllithium addition to the 19 aldehyde of **4d** occurred with concomitant cleavage of the acetate and furnished the diol **4e**. An inspection of the pmr spectra indicated that the product was a mixture of diastereoisomers, most probably resulting from stereospecific addition of methyllithium to the two aldehyde geometric isomers. The 18-methyl groups of mixture **4e** appeared as two absorptions in a ratio of 2:1. In addition, the 19a-methyl absorptions appeared as two doublets centered at 1.37 and 1.40 ppm, respectively, with J = 6 Hz for both isomers in a ratio of 2:1. No attempt was made to separate these isomers, but rather the sample was subjected directly to hydrogenation. The olefinic diol **4e** was nearly inert to reduction; however, after various catalysts and solvents were tried, it was determined that 20% palladium hydroxide on carbon in 2-propanol–ethanol gave optimum yields of material in which the $\Delta^{5,6}$ double bond had been reduced. The appearance of a 1750-cm^{-1} absorption in the infrared spectrum of the crude product indicated that some hydrolysis of the 17-ketal group had occurred during hydrogenation. The reduction product was reketalized to furnish **7a**, and then, without prior purification, oxidized with the Collins reagent to the crude diketo ethylene ketal compound **7b**. Thin layer chromatography of this initial material indicated that at least two major compounds were present. Column chromatography of the mixture furnished both **7b** and **7c**.

The structure of **7b** was readily established from its infrared and pmr spectra. Absorptions at 1715 and 1695 cm^{-1} were observed for both the 3 and 19 ketones, and the presence of a singlet at 2.12 ppm in the pmr spectrum for the 19a-methyl confirmed the structure assignment.

The structure of **7c** was also established by examination of the infrared and pmr sepctra. The infrared spectrum of **7c** showed only a 1690-cm^{-1} carbonyl absorption; however, this did not accurately establish whether the 3 or 19 ketone function was now missing. A singlet at 2.28 ppm in the pmr spectrum for the 19a-methyl of **7c** clearly indicated that the 3 ketone function was missing. As well, the absence of other functional groups and the elemental analysis of **7c** indicated that hydrogen replacement of the 3 functionality had occurred. Compound **7c** could have been formed by catalytic isomerization of the $\Delta^{5,6}$ olefin to the $\Delta^{4,5}$ position, hydrogenolysis of the 3-hydroxyl, and then reduction of the $\Delta^{4,5}$ double bond. Alternatively, **7c** could have been formed by reduction of a solvolytic intermediate such as **8** or its products.

Treatment of **7b** with alcoholic potassium hydroxide for 5 min resulted in the quantitative formation of a new product whose infrared spectrum showed a new 3500- and a 1710-cm^{-1} absorption. As well, the singlet at 2.12 ppm for the 19a-methyl was not present in the pmr spectrum of the new compound. These data were consistent with the formulation of the new product as 3,10-[2′-oxoethano]-5α-estran-3-ol-17-one 17-ethylene ketal (**9a**).

Experimentally it proved simpler to deketalize rather than reketalize the crude product from reduction of

(3) V. Grenville, D. K. Patel, V. Petrow, I. A. Stuart-Webb, and D. M. Williamson, *J. Chem. Soc.*, 4105 (1954).

(4) V. I. Maksimov, F. A. Luri, N. V. Samsonova, and L. S. Morozova, *Khim-Farm. Zh.*, **4** (2), 5 (1970).

(5) O. Halpern, I. Delfin, L. Magana, and A. Bowers, *J. Org. Chem.*, **31**, 693 (1966).

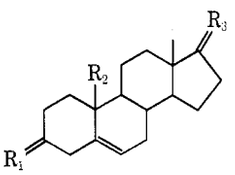
(6) E. LeGoff, *J. Org. Chem.*, **29**, 2048 (1964).

(7) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).

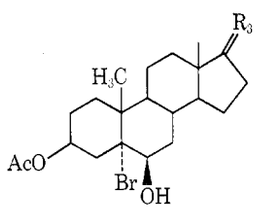
4e. This product, without purification, was directly oxidized to a mixture of triketone **7e** and diketone **7f**. Triketone **7e** could then be directly isolated by crystallization. Chromatography of the filtrates afforded additional quantities of **7e** and also the hydrogenolysis product **7f**. The infrared spectrum of **7e** showed absorptions at 1735, 1715, and 1695 cm^{-1} while **7f** showed only absorptions at 1735 and 1690 cm^{-1}. Analogous to the reaction of **7b**, treatment of **7e** with alcoholic potassium hydroxide afforded a near quantitative conversion to 3,10-[2′-oxoethano]-5α-estran-3-ol-17-one (**9b**).

Since the 17-ketal function was removed, it was necessary to manipulate either the 2′ or 17 ketone functions of **9b** so that the 2′ ketone could then be selectively removed. Examination of molecular models of **9b** indicated that the 2′-oxo position was extremely sterically hindered and quite probably a 17-keto functionality could be easily manipulated in its presence. Indeed, we found that the product **9c** from treatment of **9b** with 1 equiv of lithium tri-*tert*-butoxyaluminum hydride had no 1735-cm^{-1} absorption, but did retain the 1710-cm^{-1} peak in its infrared spectrum. In fact, the 2′ ketone function is so sterically hindered that selective reduction of the 17 ketone to furnish the 17-hydroxy compound **9c** can be accomplished with no reduction of the 2′-oxo moiety even when a large excess of reducing agent is employed.

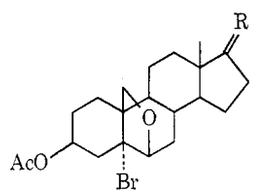
Initial attempts to reductively convert the 2′ ketones **9a** or **9c** to the corresponding methylene unit by formation of the tosylhydrazone followed by reduction with sodium borohydride were unsuccessful. The 2′-oxo position is so severely sterically hindered that the tosylhydrazone derivatives could not be formed under forcing conditions. Wolff–Kishner reduction of **9c**, employing the Huang-Minlon method for reduction of sterically hindered 11-keto steroids,[8] afforded a high yield of the ethanoestrane **10a**. Since Nagata and Itazaki[8] had successfully reduced steroid 11-keto groups in the presence of a 17-ketal moiety using the indicated conditions, we treated the ketal **9a** under similar conditions. However, the only product isolated from this reaction was 3,10-ethano-5α-estran-3-ol (**10b**). Oxidation of **10a** afforded a high yield of ketone **10c**. Ethynylation of ketone **10c** with lithium acetylide–ethylenediamine complex afforded the bicyclic 17α-ethynyl-17β-hydroxy compound **10d**.



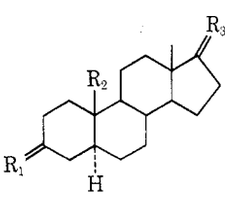
4a, R_1 = H,OAc; R_2 = CH_3; R_3 = O
b, R_1 = H,OAc; R_2 = CH_2OH; R_3 = OCH_2CH_2O
c, R_1 = H,OH; R_2 = CH_2OH; R_3 = OCH_2CH_2O
d, R_1 = H,OAc; R_2 = CHO; R_3 = OCH_2CH_2O
e, R_1 = H,OH; R_2 = $HOCHCH_3$; R_3 = OCH_2CH_2O



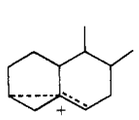
5



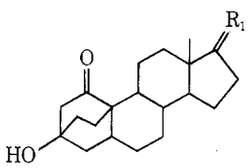
6a, R = O
b, R = OCH_2CH_2O



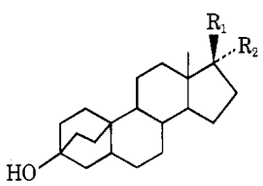
7a, R_1 = H,OH; R_2 = $HOCHCH_3$; R_3 = OCH_2CH_2O
b, R_1 = O; R_2 = O=CCH_3; R_3 = OCH_2CH_2O
c, R_1 = H,H; R_2 = O=CCH_3; R_3 = OCH_2CH_2O
d, R_1 = H,OH; R_2 = $HOCHCH_3$; R_3 = O
e, R_1 = O; R_2 = O=CCH_3; R_3 = O
f, R_1 = H,H; R_2 = O=CCH_3; R_3 = O



8



9a, R_1 = OCH_2CH_2O
b, R_1 = O
c, R_1 = α-H,β-OH



10a, R_1 = OH; R_2 = H
b, R_1 = R_2 = H
c, R_1 = R_2 = O
d, R_1 = OH; R_2 = C≡CH

The ORD and/or CD properties of only a few optically active bicyclo[2.2.2]octanones have been reported in the literature.[9-11] The back octant rule method[12] has been used to explain the sign of the Cotton effect in some cases[10,11] while other examples were explained by their antioctant behavior or the Horeau method.[9] Since no generally accepted method for the correlation of the sign of the Cotton effect exhibited by bicyclo[2.2.2]octanones and their absolute stereochemistry is yet available, we wish to report our observations with steroid A-ring bicyclo[2.2.2]octanones.

The CD spectra of **9a**, **9b**, and **9c** are shown in Figure 1. As shown in these curves, the long-wavelength Cotton effect due to the bicyclo carbonyl n–π^* transitions are all weakly negative. In the case of compound **9b** this effect is obscured by the large positive Cotton effect due to the 17-carbonyl moiety. The octant rule can be used to explain this observation.

If one considers the cyclohexanone ring formed by carbons 1, 1′, 2, 2′, 3, and 10 in these compounds, then

(8) W. Nagata and H. Itazaki, *Chem. Ind. (London)*, 1194 (1964).
(9) D. Warech and J. Jacques, *Tetrahedron*, **28**, 5671 (1972).
(10) G. Snatzke, *Tetrahedron Lett.*, 4275 (1972).
(11) P. Crabbé, L. H. Zalkow, and N. N. Girotra, *J. Org. Chem.*, **30**, 1678 (1965).
(12) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, **83**, 4013 (1961).

the observed negative Cotton effect is inconsistent with the octant rule when only the back octants are considered. Carbon atom 5 is severely skewed in a positive octant and is enhanced by carbon atom 6, also in a positive octant. These contributions are only partly canceled by carbon atom 1 in a negative octant. However, an examination of the geometry of these steroid A-ring bicyclo[2.2.2]octanones with Dreiding molecular models indicates that it is necessary to also consider the front octants.[12] Since carbon atoms 7, 14, 15, and 16 fall into a negative front octant and are only partly canceled by carbon atoms 11 and 12 in a positive front octant, one would predict a relatively large negative front octant effect. This negative front octant effect would be only partially canceled by the smaller positive back octant effects, and one would then predict that the 3,10-[2′-oxoethano]-5α-estranes **9a** and **9c** would show small negative n–π* Cotton effects. Thus, the compounds **9a** and **9c** give an excellent example of the use of the front octant method to explain the observed Cotton effect.[13]

In addition to the relatively strong negative Cotton effect exhibited by compounds **9a** and **9c**, one also observes two weaker Cotton effects at lower wavelengths. No satisfactory explanation has been found for this observation, and only tentative interpretation, such as solvation, may be suggested.

Experimental Section

Melting points were taken on a Kofler hot-stage microscope and are uncorrected. Infrared spectra were measured with a Perkin-Elmer 221 spectrophotometer. Ultraviolet spectra were run in methanol on a Cary Model 14 recording spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian Model A-100, using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in δ units. Rotations were determined with a Perkin-Elmer Model 141 polarimeter. CD measurements were made with a Jasco Model-20 spectropolarimeter at ambient temperature. Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Ill.

3β-Acetoxy-19-hydroxyandrost-4-en-17-one Ethylene Ketal (4b).—Steroid **6b**[5] (40 g, 0.085 mmol) was treated with Zn–Cu couple[6] for 10 min in refluxing 2-propanol. The hot solution was immediately filtered, and the residue was washed with chloroform. After evaporation of the solvent, the residue was taken up in chloroform and water, and washed with saturated ammonium chloride and then with water. The solution, after drying ($MgSO_4$), was evaporated, and the residue was recrystallized from acetone–hexane to yield 27.3 g (82%) of pure **4b**, mp 143–144° (lit.[5] mp 143.5–144.5°).

3β-Acetoxy-19-oxoandrost-4-en-17-one Ethylene Ketal (4d).—Chromium trioxide (47 g) was slowly added to a mechanically stirred solution of pyridine (80 ml) in methylene chloride (1500 ml) under nitrogen.[7] After the solution was stirred for 15 min, steroid **4b** (28 g, 0.072 mol) in methylene chloride (100 ml) was rapidly added dropwise; then the solution was stirred for an additional 15 min. After the methylene chloride layer was decanted, the tarry residue was leached with ether (4 × 300 ml) and the combined organic layers were washed with water (2 × 400 ml), 2% sodium hydroxide (4 × 200 ml), and water until neutral. The organic layer was dried (Na_2SO_4), filtered through Celite, and evaporated to dryness at reduced pressure. The crude product was recrystallized from acetone–water to yield 21.5 g (77%) of pure **4d**: mp 149–151° (lit.[5] mp 148°); ir (KBr) 1725 (CHO) and 1745 cm^{-1} (RCO_2R); nmr ($CDCl_3$) δ 0.84 (s, 3, CH_3), 2.10 [s, 3, $OC(=O)CH_3$], 3.86 (m, 4, $-OCH_2CH_2O-$), 5.85 (m, 1, =CH), and 9.61 ppm (d, 1, CHO).

3,19-Dihydroxy-19-methylandrost-5-en-17-one 17-Ethylene Ketal (4e).—Methyllithium (30 ml, 1.6 *M*) was added dropwise to a magnetically stirred dry ether (100 ml) suspension of aldehyde **4d** (5.6 g, 0.014 mol) under nitrogen. On completion of the addition, the ether solution was refluxed for an additional 30 min, then stirred overnight.

The excess methyllithium was decomposed by dropwise addition of water. Ethyl acetate (200 ml) and water (100 ml) were added to dissolve the residue, and the aqueous phase was extracted with additional ethyl acetate (2 × 200 ml). The combined extracts were washed with water (2 × 100 ml), dried (Na_2SO_4), evaporated, and recrystallized (methylene chloride–hexane) to give 4.8 g (94%) of **4e**: mp 179–180°; ir ($CHCl_3$) 3500 cm^{-1} (OH); nmr ($CDCl_3$) δ 0.91 and 0.93 (s, 3, 18-CH_3), 1.37 (d, ~2, J = 6 Hz, 19a-CH_3), 1.40 (d, ~1, J = 6 Hz, 19a-CH_3), 3.4 (m, 4, $-OCH_2CH_2O-$), and 5.63 ppm (m, 1, =CH). Nmr indicated the presence of two isomers.

Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.88; H, 9.45. Found: C, 72.77; H, 9.52.

19a-Methyl-5α-androstane-3,17,19-trione 17-Ethylene Ketal (7b).—A solution of **4e** (10.5 g, 0.029 mol) in 2-propanol (150 ml) and absolute ethanol (100 ml) was stirred with palladium hydroxide on carbon (2.5 g, 35%) under hydrogen for 1 hr. The catalyst was removed by filtration and the filtrate was evaporated to dryness: ir ($CHCl_3$) 1750 cm^{-1}; nmr indicates no vinyl hydrogens.

The residue and *p*-toluenesulfonic acid (250 mg) were dissolved in ethylene glycol (60 ml) and benzene (150 ml) and refluxed with water removal employing a Dean–Stark trap. After cooling, the reaction was diluted with water (500 ml) and extracted with ethyl acetate. The combined organic layers were washed with dilute bicarbonate and water, then dried (Na_2SO_4) and evaporated to dryness under reduced pressure to give crude **7a** (10.1 g).

Compound **7a** was dissolved in methylene chloride (15 ml) and added to a well-stirred solution of chromium trioxide (48 g) in methylene chloride (1.2 l.) and pyridine (60 ml), then stirred for 1 hr. The methylene chloride solution was decanted from the tarry residue, which was then thoroughly washed with methylene chloride. The combined methylene chloride solutions were repeatedly washed with water until the water washings were no longer dark. After drying (Na_2SO_4), the methylene chloride was removed at reduced pressure to give a light brown solid (8.8 g). The residue was chromatographed on alumina (activity III, 800 g). After washing with benzene (1 l.), the column was eluted with 5% ethyl acetate to furnish 19a-methyl-5α-androstane-17,19-dione 17-ethylene ketal (**7c**) (1.55 g, 15.4%): mp 93–94° [petroleum ether (bp 30–60°)]; ir ($CHCl_3$) 1690 cm^{-1} (19-C=O); nmr ($CDCl_3$) δ 0.98 (s, 3,18-CH_3), 2.12 (s, 3,19a-CH_3), and 3.86 ppm (b, m, 4, $-OCH_2CH_2O-$).

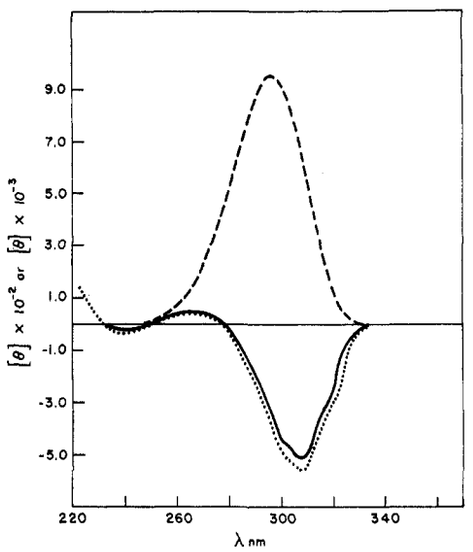


Figure 1.—The CD spectra of **9a** (——) and **9c** (· · · ·), ordinate = [θ] × 10^{-2}, and **9b** (- - - -), ordinate = [θ] × 10^{-3}, in methanol.

(13) In the steroid A-ring bicyclooctanones the ring containing the carbonyl moiety is a cyclohexane ring in the boat conformation. Therefore, since the octant rule has been based mainly for cyclohexanones in the chair conformation, this explanation will have to be considered tentative until additional information becomes available concerning the application of the octant rule to cyclohexanes in nonchair conformations.

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.22; H, 10.01.

Further elution with 7.5% ethyl acetate gave 19a-methyl-5α-androstane-3,17,19-trione 17-ethylene ketal (**7b**) (5.3 g, 50.8%): mp 148–151° (acetone–hexane); ir ($CHCl_3$) 1695 (19-C=O), 1715 cm^{-1} (3-C=O); nmr ($CDCl_3$) δ 0.80 (s, 3, 18-CH_3), 2.28 (s, 3, 19a-CH_3), and 3.86 ppm (d, 4, $-OCH_2CH_2O-$).

Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.29; H, 8.95. Found: C, 73.41; H, 9.22.

3,10-[2′-Oxoethano]-5α-estran-3-ol 17-Ethylene Ketal (9a).—A solution of **7b** (200 mg, 0.55 mmol) and potassium hydroxide (30 mg, 0.55 mmol) in absolute ethanol (4 ml) was boiled on a steam bath for 5 min, cooled, diluted with water (10 ml), and extracted with ethyl acetate. After drying (Na_2SO_4), the ethyl acetate was removed at reduced pressure to give a white solid (197 mg). Crystallization from acetone–hexane gave 178 mg (89%) of pure **9a**: mp 205–207°; ir (KBr) 3600, 3420 (OH), and 1710 cm^{-1} (2′-C=O); nmr ($CDCl_3$) δ 1.00 (s, 3, 18-CH_3), 1.71 (s, 2, CH_2C=O), and 3.86 ppm (d, 4, $-OCH_2CH_2O-$).

Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.24; H, 8.98.

19a-Methylandrostane-3,17,19-trione (7e).—Steroid **4e** (12 g, 0.033 mol) in 2-propanol (150 ml) and ethanol (100 ml) was stirred with 35% palladium hydroxide on carbon (3.0 g) under hydrogen until hydrogen uptake ceased (~1.5 hr). The catalyst was filtered and the filtrate was evaporated to dryness (nmr indicated that the reduction was complete). The residue was dissolved in a mixture of acetone (250 ml), hydrochloric acid (5 ml), and water (5 ml), and the solution was stirred overnight. After dilution with water (500 ml) and extraction with ethyl acetate, the extracts were washed with bicarbonate solution and water, then dried (Na_2SO_4). Evaporation of the solvent gave crude steroid **7d** (11.5 g).

Crude dihydroxy steroid **7d** in methylene chloride (15 ml) and pyridine (5 ml) was added to a mechanically stirred solution of chromium trioxide (48 g) in methylene chloride (900 ml) and pyridine (60 ml). The solution was stirred for 1 hr. After the methylene chloride was decanted, the tarry residue was thoroughly washed with methylene chloride (3 × 300 ml). The combined organic extracts were washed with 5% sodium hydroxide, 5% hydrochloric acid, and water and then dried ($MgSO_4$). Evaporation of the solvent and recrystallization of the residue from acetone–hexane gave **7e** (4.5 g), mp 171–172°.

The filtrate was concentrated and chromatographed (alumina III) by first eluting with benzene (1 l.). Further elution with 5% ethyl acetate gave **7f** (2.8 g, 28%): mp 161–162°; ir ($CHCl_3$) 1690 (19-C=O) and 1735 cm^{-1} (17-C=O); nmr ($CDCl_3$) δ 1.03 (s, 3, 18-CH_3) and 2.13 ppm (s, 3, 19a-CH_3).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.43; H, 10.00. Found: C, 79.59; H, 10.16.

Elution with 7.5% ethyl acetate solution gave an additional 1.5 g of **7e** (6 g total, 58%): ir ($CHCl_3$) 1695 (19-C=O), 1714 (3-C=O), 1735 cm^{-1} (17-C=O); nmr ($CDCl_3$) δ 0.82 (s, 3, 18-CH_3) and 2.31 ppm (s, 3, 19a-CH_3).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.80; H, 8.97.

3,10-[2′-Oxoethano]-5α-estran-3-ol-17-one (9b).—A solution of steroid **7e** (0.2 g, 0.69 mmol), potassium hydroxide (30 mg), and ethanol (4 ml) was refluxed on a steam bath for 30 min, then cooled, diluted with water (10 ml), and extracted with ethyl acetate. The ethyl acetate extract was washed with water, dried (Na_2SO_4), and evaporated at reduced pressure to give **9a** (197 mg) as a white solid.

Recrystallization from acetone–hexane gave pure **9b** (182 mg, 91%): mp 215–216°; ir (KBr) 3600, 3420 (broad, OH), and 1710 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.00 (s, 3, 18-CH_3), 1.71 (s, 2, CH_2C=O), and 3.86 ppm (m, 4, $-OCH_2CH_2O-$).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 73.30; H, 8.95. Found: C, 73.24; H, 8.98.

3,10-[2′-Oxoethano]-5α-estrane-3,17-diol (9c).—Steroid **9b** (3.5 g, 11.0 mmol) in dry tetrahydrofuran (100 ml), magnetically stirred at 0° under nitrogen, was treated portionwise with lithium tri-*tert*-butoxyaluminum hydride and then stirred for 2 hr more. Water was added dropwise to destroy the excess hydride; then 10% acetic acid (350 ml) was added. The precipitated steroid **9c** (2.88 g), after filtration and drying, had mp 247–248°. An additional quantity of **9c** (0.51 g, 97% total yield) was obtained by removing the tetrahydrofuran from the filtrate at reduced pressure: mp 249–249.5°; ir ($CHCl_3$), 1717 cm^{-1} (2′-C=O); nmr (DMSO-d_6) δ 0.73 (s, 3, 18-CH_3), 4.34 (d, 1, J = 5 Hz, 17-OH), and 4.61 ppm (s, 1, 3-OH).

Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.28; H, 9.52.

3,10-Ethano-5α-estrane-3,17-diol (10a).—A mixture of keto steroid **9c** (3.0 g, 9.4 mmol), hydrazine (19 ml, 97%), hydrazine dihydrochloride (7.5 g), and triethylene glycol (203 ml) was heated at 100° for 11 hr. Potassium hydroxide (11.25 g) was added, and the temperature was gradually raised to 240° with distillation of lower boiling material. The reaction was maintained at 240° for 7 hr, then cooled and diluted with water. The solid was collected, dried, and recrystallized from methanol to give steroid **10a** (2.03 g, 71%), mp 195–197°. The analytical sample prepared by recrystallization from methanol had mp 197–198°; ir (KBr) 3400 cm^{-1} (OH); nmr (DMSO-d_6–$CDCl_3$) δ 0.71 (s, 3, 18-CH_3), 3.94 (s, 1, 3-OH), and 4.2 ppm (d, 1, J = 5 Hz, 17-OH).

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.89; H, 10.60. Found: C, 78.47; H, 10.88.

3,10-Ethano-5α-estran-3-ol (10b).—The ketal **9a** (0.36 g, 10 mmol) was reduced under exactly the same conditions as described for **10a**. The crude product obtained was chromatographed on alumina (activity III) using benzene–ethyl acetate (9:1) as the eluent. The product fractions were combined, concentrated, and recrystallized from hexane to give 0.175 g (61%) of **10b**: mp 156–158°; ir ($CHCl_3$) 3600 and 3420 cm^{-1} (OH); nmr ($CDCl_3$) δ 0.67 ppm (18-CH_3).

Anal. Calcd for $C_{20}H_{32}O$: C, 83.32; H, 11.20. Found: C, 83.17; H, 11.47.

3,10-Ethano-5α-estran-3-ol-17-one (10c).—A solution of **10a** (1.2 g, 3.9 mmol) in methylene chloride (5 ml) and pyridine (11 ml) was added dropwise to a mechanically stirred solution of chromium trioxide (2.4 g) in methylene chloride (85 ml) and pyridine (4 ml) and stirred for 1 hr. The methylene chloride was decanted from the tarry residue, which was then washed thoroughly with methylene chloride. After the combined organic extracts were washed with 5% sodium hydroxide, 5% hydrochloric acid, and water, the methylene chloride solution was dried (Na_2SO_4) and evaporated at reduced pressure to give **10c** (1.03 g, 86%), mp 163–164°. The analytical sample, recrystallized from acetone–hexane, had mp 165–166°; ir ($CHCl_3$) 3600, 3420 (OH), and 1735 cm^{-1} (17-C=O).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 9.99. Found: C, 79.25; H, 10.12.

17α-Ethynyl-3,10-ethano-5α-estrane-3,17β-diol (10d).—Steroid **10c** was ethynylated with lithium acetylide–ethylenediamine complex in dioxane by a method used for other five-membered ketones.[14] Several recrystallizations from methanol–water and chloroform gave pure **10d**: mp 290–291° (sealed capillary, sublimes); ir (KBr) 3450 (OH) and 3260 cm^{-1} (C≡CH); nmr ($CDCl_3$–CD_3OD) δ 0.78 (s, 3, 18-CH_3) and 2.55 ppm (s, 1, C≡CH).

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.16; H, 9.81.

Registry No.—**4b,** 41563-98-8; **4d,** 4119-21-5; **4e,** 41564-00-5; **7a,** 41564-01-6; **7b,** 41564-02-7; **7c,** 41564-03-8; **7e,** 24124-71-8; **7f,** 41564-05-0; **9a,** 41564-06-1; **9b,** 41564-07-2; **9c,** 41564-08-3; **10a,** 41564-09-4; **10b,** 41564-10-7; **10c,** 41564-11-8; **10d,** 41564-12-9.

(14) J. W. Huffman and P. G. Arapakos, *J. Org. Chem.*, **30**, 1604 (1965).