tain >99.5% endo diastereomer. Equal portions of this solution were transferred into two 40-ml centrifuge tubes containing magnetic stirring bars immersed in a Dry Ice–acetone bath. The tubes were warmed to 0° with stirring. Mesityl oxide (0.5 equiv) was added to one tube. Aliquots from both solutions were taken periodically by transferring into 40-ml centrifuge tubes held at Dry Ice temperatures. These aliquots were analyzed for the diastereomeric content of the remaining **2**. Immediately after warming to 0°, the diastereomeric purity of the **2** in the solution not containing mesityl oxide was 98.5%; after standing for 5 min at 0°, it was 97.1%. The sample containing mesityl oxide contained **2** that was 98.6% endo immediately after warming to 0°, 99.5% after 1 min at 0°, and 93.7% after 15 min.

Competition of a Mixture of *endo*- and *exo*-2 for Limiting Quantities of Mesityl Oxide.—An epimeric mixture of **2** was prepared at −78° and was shown to be 74% endo and 26% exo. Aliquots calculated to contain 1.19 mmol of **2** were transferred to 40-ml centrifuge tubes and warmed to 0°. Calculated amounts of mesityl oxide were added, and the reaction mixtures were stirred at 0° for *ca.* 2 min. The reaction mixtures were then cooled to −78°, and the remaining **2** was analyzed for epimeric composition by treatment with methyllithium and oxidation with nitrobenzene. The conjugate additions of **2** and of lithium methyl-2-norbornylcuprate to mesityl oxide at −78° are very slow. The results of these experiments are as follows: for 0.250 equiv of mesityl oxide/equiv of **2**, the epimeric composition of the **2** remaining after quenching was 67.8% endo; for 0.336 equiv, 69.6% endo; for 0.505 equiv, 74.8% endo; for 0.675 equiv, 77.6% endo.

Registry No.—*endo*-**1**, 13058-87-2; *endo*-**2**, 24473-67-4; *exo*-**2**, 35616-99-0; **3**, 35623-77-9; **4**, 35623-78-0; *exo*-**5**, 35623-75-7; *endo*-**5**, 35623-79-1; mesityl oxide, 141-79-7; *endo*-2-norbornyl methyl ketone, 824-58-8; *exo*-2-norbornyl methyl ketone, 824-59-9; bromobis(trimethyl phosphite)copper(I), 35617-00-6.

Acknowledgments.—Samples of dibromobis(triphenylphosphine)nickel(II) were supplied by Dr. T. L. Newirth, and dichlorobis(triphenylphosphine)platinum(II) was obtained from Dr. S. L. Regen.

The Reaction of Steroidal 3-Keto-19-carboxylic Acids and 19-Nor Steroidal Dienones in Solutions of Iodine in Pyridine[1]

FRANCISCO S. ALVAREZ* AND ALEXANDER N. WATT

Institute of Organic Chemistry, Syntex Research, Palo Alto, California 94304

Received May 24, 1971

The treatment of 3,17-dioxoestr-4-en-19-oic acid (**1**) with iodine in pyridine yielded estra-4,9-diene-3,17-dione (**6**). This compound reacted further with iodine to give 3-hydroxyestra-1,3,5(10),9(11)-tetraen-17-one (**7**). The reaction of estra-4,6-diene-3,17-dione (**11**) under the same conditions afforded 3-hydroxyestra-1,3,5(10),6-tetraen-17-one (**12**). When 3,17-dioxoandrosta-4,6-dien-19-oic acid (**10**), 3,17-dioxo-5α-androstan-19-oic acid (**16**), and 3,17-dioxo-5β-androstan-19-oic acid (**16a**) were treated with iodine in pyridine, they yielded, respectively, the lactones **15**, **17**, and **17a**. Pyridine–iodine appears to be a new reagent capable of yielding γ-lactones and unsaturated phenols from suitable γ-keto carboxylic acids and conjugated dienones. A deviation from the helicity rule of the homoannular diene **13a** is reported.

In 1960 Hagimara, *et al.*,[2] reported that treatment of androst-4-en-3,17-dion-19-oic acid (**1**) in hot pyridine solution afforded estr-5(10)-ene-3,17-dione (**2**) in almost quantitative yield. Subsequently, Perelman, *et al.*,[3] reported the synthesis of estra-4,9-diene-3,17-dione (**6**) in unspecified yield by the reaction of estr-5(10)-ene-3,17-dione (**2**) with bromine in pyridine solution. These authors reported that pyridine is unique in transforming the resulting 5,10-dibromo · intermediate into the dienone **6** instead of phenolic products, obtained when the reaction is carried out in other solvents.

The possibility of obtaining the dienone **6** in a single reaction by decarboxylation of the acid **1** in pyridine solution in the presence of halogen was considered. This type of decarboxylation should produce the intermediate enol **4** *via* the anion **3**, which in principle may be "trapped" by an electrophilic reagent, such as positive halogen.[4]

With this aim, the following transformations were carried out. Reaction of androst-4-ene-3,17-dion-19-oic acid (**1**) in pyridine solution with 1 mol of iodine at 60–65° led to an immediate evolution of carbon dioxide and formation of a heavy crystalline precipitate of pyridine hydriodide. After isolation of the products, an oil with strong ultraviolet absorption at 302 mμ, characteristic of a $\Delta^{4,9}$-3-ketone chromophore,[3] was obtained. Purification of the reaction mixture by elution chromatography on activated alumina yielded 59% of estra-4,9-diene-3,17-dione (**6**).

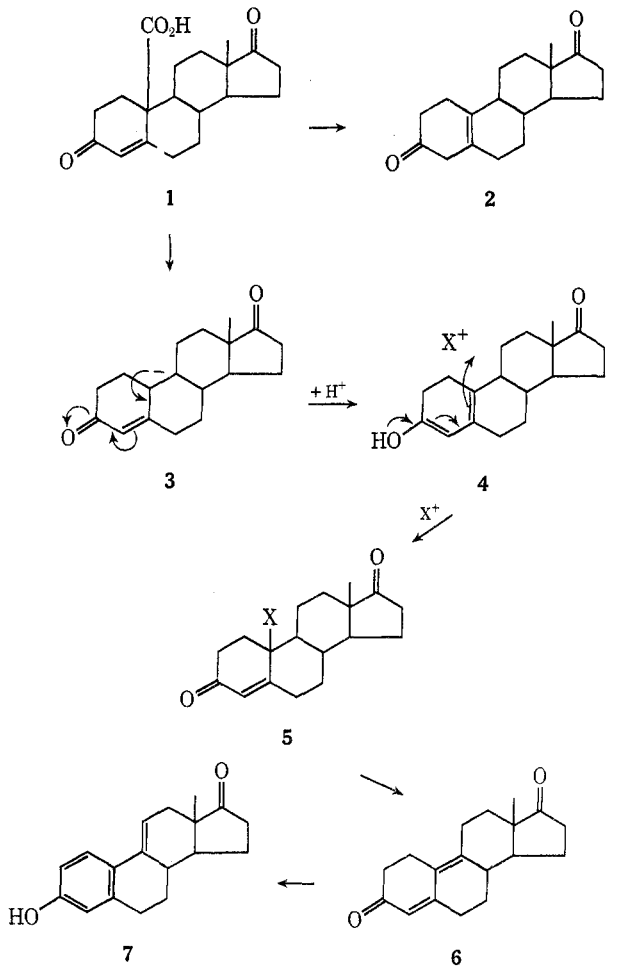
Under the conditions of the experiment, the C-10 iodo derivative **5** (X = I) (probably with the 10β configuration) proved to be unstable, decomposing rapidly with elimination of 1 mol of hydrogen iodide to produce the dienone **6**. In the more polar fractions, a mixture of ring A phenolic steroids with ultraviolet absorption at 264 mμ was obtained, suggesting the presence of an estra-1,3,5,9(11)-tetraene chromophore. Apparently estra-4,9-diene-3,17-dione (**6**) undergoes further attack by iodine, the intermediate iodo compound being transformed into 3-hydroxyestra-1,3,5,9-(11)-tetraen-17-one (**7**) by elimination and rearrangement. To support this proposal, the following experiments were carried out. Treatment of the dienone **6** with 1 mol of iodine in pyridine solution at reflux for 6 hr yielded 48% of 3-hydroxyestra-1,3,5,9(11)-tetraen-17-one (**7**). Treatment of the acid **1** with 2 mol of iodine in refluxing pyridine afforded the $\Delta^{9(11)}$ compound **7** in 30% yield. This appears to be the first example of

(1) This paper represents Contribution No. 389 from Syntex Research, Institute of Organic Chemistry, Palo Alto, Calif.

(2) H. Hagimara, S. Noguchi, and M. Nishikama, *Chem. Pharm. Bull.*, **8**, 84 (1960).

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

(4) K. S. Pedersen, *ibid.*, **51**, 2098 (1929); **58**, 250 (1936); F. S. Fawcet, *Chem. Rev.*, **47**, 219 (1950). For a similar type of trapping of carbanion intermediates derived from carboxylic acids having strong electron-attracting groups, see K. S. Pedersen, *J. Phys. Chem.*, **38**, 559 (1934).

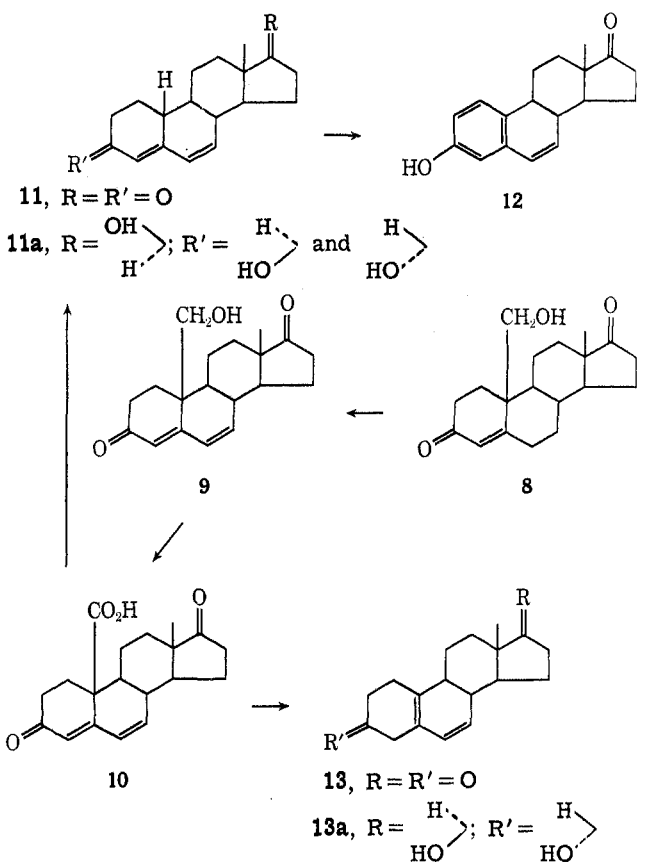


a one-step transformation of a C-19 steroid into an estra-1,3,5,9-(11)-tetraene derivative.[5]

Because of alternate possibilities of enolization of the dienone **6**, it is uncertain whether electrophilic attack by iodine takes place at C-2 or C-11. In either case, subsequent elimination and rearrangement can yield the $\Delta^{9(11)}$ derivative **7**.

19-Hydroxyandrost-4-ene-3,17-dione[6] (**8**) was dehydrogenated with chloranil in refluxing *tert*-butyl alcohol to yield 19-hydroxyandrosta-4,6-diene-3,17-dione (**9**) in 50% yield. Oxidation of this material in acetone–dichloromethane solution with Jones reagent yielded 3,17-dioxoestra-4,6-dien-19-oic acid[7] (**10**) in good yield. Decarboxylation of this material in refluxing methanol containing hydrochloric acid afforded estra-4,6-diene-3,17-dione (**11**).

When estra-4,6-diene-3,17-dione (**11**) was treated with iodine in pyridine as described before, estra-1,3,5(10),6-tetraen-17-one (**12**) was obtained in moderate yield.



Treatment of androsta-4,6-diene-3,17-dion-19-oic acid (**10**) in pyridine solution at 60–65° yielded 60% of crude estra-5(10),6-diene-3,17-dione[7] (**13**). Thin layer chromatography showed that the product was contaminated with about 5% of estra-4,6-diene-3,17-dione (**11**). Reduction of **13** with lithium tri-*tert*-butoxyaluminum hydride and purification by preparative tlc yielded 3α,17β-dihydroxyestra-5(10),6-diene (**13a**). The ultraviolet absorption at 264 mμ (ε 4274) is compatible with the homoannular diene chromophore.[8] The nmr spectrum shows two resonances for chemically equivalent protons as a singlet at 5.63 ppm in support of structure **13a**.

Examination of Dreiding models for the homoannular diene **13a** shows a positive helix formed by the C_{10}–C_5–C_6–C_7 carbon chain, and consequently a positive Cotton effect was expected for this system.[9] Experimentally, the Cotton effect was found to be negative.[10] In order to determine if contamination of the homoannular diene **13a** with the diene **11a** is responsible for this unexpected result, the latter compound was prepared by reduction of the dienone **11** with lithium tri-*tert*-butoxyaluminum hydride. However, its Cotton effect was also negative, although of a much smaller magnitude (see Experimental Section) than that observed for **13a**. The variance of the helicity rule with experimental observation has already been reported by Beechmann and Mathieson.[10]

Having established that the carboxylic acid **10** is capable of being transformed into the nonconjugated

(5) (a) The transformation of steroidal $\Delta^{1,4,9(11)}$-3 ketones into estra-1,3,5(10),9(11)-3-ol derivatives has been described; *cf.* K. Tsuda, E. Ohki, and S. Nozoe, *J. Org. Chem.*, **28**, 783, 786, 789, 795 (1963). However, the $\Delta^{9(11)}$ double bond was already present in the starting material. (b) Farkas and Owen have reported the transformation of 9α,10α-oxidoestr-4-en-17β-ol-3-one into estra-1,3,5(10),9(11)-tetraene-3,17β-diol under acidic conditions; *cf.* E. Farkas and J. M. Owen, *J. Med. Chem.*, **9**, 510 (1966).

(6) A. Bowers, R. Villotti, J. A. Edwards, E. Denot, and O. Halpern, *J. Amer. Chem. Soc.*, **84**, 3204 (1962).

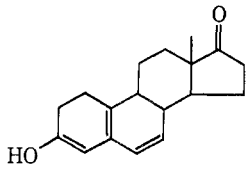
(7) When this work was completed, a paper appeared in the literature describing the transformation of 19-hydroxyandrosta-4,6-diene-3,17-dione (**9**) into estra-5(10),6-diene-3,17-dione (**13**) and estra-4,6-diene-3,17-dione (**11**) by procedures similar to the ones described here; *cf.* J. Kalvoda and G. Anner, *Helv. Chim. Acta*, **50**, 269 (1967).

(8) L. Dorfman, *Chem. Rev.*, **53**, 47 (1953).

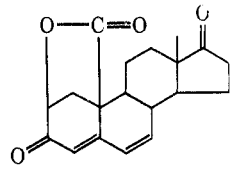
(9) P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, San Francisco, Calif., 1965, Chapter 10.

(10) A. F. Beechmann and A. Mc. L. Mathieson, *Tetrahedron Lett.*, 3139 (1966). These authors determined the absolute chilarity of gliotoxin by X-ray analysis and found that a "left-handed twist" is associated with a strong positive Cotton effect.

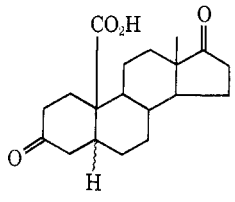
ketone **13**, the following experiments were carried out in order to "trap" the intermediate trienol **14**, as in the preceding transformations.



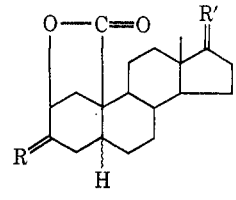
14

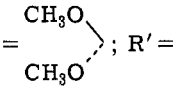
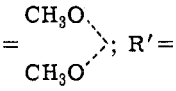
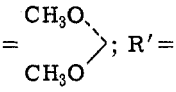


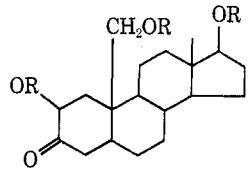
15



16, 5α-H
16a, 5β-H



17, 5α-H; R = R′ = O
17a, 5β-H; R = R′ = O
17b, 5α-H; R =  ; R′ = O
17c, 5β-H; R =  ; R′ = O
17d, 5α-H; R = O; R′ = 
17e, 5β-H; R = O; R′ = 
17f, 5β-H; R =  ; R′ = 



18, 5α-H; R = H
18b, 5α-H; R = Ac
18c, 5β-H; R = H
18d, 5β-H; R = Ac

When 3,17-dioxoandrosta-4,6-dien-19-oic acid (**10**) was treated at room temperature with 1 mol of iodine in pyridine, a complex mixture was obtained. Resolution of this mixture by chromatography on silica gel yielded ring A phenolic steroids and estra-4,6-diene-3,17-dione (**11**) in addition to the major compound isolated in 60% yield. The presence of a carbonyl band at 1775 cm^{-1} in the infrared spectra of the latter product suggested the presence of a γ-lactone, *e.g.*, **15**. The nmr spectrum shows a narrow multiplet at 6.5–6.6 ppm characteristic of an equatorial proton attached to a carbon bearing oxygen. This is consistent with a lactone structure and suggests intramolecular attack by the carboxylate anion, most probably at C-2. A reasonable path may involve initial formation of a C-19 hypoiodite function, followed by hydrogen abstraction and ring closure. However, the possibility of iodination at C-2, followed by ring closure, is not excluded.

Two physical characteristics of **15** are worth noting.

A. The observed 9-mμ bathochromic shift in the ultraviolet absorption spectra shown by **15**, as compared with the precursor $\Delta^{4,6}$-3-keto 19-oic acid (**10**), suggests the existence of electronic interaction between the lactone and the $\Delta^{4,6}$-3-keto group.

B. The 7.8-Hz paramagnetic shift experienced by the C-18 protons of **15**, as compared to **10**, shows a deshielding effect of the carbonyl dipole of the lactone on these protons. Examination of Prentice Hall molecular orbital models shows that the C-18 methyl protons in structure **15** lie close to the plane of the C-19 trigonal carbon atom. Under these circumstances a deshielding effect should be expected.[11]

It is noteworthy that no evidence of a lactonization process was encountered on careful examination of the reaction mixture obtained from the treatment of androst-4-en-3,17-dion-19-oic acid (**1**) with iodine in pyridine solution. Even when this reaction was allowed to proceed at room temperature, only products derived from decarboxylation were present.

A more favorable situation for lactone formation would be expected with a 3-keto saturated C-19 carboxylic acid such as 5α- and 5β-androsta-3,17-dion-19-oic acids, since, with these compounds, the competitive decarboxylation process should be fully prevented, considering the mild reaction conditions used. In fact, when 5α-androsta-3,17-dion-19-oic acid[12] (**16**) was treated in pyridine solution with 1 mol of iodine at 60–65° for 2 hr, it was transformed in high yield into 3,17-dioxo-2β-hydroxy-5α-androstan-19-oic acid 2,19-lactone (**17**). This compound was previously prepared in low yield in a multistep process by Kwok and Wolff[13] *via* photolysis of the nitrite ester of 5α-androstane-2β,3α,17β-triol-3,17-diacetate.

When 3,17-dioxo-2β-hydroxyandrosta-4,6-dien-19-oic acid 2,19-lactone (**15**) was treated in ethanol solution with 5% Pd/C at a hydrogen pressure of 50 psi, it was transformed into **17**, identical in all respects with 3,17-dioxo-2β-hydroxy-5α-androstan-19-oic acid 2,19-lactone described above. This result yields conclusive evidence that structure **15** is correct for the lactone obtained from androsta-4,6-diene-3,17-dion-19-oic acid (**10**).

Similarly, reaction of 5β-androstane-3,17-dion-19-oic acid[12] (**16a**) with the iodine–pyridine reagent at 95–100° for 2 hr (no reaction occurred at 60–65°) gives a new lactone characterized as **17a**.

Examination of the Prentice Hall flexible molecular orbital models for the saturated 5β-19-oic acid **16a** shows that it can be closed to the lactone **17a**, provided that ring A and ring B are transformed into a boat conformation (see Scheme I). Under these circumstances the molecule is reasonably strain free, although the hydrogen atoms at C-1α–C-4α, C-1β–C-11β, and C-6α–C-9α are in an eclipsed conformation. This unusual structure containing three cis-fused rings[14] was confirmed as follows.

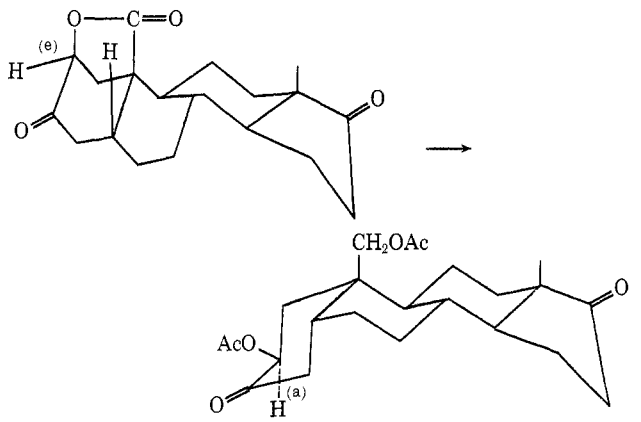
(11) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, pp 122–124.

(12) L. H. Knox, E. Blossey, H. Carpio, L. Cervantes, P. Crabbé, E. Verlarde, and J. A. Edwards, *J. Org. Chem.*, **30**, 2198 (1965)

(13) R. Kwok and M. Wolff, *ibid.*, **28**, 422 (1963).

(14) *Cf.* J. S. McKechnie and I. C. Paul, *J. Amer. Chem. Soc.*, **90**, 2144 (1968) for a structure containing three five-membered cis-fused rings.

SCHEME I

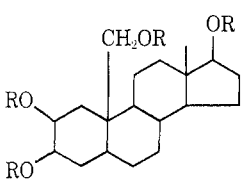


Examination of the nmr spectrum of **17a** shows a narrow multiplet at 4.05–4.25 ppm, indicating an equatorial hydrogen attached to a carbon-bearing oxygen. Conversion of **17a** into the triacetate **18d** allows ring A to flip from boat to chair (Scheme I), producing a C-2 axial proton. The resonance of this proton should appear as an ABX system, as found[15] in the case of 2α-acetoxycholestanone.

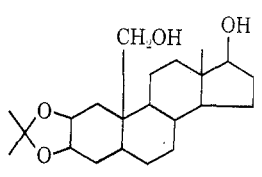
When the lactone **17a** was treated with anhydrous methanol in the presence of perchloric acid, it was transformed smoothly into the C-3 methyl ketal **17c** which, on reduction with lithium aluminum hydride followed by acid hydrolysis, yielded 2β,17β-19-trihydroxy-5β-androstan-3-one (**18c**). This compound was transformed into its triacetate **18d** by acetic anhydride in pyridine.

The nmr spectrum of this triacetate shows the C-2 axial proton as a quartet at 5.14, 5.2, 5.27, and 5.34 ppm with coupling constants $J_{1\alpha,2\alpha}$ and $J_{1\beta,2\alpha}$ of 6.5 and 13.5 Hz. These results are in full agreement with the corresponding resonances in 2α-acetoxycholestanone and in agreement with the structure **17a**.

Reduction of lactones **17** and **17a** with lithium aluminum hydride yielded the 2β,3β,17β,19-tetrols **19** and **19b**, which were transformed into the corresponding



19, 5α-H; R = H
19a, 5α-H; R = Ac
19b, 5β-H; R = H
19c, 5β-H; R = Ac



20, 5α-H
20a, 5β-H

tetraacetates **19a** and **19c** in the usual manner. Treatment of the tetrols **19** and **19b** with acetone in the presence of *p*-toluenesulfonic acid afforded the acetonides **20** and **20a**, providing additional support for the vicinal oxygenation pattern at C-2 and C-3 in the lactones **17** and **17a**.

Lactones **17** and **17a** were transformed into the corresponding C-3 methyl ketals **17b** and **17c** by treatment with anhydrous methanol in the presence of strong acid. These ketals were reduced with sodium borohydride to yield the corresponding 17β alcohols, which, on acid hydrolysis, afforded the 3-keto 17β-hydroxy lactones **17d** and **17e**. Examination of the ORD curves for these lactones shows the correct Cotton effects for steroidal C-3 ketones epimeric at C-5[16] (see Experimental Section).

(15) K. L. Williamson and W. S. Johnson, *J. Amer. Chem. Soc.*, **83**, 4623 (1961).

Experimental Section[17]

Estra-4,9-diene-3,17-dione (6).—A solution of 248.1 g of iodine in pyridine (previously distilled over potassium hydroxide) was prepared. To this solution, 294 g of androst-4-ene-3,17-dion-19-oic acid (1) was added, and the mixture was heated with stirring to 80° for 20 min. The mixture was cooled to room temperature and poured into a solution of 3 l. of concentrated hydrochloric acid in 30 l. of water. The resulting mixture was extracted three times with 2-l. portions of methylene chloride; the extracts were washed with water until neutral and concentrated to 1 l. at atmospheric pressure. The resulting extract was filtered through a column of 3 kg of washed alumina. The column was eluted with methylene chloride until no more product could be eluted. The eluates were concentrated to dryness under reduced pressure and the residue was crystallized from ethyl acetate–hexane to yield 150.7 g (59.5%) of **6**: mp 119–121°; $[\alpha]_D$ −134°; λ_{max}^{MeOH} 302 mμ (ϵ 19,400). A pure specimen was obtained after several crystallizations from ethyl acetate–hexane and showed mp 128–130° (reported[3] mp 130–131°).

3-Hydroxyestra-1,3,5,9(11)-tetraen-17-one (7). **A.**—A solution of 150 g of estra-4,9-diene-3,17-dione (6) in 1.5 l. of pyridine containing 150 g of iodine was refluxed for 6 hr. The mixture was cooled to room temperature and poured into 15 l. of water. The mixture was extracted three times with 2 l. of methylene chloride each time. The combined extracts were washed with excess 10% aqueous hydrochloric acid and then with water until neutral. The solution was dried with anhydrous sodium sulfate and the solvent was eliminated under reduced pressure. The residue was crystallized from methylene chloride–ether to yield 71 g of 3-hydroxyestra-1,3,5,9(11)-tetraen-17-one: mp 243–246°; $[\alpha]_D$ 265°; λ_{max}^{MeOH} 264 mμ (ϵ 18,120) [reported[6] mp 256–258°; λ_{max}^{MeOH} 262.5 mμ (ϵ 18,000)].

B.—Similarly, when 50 g of androst-4-en-3,17-dion-19-oic acid in 1000 ml of pyridine containing 100 g of iodine was refluxed for 6 hr and worked up as described above, 15.2 g of 3-hydroxyestra-1,3,5,9(11)-tetraen-17-one, mp 250–251°, was isolated. The material was shown to be identical with the material prepared previously.

19-Hydroxyandrosta-4,6-diene-3,17-dione (9).—A solution of 260 g of 19-hydroxyandrost-4-ene-3,17-dione[7] (8) in 2500 ml of *tert*-butyl alcohol was treated with 265 g of chloranil under reflux for 2 hr. The reaction mixture was cooled to room temperature and the precipitate of tetrachlorohydroquinone formed during the reaction was collected by filtration. The filtrate was concentrated under vacuum to dryness, and benzene was added at the end of the evaporation to help the elimination of the residual *tert*-butyl alcohol. The crystalline residue so obtained was taken up in 5 l. of dichloromethane and refluxed for 1 hr. The residual tetrachlorohydroquinone was filtered off and the filtrates were washed two times with 2.5 l. of 5% aqueous sodium hydroxide each time, then with water until neutral. The dichloromethane layer was dried with anhydrous sodium sulfate and decolorized with charcoal. The solution was concentrated to a small volume

(16) C. Djerassi, "Optical Rotatory Dispersion: Applications to Organic Chemistry," McGraw-Hill, New York, N. Y., 1960.

(17) Melting points are corrected. Optical rotations were measured in chloroform solution unless stated otherwise using an O. C. Rudolph and Sons Model 80 polarimeter. Ultraviolet spectra were measured in methanol using a Cary Model 14 spectrometer. Infrared spectra were measured using a Perkin-Elmer Model 137 spectrophotometer Nmr spectra were recorded on Varian HA-100 and A-60 spectrometers using deuteriochloroform or DMSO-d_6 as solvent. Chemical shifts are recorded in parts per million. We wish to thank Mrs. J. Nelson for these measurements and Miss Irma Delfin for her able technical assistance. Optical rotatory dispersion (ORD) curves were measured in dioxane or methanol on a Jasco ORD/UV-5 spectrometer. Sufficient values are quoted to allow a rough curve to be plotted. Analytical tlc plates with a thickness of 0.25 mm silica gel GF_{254} (E. Merk, A. G. Darmstadt) and preparative tlc plates with a thickness of 0.25 mm silica gel GF_{254} were used.

and the material was crystallized by addition of methanol to yield 130 g of title compound. This material was crystallized once more from dichloromethane, affording 104 g of pure compound, mp 195–196°. The analytical sample was obtained after several crystallizations from dichloromethane: mp 197–198°; $[\alpha]_D$ 128°; λ_{max}^{MeOH} 284 mμ (ε 26,650) [reported[7] mp 196–199°; $[\alpha]_D$ 135.6°; λ_{max} 283 mμ (ε 25,400)]. *Anal.* Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05; O, 15.98. Found: C, 75.63; H, 7.97; O, 16.04.

3,17-Dioxoestra-4,6-dien-19-oic acid (10)[18] had mp 133–135° dec; $[\alpha]_D$ 128°; λ_{max}^{MeOH} 287 mμ (ε 22,300) [reported[7] mp 134–135°; $[\alpha]_D$ 125°; λ_{max} 287 mμ (ε 22,800)]. *Anal.* Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65; O, 20.23. Found: C, 71.96; H, 7.81; O, 20.04.

Estra-4,6-diene-3,17-dione (11)[18] had mp 180–182°; $[\alpha]_D$ 61°; λ_{max}^{MeOH} 282 mμ (ε 26,250) [reported[7] mp 181.5–182.5°; $[\alpha]_D$ 58.3°; λ_{max} 282 mμ (ε 26,600)]. *Anal.* Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20; O, 11.84. Found: C, 80.01; H, 8.31; O, 12.01.

3α,17β-Dihydroxyestra-5(10),6-diene (13a).—A solution of 1 g of androst-4,6-diene-3,17-dion-19-oic acid (10) in 5 ml of pyridine was heated on the steam bath for 10 min. Evolution of carbon dioxide started almost at once. The reaction mixture was poured into 75 ml of water saturated with sodium chloride, and the solid material that precipitated was collected by filtration and washed with water. This compound was dried under vacuum over calcium chloride to yield 0.510 g of the crude homoannular dienone **13**. Examination of this material on tlc in a 1:1 hexane–ethyl acetate system showed it to be contaminated with about 5% of the conjugated dienone **11**. A solution of this compound in 5 ml of anhydrous tetrahydrofuran was treated with 2 g of lithium tri-*tert*-butoxyaluminum hydride at room temperature for 2 hr, then poured into 150 ml of 5% aqueous acetic acid. The mixture was extracted with ether; the combined extract was washed with water, dried over anhydrous sodium sulfate, and filtered. The solvent was evaporated under reduced pressure. The material thus obtained was dissolved in 75 ml of dichloromethane and filtered through 5 g of acid-washed alumina, eluting with the same solvent. The crystalline fractions were combined and purified on a preparative tlc plate to yield, after crystallization from acetone–hexane, 17.8 mg of pure title compound: mp 165–167°; ORD $[\Phi]_{600}$ −272°, $[\Phi]_{350}$ −1850°, $[\Phi]_{293}$ −9900°, $[\Phi]_{272}$ ±0°, $[\Phi]_{240}$ 13,800°, $[\Phi]_{211}$ 6260°; λ_{max} 265 mμ (ε 4274); ν_{max} 3410 (s), 726 cm^{-1} (m); nmr (DMSO-d_6) 0.64 (18-H), 3.34–3.83 (3β- and 17α-H), 4.5 (2 OH), singlet at 5.63 ppm (6-H and 7-H). *Anal.* Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.84; H, 9.37.

3ξ,17β-Dihydroestra-4,6-diene (11a).—Similarly, **11a** was prepared from **11**: mp 190–195°; ORD $[\Phi]_{600}$ −130.5°, $[\Phi]_{350}$ −721°, $[\Phi]_{260}$ −2740°, $[\Phi]_{256}$ −2500°, $[\Phi]_{259}$ −3290°, $[\Phi]_{253}$ ±0°, $[\Phi]_{250}$ 1690°, $[\Phi]_{240}$ ±0°; nmr (DMSO-d_6) 0.67 (18-H), 3.17–3.67 (17α-H), 3.84–4.42 (3-H), 4.5, 4.6, 4.68 (2 OH), 5.4 (4-H), 5.48, 5.67, 5.87, and 6.05 ppm (6-H and 7-H). *Anal.* Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.54; H, 9.73.

3-Hydroxyestra-1,3,5(10),6-tetraen-17-one (12).—A solution of 1 g of estra-4,6-diene-3,17-dione (11) in 10 ml of pyridine was treated with 2.2 g of iodine under reflux for 6 hr. The reaction mixture was cooled to room temperature and then poured into 150 ml of water. The solid that precipitated was collected by filtration, washed with water, and air dried to give 0.54 g of crude **12**. A pure specimen was obtained after several crystallizations from methanol: mp 258°; $[\alpha]_D$ −115° (dioxane); λ_{max}^{MeOH} 264 mμ (ε 8560) and 304 (2620); nmr 0.93 (18-H), quartet at 5.83, 6.03, 6.33, and 6.5 (C-6, C-7 olefinic protons), and 9.07 ppm (phenolic OH). The infrared spectrum of this material was superimposable with the one of an authentic sample [reported[19] mp 261–263°; $[\alpha]_D$ −127° (dioxane); λ_{max} 262 mμ (ε 8900) and 304 (2750)].

2β-Hydroxy-3,17-dioxoandrosta-4,6-dien-19-oic Acid 2,19-Lactone (15).—A solution of 15.83 g of iodine in 84.6 ml of pyridine was prepared. To this solution, 28.2 g of 3,17-dioxoandrosta-4,6-dien-19-oic acid (10) was added, and the mixture was stirred at room temperature for 72 hr. The precipitate of pyridine hydriodide was collected by filtration and washed with methylene chloride. The filtrates were concentrated to dryness under reduced pressure and the residue was dissolved in methylene chloride. An insoluble residue of pyridine hydriodide was filtered off. The filtrates were passed through a column of 400 g of silica gel. The fractions eluted with a mixture of 2% ether–98% methylene chloride were combined and concentrated to dryness. The residue was crystallized from acetone–hexane to yield 16.8 g (59.7%) of **15**: mp 256–258°; $[\alpha]_D$ −104°; λ_{max}^{MeOH} 294 mμ (ε 19,600). The analytical sample was prepared by crystallization from methylene chloride–ether twice: mp 268–270°; $[\alpha]_D$ −108°; λ_{max}^{MeOH} 294 mμ (ε 20,600), ν_{max}^{KBr} 1775, 1740, 1695, 1615 cm^{-1}; nmr 1.06 (18-H), 5.59 (4-H), 6.47–6.56 (6-H and 7-H), 6.50–6.60 ppm (2α-H); molecular ion *m/e* 312. *Anal.* Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45; O, 20.49. Found: C, 73.25; H, 6.66; O, 20.60.

3,17-Dioxo-2β-hydroxy-5α-androstan-19-oic Acid 2,19-Lactone (17). A.—A suspension of 100 mg of lactone **15** in 2 ml of absolute ethanol plus 30 mg of 5% Pd/C was shaken in a hydrogen atmosphere under a pressure of 50 psi for 2 hr. The mixture was filtered and the filtrate was concentrated under vacuum. The residue was dissolved in methylene chloride and extracted in turn with 3% sodium bicarbonate and water until neutral. The organic solution was dried with anhydrous sodium sulfate and filtered through a column of 3 g of silica gel. The fractions eluted with 3% ether–97% methylene chloride yielded a crystalline material homogeneous on tlc analysis: mp 202–204°; $[\alpha]_D$ 200°; ν_{max} 1740, 1775 cm^{-1}. The infrared spectrum of this material was superimposable with that of the material obtained by lactonization with iodine in pyridine of the 3,17-dioxo-5α-androstan-19-oic acid (**16**) as described below. No depression was observed on mixture melting point determination with this same sample.

B.—A solution of 83.5 g of iodine in 285 ml of pyridine was prepared. To this solution, 95 g of 3,17-dioxo-5α-androstan-19-oic acid (**16**) was added and the mixture was heated to 60–70° for 2 hr. A precipitate of pyridine hydriodide was formed during the reaction. The mixture was cooled to room temperature and dilued with methylene chloride. This solution was washed with 5% aqueous sodium thiosulfate solution, 5% aqueous sodium bicarbonate solution, water, dilute hydrochloric acid, and finally water until neutral. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The crystalline residue was crystallized from acetone–hexane to yield 63 g in the first crop, mp 195–198°, and 23.5 g in the second crop, mp 193–196° (total 96%). The analytical sample obtained after three crystallizations from acetone–hexane showed mp 202–203.5°; $[\alpha]_D$ 200°;[20] ORD $[\Phi]_{280}$ −10,650°, $[\Phi]_{238}$ −4310°, $[\Phi]_{212}$ −10,590°; ν_{max} 1775, 1740 cm^{-1}; nmr 0.97 (18-H), 4.48–4.59 ppm (2α-H). *Anal.* Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65; O, 20.23. Found: C, 72.09; H, 7.75; O, 20.13.

3,17-Dioxo-2β-hydroxy-5β-androstan-19-oic Acid 2,19-Lactone (17a).—A solution of 65 g of iodine in 140 ml of pyridine was prepared. To this solution 46.3 g of 3,17-dioxo-5β-androstan-19-oic acid (**16a**) was added, and the mixture was heated on the steam bath for 2 hr. The reaction mixture was worked up as described above. Crystallization of the crude material from acetone yielded 27.1 g (59%) of **17a**, mp 221.5–223.5°. A pure specimen was obtained after two crystallizations from acetone: mp 223.5–224.5°; $[\alpha]_D$ 89°; ORD $[\Phi]_{600}$ 0°, $[\Phi]_{340}$ 570°, $[\Phi]_{320}$ 6320°, $[\Phi]_{300}$ 0°, $[\Phi]_{276}$ −6990°, $[\Phi]_{244}$ −5110°, $[\Phi]_{222}$ −9070°; ν_{max} 1770, 1735 cm^{-1}; nmr 0.95 (18-H), 4.00–4.40 ppm (2α-H). *Anal.* Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65; O, 20.23. Found: C, 72.16; H, 7.52; O, 20.12.

2β,3β,17β,19-Tetrahydroxy-5β-androstane (19b).—Reduction of **17a** with lithium aluminum hydride in the usual manner[21] yielded **19b**: mp 228–229°; $[\alpha]_D$ 0° (dioxane); ν_{max} 3400 cm^{-1}; nmr poor resolution (see below for the tetraacetate). *Anal.* Calcd for $C_{19}H_{32}O_4$: C, 70.33; H, 9.94; O, 20.73. Found: C, 69.69; H, 9.55; O, 20.53.

The acetonide **20a** was prepared from **19b** in the usual manner:[22] mp 175.5–177.8°; $[\alpha]_D$ 82°; ν_{max} 3450, 1155, 1135, 1080 (shoulder), 1075 cm^{-1} (strong); nmr 0.72 (18-H), 1.33 and 1.52

(18) Prepared as described by Kalvoda, *et al.*; *cf.* ref 7.

(19) St. Kaufmann, J. Pataki, G. Rosenkranz, J. Romo, and C. Djerassi, *J. Amer. Chem. Soc.*, **72**, 4531 (1950).

(20) The physical constants reported[18] for the 5α-lactones **17** and **17b** are in good agreement with those observed by us, with the exception of the $[\alpha]_D$ values, which are almost twice those reported. We can offer no sure explanation for this difference.

(21) See, for example, H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, Chapter 2.

(22) See, for example, C. Djerassi in "Steroid Reactions," Holden-Day, San Francisco, Calif., 1963, p 67.

(acetonide H), 1.54–1.72, and 3.00–3.25 (2 OAc), 4.3–4.41 (2α-H + 3α-H), 3.61 (17α-H), quartet 3.43, 3.54, 3.70, and 3.8 ppm (C-19 H). *Anal.* Calcd for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96; O, 17.56. Found: C, 72.44; H, 9.81; O, 17.45.

The tetraacetate **19c** was prepared in the usual manner:[23] mp 182–183°; $[\alpha]_D$ −2°; ν_{max} 1730, 1235 cm^{-1}; nmr 1.75 (18-H), 1.97 (acetate H), 2.00 (acetate H), 2.07 (2 acetate H), quartet centered on 4.19 (19-H), quartet centered on 4.55 (17α-H), multiplet spread over 4.70–4.95 (2α-H), narrow multiplet centered on 5.28 ppm (3α-H). *Anal.* Calcd for $C_{27}H_{40}O_8$: C, 65.83; H, 8.19; O, 25.99. Found: C, 65.91; H, 8.17; O, 26.02.

2β,3β,17β,19-Tetrahydroxy-5α-androstane (19).—Lithium aluminum hydride reduction of **17** in the usual manner[21] yielded **19**: mp 234°; $[\alpha]_D$ 20° (dioxane). *Anal.* Calcd for $C_{19}H_{32}O_4 \cdot CH_3COCH_3$: C, 69.07; H, 10.01; O, 20.91. Found: C, 68.84; H, 10.00; O, 21.32.

The acetonide **20** was prepared from **19** in the usual manner:[22] mp 183–184°; $[\alpha]_D$ 34°; ν_{max} 3445, 1148, 1125, 1080 (shoulder), 1050 cm^{-1} (strong); nmr 0.75 (18-H), 1.33 and 1.51 (acetonide H), multiplet centered at 2.73 (1β-H), 3.38 (methanol H), 3.7 (broad) (19-H), 4.2 (narrow multiplet) (2α-H), 3.74–4.4 ppm (broad multiplet) (3α-H). *Anal.* Calcd for $C_{22}H_{36}O_4 \cdot CH_3OH$: C, 69.66; H, 10.17; O, 20.17. Found: C, 70.20; H, 10.32; O, 19.94.

The tetraacetate **19a** was prepared as described above: mp 175.5–176.5°; $[\alpha]_D$ 20°; ν_{max} 1735, 1280 cm^{-1}; nmr 0.74 (18-H), 1.97 (2 acetate H), 2.01 (2 acetate H), quartet centered at 2.61 (1β-H), quartet centered at 4.33 (19-H), quartet centered at 4.54 (17α-H), broad multiplet spread over 4.70–4.95 (3α-H), narrow multiplet centered at 5.24 ppm (2α-H). *Anal.* Calcd for $C_{27}H_{40}O_8$: C, 65.83; H, 8.19; O, 25.99. Found: C, 65.78; H, 8.10; O, 26.07.

2β-Hydroxy-3,3-dimethoxy-17-oxo-5β-androstan-19-oic acid 2,-19-lactone (17c) was prepared in the usual manner:[13] mp 159.5–160°; $[\alpha]_D$ 137°; ν_{max} 1935, 1775, 1040 (shoulder), 1060, 1107, 1120 cm^{-1}. *Anal.* Calcd for $C_{21}H_{30}O_5$: C, 69.58; H, 8.53; O, 22.07. Found: C, 69.68; H, 8.32; O, 22.20.

2β,17β,19-Trihydroxy-5β-androstan-3-one (18c) was prepared from **17c** by lithium aluminum hydride reduction in the usual manner:[21] mp 234.5–237°; $[\alpha]_D$ 16°; ORD $[\Phi]_{600}$ 92°, $[\Phi]_{589}$ 92°, $[\Phi]_{334}$ 0°, $[\Phi]_{304}$ −690°, $[\Phi]_{298}$ −690°, $[\Phi]_{288}$ 0°, $[\Phi]_{260}$ 2300°, $[\Phi]_{230}$ 2600°, $[\Phi]_{210}$ 4540° (in methanol); ν_{max} 3525, 3400, 1735 cm^{-1}; nmr (DMSO-d_6) 0.67 (18-H), multiplet spread over 4.05–4.25 (2α-H). *Anal.* Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38; O, 19.85. Found: C, 71.25; H, 9.51; O, 19.22.

The triacetate **18d** was prepared from **18c** in the usual manner:[23] mp 168–170°; $[\alpha]_D$ +4°; ORD $[\Phi]_{600}$ 18°, $[\Phi]_{589}$ 18°, $[\Phi]_{420}$ −73°, $[\Phi]_{330}$ −405°, $[\Phi]_{304}$ −1505°, $[\Phi]_{299}$ 0°, $[\Phi]_{270}$ 2165°, $[\Phi]_{260}$ 2310°, $[\Phi]_{248}$ 2260°, $[\Phi]_{232}$ 2905°; ν_{max} 1735, 1225 cm^{-1}; nmr 0.82 (18-H), 2.03, 2.05, 2.14 (3 AcO), quartet centered at 4.25 (19-H), multiplet spread over 4.55–4.74 (17α-H), quartet 5.14, 5.2, 5.27, 5.34 ppm (2α-H) ($J_{1\beta,2\alpha}$ = 13.5, $J_{1\alpha,2\alpha}$ = 6.5, $J_{1\beta,2\alpha} + J_{1\alpha,2\alpha}$ = 20 Hz). *Anal.* Calcd for $C_{25}H_{36}O_7$: C, 67.24; H, 7.68; O, 25.08. Found: C, 67.49; H, 8.06; O, 24.28.

3,3-Dimethoxy-2β,17β-dihydroxy-5β-androstan-19-oic Acid 2,19-Lactone (17f).—Reduction of **17c** with lithium tri-*tert*-butoxyaluminum hydride as usual[21] gave **17f**: mp 165–166°; $[\alpha]_D$ −46°; ν_{max} 3450, 1775, 1130, 1060, 1023 cm^{-1}. *Anal.* Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85; O, 21.95. Found: C, 68.60; H, 9.04; O, 22.48.

2β,17β-Dihydroxy-3-oxo-5β-androstan-19-oic Acid 2,19-Lactone (17e).—A solution of 150 mg of ketal **17f** in 3 ml of methanol and 1 ml of water was treated with 1 ml of concentrated hydrochloric acid. The mixture was heated on the steam bath until most of the methanol had evaporated. The product crystallized as long needles and was collected by filtration. The pure specimen was prepared by crystallization from acetone–hexane: mp 194–195°; $[\alpha]_D$ −48°; ORD $[\Phi]_{600}$ −242°, $[\Phi]_{560}$ −341°, $[\Phi]_{370}$ −712°, $[\Phi]_{338}$ −1697°, $[\Phi]_{307}$ 725°, $[\Phi]_{260}$ −1515°, $[\Phi]_{234}$ −1775°, $[\Phi]_{209}$ −11,580° (in dioxane); ν_{max} 3500, 1750 cm^{-1}; nmr 0.83 (18-H), multiplet spread over 1.3–1.6 (17β-OH), multiplet spread over 3.5–3.7 (17α-H), and 4.45 and 4.51 ppm (2α-H). *Anal.* Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23; O, 20.10. Found: C, 71.31; H, 8.95; O, 20.75.

3,3-Dimethoxy-2β-hydroxy-17-oxo-5α-androstan-19-oic acid 2,19-lactone (17b) was prepared from **17** as usual:[13] mp 208–209°; $[\alpha]_D$ 118°; ν_{max} 1125, 1082, 1058, 1048, 1780, 1740 cm^{-1}; nmr 0.95 (18-H), 3.22 and 3.24 (2 MeO), 4.34–4.60 ppm (2α-H) (reported[13,20] mp 210–212°; $[\alpha]_D$ 55°). *Anal.* Calcd for $C_{21}H_{30}O_5$: C, 69.45; H, 8.34; O, 22.07. Found: C, 69.47; H, 8.38; O, 22.01.

2β,17β-Dihydroxy-3-oxo-5α-androstan-19-oic Acid 2,19-Lactone (17d).—Reduction of **17b** with sodium borohydride as usual[21] followed by acid hydrolyses as described before yielded **17d**: mp 182–182.5°; $[\alpha]_D$ 133.5°; ORD $[\Phi]_{600}$ −131°, $[\Phi]_{400}$ −412°, $[\Phi]_{350}$ 1385°, $[\Phi]_{330}$ 3455°, $[\Phi]_{300}$ 0°, $[\Phi]_{280}$ −4912°, $[\Phi]_{250}$ −3004° (in dioxane); ν_{max} 3420, 1775, 1730 cm^{-1}; nmr 0.85 (18-H), quartet centered at 3.0 (1β-H), multiplet spread over 3.5–3.8 (17α-H) and doublet at 4.23 and 4.3 ppm (2α-H) (reported[13] mp 182.5–183.5°; $[\alpha]_D$ 145°). *Anal.* Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23; O, 20.10. Found: C, 70.89; H, 8.23; O, 20.02.

Registry No.—**9,** 14507-55-2; **11a,** 35672-38-9; **13a,** 35672-39-0; **15,** 35672-40-3; **17,** 35672-41-4; **17a,** 35672-42-5; **17b,** 35672-43-6; **17c,** 35672-44-7; **17d,** 35672-45-8; **17e,** 35661-30-4; **17f,** 35661-31-5; **18c,** 35661-32-6; **18d,** 35661-33-7; **19,** 35661-34-8; **19a,** 35737-08-7; **19b,** 35737-09-8; **19c,** 35661-35-9; **20,** 35661-36-0; **20a,** 35661-37-1.

(23) See, for example, J. March, "Advanced Organic Chemistry," McGraw-Hill, New York, N. Y., 1968, p 320.