(110 mg) were dissolved in 3 ml of methanol. The solution was heated for a few minutes whereupon a heavy, crystalline precipitate appeared. The resulting suspension was cooled in an ice bath, the crystals were collected by filtration, washed well with cold methanol, and dried at room temperature under reduced pressure (1.0 mm). The resulting tosylhydrazone derivative (XXXVI, (132 mg, 82%, mp 149–158° dec) contained traces of a ketonic contaminant according to its infrared spectrum.

A slurry of the crude tosylhydrazone (XXXVI, 90 mg) and lithium aluminum deuteride (90 mg) in dry dioxane (3 ml, reagent grade) was heated under reflux for 2 hr. After this period, the excess deuteride was decomposed with a few drops of deuterium oxide and the mixture was heated again for 5 min. The crystalline residue which was obtained, upon removal of the inorganic salts by filtration and evaporation of the dioxane under reduced pressure, was dissolved in methanol which contained a few drops of dilute hydrochloric acid. After heating under reflux for 1 hr the methanol was evaporated under reduced pressure, the residue was dissolved in ether, and the ether solution was washed with water and dilute sodium bicarbonate solution and dried over magnesium sulfate. Evaporation of the ether gave the crude product which was purified by tlc with benzene, yielding 28 mg (55%) of pure **3,3-d_2-5α-pregnan-20-one** (XXXVII), mp 136–138°; the isotope composition was 6% d_1 and 94% d_2.

Registry No.—VII, 7704-78-1; X, 848-62-4; XXXII, 7733-99-5; XXVIII, 7721-36-0; XVI, 7704-79-2; XXXVII, 7704-80-5; XX, 7704-81-6; XV, 7704-82-7; V, 7704-83-8; XIII, 7704-84-9; XVII, 7704-85-0; XXI, 7721-37-1; XI, 7704-86-1; XIV, 7704-87-2; II, 7721-38-2; VIII, 7704-88-3; III, 7721-39-3; IX, 3752-04-3; IV, 7704-89-4; XII, 7704-90-7; XIX, 7718-52-7; XXIV, 7704-91-8; XXIII, 7738-86-5; XXV, 7704-92-9; XXVII, 7704-93-6; XXVI, 7704-94-1; XXXV, 1452-23-9; XXXVI, 7721-40-6.

C-19 Functional Steroids. XI.[1a] Some Reactions of C-19 Aldehydes[1b,c]

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Degradation of 19-oximino steroidal 5,6-chlorohydrins gave 6,19-hemiacetals which with zinc in acetic acid furnished Δ^5-19 aldehydes in the androstane series. Reduction of the double bond (Pd–H_2) in alcoholic solution gave the 5α-steroidal 19-alkyl acetal. These compounds were hydrolyzed and oxidized to form 3,19-lactones. 19-Oxo-5α-androstane-3β,17β-diol diacetate on ultraviolet irradiation in ethyl acetate in the presence of oxygen gave 5α-androstane-3β,10β,17β-triol 3,17-diacetate.

During the preparation of derivatives of **17**[2] for biological evaluation[3] reactions of steroidal C-19 aldehydes were studied. These results are now described. Treatment of **1**[4] and **2**[5] with nitrous acid gave **3** and **4**, respectively. These compounds were mixtures of C-19 anomers as shown by their nmr spectra. After deuteration of the hydroxyl hydrogen in **3** to obviate spin splitting of the C-19–H resonance, two signals from this proton at 5.30 and 5.78 ppm in a ratio of approximately 75:25 were seen, and two C-18–H signals at 0.80 and 0.85 in the same ratio were observed. The two high-field peaks of each pair clearly arise from the (19*S*)-hydroxy anomer (Figure 1) in which relative to the (19*R*)-hydroxy anomer the C-19–H is more distant from the deshielding C-3 oxygen function and C-18 is more distant from the deshielding hydroxy group. A similar situation prevails in the case of **4**, in which the C-19 and C-18 peaks occur at 5.36 and 0.88 ppm, respectively, in the (19*S*) hydroxy isomer, and at 5.83 and 0.93 for the (19*R*) isomer. (See Scheme I.)

Treatment of **3** and **4** with zinc in acetic acid resulted in elimination of the elements of hypochlorous acid and gave directly **5**[5] and **7**,[6,7] respectively. The over-all yield of the aldehyde from the oxime was approximately 70% in both cases, making this an especially good way for obtaining Δ^5-C-19 aldehydes. Saponification of **5** and **7** gave **6**[5] and **8**,[7] respectively. Reduction of **6** with palladium and hydrogen in methanol solution readily gave acetal **9**. This material had mp 154–156°, but showed two spots on tlc and glpc. The nmr spectrum showed two C-19–H bands in 1:1 ratio at 4.75 and 4.95 ppm and two methoxyl peaks at 3.40 and 3.42 ppm. The C-18 resonance occurred at 0.73 and 0.75 ppm. Unlike the situation in 6,19-hemiacetals **3** and **4**, it is not possible in this case to determine the sterically favored C-19 isomer from an inspection of models, nor is it possible to assign the individual nmr peaks to one or the other isomer. Even when the reduction was performed in isopropyl alcohol solution, two isomers corresponding to **10** were obtained, as shown by C-19–H resonance at 4.91 and 5.13 ppm in the ratio 2:1. The minor component was obtained in pure form after chromatography and recrystallization, and it was found that the low-field C-19 resonance and the high-field C-18 resonance are produced by this isomer.

By contrast to 6,19-hemiacetals **3** and **4**, in which ring B is in a stable chair, ring A must form a boat in **9** and **10**. Therefore, the hydrolysis of **9** and **10** gives open aldehyde **14**, rather than the cyclic hemiacetal, as the sole isolable product.

(1) (a) Paper X: M. E. Wolff and T. Morioka, *J. Org. Chem.*, **30**, 2553 (1965). (b) This investigation was supported in part by a Public Health Service research grant (AM-05016) from the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service. (c) A preliminary account of portions of this work has been presented: M. E. Wolff and S.-Y. Cheng, *Tetrahedron Letters*, 2507 (1966). (d) From the Ph.D. Thesis of S.-Y. Cheng, University of California at San Francisco, 1966.

(2) This study was initiated in this laboratory by Dr. Timothy Jen, who prepared compounds **16** and **17**: T. Jen, Ph.D. Thesis, University of California at San Francisco, 1963, pp 46–47, 70–71, 80–81.

(3) Evaluation of **16** for its ability to antagonize the myotrophic–androgenic effect of testosterone propionate showed that it had slight activity when measured by the method of L. O. Randall and J. J. Selitto, *Endocrinology*, **62**, 693 (1958). However, compounds **18**, **19**, **20**, and **21** were inactive in this test. All tests were conducted using ten times as much antagonist as testosterone propionate, and were performed at Endocrine Laboratories, Madison, Wis.

(4) T. Jen and M. E. Wolff, *J. Med. Pharm. Chem.*, **5**, 876 (1962); *J. Med. Chem.*, **6**, 726 (1963).

(5) T. Jen and M. E. Wolff, *J. Org. Chem.*, **28**, 1573 (1963).

(6) K. Tanabe, R. Takasaki, K. Sakai, R. Hayashi, and Y. Morisawa, *Chem. Pharm. Bull.* (Tokyo), **10**, 1126 (1962).

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

stirring for 30 min. The resulting mixture was cooled to 27°, filtered, and poured into 1 l. of ice–water. The precipitated steroid was filtered, dried, and recrystallized from hexane–acetone to afford 6.2 g (90%) of the product, mp 145–147°. Further recrystallization alternately from acetone–hexane and ethanol–water gave the analytical sample: mp 146–148° (lit.[6,7] 148–150°, 151–152°); ν_{max}^{KBr} 1745, 1725, 1720, 1240 cm^{-1}.

Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.48; H, 8.08.

3β-Hydroxy-19-oxoandrost-5-e-17-one (8).—A solution of 4.2 g (0.012 mole) of **7** in 120 ml of 5% methanolic potassium hydroxide was refluxed for 30 min. The resulting solution was concentrated *in vacuo* and poured into 800 ml of ice–water. The precipitated steroid was collected by filtration, dried, and recrystallized from acetone–hexane to afford 3.0 g (83%) of the hydrolyzed product, mp 145–149°. Further recrystallization gave the analytical sample: mp 149–151°; $[\alpha]^{20}D$ −179° (*c* 1, $CHCl_3$) (lit.[7] mp 141–146°, $[\alpha]^{20}D$ −165°); ν_{max}^{KBr} 3390, 1725, 1715 cm^{-1}.

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.46; H, 8.45.

3β,19-Epoxy-19-methoxyandrostan-17β-ol (9).—A mixture of 1.50 g (0.00493 mole) of **6** and 0.5 g of 10% palladium on charcoal in 120 ml of methanol was shaken under hydrogen at 30 psi until 1 mole of gas was absorbed (20 min). The catalyst was removed by filtration and the solvent was evaporated *in vacuo*. The crystalline product was recrystallized from acetonitrile to afford 0.85 g (54%) of **9**, mp 150–156°. Further recrystallization from acetone–hexane gave the analytical sample: mp 154–156°; ν_{max}^{KBr} 3400 cm^{-1}; $[\alpha]^{25}D$ +35° (*c* 1, $CHCl_3$); glpc two peaks, relative retention time as compared with cholesterol (0.285, 0.295); nmr 0.73, 0.75 (C-18 methyls), 3.40, 3.42 (methoxy methyls), 4.75, 4.95 (C-19 H) ppm and 210–245 cps (low hump, 3α-H, 17α-H).

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 74.56; H, 9.71.

3β,19-Epoxy-19-isopropoxy-5α-androstan-17β-ol (10).—A mixture of 0.3 g (0.001 mole) of **6** and 0.20 g of 10% palladium on charcoal in 50 ml of 2-propanol was shaken under hydrogen at 30 psi until 1 mole of gas was absorbed (20 min). The catalyst was removed by filtration and the solvent was evaporated to dryness *in vacuo*. Upon recrystallization of the residue from acetonitrile, 0.08 g (23%) of **10** was obtained. Further recrystallization gave the analytical sample: mp 189–191°; $[\alpha]^{20}D$ −44° (*c* 0.1, $CHCl_3$); ν_{max}^{KBr} 3250 cm^{-1}; nmr 0.73 (C-18 methyl), 1.18, 1.23 (doublet, isopropoxy methyls), 5.1 (C-19 acetal H) ppm and 200–255 (multiplet, 17α-H and isopropoxy H) cps.

Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.82; H, 10.41. Found: C, 76.30; H, 10.15.

5α-Androstane-3,17-dion-19-oic Acid (11).—To a solution of 0.05 g (0.00015 mole) of **13** in 250 ml of acetone there was added slowly 2.0 ml (excess) of 8 *N* chromic acid reagent and the mixture was kept at 25° for 1 hr. The excess oxidizing reagent was destroyed with 2-propanol and the residue was removed by filtration. After the addition of a small quantity of water, the mixture was evaporated *in vacuo* to give a crystalline precipitate. The precipitate, on recrystallization from acetone, yielded 0.04 g (80%) of **11**, mp 195–196° (lit.[8] 199.5–201.5°).

3β,17β-Dihydroxy-5α-androstan-19-oic Acid 3,17-Diacetate (12).—To a solution of 0.12 g (0.00032 mole) of **15** in 5 ml of acetone was added, slowly with stirring, 0.5 ml (excess) of 8 *N* chromic acid reagent and the mixture was kept at 25° for 30 min. The excess oxidizing reagent was destroyed by the addition of 2-propanol. After the addition of a small quantity of water, the mixture was evaporated under reduced pressure and the oily residue was extracted with 80 ml of ether. The ether extract was dried over anhydrous sodium sulfate and evaporated *in vacuo*. Upon treatment of the residue with hexane, a crystalline product precipitated and was filtered to afford 0.10 g (77%) of material, mp 158–160°. Recrystallization from methanol–water raised the melting point to 191–194°. Further recrystallization gave the analytical sample: mp 193–194°; $[\alpha]^{20}D$ −4° (*c* 1, $CHCl_3$); ν_{max}^{KBr} 1740, 1700, 1250 cm^{-1}.

Anal. Calcd for $C_{23}H_{34}O_6$: C, 67.96; H, 8.43. Found: C, 68.08; H, 8.12.

19-Oxo-5α-androstane-3β,17β-diol (14).—A mixture of 0.50 g (0.00156 mole) of **9** in 30 ml of methanol–water (1:1), containing 1% of hydrochloric acid was refluxed for 50 min. While the resulting solution was hot, water was added until turbidity occurred. Upon standing, crystals separated slowly from the cold solution. The crystals were collected by filtration and dried to afford 0.45 g (94%) of the product. Several recrystallizations from acetone–hexane gave the analytical sample: mp 167–169°; mass spectrum M$^+$ 390; λ_{max}^{EtOH} 380 mμ (ε 22); $[\alpha]^{20}D$ +30° (*c* 1, $CHCl_3$); ν_{max}^{KBr} 3480, 3400, 3230, 1710 cm^{-1}; nmr (DMSO-d_6–$CDCl_3$) 0.63 (C-18 methyl), 9.95 (aldehyde H) ppm and 192–230 (3α-H, 17α-H) cps.

Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.26; H, 9.53.

19-Oxo-5α-androstane-3β,17β-diol 3,17-Diacetate (15).—A solution of 0.100 g (0.00033 mole) of **14** in 1.5 ml of pyridine and 0.2 ml of acetic anhydride was kept for 18 hr at 27°. The resulting solution was diluted with water until turbid and chilled. The crystalline product was collected, washed with water, and dried to afford 0.125 g (97%) of the crude diacetate, mp 104–107°. Several recrystallizations from methanol gave the analytical sample: mp 116–117°; λ_{max}^{EtOH} 308 mμ (ε 26); $[\alpha]^{20}D$ +6° (*c* 1, $CHCl_3$); ν_{max}^{KBr} 1740, 1245–1235 cm^{-1}; nmr (C_6H_6) 0.65 (C-18 methyl), 1.73, 1.74 (acetate methyls), 9.83 (aldehyde H) ppm and 263–294 (3α-H, 17α-H, low hump) cps.

Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.67; H, 8.52.

3β-Hydroxy-17-oxo-5α-androstan-19-oic Acid 3,19-Lactone (16). Procedure A.—A solution of 0.6 g (0.00187 mole) of **9** in 100 ml of acetone was treated with 2.5 ml (excess) of 8 *N* chromic acid reagent at 25° for 30 min. The excess oxidizing reagent was destroyed with 2-propanol and the solution was filtered. After additon of a small quantity of water, the mixture was evaporated *in vacuo* to give a crystalline precipitate which was recrystallized from acetone–hexane, gave 0.3 g (53%) of **16**: mp 250–252° (lit.[8] 272–274°); $[\alpha]^{25}D$ +75° (*c* 1, $CHCl_3$); ν_{max}^{KBr} 1725, 1095 cm^{-1}; nmr 1.02 (C-18 H), 4.66 (3a-H) ppm.

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.61; H, 8.45.

The residue from evaporation of the mother liquor was dissolved in ether and extracted with 4% potassium hydroxide solution. The aqueous extracts were combined, acidified with 10% hydrochloric acid solution, aged in the cold, filtered, and dried to afford 0.1 g (17%) of **11**, mp 187–191°. One recrystallization from acetone raised the melting point to 195–197° (lit.[8] 199.5–201.5°).

Procedure B.—A mixture of 2.10 g (0.0069 mole) of **8** and 0.4 g of palladium on charcoal (10%) in 50 ml of methanol was shaken under hydrogen at 30 psi until 1 mole of hydrogen was absorbed (20 min). The catalyst was removed by filtration and the methanol was evaporated *in vacuo*. The oily residue was dissolved in 50 ml of acetone and treated with 1.5 ml (excess) of 8 *N* chromic acid at 25° for 30 min. The excess oxidizing reagent was destroyed with 2-propanol. After the addition of small quantity of water, the mixture was evaporated *in vacuo* to give a crystalline precipitate. The precipitate, upon recrystallization from acetone–hexane, afforded 0.66 g (31%) of **16**, mp 249–252°.

3β,17β-Dihydroxy-5α-androstan-19-oic Acid 3,19-Lactone (17).—A solution of 0.10 g (0.00033 mole) of **16** and 0.15 g of tri-*t*-butoxylithium aluminohydride in 15 ml of tetrahydrofuran was kept at 0° for 1 hr. It was first acidified with 20% hydrochloric acid solution until the mixture turned clear and then neutralized to pH 5 by means of 10% sodium bicarbonate solution. Evaporation of the solvent gave 0.09 g (90%) of **17**, mp 199–202°. The analytical sample, recrystallized from acetone–hexane, had mp 204–204°; $[\alpha]^{25}D$ +6° (*c* 1, $CHCl_3$); ν_{max}^{KBr} 3550, 1725 cm^{-1}.

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 75.02; H, 9.03.

3β,17β-Dihydroxy-5α-androstan-19-oic Acid 17-Acetate 3,19-Lactone (18).—A solution of 0.10 g (0.00033 mole) of **17** in 1 ml of pyridine and 0.5 ml of acetic anhydride was kept for 18 hr at 27°. The resulting solution was poured into 30 ml of ice–water. The precipitated steroid was collected and recrystallized from methanol to furnish 0.07 g (61%) of colorless needles, mp 195–198°. Eurther recrystallization gave the analytical sample: mp 198–199°; $[\alpha]^{20}D$ −3° (*c* 1, $CHCl_3$); ν_{max}^{KBr} 1725, 1245 cm^{-1}.

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 73.04; H, 8.49.

3β,17β-Dihydroxy-5α-androstan-19-oic Acid 3,19-Lactone 17-Propionate (19).—This compound was prepared using propionic anhydride and the procedure described for **18**. Recrystallization from hexane furnished the analytical sample: mp 171–173°; ν_{max}^{KBr} 1720, 1740, 1190 cm^{-1}; $[\alpha]^{20}D$ −7° (*c* 1, $CHCl_3$).

configuration, the proton at C-3 can be axial only in an A/B *trans* system. The hydroxyl group at C-10 can therefore only be β oriented, since a 5α proton has already been demonstrated. A quartet owing to the 17α proton overlies the C-3 band, but this does not interfere with the analysis.

The presence of a carboxyl group in **12** was established[12] by examination of its infrared spectrum in chloroform solution; on treatment with triethylamine, a carbonyl stretching band (1710 cm^{-1}) disappeared, whereas a carboxylate band (1550 cm^{-1}) appeared. An authentic sample of **12** was prepared by chromic acid oxidation of **15**. The true yields of **12** (50%) and **22** (20%) were determined by diazomethane treatment of a reaction mixture obtained under optimum conditions and quantitative gas chromatography of the resulting **24** and **22**. A study of the optimum conditions for this oxidative decarbonylation showed that the reaction is accelerated by oxygen and is catalyzed by light or azobisisobutyronitrile but not by hydrogen peroxide in the presence of either acid or alkali. The reaction is inhibited by tolylthiol. The activating wavelength is transmitted by Vycor No. 7910 filters but not by Pyrex No. 7740 and thus lies approximately between 240 and 310 mμ. Compound **15** was found to have λ_{max}^{EtOH} 308 mμ (ϵ 26) and presumably this n–π^* band is involved in the photochemical step.

The simplest sequence which accommodates these data is photochemical oxidation of the aldehyde to the corresponding per acid[13] or a related excited species. Disproportionation of this product to form **12**, **22**, and carbon dioxide would follow.[14] The fact that no formate ester of **22** was observed by gas chromatography argues against a Baeyer–Villiger mechanism. A stereospecific hydroxyl transfer and a chain mechanism clearly are involved, but it is not possible to state which portions of the process are ionic and which are free radical in nature. Likewise, the stereospecificity could be explained equally well by a concerted or tight-pair scheme. These results are in contrast to the photochemical decarbonylation of steroidal Δ^5-19-aldehydes[15,16] which is unaffected by oxygen. The reported autoxidation of strophanthidin[17] appears to be similar to the present process, and thus the 5β-hydroxy group appears not to be involved in the process.

Experimental Section[18]

5α-Chloro-6β,19-epoxyandrostane-3β,17β,19-triol 3,17-Diacetate (3).—To a solution of 4.8 g (0.0105 mole) of **1**[4] in 65 ml of 20% glacial acetic acid in dioxane there was added slowly a solution of 7.2 g of sodium nitrite in 35 ml of water. The resulting solution was kept for 2 hr at 27° and poured into 800 ml of ice–water. The precipitated steroid was collected and dried to afford 3.6 g (80%) of the product, mp 173–178°. Several recrystallizations from methanol gave the analytical sample: mp 181–182°; ν_{max}^{KBr} 3500, 1720, 1740, 1235, 1260 cm^{-1}; nmr 0.80, 0.85 (C-18 methyls), 5.30, 5.78 (C-19 acetal H) ppm and 238–256 (6α-H), 266–290 (17α-H), 293–330 (3α-H) cps; $[\alpha]^{20}D$ −7° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{23}H_{33}ClO_6$: C, 62.64; H, 7.54. Found: C, 62.48; H, 7.47.

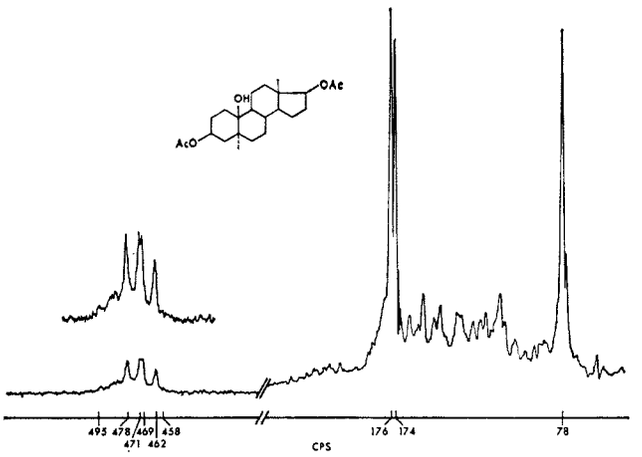


Figure 3.—Nmr spectrum (100 Mc in deuteriobenzene) of 5α-androstane-3β,10β,17β-triol 3,17-diacetate.

5α-Chloro-6β,19-epoxyandrostan-17-oxo-3β,19-diol 3-Acetate (4).—Treatment of **2**[5] by the procedure described for **3** gave 75% of **4**, mp 198–201°, after recrystallization from chloroform–hexane. Further recrystallization gave the analytical sample: mp 198–201°; $[\alpha]^{20}D$ +54° (*c* 1, $CHCl_3$); ν_{max}^{KBr} 3400, 1730, 1700, 1265, 1350 cm^{-1}; nmr 0.88, 0.93 (C-18 methyls), 5.36, 5.38 (C-19 acetal H) ppm and 244–252 (6α-H), 297–335 (3α-H) cps.

Anal. Calcd for $C_{21}H_{29}ClO_5$: C, 63.55; H, 7.37. Found: C, 63.31; H, 7.17.

19-Oxoandrost-5-ene-3β,17β-diol 3,17-Diacetate (5).—To a warm solution of 2.8 g (0.0063 mole) of **3** in 80 ml of glacial acetic acid was added 5.6 g of zinc dust (CP zinc 60–200 mesh, J. T. Baker Chemical Co., Phillipsburg, N. J.) and the stirred mixture was refluxed for 30 min. The mixture was cooled to 27°, filtered, and poured into 1 l. of ice–water. The precipitated steroid was filtered, dried, and recrystallized from aqueous ethanol to afford 2.1 g (88%) of colorless crystals, mp 149–151° (lit.[5] 150–153°).

19-Oxoandrost-5-ene-3β,17β-diol (6).—A solution 2.10 g (0.0054 mole) of **5** in 60 ml of 5% methanolic potassium hydroxide was refluxed for 30 min. The resulting solution was cooled to 27°, concentrated *in vacuo*, and poured into 500 ml of ice–water. The precipitated steroid was filtered, dried, and recrystallized from aqueous ethanol to give 1.45 g (88%) of the product, mp 188–191° (lit.[5] 185–188°).

19-Oxo-3β-hydroxyandrost-5-en-17-one 3-Acetate (7).—A warm solution of 7.5 g (0.02 mole) of **4** in 80 ml of glacial acetic acid was treated with 15 g of zinc dust and refluxed under mechanical

(12) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, p 44.

(13) Photochemical oxidation of benzaldehyde to perbenzoic acid has been reported by P. van der Beek, *Rec. Trav. Chim.*, **47**, 300 (1928).

(14) Disproportionation of several long-chain per acids to form the corresponding alcohols with one less carbon has been described by D. Lefort, C. Paquot, and J. Sorba, *Bull. Soc. Chim. France*, 1385 (1959).

(15) M. Akhtar, *Tetrahedron Letters*, 4727 (1965).

(16) (a) J. Iriarte, J. Hill, K. Schaffner, and O. Jeger, *Proc. Chem. Soc.*, 114 (1963); *Helv. Chim. Acta*, **49**, 292 (1966); (b) K. Schaffner, *Chimia*, **19**, 575 (1965).

(17) A. von Wartburg, J. Binkert, and E. Angliker, *Helv. Chim. Acta*, **45**, 2139 (1962).

(18) Melting points were taken with a Thomas–Hoover apparatus equipped with a corrected thermometer. Infrared spectra were obtained with a Beckman IR-8 or Perkin-Elmer 337 instrument. Ultraviolet spectra were obtained with a Cary 14 instrument. Microanalyses were carried out by the Microanalytical Laboratory, Chemistry Department, University of California at Berkeley, Berkeley, Calif. Optical rotations were obtained in a 0.5-dm tube with a Rudolph photoelectric polarimeter. Analyses by gas chromatography were carried out with a Barber–Coleman 5000 Selecta-System instrument equipped with glass columns, 1.8 m × 4 mm i.d., packed with 100–120 mesh Gas-Chrom Q coated with SE-30 or QF-1 (3% by weight), maintained at 215°, using helium carrier (20 psi). A flame detection system was used. Nmr spectra were obtained at a field strength of 60 Mc on samples in deuteriochloroform solution on Varian A-60 or A-60A instruments using tetramethylsilane as the internal standard, unless otherwise specified. A Varian C-1024 computer was used for time averaging. We thank Dr. Norman S. Bhacca and Varian Associates for the 100-Mc spectrum (compound **22**). Resonance positions are reported in δ units where possible; unresolved humps are described in cps units. Mass spectra were obtained on a Hitachi-Perkin-Elmer RMU-6D instrument by Morgan-Schaffer Corp., Montreal, Que., Canada. Silica gel G (according to Stahl, Brinkmann Instrument Inc., Hesburg, N. Y.) was used as the absorbent in the thin layer chromatography. Solvent systems of petroleum ether (bp 30–60°)–ether mixtures in different proportions were used in developing the plates and ceric ammonium sulfate in 15% H_2SO_4 was used as the spraying agent.

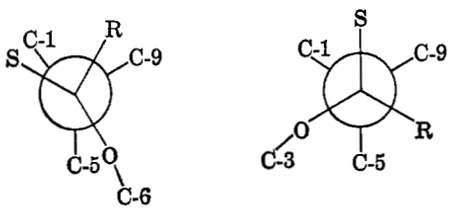


Figure 1.—Conformations and configurations of 3,19- and 6,19-acetals and -hemiacetals.

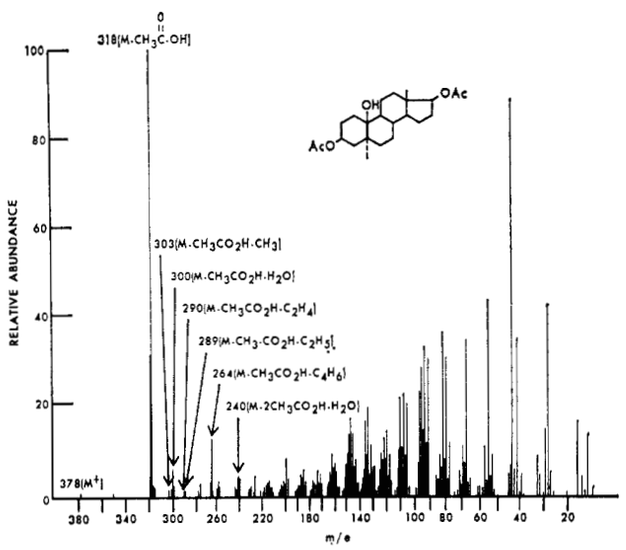


Figure 2.—Mass spectrum of 5α-androstane-3β,10β,17β-triol 3,17-diacetate (**22**).

Catalytic reduction of various Δ^4- and Δ^5-steroids has been shown to give varying proportions of 5α- and 5β-steroids depending on the material being reduced.[8] In the present study, only 5α-steroids were obtained in the catalytic reductions. The configuration at C-5 was established by conversion of **9** or **14** to dithiomercaptal **23** with ethanedithiol containing 5% hydrogen chloride. Product **23** was isolated as a stable ethyl acetate solvate as shown by analysis and nmr and mass spectrometry. Reductive desulfurization of **23** with Raney nickel in absolute ethanol gave 5α-androstane-3β,17β-diol, identical with an authentic sample[9] and thus establishing the configuration at C-5.

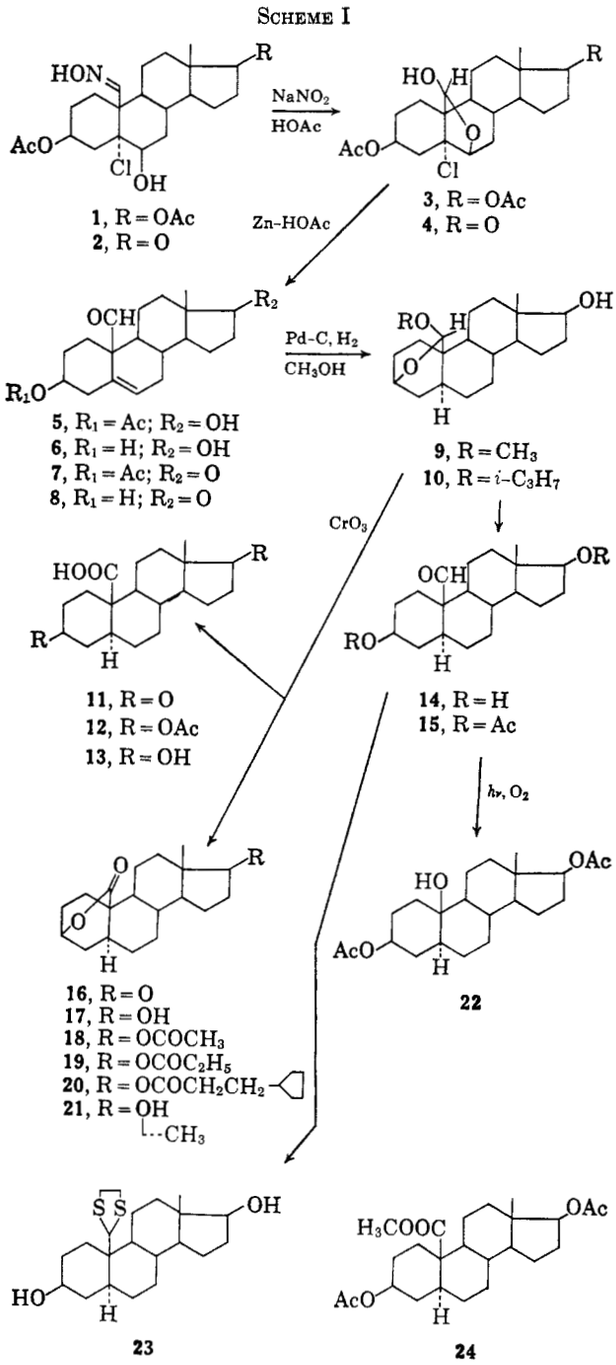
Oxidation of **9** with chromic acid in acetone gave a readily separable mixture of **11** (17%), which could also be obtained by chromic acid oxidation of **13**, and **16** (53%). Apparently, the methoxy acetal is first cleaved under the conditions of the reaction. Compound **16** could also be obtained by reduction of **8** followed by oxidation with chromic acid. After the initial preparation of **16**, mp 250–252°, in this laboratory[2] it was described by Knox, *et al.*,[8] as having mp 272–274°.[10] Reduction of **16** with lithium tri-*t*-butoxyaluminohydride gave 17β-hydroxy lactone **17**, which formed esters **18**, **19**, and **20** upon treatment with the appropriate acyl chloride. The action of methylmagnesium bromide on **16** gave 17α-methyl derivative **21**.

(8) (a) L. H. Knox, E. Blossey, H. Carpio, L. Cervantes, P. Crabbé, E. Velarde, and J. A. Edwards, *J. Org. Chem.*, **30**, 2198 (1965); (b) Y. Watanabe, U. Mizuhara, and M. Shiota, *ibid.*, **31**, 3785 (1966).

(9) A. Butenandt, K. Tshernig, and G. Hanisch, *Ber.*, **68**, 2097 (1935).

(10) During correspondence with Dr. Edwards it was learned that he had no material remaining so that a direct comparison could not be made.

SCHEME I



Acetylation of **14** gave **15**. During recrystallization of **15** from ethyl acetate, the spontaneous formation of two new compounds, shown to be **12** and **22**, was observed. Compound **22** showed a hydroxyl group in the infrared spectrum at 3500 cm^{-1}, but lacked aldehyde and vinyl proton signals in the nmr. The molecule weight of **22** was 378 (mass spectrometry; Figure 2) and an isotopic analysis at the parent ion ($M - CH_3CO_2H$) gave an empirical formula of $C_{20}H_{30}O_3$, corresponding to $C_{22}H_{34}O_5$ for **22**. A peak at *m/e* 300 corresponding to the loss of acetic acid and water, confirmed the presence of a hydroxyl group. The nmr spectrum of **22** (Figure 3) shows a broad band (458–495 cps) typical of axial protons geminal to an acetate function.[11] Since the acetate is known to have a 3β

(11) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964 pp 79–81.

Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.32; H, 8.70.

3β,17β-Dihydroxy-5α-androstan-19-oic Acid 3,19-Lactone 17-Cyclopentylpropionate (20).—This compound was prepared using cyclopentylpropionyl chloride and the procedure described for **18**. The crude product was extracted with chloroform, and the chloroform solution was washed successively with dilute hydrochloric acid, 5% sodium bicarbonate solution, and water, and dried (Na_2SO_4). The oily residue remaining after evaporation of the chloroform was dissolved in several drops of methanol and extracted with hexane. The hexane extracts were combined and evaporated to dryness *in vacuo*. Upon treating the residue with a few drops of methanol, the product crystallized and was collected by filtration to afford 0.06 g (61%) of the crude ester, mp 169–171°. Recrystallization from ethyl acetate and then acetonitrile furnished the analytical sample: mp 171–173°; $[\alpha]^{20}D$ +3° (*c* 1, $CHCl_3$); ν_{max}^{KBr} 1740, 1170 cm^{-1}.

Anal. Calcd for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 75.41; H, 9.20.

3β,17β-Dihydroxy-17α-methyl-5α-androstan-19-oic Acid 3,19-Lactone (21).—A solution of 0.155 g (0.0005 mole) of **16** in 1.50 ml of anhydrous tetrahydrofuran–ether was treated slowly with 5 ml of an ethereal solution of methylmagnesium bromide (3 *M*, Arapahoe Chemicals, Inc., Boulder, Col.) and refluxed for 18 hr. The resulting solution was poured into crushed ice, acidified with 20% hydrochloric acid to pH 1, and extracted with ether (three 100-ml portions). The combined extract was washed with water until the washings were neutral, dried (Na_2SO_4), and evaporated. The product was recrystallized from ethanol–water to afford 0.110 g (70%) of **21**, mp 229–233°. Further recrystallization furnished the analytical sample: mp 239–242°; $[\alpha]^{20}D$ −13° (*c* 1, $CHCl_3$); ν_{max}^{KBr} 3600, 1720 cm^{-1}.

Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.20; H, 9.28.

Oxidative Photochemical Decarbonylation of 15. A. Preparative Procedure.—A solution of 0.80 g (0.002 mole) of **15** in 15 ml of ethyl acetate (reagent grade, Eastman Organic Chemicals, Rochester, N. Y.) in a 500-ml, quartz, round-botton flask was irradiated under a stream of oxygen for 1 hr at 25° by a Hanovia 450 w high-pressure mercury arc equipped with a Vycor No. 7910 filter (Corning Glass Works, Corning, N. Y.). When a Pyrex No. 7740 filter was used, no product was obtained. The solvent was evaporated *in vacuo* and the oily residue was chromatographed on 60 g of Florisil. Elution with 26–32% of ether in petroleum ether and recrystallization from ether–hexane, gave 0.05 g (6%) of colorless needles of **5α-androstane-3β,10β,17β-triol 3,17-diacetate (22)**, mp 174–175°. Further recrystallization furnished the analytical sample: mp 174–175°; mass spectrum M^+ 378; ν_{max}^{KBr} 3500, 1740, 1720, 1262, 1240 cm^{-1}; $[\alpha]^{20}D$ −21° (*c* 1, $CHCl_3$); nmr (C_6D_6, 100 Mc) 0.78 (C-18 methyl), 1.74, 1.76 (acetate methyls) ppm and 462, 469, 471, 478 (17α-H quartet), 458–495 (3α-H, multiplet) cps.

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.84; H, 9.26.

A second crystalline fraction was obtained from the elution with 30–40% petroleum ether in ether. The fractions were combined and extracted with 50 ml of 4.5% sodium hydroxide solution. After washing the sodium hydroxide aqueous extracts with 20 ml of ether, the solution was acidified with 20% hydrochloric acid and the crystalline steroid precipitate was filtered and dried to afford 0.30 g (47%) of **3β,17β-dihydroxy-5α-androstan-19-oic acid (13)**, mp 271–272°, formed from **12** by hydrolysis during the work-up. Several recrystallizations from methanol–water gave the analytical sample: mp 271–272°; ν_{max}^{KBr} 3465, 1700 cm^{-1}; $[\alpha]^{20}D$ +29° (*c* 0.2, dioxane).

Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.78; H, 9.12.

In another run, 0.5 g (0.0012 mole) of **15** was irradiated in the same way and 0.1 g of pure **12**, mp 186–189° was directly obtained after column chromatography.

B. Determination of the Exact Yield of 12 and 22.—One microliter of a 0.10% ethyl acetate solution of **22** was injected into a gas chromatograph to give a peak of standard area. Ten milliliters of 0.10% ethyl acetate solution of **15** was irradiated as described above. After the reaction had been completed, the mixture was transferred to a 10-ml volumetric flask and additional ethyl acetate was added to the mark. This solution was then divided into two equal parts (A and B). Glpc of 5 μl of A gave a peak with an area exactly equal to the one shown by known standard solution. The yield of **22** was calculated to be 20%.

Part B was treated with diazomethane to obtain **24** (detailed procedure described under compound **24**). Similarly, using a 0.10% ethyl acetate solution of **24** as the standard, the yield of **12** from the photochemical decarbonylation reaction was determined to be 50%.

C. Effect of Oxygen, Hydrogen Peroxide, and Other Reagents. (1).—After a stream of oxygen was passed through a 0.2% ethyl acetate solution of **15** for 30 min, it was capped. A second solution of the same concentration but without oxygen treatment was left exposed to atmospheric oxygen. Both solutions were then kept under ordinary room light. Quantitative gas chromatographic analysis of both reaction mixtures after 17 hr indicated the complete conversion of **15** in the solution which had been treated with oxygen, while the control still showed the presence of 60% of **15** which disappeared completely only after 72 hr.

(2).—Several drops of various aqueous hydrogen peroxide solutions (5, 10, 15, 20, 25, and 30%) were added to 1 ml of a 0.2% ethyl acetate solution of **15**. No accelerated conversion to **22** was observed by gas chromatography. The addition of 10% hydrochloric acid or 10% sodium hydroxide to the peroxide solution did not change the results. The addition of 25 and 30% aqueous hydrogen peroxide simply oxidized **15** to **12**.

(3).—When a few crystals of azoisobutyronitrile were added to a 0.2% ethyl acetate solution of **15** followed by passing through a stream of oxygen for 15 min, reaction was completed within 5 hr. However, if a few drops of tolylthiol were added into the solution instead of azoisobutyronitrile, no conversion was observed at all.

3β,17β-Dihydroxy-19-oxo-5α-androstanethylene Thioketal (23).—A solution of 0.30 g (0.0009 mole) of **9** in 1.5 ml of ethanedithiol was cooled to 0° in an ice–salt bath and dry HCl gas was slowly bubbled into the stirred solution until approximately 0.085 g of gas was absorbed (5%, w/v). Stirring was continued for 10 min at 0° and at 27° for 2.5 hr, during which time the product crystallized. It was collected and washed successively with dilute hydrochloric acid solution, 5% sodium bicarbonate solution, and distilled water. There was obtained 0.35 g (93%) of the crude ketal, mp 108–115°. Several recrystallizations from ethyl acetate gave the analytical sample as the ethyl acetate solvate: mass spectrum, two components, M^+ 88 (volatilized at 110°, ethyl acetate), M^+ 382 (volatilized at 150°, compound **23**); mp 113–115°; ν_{max}^{KBr} 3400 cm^{-1} (broad); $[\alpha]^{20}D$ +24° (*c* 1, $CHCl_3$); nmr 0.80 (C-18 methyl), 4.92 (C-19 H) ppm and 177–200 (ethylene H, multiplet) 201–230 (3α-H 17α-H, low hump) cps and 1.25 (triplet), 2.03, 4.12 (quartet) ppm owing to ethyl acetate.

Anal. Calcd for $C_{21}H_{34}O_2S_2 \cdot C_4H_8O_2$: C, 63.81; H, 9.00; S, 13.59. Found: C, 63.92; H, 8.76; S, 13.55.

5α-Androstane-3β,17β-diol.—A mixture of approximately 2.0 g of Raney nickel (W. R. Grace & Co., Raney Catalyst Division, Pittsburgh, Pa.) in 10 ml of absolute ethanol and 0.2 g (0.00052 mole) of **23** in 6 ml of absolute ethanol was stirred magnetically for 18 hr at 25° and filtered. The gummy residue from evaporation of the filtrate was treated with a small amount of ether and 0.1 g (66%) of the product precipitated. Recrystallization from ethanol and then acetone gave a sample, mp 159–161° (lit.[9] 162–164°); with an authentic sample mixture melting point was 160–162°. The infrared spectrum was indistinguishable from that of an authentic sample, and the glpc retention time (QF-1) was the same as that of the authentic sample.

3β,17β-Dihydroxy-19-carbomethoxy-5α-androstane 3,17-Diacetate (24).—To a solution of 0.15 g (0.0037 mole) of **12** in 60 ml of ethyl acetate, there was added slowly 0.1 g of diazomethane in 5 ml of ether and the mixture was kept at 27° for 1 hr. Several drops of 10% acetic acid was added to decompose the excess diazomethane. The resulting solution was washed with 30 ml of 1% sodium bicarbonate and the aqueous bicarbonate solution was extracted once with ether. The ether solution was combined with ether–ethyl acetate solution and dried (Na_2SO_4). The solvent was evaporate *in vacuo* and the product was crystallized to give 0.09 g (60%) of **24**, mp 128–130°. Several recrystallizations from methanol–water afforded the analytical sample: mp 129.5–131°; $[\alpha]^{20}D$ +5° (*c* 0.7, $CHCl_3$); ν_{max}^{KBr} 1720, 1735, 1240 cm^{-1}.

Anal. Calcd for $C_{24}H_{36}O_6$: C, 68.55; H, 8.63. Found: C, 68.30; H, 8.65.

Registry No.—**3**, 7677-63-6; **4**, 7641-53-4; **5**, 2951-52-2; **6**, 7677-64-7; **7**, 2067-71-2; **8**, 5833-76-1; **9**, 7641-56-7; **10**, 7641-57-8; **11**, 2059-60-1; **12**, 6986-19-2; **14**, 7641-59-0; **15**, 7090-12-2; **16**, 2229-22-3; **17**, 7641-62-5; **18**, 7641-63-6; **19**, 7641-64-7; **20**, 7677-66-9; **21**, 7641-65-8; **22**, 6986-20-5; **13**, 7641-67-0; **23**, 6992-20-7; 5α-androstane-3β,17β-diol, 1892-77-9; **24**, 7641-68-1.

Conformational Transmission. I. The Effect of an 11β-Hydroxyl Group on the Enolization Properties of 3-Oxo 5β-Steroids

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A comparison of the enol acetylation properties of 11β-hydroxy-3-oxo 5β-steroids and 3-oxo 5β-steroids has demonstrated that, in the isopropenyl acetate (kinetic control) and acetic anhydride–perchloric acid (thermodynamic control) enol acetylation reactions, the 11β-hydroxyl group caused an increase in Δ^2-enol acetate formation. In the perchloric acid catalyzed acetic anhydride enol acetylation, the 11β substituent had a rate-retarding influence which was due to a preferential retardation of Δ^3-enol acetate formation. Equilibration studies indicate that the $\Delta F°_{25}$ for the 11β-hydroxyl group effect is approximately 1.0 kcal/mole. Evidence is presented which indicates that a C-17β acetoxyl group contributes about 0.25 kcal/mole to the 11β-hydroxyl group effect.

Chemical modification of the natural hormone cortisol has led to the conclusion that the most structurally specific portion of the corticoid is the 11β-hydroxyl group.[2] Speculation about the role of this substituent evolved from the work of Fried[3,4] who discovered the parallel between corticoid activity and the acidity of the 11β-hydroxyl group as influenced by vicinal substituents. It was postulated that protein–steroid binding at the receptor site was dependent on hydrogen bond formation to the C-11 hydroxyl group. However, the subsequent discovery that some 11-deoxy steroids such as 16α,17α-isopropylidenedioxy-6α-methylpregna-1,4-diene-3,20-dione[5] and 1α-acetylthio-17,21-dihydroxypregn-4-ene-3,20-dione[6] possess corticoid activity suggested that the role of the 11β-hydroxyl group was more complex than originally had been estimated. The absence of corticoid activity in a 2α-methyl-17α,21-dihydroxypregn-4-ene-3,11,20-trione as opposed to the activity of 2α-methyl-11β,17α,21-trihydroxypregn-4-ene-3,20-dione[7] and the significant activity of 21-acetoxy-9α,11β-dichloro-17α-hydroxypregna-1,4-diene-3,20-dione[8] led to speculation that perhaps the 11β substituents exerted their influence by steric as well as polar effects.

Since electron density and sp^2 hybridization are known to influence other types of hormone action[9,10] it was decided to investigate the effect of the 11β-hydroxyl group on the enolization properties of the C-3 carbonyl group of steroids. It also was of interest to determine the magnitude of the forces involved in the distortion of the steroid nucleus upon insertion of the 11β-hydroxyl group. This required a model steroid in which there was a dual enolization of the C-3 carbonyl group. Our previous work on the enolization properties of 3-oxo 5β-steroids indicated that these compounds were suitable for this study.[11] Although they do not possess the planar structure of the Δ^4-3-oxo steroids, the B, C, and D rings are such that the nonbonded interactions introduced upon the insertion of an 11β-hydroxyl group should be identical.

Thermodynamically controlled enol acetylation using perchloric acid catalyst and acetic anhydride[12] has been an excellent method of determining the enolization of cyclic ketones[11,13] and was employed for our investigation. Two model steroids were chosen, the first compound, 17β-acetoxy-11β-hydroxy-5β-androstan-3-one (**10a**), is the 11β-hydroxy analog of 17β-acetoxy-5β-androstan-3-one (**10c**) while the second compound, 11β-hydroxy-5β-androstan-3-one (**10b**), is the unacetylated positional isomer of **10c**. These steroids were studied to demonstrate the effect of the 11β-hydroxyl group and also to determine if a C-17 substituent exerted a buttressing effect on the C-18 angular methyl group.

The compounds were prepared from cortisone acetate (1) by selective ketalization of the conjugated ketone to yield 3,3-ethylenedioxy-21-acetoxy-17α-hydroxypregn-5-ene-11,20-dione (2).[14] The ketal (2) was reduced by sodium borohydride in aqueous alkali to a C-20 epimeric mixture of tetrols (3) and cleaved with sodium periodate to yield 3,3-ethylenedioxy-11β-hydroxyandrost-5-en-17-one (**4**)[15,16] which served as a

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