Steroidal Spirolactols (17→22)[1]

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A practical synthesis of lactols from lactones employs sodium in ammonia. The method is used to transform a number of C-17 spirolactones to their lactols; *e.g.*, the lactone **12b** yields 3-[3-methoxy-17β-hydroxyestra-1,3,5(10)-trien-17-yl]propionaldehyde lactol (**12a**). In contrast, the use of lithium metal produces **14**, in which the lactone group has been reduced to a diol and the aromatic ring to a dihydroaromatic system. The mechanism of the reaction is discussed with regard to these differences. An alternate synthesis of the lactol (**5a** or **12a**) is also presented, entailing oxidation of the 17-acetoxy-22-hydroxy steroid **1c** or (**8b**) to its 22-aldehyde and subsequent acetal formation, ester hydrolysis, and acetal hydrolysis.

The success of the spirolactones as potent aldosterone blockers[2] has produced a continuing stimulus to synthesize related derivatives.[1b,3] As part of this program the corresponding spirolactols[4] were prepared, a choice suggested by the structure of the physiologically potent mineralocorticoid, aldosterone. Early exploration of an oxidative synthesis of the spirolactol system from 17,22-diols (such as **1a**) produced mixtures of lactone and starting material.[5] This result is reasonably explained by the greater ease of oxidation of the lactol compared with the starting diol. Esterification of the 17-hydroxyl before oxidation, thus preventing lactol formation, was expected to allow isolation of the desired aldehyde and eliminate lactone production.

Passage of the triacetate **1b** over alumina effected hydrolysis of the primary acetate group (to **1c**) leaving the secondary and tertiary functions protected.[6] Subsequent oxidation with either chromium trioxide–pyridine or *t*-butyl chromate afforded the aldehyde **2a** as the principle product. Attempts to separate this compound from by-products by chromatographic purification led to the isolation of a crystalline product of higher molecular weight (859).

Since the aldehyde **2a** was relatively unstable, it was converted to its acetal **2b** prior to hydrolysis of the 17-acetate group. Hydride reduction or vigorous base treatment of the diacetate **2b** led to the diol **2c**. Base treatment also afforded the monoacetate **2d**. Hydrolysis of the acetal with dilute acetic acid afforded a product (**5a**) lacking carbonyl absorption in the infrared. The material obtained was a mixture of roughly equal parts of two lactols, epimeric at C-22, as evidenced by the two 18-methyl signals in the nmr. Support for the lactol structure was furnished by the ready formation of a mixture of epimeric lactol ethers **5b** with methanol and a trace of acid. The structure proof was completed by chromic acid oxidation of the lactol group of **6a** to the known lactone **6c** in high yield.

Oxidation of the lactol ethers **5b** under Oppenauer conditions produced the unsaturated ketone grouping in the A ring (**6b**). In this case one of the epimers was separated by crystallization. The pure compound displayed a signal for the 18-methyl group at 58 cps, in contrast to the remaining component's signal at 56 cps, a difference too small to allow a firm assignment of the methoxyl configuration.

Oppenauer oxidation of the acetal **2c** afforded the corresponding unsaturated ketone **3**. Subsequent hydrolysis of the acetal group afforded the desired lactols **6a** as a mixture of C-22 epimers. The same mixture was also obtained by hydrolysis of the lactol ethers **6b**.

The aromatic A-ring lactol mixture **12a** was prepared by a similar sequence of reactions starting with the diacetate of **8a**. Bicarbonate hydrolysis afforded the monoalcohol **8b** which was oxidized to a mixture of the aldehyde **8c** and its acid **8d**. Methanol and acid converted a mixture of these compounds to the corresponding acetal and methyl ester. The structure of the ester was demonstrated by its hydrolysis to the known lactone. Lithium aluminum hydride reduction of the acetal afforded the 17-alcohol **8e** which was then hydrolyzed to the lactols **12a**.

An alternate approach to the synthesis of the lactol system was sought through direct reduction of the lactone ring. Lactols have been successfully produced from lactones by use of various hydrides,[7] a recent example employing diisobutylaluminohydride.[8] When applied to the lactone **12b** this reagent afforded lactols **12a** contaminated with varying amounts of overreduced material (**8a**) and compounds of higher molecular weight, such as the bisether **13**. Similar results were obtained with the fluorohydrin **10a** and the lactone **4a**.

Of greater interest, both theoretically and practically, were the results obtained from the studies with the 3-chloro spirolactone **4b**, a compound prepared by reaction of thionyl chloride with the 3-alcohol **4a**.[9] Reductive removal of the chlorine atom with a large excess of sodium in ammonia[10] also effected reduction of the lactone ring to give in good yield the 3-desoxy spirolactols **5c**. Subsequent reduetions of the pyranyl

(1) (a) Paper IX: Aldosterone Blockers. (b) For paper VIII, see R. C. Tweit, E. A. Brown, S. Kraychy, S. Mizuba, R. D. Muir, and R. T. Nicholson, *Chem. Pharm. Bull.* (Tokyo), **12**, 859 (1964).

(2) See, among others, "The Clinical Use of Aldosterone Antagonists," F. C. Bartter, Ed., C. C. Thomas, Springfield, Ill., 1960; R. R. Burtner, "Hormonal Steroids," Proceedings of the First International Congress on Hormonal Steroids, L. Martini and A. Pecile, Ed., Academic Press Inc., New York, N. Y., 1965, p 31.

(3) (a) L. N. Nysted and R. R. Burtner, *J. Org. Chem.* **27**, 3175 (1962); (b) G. E. Arth, H. Schwam, L. H. Sarett, and M. Glitzer, *J. Med. Chem.* **6**, 617 (1963); (c) E. Farkas and J. A. Swallow, *ibid.*, **7**, 739 (1964).

(4) After completion of this work, an alternate synthesis of **6a** and **6b** appeared. See D. Bertin and J. Perronnet, *Bull. Soc. Chim. France*, 564 (1964).

(5) Private communication from Dr. R. R. Burtner of these laboratories.

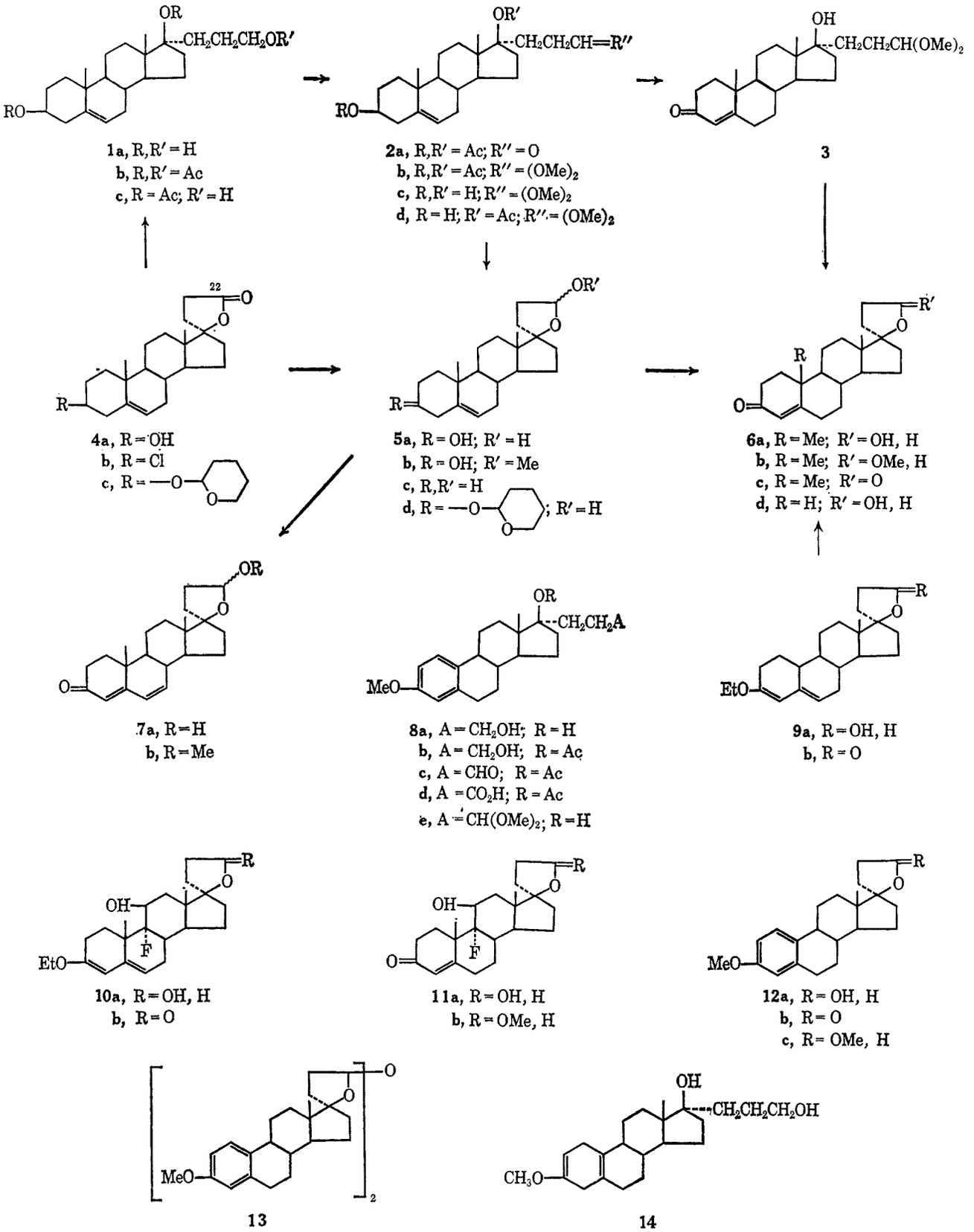
(6) W. F. Johns and D. M. Jerina, *J. Org. Chem.*, **28**, 2922 (1963).

(7) See, among others, J. T. Edward, P. F. Morand, and I. Puskas, *Can. J. Chem.*, **39**, 2069 (1961); G. R. Pettit and T. R. Kasturi, B. Green, and J. C. Knight. *J. Org. Chem.*, **26**, 4773 (1961).

(8) J. S. Baran, *ibid.*, **30**, 3564 (1965); J. Schmidlin and A. Wettstein, *Helv. Chim. Acta*, **46**, 2799 (1963). See also L. I. Zakharkin and I. M. Khorlina, *Tetrahedron Letters*, 619 (1962).

(9) The configuration of the chlorine atom is assigned in analogy to that in cholesteryl chloride. See C. W. Shoppee, "Steroids," 2nd ed, Butterworth and Co. (Publishers) Ltd., Washington, D. C., 1964, p 50.

(10) R. E. Ireland, T. I. Wrigley, and W. G. Young, *J. Am. Chem. Soc.*, **80**, 4604 (1958).



ether **4c** and then its 3-hydroxy precursor **4a** showed the ready production in each case of the spirolactol system.

Sodium–ammonia reduction of lactones was successfully employed in two other compounds which further demonstrated the mildness and selectivity of the reagent. The 3,5-dienol ether lactone **10b** was transformed smoothly to its lactol, without evidence of diene reduction. Hydrolysis of the enol ether gave the unsaturated ketone **11a** in good yield, and this compound was converted to its lactol ether **11b**. Also, the A-ring aromatic derivative **12b** was reduced to its lactol **12a** without affecting the A ring. However, the substitution of lithium metal for sodium led to reduction of both A ring and lactol, affording the diol **14** (see below).

When either the acetal **8e** or the lactol ether **12c** was subjected to Birch reduction followed by acid hydrolysis, mixtures were obtained which contained a substantial amount of nonconjugated (or possibly saturated) ketone. Separation of this impurity by several chemical methods in combination with chromatography proved unsuccessful. To obtain the desired 19-nor lactol **6d**, the enol ether (**9a**) of the 19-nor lactone was reduced with sodium–ammonia. The crystalline lactol which resulted was purified and the enol ether grouping carefully hydrolyzed to produce the amorphous lactol **6d**. This material was unstable to purification attempts and held tightly 0.5 equiv of water. The spectral data, however, were in good agreement with those expected: the 22-proton showed a typical signal at 327 cps and the lactol hydroxyl exhibited a 2.75-μ band.

A final series of compounds was prepared by treatment of the lactol ether **5b** with bromine in buffered solution,[11] resulting in a direct formation of the 4,6-dien-3-one system **7b**. A small amount of the corresponding 4-bromo compound was also isolated on chromatography. Acid hydrolysis of the lactol ether **7b** afforded the lactols **7a**.

The unexpected selectivity of sodium in ammonia in these reductions, especially as compared with lithium, deserves additional comment. The inability of sodium in ammonia to reduce the aromatic A ring (in **12**) is in agreement with earlier work: aromatic systems of this type are normally stable to metal–ammonia combinations in the absence of a proton donor.[12] When the reaction is quenched by addition of a proton source (ethanol), the rate of reduction of the aromatic system is too slow to compete with the reaction of sodium with alcohol.[12,13] (A parallel argument may be applied to explain the stability of the dienol ether system in **10**.) In contrast, lithium effects a faster rate of reduction of aromatic systems (*ca.* 200 times that of sodium),[13] allowing the reduction of the A ring to compete favorably with the reaction of metal with alcohol. Accentuating this difference in inherent reductive power of the metals is the much faster rate of reaction of sodium with alcohol compared with that of lithium, especially in the presence of small amounts of metal salts.[12]

The difference in lactone reduction by sodium compared with lithium may be explained in the same general way: in the course of reduction the lactone is rapidly transformed to the lactol, an entity relatively stable to excess metal in the absence of a proton source and in the short time intervals used (from 10 to 30 min). When ethanol is added to quench the reaction the sodium metal reacts much more quickly with the ethanol than with the lactol (or the free carbonyl compound formed from it by a rate-determining dissociation); with lithium metal, the relative rates are changed, allowing sufficient time for lactol reduction. When methyl iodide, instead of a proton donor, was used to quench the lithium reaction, this second reduction (lactol to diol) could not occur, and the product obtained in good yield was the lactol **5a**. This last experiment adds substantial support to the mechanistic picture described.

Another possible explanation of the lactol stability to reduction is that an intermediate lactol salt precipitates in one or both cases. The difference in reaction products would then be a function of the relative solubilities created by the different cations involved. Owing to the opacity of the reaction mixture this possibility could not be ruled out completely, but it is thought to be unlikely.

Extension of this reduction to carboxylic acid salts was unwarranted since their stability to lithium–ammonia reductions (even in the presence of alcohol) has been recorded.[14] With free carboxylic acids, intermediate aldehydes are isolable, although in widely varying yields, by use of lithium–ethylamine in a procedure formally similar to that described here.[15]

Application of this reduction method to esters was briefly explored.[16] Methyl desoxybisnorcholanate afforded the corresponding alcohol which was alternately synthesized by lithium aluminum hydride reduction of the same ester. This result is in agreement with the well-known reduction of esters to alcohols with metal–alcohol combinations in ammonia.[16b] The failure to stop at the intermediate hemiacetal stage, in analogy to the lactol is best explained by the inherent geometric stability of the lactol; that is, the hemiacetal dissociates faster than the lactol to form a rapidly reduced carbonyl group.

Experimental Section[17]

3-(3β,17β-Diacetoxyandrost-5-en-17-yl)propionaldehyde (2a). A. Chromium Trioxide–Pyridine.—A solution of 10.2 g of the 3-(3β,17β-diacetoxyandrost-5-en-17-yl)propanol (**1c**)[6] in 100 ml of cold pyridine was added to a slurry of 10 g of chromium trioxide in 100 ml of pyridine[18] at 5° over a 10-min period. After 65 hr the mixture was poured into water and extracted with ether. The ether soluble portion (9.0 g) was chromatographed[19] and yielded fractions, eluted with 10% ethyl acetate–benzene, which were combined and triturated with ether. The crystalline material (0.7 g) thus obtained was recrystallized from methylene chloride–methanol to yield 0.53 g of an unknown (dimer?): mp 198–199°; λ_{max} 5.74 μ; $\Delta\nu$ 243 (22-H) cps; $[\alpha]D$ −79°.

Anal. Calcd for $C_{52}H_{76}O_{10}$: C, 72.52; H, 8.90; mol wt, 860. Found: C, 72.81; H, 8.91; mol wt, 859.

Attempted sublimation of this material or treatment with methanolic hydrochloric acid or potassium carbonate failed to give a tractable monomer.

Continued elution of the above chromatographic column with 10% ethyl acetate in benzene gave 4.9 g of the amorphous aldehyde **2a**: λ_{max} 3.65 and 5.78 μ; $\Delta\nu$ 587 (–CHO) cps.

(11) M. J. Kalm and H. L. Dryden, Jr., patent applied for.

(12) H. L. Dryden, Jr., G. M. Webber, R. R. Burtner, and J. A. Cella, *J. Org. Chem.*, **26**, 3237 (1961).

(13) A. P. Krapcho and A. A. Bothner-By, *J. Am. Chem. Soc.*, **81**, 3658 (1959).

(14) J. A. Cella, E. A. Brown, and R. R. Burtner, *J. Org. Chem.*, **24**, 743 (1959).

(15) A. W. Burgstahler, L. R. Worden, and T. B. Lewis, *ibid.*, **28**, 2918 (1963).

(16) With limited amounts (1–2 equiv) of metal, some esters have been partially converted to aldehydes. See (a) M. S. Kharasch, E. Sternfeld, and F. R. Mayo, *ibid.*, **5**, 362 (1940); (b) H. Smith, "Organic Reactions in Liquid Ammonia," Interscience Publishers, Inc., New York, N. Y., 1963, p 173.

(17) (a) The lactols described, unless otherwise indicated, were approximately 1:1 mixtures of the two C-22 epimers. (b) The infrared spectra and rotations were determined in chloroform, and the ultraviolet spectra in methanol. The nmr spectra were determined in deuteriochloroform with a Varian A-60 spectrometer (60 Mc, tetramethylsilane as an internal standard, $\Delta\nu$ = 0 cps). We wish to thank Dr. R. T. Dillon and staff for this data and the elemental analyses. Melting points were determined on a Fisher-Johns melting point apparatus.

(18) For precautions, see G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(19) All of the chromatograms in this paper were run on silica gel (60 × the weight of the steroid used). We wish to thank Dr. E. G. Daskalakis and staff for this service.

Anal. Calcd for $C_{26}H_{38}O_5$: C, 72.52; H, 8.90. Found: C, 72.26; H, 9.16.

Elution of the column with 30% ethyl acetate in benzene gave fractions which yielded 0.75 g of starting material (**1c**).

B. *t*-Butyl Chromate (Procedure A).—A solution of 36 g of the alcohol **1c** in 350 ml of cold carbon tetrachloride and a cold solution of 150 ml of 1 *M* *t*-butyl chromate[20] in carbon tetrachloride were mixed and maintained at 5° for 3 hr. The mixture was poured onto a slurry of 150 g of oxalic acid and ice. The resulting mixture was stirred for 2 hr and filtered. The filtrate was extracted with chloroform, yielding 44 g of a green amorphous material. A portion (2.8 g), on chromatography, afforded fractions which were combined to yield 0.10 g of a pure crystalline unknown (see above). Subsequent fractions yield 0.8 g of amorphous aldehyde (**2a**).

3-(3β-Hydroxy-17β-acetoxyandrost-5-en-17-yl)propionaldehyde Dimethyl Acetal (2d).—A solution of 9.0 g of the crude aldehyde **2a** and 0.20 g of *p*-toluenesulfonic acid in 100 ml of methanol was allowed to stand at room temperature for 30 min and was then diluted with excess aqueous potassium carbonate. The product (6.6 g) was extracted with methylene chloride and chromatographed. Fractions eluted with 10% ethyl acetate in benzene were combined as the amorphous acetal **2b**: λ_{max} 5.78 μ; Δν 49 (18-CH_3), 62 (19-CH_3), and 199 (OCH_3) cps.

A solution of 3.2 g of the acetal **2b** in 50 ml of methanol and 10 ml of water containing 0.5 g of potassium carbonate was heated at reflux for 40 min. The solution was concentrated and water was added. The resulting crystalline product (2.6 g) was collected on a filter, washed with water, dried, and recrystallized from acetone–petroleum ether, affording 1.90 g (mp 155–158°) and 0.40 g (mp 154–156°) of the monoacetate **2d**: λ_{max} 2.78, 5.79 μ; Δν 198 (OCH_3) and 260 (triplet, 22-H) cps; $[\alpha]_D$ −79°.

Anal. Calcd for $C_{26}H_{42}O_5$: C, 71.85; H, 9.74. Found: C, 72.06; H, 9.76.

3-(3β,17β-Dihydroxyandrost-5-en-17-yl)propionaldehyde Dimethyl Acetal (2c) A. Base Hydrolysis.—A solution of 0.90 g of the amorphous acetal **2b** in 50 ml of methanol and 5 ml of 10% aqueous potassium hydroxide was heated at reflux for 18 hr. The product was isolated by methylene chloride extraction of the cooled and diluted reaction mixture. Chromatography yielded fractions, eluted with 20% ethyl acetate–benzene, containing 0.15 g of the monohydroxy compound **2d**. Elution with 40% ethyl acetate–benzene afforded fractions which were combined and recrystallized from ether to yield the pure diol **2c**: mp 146–147°; λ_{max} 2.75 μ; $[\alpha]_D$ −66°.

Anal. Calcd for $C_{24}H_{40}O_4$: C, 73.43; H, 10.27. Found: C, 73.62; H, 10.13.

B. Hydride Reduction (Procedure B).—A solution of 0.45 g of the alcohol **2d** in 10 ml of tetrahydrofuran was added to a solution of 0.4 g of lithium aluminum hydride in 20 ml of ether. The mixture was stirred for 18 hr at room temperature and was then diluted cautiously with 1 ml of water and 1 ml of 10% aqueous potassium hydroxide. The mixture was filtered through Super-Cel and concentrated to dryness. The residue (0.51 g) was crystallized from aqueous methanol to yield 0.30 g of the diol **2c**, mp 135–140°, identical in the infrared with the above product.

3-(3β,17β-Dihydroxyandrost-5-en-17-yl)propionaldehyde Lactols (5a). A. Acetal Hydrolysis.—A solution of 0.65 g of the acetal **2d** in 5 ml of tetrahydrofuran and 20 ml of 70% aqueous acetic acid was allowed to stand at room temperature for 18 hr. Dilution with water afforded a precipitate (0.55 g, mp 195–205°) which was separated by filtration, air dried, and recrystallized from methylene chloride–acetone, yielding 0.33 g of the lactols **5a** (epimeric at C-22): mp 213–215°; λ_{max} 2.75 μ; Δν 54 and 59 (18-CH_3) and 62 (19-CH_3) cps.

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.05; H, 9.97.

B. Sodium Reduction of the Lactone 4a (Procedure C).—A solution of 30 g of 3-(3β,17β-dihydroxy-5-androsten-17α-yl)propionic acid lactone **4a**[14] in 1 l. of tetrahydrofuran was added to a solution of 20 g of sodium in 2 l. of ammonia with stirring over a 20-min period. After 15 min absolute ethanol was added dropwise until the blue color was gone (*ca.* 30 ml used). The ammonia was distilled and the residue was diluted with water. The mixture was neutralized and slurried with chloroform and then methanol. Filtration through Super-Cel yielded a solution which on concentration to a volume of 100 ml provided a crystalline product. Filtration gave 18 g of the lactols **5a**, mp 190–215°, and 5.5 g, mp 180–195°. Thin layer chromatographic analysis of the mother liquors (1.6 g) showed product and a little starting material (**4a**), but only small amounts of triol **1a** were seen.

C. Lithium Reduction of the Lactone 4a (Methyl Iodide Quench).—A solution of 4.0 g of the lactone **4a** in 100 ml of tetrahydrofuran was added to a solution of 1.5 g of lithium in 300 ml of ammonia over a 10-min period. After a total of 20 min, a solution of 12 ml of methyl iodide in 30 ml of ether was added over a 5-min period. Anhydrous ethanol (50 ml) was added to the colorless solution and the ammonia was distilled. The mixture was diluted with water and extracted with benzene. Concentration of the extract afforded 3.2 g of the lactols **5a**, mp 198–202°.

3-(3β,17β-Dihydroxyandrost-5-en-17yl)propionaldehyde Lactol Methyl Ethers (5b).—To a slurry of 11.7 g of the lactols **5a** in 150 ml of methanol was added 0.50 g of *p*-toluenesulfonic acid. Solution occurred rapidly. After 10 min aqueous potassium bicarbonate was added to the solution providing 11.7 g of a crystalline precipitate. Recrystallization from aqueous acetone afforded 10.3 g of a mixture of the epimeric ethers **5b**: mp 85–105°; λ_{max} 2.75 μ; Δν 52 and 54 (18-CH_3; equal intensities), 59 (19-CH_3), 198 (OCH_3), and 296 (22-H) cps.

Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.41; H, 10.16.

The lactol ethers **5b** in 70% aqueous acetic acid at room temperature for 18 hr afforded a high yield of the lactols **5a**.

3-(3β-Tetrahydropyranyloxy-17β-hydroxyandrost-5-en-17-yl)-propanoic Acid Lactone (4c).—Phosphorus oxychloride (1 ml) was added to a stirred solution of 20.0 g of the lactone **4a** in 200 ml of 2,3-dihydropyran over a 6-min period. After 3.5 hr at ambient temperature a solution of 2.0 g of potassium hydroxide in 240 ml of methanol was added followed by 100 ml of water, producing two liquid layers. The lower layer was separated; the solvent was removed *in vacuo* to produce a solid residue. This material was digested with 50 ml of *n*-hexane to yield 13.35 g of **4c**, mp 186–188°, λ_{max} 5.66 μ (no hydroxyl).

Anal. Calcd for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 75.43; H, 9.28.

In addition, the upper liquid layer was evaporated to afford 4.8 g of residue which was recrystallized from methanol to yield 2.7 g. of **4c**, mp 184–187°.

3-(3β-Tetrahydropyranyloxy-17β-hydroxyandrost-5-en-17-yl)-propionaldehyde Lactols (5d). A. Sodium Reduction.—The lactone **4c** (2.0 g) was reduced with sodium–ammonia by procedure C providing a residue which was digested with 25 ml of boiling chloroform. Two recrystallizations from ethyl acetate yielded 550 mg of **5d**: mp 163–172°; λ_{max} 2.73 and 2.91 μ; Δν 52 and 54 (18-CH_3) and 62 (19-CH_3) cps.

Anal. Calcd for $C_{27}H_{42}O_4$: C, 75.30; H, 9.83. Found: C, 74.92; H, 9.80.

Hydrolysis of the lactols **5d** in 70% aqueous acetic acid for 6 hr afforded a good yield of the lactols **5b**.

B. Hydride Reduction (Procedure D).—To a solution of 430 mg of **4c** in 15 ml of dry toluene at −70° was added 0.72 ml of a toluene solution of diisobutylaluminum hydride (*ca.* 1.4 *M*). The solution was stirred at −70° for 45 min and then hydrolyzed by the addition of 0.5 ml of saturated aqueous ammonium chloride. After warming to room temperature, the toluene solution, washed twice with water and evaporated to dryness, afforded a residue which was recrystallized twice from methanol to yield 40 mg of lactols **5d**, mp 175–180°, identical in the infrared with the material obtained above.

3-(17β-Hydroxy-3-oxoandrost-4-en-17-yl)propionaldehyde Dimethyl Acetal (3).—A solution of 1.2 g of the acetal **2c** in 150 ml of toluene and 5 ml of cyclohexanone was dried by distillation of 30 ml of solvent. To the boiling solution under an atmosphere of nitrogen was added a solution of 0.6 g of aluminum isopropoxide in 20 ml of toluene over 5 min. After 15 min more the solution was cooled and diluted with 30 ml of saturated aqueous Rochelle salt solution. The mixture was steam distilled for 1.5 hr, cooled, and extracted with benzene. The product, 1.2 g, crystallized from ether yielding 0.65 g of **3**, mp 128–136°. Recrystallization from ether gave 0.42 g of the pure ketone **3**: mp 143–145°; λ_{max} 2.75 and 6.01 μ; λ_{max} 241 mμ (15,200); Δν 200 (OCH_3) and 264 (22-H) cps; $[\alpha]_D$ 60°.

(20) R. V. Oppenauer and H. Oberrauch, *Chem. Abstr.*, **44**, 3871c (1950).

Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 74.07; H, 9.79.

3-(17β-Hydroxy-3-oxo-androst-4-en-17-yl)propionaldehyde Lactol Methyl Ether (6b).—The lactol ethers **5b** (3.0 g) were oxidized by the procedure immediately above. Chromatography of the crude product afforded fractions, eluted with 5% ethyl acetate–benzene, which were combined and recrystallized from petroleum ether to yield 0.24 g of a single pure epimer: mp 138–141°; λ_{max} 5.99 μ; λ_{max} 241 mμ (15,500); Δν 58 (18-CH_3), 72 (19-CH_3), and 296 (quartet, 22-H) cps; $[\alpha]_D$ 136°.

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.36; H, 9.51.

The second epimer was seen in the mother liquors by nmr [Δν 56 (18-CH_3) cps].

3-(17β-Hydroxy-3-oxo-androst-4-en-17-yl)propionaldehyde Lactols (6a). A. Acetal Hydrolysis.—Hydrolysis of 0.35 g of the acetal **3** in 20 ml of 70% aqueous acetic acid for 3 hr yielded 0.24 g of the lactols **6a**, mp 138–141°. Recrystallization from ether gave a sample: mp 143–148°; λ_{max} 2.74 and 5.98 μ; Δν 54 and 56 (18-CH_3, equal intensities), 72 (19-CH_3), and 328 (22-H) cps.

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.54; H, 9.39.

B. Lactol Ether Hydrolysis.—A solution of 1.9 g of the crude lactol ethers **6b** was hydrolyzed in 20% aqueous acetic acid for 20 hr. The product was extracted with benzene and recrystallized from ether yielding 0.58 g of the lactols **6a**, mp 150–155°, identical in the infrared with the above product.

Oxidation of the Lactols 6a.—A solution of 50 mg of the lactols **6a** in 2 ml of acetone at −5° was treated with an excess of 4 *N* chromic acid solution.[21] After 5 min the solution was diluted with water and 0.5 ml of methanol. The product was isolated by benzene extraction, yielding 50 mg of material which was identical in the infrared with the authentic spirolactone **14**.

3-[3-Methoxy-17β-acetoxyestra-1,3,5(10)-trien-17-yl]propyl Acetate (8a Diacetate).—A solution of 1.5 g of the 3-(3-methoxy-17β-hydroxyestra-1,3,5(10)-trien-17-yl)propanol[22] (**8a**) in 300 ml of isopropenyl acetate containing 0.6 g of *p*-toluenesulfonic acid was stirred at room temperature for 10 min and then distilled to one-half volume over a 3-hr period. The product was extracted with ether and was chromatographed. Fractions eluted with 10% ethyl acetate–benzene were recrystallized from aqueous methanol to yield 0.30 g of the diacetate, mp 88–89°, λ_{max} 5.78 and 7.95 μ.

Anal. Calcd for $C_{25}H_{36}O_5$: C, 72.86; H, 8.47. Found: C, 73.12; H, 8.41.

3-[3-Methoxy-17β-acetoxyestra-1,3,5(10)-trien-17-yl]propanol (8b).—A solution of 0.23 g of **8a** diacetate in 20 ml of methanol and 2 ml of water containing 0.5 g of potassium bicarbonate was boiled for 1 hr. The solution was diluted with water and the resulting product was collected on a filter, yielding 0.15 g of crystals, mp 161–163°. Recrystallization from acetone–petroleum ether yielded the pure material: mp 163–165°; λ_{max} 2.72 and 5.79 μ; $[\alpha]_D$ 13°.

Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.62; H, 8.73.

3-[3-Methoxy-17β-acetoxyestra-1,3,5(10)-trien-17-yl]propionaldehyde (8c).—A solution of 0.45 g of **8b** in 3 ml of pyridine was added dropwise over 1 min to a slurry of 0.7 g of chromium trioxide in 7 ml of pyridine at 5°.[18] After 1.5 hr (final temperature: 25°) the mixture was diluted with water and the product was isolated by ether extraction. Chromatography of the product (0.34 g) afforded fractions eluted with 5% ethyl acetate–benzene which were recrystallized from ether–petroleum ether to yield 50 mg of the pure aldehyde **8c**: mp 142–143°; λ_{max} 3.63 and 5.78 μ.

Anal. Calcd for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 75.08; H, 8.22.

Fractions eluted with 30% ethyl acetate–benzene yielded 0.12 g of starting material (**8b**).

Oxidation of the alcohol **8b** (105 mg) with *t*-butyl chromate (procedure A)[20] and chromatography of the resulting product yielded 50 mg of the aldehyde **8c**, mp 135–142°, from fractions eluted with 10% ethyl acetate–benzene. Repetition of this experiment on a larger scale gave much lower yields.

3-[3-Methoxy-17β-hydroxyestra-1,3,5(10)-trien-17-yl]propionaldehyde Dimethyl Acetal (8e).—To a slurry of 25 mg of the aldehyde **8c** in 0.5 ml of methanol was added 3 mg of *p*-toluenesulfonic acid. The mixture became homogeneous immediately. After 10 min aqueous potassium bicarbonate was added. The product (25 mg) was isolated by methylene chloride extraction and eluted from a chromatographic column with 2% ethyl acetate–benzene, affording the amorphous acetate of **8e**: λ_{max} 5.79 μ; ν 200 (OCH_3) and 318 (22-H) cps.

Reduction of 1.6 g of **8e** acetate by procedure B gave 1.40 g of an amorphous product. A portion (0.42 g) of this material was chromatographed and yielded fractions, eluted with 1% ethyl acetate–benzene, which crystallized in part to yield the acetal **8e**: mp 148–149°; λ_{max} 2.75 μ.

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.20; H, 9.16.

Standard Birch reduction[12] of **8e** followed by acid hydrolysis gave amorphous mixtures from which the pure lactol **6d** could not be isolated.

Methyl 3-[3-Methoxy-17β-acetoxyestra-1,3,5(10)-trien-17-yl]-propionate (Ester of 8d).—The methyl ester of **8d** was isolated by chromatography of the mixture resulting from the treatment of the crude aldehyde **8c** (containing some **8d**) with methanol and acid (as above). The material eluted with 5% ethyl acetate–benzene was recrystallized from methylene chloride–methanol and afforded the ester of **8d**: mp 123–124°; λ_{max} 5.75 μ; Δν 222 (CO_2CH_3) and 227 (OCH_3) cps; $[\alpha]_D$ 18°.

Anal. Calcd for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.49; H, 8.45.

The basic aqueous extracts of this ketalization experiment were acidified and the resulting precipitate was collected. Recrystallization from aqueous acetone afforded pure 3-[3-methoxy-17β-acetoxyestra-1,3,5(10)-trien-17-yl]propanoic acid (**8d**), mp 168–169°, λ_{max} 5.75 μ.

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.79; H, 8.10.

Saponification of the methyl ester (0.15 g) in 20 ml of ethanol containing 3 ml of 10% aqueous potassium hydroxide for 4 hr followed by dilution, concentration, and acidification afforded 0.15 g of the lactone **12b**, identical with the known lactone[14] by comparison of infrared spectra.

3-[3-Methoxy-17β-hydroxyestra-1,3,5(10)-trien-17-yl]propionaldehyde Lactols (12a). A. Sodium–Ammonia Reduction (Procedure E).—A solution of 12 g of the lactone **12b**[14] in 200 ml of tetrahydrofuran was added to 0.5 l. of ammonia with efficient stirring, producing a suspension of the compound in ammonia. Sodium (1.5 g) was added. After 1 hr, the deep blue color was discharged with methanol. The ammonia was distilled and the solution was diluted with water and then with excess acetic acid. The resulting precipitate (11.4 g, mp 63–68°) was separated by filtration, washed with water, and dried. The ultraviolet spectrum showed only the anisole chromophore and was unchanged by acid hydrolysis, indicating no reduction of the A ring had occurred. Two recrystallizations from ethyl acetate yielded 3.37 g of **12a**: mp 120–134°; λ_{max} 2.91, 6.20, and 6.62 μ; Δν 53 and 56 (18-CH_3), 227 (OCH_3), and 330 (22-H) cps.

Anal. Calcd for $C_{22}H_{30}O_3$: C, 77.15; H, 8.33. Found: C, 77.21; H, 8.53.

B. Hydride Reduction.—A stirred solution of 1.07 g of **12b** was reduced with diisobutylaluminum hydride solution according to procedure D. Two recrystallizations of the resulting product from ethyl acetate yielded 80 mg of the dimer **13**: mp 199–201°; λ_{max} 6.17, 6.32, and 6.62 μ.

Anal. Calcd for $C_{44}H_{58}O_5$: C, 79.24; H, 8.77; mol wt, 666. Found: C, 79.32; H, 8.81; mol wt, 621.

Similar amounts of dimer were obtained in a run of equal size in which the relative amount of hydride was halved. Chromatography of the combined mother liquors (1.5 g) from these two runs afforded fractions, eluted with 5% ethyl acetate–benzene, which were recrystallized from ethyl acetate to yield 250 mg of **12a**.

Further elution gave fractions combined to yield 0.30 g of the diol **8a**, mp 164–166°. Also isolated was 0.75 g of the starting lactone (**12b**).

3-[3-Methoxy-17β-hydroxyestra-2,5(10)-dien-17-yl]propanol (14).—Lithium wire (5.0 g) was added over a 5-min period to a stirred solution of 10.0 g of lactone **12b** in 500 ml of tetrahydrofuran and 500 ml of ammonia. After an additional 5 min, 35 ml of ethanol was added dropwise over an 18-min period. Decolorization of the reaction mixture occurred after 2 more min

(21) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(22) R. Pappo, U. S. Patent 2,913,467 (1958). See also ref 3b.

(total "blue time" 30 min). The ammonia was allowed to evaporate and then 2.5 l. of water was added. The resulting precipitate was collected on a funnel, washed with water, and air dried to yield 9.65 g of crude product: λ_{max}^{KBr} 2.98, 3.05, 5.88, and 5.99 μ; λ_{max} 278 mμ (230) (representing roughly 15% of unreduced material). On acid hydrolysis the crude material showed λ_{max} 241 mμ (ϵ 11,000 or about 80% of the pure unsaturated ketone). A portion of the product was recrystallized from a large volume of ethyl acetate to yield 0.92 g of the diol **14**: mp 196–197°; $\Delta\nu$ 68 (18-CH_3), 115 (C$_4$–CH_2), 211 (OCH_3), and 281 (C$_5$–H) cps.

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.29; H, 9.89. Found: C, 76.65; H, 9.56.

3-[3-Methoxy-17β-hydroxyestra-1,3,5(10)-trien-17-yl]propionaldehyde Lactol Methyl Ether (12c).—Addition of 0.5 g of *p*-toluenesulfonic acid to a solution of 11.3 g of the lactol **12a** in 10 ml of methanol resulted in the fast precipitation of an oil. After 10 min aqueous potassium bicarbonate was added and the product was extracted with benzene. Chromatography of the product yielded the ether **12c**, eluted with 2% ethyl acetate–benzene, which was recrystallized from ether to yield 0.65 g of **12c**, mp 121–124°. Recrystallization from acetone–petroleum ether afforded one pure epimer: mp 129–131°; $\Delta\nu$ 54 (18-CH_3), 200 (22-OCH_3), 226 (3-OCH_3), and 296 (22-H) cps; $[\alpha]_D$ −55°.

Anal. Calcd for $C_{23}H_{32}O_3$: C, 7.49; H, 9.05. Found: C, 77.62; H, 8.82.

The second epimer was seen in the nmr spectrum of the mother liquors by its 18-methyl signal at 58 cps.

3-(3-Ethoxy-17β-hydroxy-19-norandrosta-3,5-dien-17-yl)propionaldehyde Lactols (9a).—A homogeneous solution of 0.57 g of 3-(3-ethoxy-17β-hydroxy-19-norandrosta-3,5-dien-17-yl)propanoic acid lactone[23] (**9b**) was reduced with 0.2 g of sodium according to procedure E. The product was recrystallized from ether–petroleum ether to provide 65 mg of the lactols **9a**: mp 178–181°; λ_{max} 2.78, 6.05 (m), and 6.15 (m) μ.

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.20; H, 9.71.

The remainder of the material was extracted from the aqueous mother liquors, yielding 0.47 g of an amorphous material, judged to consist largely of the lactol epimers **9a** by the similarity of its infrared spectrum to that of pure **9a**.

Hydrolysis of the Enol Ether 9a.—A solution of 30 mg of the lactols **9a** and 20 mg of *p*-toluenesulfonic acid in 8 ml of acetone and 2 ml of water was allowed to stand at room temperature for 2.5 hr. The product was extracted from the diluted mixture with methylene chloride, affording 30 mg of the amorphous lactols **6d** containing 0.5 equiv of water: λ_{max} 2.76 and 6.01 μ; λ_{max} 240 mμ (16,800); $\Delta\nu$ 54 and 57 (18-CH_3), 327 (22-H), and 348 (4-H) cps.

Anal. Calcd for $C_{21}H_{30}O_3 \cdot 0.5H_2O$: C, 74.30; H, 9.12. Found: C, 74.52; H, 9.12.

Attempts to prepare the lactols **6d** by Birch reduction[12] of the lactol ethers **12c** followed by acid hydrolysis and chromatography gave materials containing both saturated and unsaturated carbonyl absorption in the infrared. No separation of the saturated component was affected by formation of the derivative lactol ether, bisulfite adduct, or enamine.

3-(3β-Chloro-17β-hydroxyandrost-5-en-17-yl)propanoic Acid Lactone (4b).—To a stirred solution of 10.0 g of the lactone **4a** in 40 ml of methylene chloride was added 12.5 ml of thionyl chloride over a 10-min period.[10] After 10 hr at room temperature, the reaction solution was poured into 200 ml of ice–water. The product, extracted with methylene chloride, was recrystallized from ethyl acetate to yield 6.4 g of **4b**, mp 179–181°, $[\alpha]_D$ −26°.

Anal. Calcd for $C_{22}H_{31}ClO_2$: C, 72.80; H, 8.61; Cl, 9.77. Found: C, 72.81; H, 8.59; Cl, 9.61.

3-(17β-Hydroxyandrost-5-en-17-yl)propionaldehyde Lactols (5c).—A solution of 2.0 g of **4b** in 100 ml of ether was added over a 10-min period to a solution of 1.0 g of sodium in 100 ml of ammonia. After 10 min, the blue color was discharged by addition of ethanol; the solvent was distilled affording 2.0 g of crude product. Recrystallization from 60 ml of methanol yielded 700 mg of **5c**: mp 167–171°; λ_{max} 2.73 and 2.90 μ; $\Delta\nu$ 53 and 55 (18-CH_3), 60 (19-CH_3), 319 broad (6-H), and 330 broad (22-H) cps.

Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.04. Found: C, 79.94; H, 10.51.

3-(3-Ethoxy-9α-fluoro-11β,17β-dihydroxyandrosta-3,5-dien-17-yl)propionaldehyde Lactols (10a).—Sodium reduction of 2.0 g of 3-(3-ethoxy-9α-fluoro-11β,17β-dihydroxyandrost-3,5-dien-17-yl)propanoic acid lactone (**10b**)[24] in tetrahydrofuran was effected by procedure E. The yellowish suspension remaining after evaporation of the ammonia was diluted with water and the precipitate was collected, washed with water, dried, and recrystallized from ethyl acetate to yield 410 mg of **10a**: mp 166–170°; λ_{max} 2.73, 2.95, 3.08, 6.02, and 6.12 μ.

Anal. Calcd for $C_{24}H_{35}FO_4$: C, 70.90; H, 8.68. Found: C, 70.73; H, 8.83.

3-(9α-Fluoro-11β,17β-dihydroxy-3-oxoandrost-4-en-17-yl)propionaldehyde Lactols (11a).—A suspension of 400 mg of **10a** in 15 ml of 70% aqueous acetic acid was stirred at 60° until homogeneous (5 min) and then allowed to cool to 25° over 40 min. Addition of 50 ml of water produced a precipitate which was collected, washed with water, dried, and recrystallized from ethyl acetate to yield 80 mg of **11a**: mp 207–215° (dried *in vacuo* at 150°); λ_{max} 2.92 and 6.01 μ; $\Delta\nu$ (pyridine) 92 and 96 (18-CH_3) and 101 (19-CH_3) cps.

Anal. Calcd for $C_{22}H_{31}FO_4$: C, 69.81; H, 8.26. Found: C, 69.61; H, 8.64.

An alternate synthesis of **11a** entailed hydride reduction of 1.6 g of lactone **10b** by procedure D, yielding 1.1 g of product. This material was hydrolyzed in dioxane containing aqueous hydrochloric acid and afforded lactol **11a** in low yield by crystallization of the product.

3-(9α-Fluoro-11β,17β-dihydroxy-3-oxoandrost-4-en-17-yl)propionaldehyde Lactol Methyl Ethers (11b).—To a suspension of 250 mg of **10a** in 5 ml of methanol was added 10 ml of water and 1.0 ml of 1 *N* hydrochloric acid. Solution occurred in 2–3 min followed by formation of a crystalline precipitate. After 45 min at room temperature the precipitate was collected, washed with a little methanol, and dried to yield 140 mg of **11b**: mp 214–219°; λ_{max} 2.98 and 6.05 μ; λ_{max} 238.5 mμ (15,500); $\Delta\nu$ 71 and 72 (18-CH_3), 93 (19-CH_3), 200 (OCH_3), 250–265 (11-αH), 292–298 (22-H), and 347 (4-H) cps.

Anal. Calcd for $C_{23}H_{32}FO_4$: C, 70.38; H, 8.47. Found: C, 70.48; H, 8.61.

3-(17β-Hydroxy-3-oxoandrosta-4,6-dien-17-yl)propionaldehyde Lactol Methyl Ether (7b).—Bromine (9.6 g) was added to 25 ml of cold dimethylformamide.[11] The resulting solution was added dropwise over 70 min to a stirred mixture of 9.8 g of the lactol ether **5b**, 6.4 g of magnesium oxide, and 4.73 g of N-methyl-2-pyrrolidone at 75°. One hour after the addition was completed, the solution was poured into 110 ml of water. The salts were filtered off, the product was extracted with benzene, and the extract was washed generously with water. Chromatography of the residue (9.8 g) afforded first **the 3-(17β-hydroxy-3-oxo-4-bromoandrosta-4,6-dien-17-yl)propionaldehyde lactol methyl ethers**, eluted with 5% ethyl acetate–benzene: λ_{max} 5.96 μ; λ_{max} 300 mμ (16,900).

Anal. Calcd for $C_{23}H_{31}BrO_3$: C, 63.44; H, 7.18. Found: C. 63.27; H, 7.28.

Following this material, eluted with 10% ethyl acetate–benzene, were fractions weighing 6.2 g which were crystallized and recrystallized from petroleum ether to afford 1.40 g of one pure epimer of lactol ether **7b**: mp 155–158°; λ_{max} 6.01 and 6.17 μ; λ_{max} 284 mμ (25,600); $\Delta\nu$ 60 (18-CH_3), 68 (19-CH_3), 338 (4-H), and 365 (6,7-H) cps; $[\alpha]_D$ 76°.

Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.37; H, 9.19.

3-(17β-Hydroxy-3-oxo-androsta-4,6-dien-17-yl)propionaldehyde Lactols (7a).—The lactol ether **7b** (6 g) was dissolved in 120 ml of 70% acetic acid over a 30-min period. After 2.5 hr the solution was diluted with water and the product was extracted with benzene, yielding 5.3 g of an amorphous material which crystallized slowly from petroleum ether. Recrystallization from ethyl acetate afforded 1.3 g of **7a**, mp 168–173°. A further recrystallization from acetone afforded a sample: mp 170–176°; λ_{max} 2.72, 6.01, and 6.18 μ; λ_{max} 283 mμ (25,800); $\Delta\nu$ 56 and 58 (18-CH_3, equal intensities) cps; $[\alpha]_D$ 36°.

Anal. Calcd for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 76.86; H, 8.81.

20-Hydroxymethyl-5β-pregnan-3α,12α-diol.—A solution of 2 g of methyl desoxybisnorcholanate in 50 ml of tetrahydrofuran was added to a solution of 0.7 g of sodium in 200 ml of ammonia over a 5-min period. After a total of 11 min, anhydrous ethanol was added. The blue color disappeared within 1 min affording

(23) F. B. Colton and J. A. Cella, U. S. Patent 3,194,803.

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a homogeneous solution. The ammonia was distilled, affording 1.85 g of crystalline material. Recrystallization from acetone gave 1.15 g of the pure triol: mp 217–219°; λ_{max} 2.72 μ; Δν [$(CD_3)_2SO$] 37(18-CH_3), 51 (19-CH_3), and 61 (21-CH_3) cps; $[\alpha]_D$ 52 (MeOH).

Anal. Calcd for $C_{22}H_{38}O_3$: C, 75.38; H, 10.93. Found: C, 75.52; H, 10.97.

Hydride reduction of 1.0 g of methyl desoxybisnorcholanate by procedure B gave 0.67 g of the same triol.

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The Enol Acetylation of 3-Oxo 5β-Steroids

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The enol acetylation of 17β-acetoxy-5β-androstan-3-one has been investigated under conditions of kinetic and thermodynamic control. Both methods lead to mixtures of enol acetates. The results of thermodynamically controlled enol acetylation are discussed in terms of nonbonded interactions in the enolic forms of the parent ketone.

During an investigation of structure–reactivity relationships it became necessary to find a model keto steroid which has a dual enolization. The 3-oxo steroids of the 5α series such as cholestan-3-one (**3c**) are known to form a single Δ^2-enol since bromination[1,2] and sulfonation[3,4] yield C-2 monosubstituted products. An examination of the literature revealed that the 3-oxo 5β-steroids present a more ambiguous pattern of enolization since bromination of 5β-cholestan-3-one (**2c**) gave only a 40% yield of the 4β-bromo-5β-cholestan-3-one (**5b**).[1] Bromination–dehydrobromination studies with this compound have yielded reaction products whose ultraviolet spectra suggested the presence of some 5β-cholest-1-en-3-one (**8b**).[5] Similarly, sulfonation of 5β-cholestan-3-one gave a mixture of C-2 and C-4 monosubstituted products.[3,4] In contrast with these results, enamine formation with 5β-cholestan-3-one (**2c**) led to a single Δ^3-enamine[6] and enol acetylation using acetyl chloride–acetic anhydride[7] or isopropenyl acetate[8] yielded only 3-acetoxy-5β-cholest-3-ene (**6b**). Steric considerations discussed below suggested that some of the less favored Δ^2-enol of 3-oxo 5β-steroids should be formed. For these reasons it was decided to investigate the enolization of 3-oxo 5β-steroids.

Enol acetylation was chosen for this study since the compounds are easily prepared and can be readily analyzed by gas chromatography.[9] There are several methods for preparing enol acetates and Hartshorn and Jones[10] and Berkoz, Chavez, and Djerassi[11] have shown that the ratio of enol acetates formed depends on the reaction conditions chosen and that bromination, which proceeds *via* the intermediate enols, does not necessarily parallel the enol acetylation results. It is essential for this study that the enol acetylation conditions chosen reflect the enolization properties of the parent ketone. In studying the enolization of 3,3-dimethylcyclohexanone, it was demonstrated[12] that the perchloric acid catalyzed acetic anhydride enol acetylation[13] was thermodynamically controlled and each isomeric enol acetate, when subjected to the acetylating conditions, was capable of regenerating the equilibrium mixture. It was also demonstrated that the ratio of enol acetates formed under equilibrium conditions corresponded to the bromination and nitric acid oxidation results.

The steroid model used for this investigation was 17β-acetoxy-5β-androstan-3-one (**2a**). The compound was prepared by catalytic hydrogenation of testosterone (**1b**) using palladium catalyst[14,15] to yield a 3:1 ratio of 5β and 5α isomers **2b** and **3b**, respectively. The 5β isomer can be isolated by fractional crystallization of the corresponding acetates **2a** and **3a**. Column chromatography with Florisil was required to obtain pure 5α isomer **3a**.

The perchloric acid catalyzed enol acetylation of carbonyl compounds is often accompanied by dark intractable material,[9] and it was found expedient to use the isopropenyl acetate–sulfuric acid method[8] to prepare the enol acetates of **2a** in sufficient quantity for purification and identification. Gas–liquid partition chromatographic (glpc) analysis of the reaction product revealed 71% 3,17β-diacetoxy-5β-androst-3-ene (**6a**) and 29% 3,17β-diacetoxy-5β-androst-2-ene (**7a**).

Proof of the isomeric nature of the two enol acetates was obtained by saponifying the reaction product under mild conditions.[16] Glpc and thin layer chromatography (tlc) detected a single saponification product, identified as 17β-acetoxy-5β-androstan-3-one (**2a**).

The enol acetates **6a** and **7a** were separated by preparative glpc and their nmr spectra were recorded. The major constituent of the mixture of enol acetates showed a vinylic proton singlet at 5.05 ppm. The compound was tentatively assigned the Δ^3-enol acetate

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