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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(2) For a review of this subject, see I. E. Bush, *Pharmacol. Rev.*, **14**, 317 (1962).

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(16) The reported rotation for 3,3-ethylenedioxy-11β-hydroxyandrost-5-en-17-one,[15] $[\alpha]D$ −100°, and the value obtained herein, $[\alpha]D$ +5.1°, suggest that the compound we have isolated may contain a significant amount of the Δ^4 isomer which normally possesses a more positive rotation.[17,18]

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(18) J. W. Dean and R. G. Christiansen, *J. Org. Chem.*, **28**, 2110 (1963).

common starting material in the preparation of both **10a** and **10b**.

Sodium borohydride reduction of 3,3-ethylenedioxy-11β-hydroxyandrost-5-en-17-one (**4**) gave 3,3-ethylenedioxyandrost-5-ene-11β,17β-diol (**5**). Acetylation by the usual method using acetic anhydride–pyridine gave 17β-acetoxy-3,3-ethylenedioxyandrost-5-en-11β-ol (**6**). Mild hydrolysis using acetic acid[19] yielded 17β-acetoxy-11β-hydroxyandrost-4-en-3-one (**8a**).

The corresponding 17-deoxy steroid (**8b**) was prepared from **4** by Wolff–Kishner reduction to give 3,3-ethylenedioxyandrost-5-en-11β-ol (**7**) which upon acid hydrolysis[19] yielded 11β-hydroxyandrost-4-en-3-one (**8b**).

Catalytic hydrogenation of Δ^4-3-ketones yields predominantly 3-oxo 5β-steroids;[20,21] however, the introduction of an 11β-hydroxyl group is reported[22,23] to reverse the usual course of the hydrogenation and 3-oxo 5α-steroids are formed preferentially. The catalytic hydrogenation of 17β-acetoxy-11β-hydroxyandrost-4-en-3-one (**8a**) yielded 62% 17β-acetoxy-11β-hydroxy-5β-androstan-3-one (**10a**) and 38% 17β-acetoxy-11β-hydroxy-5α-androstan-3-one (**9b**). A similar 60:40 ratio of 11β-hydroxy-5β-androstan-3-one (**10b**) to 11β-hydroxy-5α-androstan-3-one (**9c**) was obtained from the catalytic hydrogenation of 11β-hydroxyandrost-4-en-3-one (**8b**). The isomer ratios were determined by gas chromatography (glpc).

The mixture of 17β-acetoxy-11β-hydroxy-5β-androstan-3-one (**10a**) and 17β-acetoxy-11β-hydroxy-5α-androstan-3-one (**9b**) was separated by column chromatography and the identity of the isomers was established by nuclear magnetic resonance spectroscopy (nmr) and the usual chemical means. The unambiguous synthesis of the 5α isomer (**9a**) by lithium–ammonia reduction of the Δ^4-3-ketone (**8a**)[24,25] followed by acetylation in the usual manner gave **9b** which was used to identify the isomers. The mixture of 11β-hydroxy-5β-androstan-3-one (**10b**) and 11β-hydroxy-5α-androstan-3-one (**9c**) from catalytic hydrogenation was also separated by column chromatography and chemical identification was carried out by preparing known 5α-androstan-11β-ol (**9d**) from 11β-hydroxy-5α-androstan-3-one (**9c**) by Wolff–Kishner reduction of the carbonyl group at C-3.[26]

The stereochemical assignments were verified by nmr using the method of Williamson, Howell, and Spencer[27] which is based on the observation that the line width at half-height ($W_{h/2}$) of the C-19 angular methyl group is larger for AB *trans* steroids than for the isomeric AB *cis* compounds. The nmr spectra were recorded under the conditions given in the original article[27] and the results are recorded in Table I. The $\Delta W_{h/2}$ values were calculated as follows: $W_{h/2}$ − TMS $W_{h/2}$ = $\Delta W_{h/2}$ (cps).

TABLE I

LINE WIDTHS AT HALF-HEIGHT FOR ANGULAR METHYL GROUPS

	$W_{h/2}$, cps			$\Delta W_{h/2}$, cps	
Compd	C-19	C-18	TMS	C-19	C-18
9c	1.35	1.50	0.55	0.80	0.95
10b	0.92	1.52	0.48	0.44	1.04
9b	1.40	1.70	0.60	0.80	1.10
10a	0.80	1.70	0.40	0.40	1.30

Isopropenyl acetate enol acetylation of 17β-acetoxy-11β-hydroxy-5β-androstan-3-one (**10a**) and 11β-hydroxy-5β-androstan-3-one (**10b**) led to mixtures of enol acetates which were analyzed by glpc. The results are recorded in Table II and compared to the enol acetylation result previously obtained with a similar 11-deoxy steroid.[11] As anticipated, since vigorous acetylating conditions are known to acetylate the C-11 hydroxyl group of steroids,[28,29] the infrared spectrum of the mixture of enol acetates indicated that enol acetylation proceeded with concomitant acetylation of the 11β-hydroxyl group. The isomeric nature of the enol acetates 3,11β,17β-triacetoxy-5β-androst-3-ene (**11a**) and 3,11β,17β-triacetoxy-5β-androst-2-ene (**12a**) was demonstrated by mild hydrolysis which yielded a single product identified as 11β,17β-diacetoxy-5β-androstan-3-one (**10e**). This compound was prepared from **10a** using acetic anhydride–perchloric acid and compared with the hydrolysis product (see Scheme I).

TABLE II

ISOPROPENYL ACETATE–SULFURIC ACID ENOL ACETYLATION RESULTS

Compd	Δ^2-Enol acetate, %	Δ^3-Enol acetate, %
10a	47 (**12a**)	53 (**11a**)
10b	45 (**12b**)	55 (**11b**)
10c	29 (**12c**)	71 (**11c**)

The mixtures of enol acetates **11a** and **12a**, and **11b** and **12b** were separated by preparative glpc and the nmr spectra of the individual enol acetates were recorded. It was demonstrated previously that the vinylic hydrogen at C-4 of a Δ^3-enol acetate such as 3,17β-diacetoxy-5β-androst-3-ene (**11c**) appears as a singlet at 5.05 ppm ($W_{h/2}$ = 4 cps),[11,30] whereas the isomeric Δ^2-enol acetate (**12c**) vinylic hydrogen at C-2 appears as an unresolved multiplet centered at 5.27 ppm ($W_{h/2}$ = 13 cps).[11] Structural assignments were made by virtue of the similar spectra recorded for the vinylic hydrogens of **11a** and **11b** and **12a** and **12b**.

Verification of the structural assignments based on nmr spectroscopy was made by brominating enol acetates **12a** and **11a** in the presence of epichlorohydrin to obtain the kinetically controlled bromination products.[31] The bromo ketones 11β,17β-diacetoxy-4ξ-bromo-5β-androstan-3-one (**13a**) and 11β,17β-diacetoxy-2ξ-bromo-5β-androstan-3-one (**14a**) failed to crystallize from the usual solvents. Their identity was proven by dehydrobromination with a lithium chloride–lithium

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(20) C. Djerassi, R. Yashin, and G. Rosenkranz, *ibid.*, **74**, 422 (1952).
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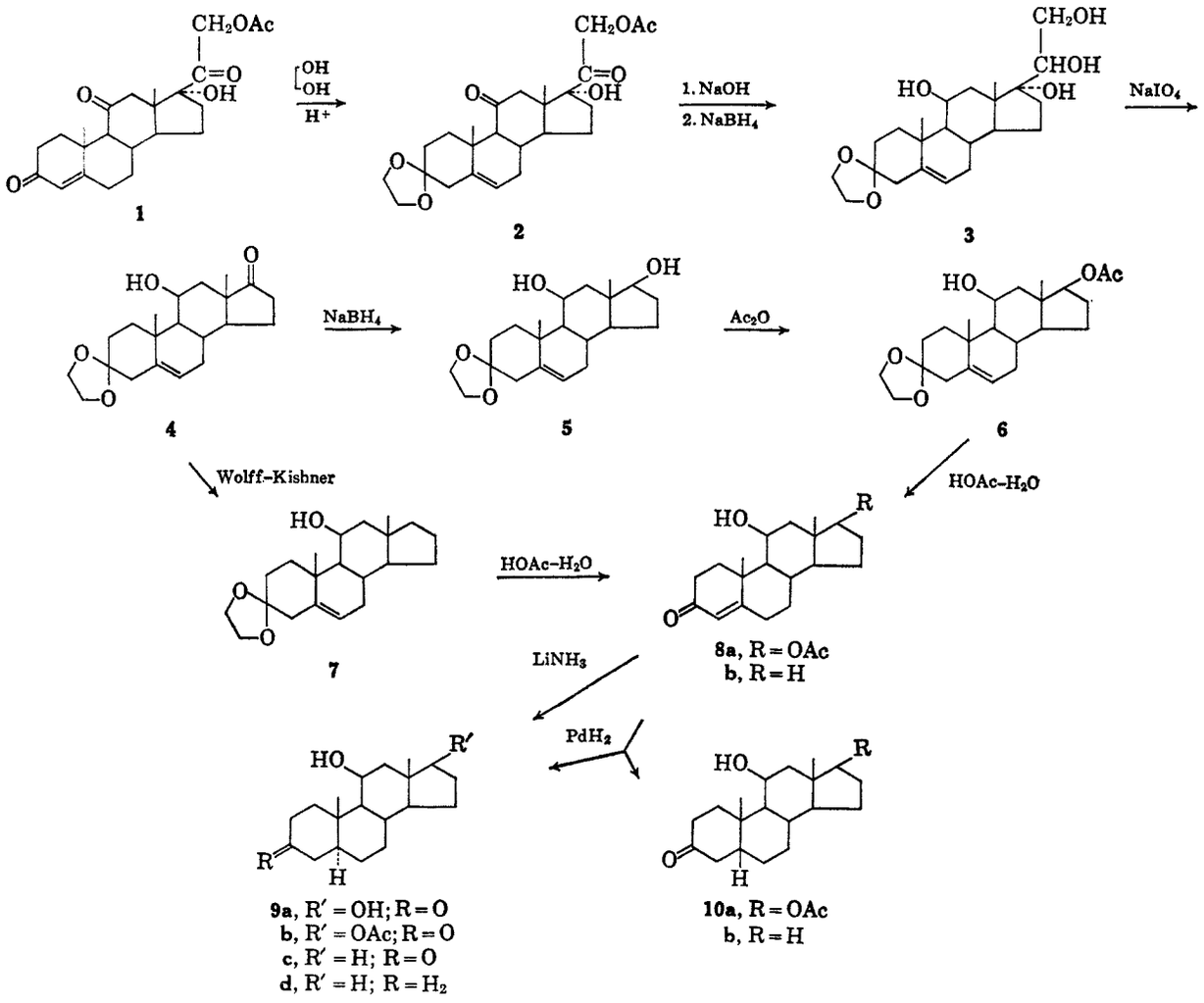
(31) M. P. Hartshorn and E. R. H. Jones, *J. Chem. Soc.*, 1312 (1962).

SCHEME I



carbonate mixture in refluxing dimethylformamide.[32] The dehydrobromination product of the 4ξ-bromo ketone (**13a**) was identified by comparing the ultraviolet[33] and infrared spectra and glpc with those of authentic 11β,17β-diacetoxy-androst-4-en-3-one (**15a**).[28] Compound **15a** was prepared from 3,3-ethylenedioxyandrost-5-ene-11β,17β-diol (**5**) by isopropenyl acetate acetylation to yield the diacetate (**17a**) which was then hydrolyzed with aqueous acetic acid[19] (see Scheme II).

Dehydrobromination of 2ξ-bromo-11β,17β-diacetoxy-5β-androstan-3-one (**14a**) yielded crystalline 11β,17β-diacetoxy-5β-androst-1-en-3-one (**16a**) whose ultraviolet spectrum (λ_{max} 230 mμ) confirmed the structural assignment.[33]

The chemical proof of structure for the isomeric enol acetates (**11a** and **12a**) confirmed the validity of the structural assignments based on the nmr spectra. Since the spectra of **11b** and **12b** were superimposable on those of **11a** and **12a** in the vinylic proton region no further proof of structure was deemed necessary.

The thermodynamically controlled enol acetylation reaction using perchloric acid catalyst and acetic anhydride next was studied using 17β-acetoxy-11β-hydroxy-5β-androstan-3-one (**10a**) and 11β-hydroxy-5β-androstan-3-one (**10b**). The reaction products were analyzed by glpc; the results for the equilibrium mixtures were compared (Table III) with those previously obtained with the 11-deoxy steroid 17β-acetoxy-5β-androstan-3-one (**10c**).[11]

TABLE III
THERMODYNAMICALLY CONTROLLED ENOL ACETYLATION RESULTS

Compd	Δ^2-Enol acetate, %	Δ^1-Enol acetate, %
10a	25 (**12a**)	75 (**11a**)
10b	18 (**12b**)	82 (**11b**)
10c	6 (**12c**)	94 (**11c**)

The perchloric acid–acetic anhydride rates of enol acetylation of ketones **10a**, **10b**, and **10c** were determined by glpc. The concentration of catalyst was adjusted so that acetylation of the 11β-hydroxyl group was instantaneous while enol acetylation required approximately 1 hr to be essentially complete. Under these conditions it was possible to obtain pseudo-first-order reaction rates during the first half of the reaction. The results are plotted in Figure 1. Since the ratios of enol acetates formed during the first 30 min of these reactions remained constant in each case, no significant equilibration occurred between isomeric enol acetates during that period.

The concentration of each isomeric enol acetate reflected the relative rate of formation of that isomer and the latter was calculated by multiplying the over-all rate of formation obtained from the curves in Figure 1 by the concentration of the individual enol acetate. The results are summarized in Table IV.

(32) R. Joly and J. Warrant, *Bull. Soc. Chim. France*, 367 (1958).
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SCHEME II

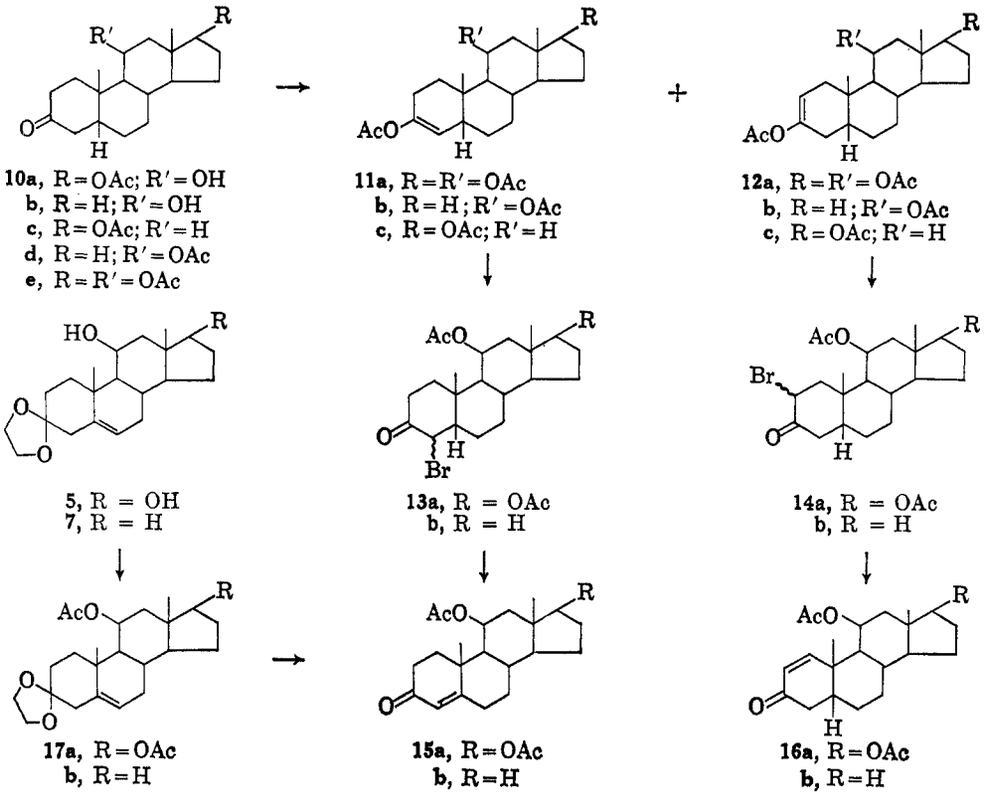

TABLE IV

RATE OF ENOL ACETATE FORMATION BY THE PERCHLORIC ACID–ACETIC ANHYDRIDE METHOD

Compd	Over-all rate constant, $k \times 10^{-2}$ (min^{-1})	% compn		Rate constant, $k \times 10^{-2}$ (min^{-1})	
		Δ^2-Enol	Δ^3-Enol	Δ^2-Enol	Δ^3-Enol
10a	9.6	32.1	67.9	3.0	6.7
10b	5.5	40.6	59.4	2.2	3.3
10c	15.2	17.7	82.3	2.7	12.5

Discussion

The introduction of an 11β-hydroxyl group into 3-oxo 5β-steroids has a significant effect on the ratio of Δ^2- and Δ^3-enol acetates formed during the kinetically controlled isopropenyl acetate enol acetylation reaction. The results listed in Table II indicate that the introduction of an 11β-hydroxyl group caused a 16 to 18% increase in the amount of Δ^2-enol acetate formed. In view of the longer reaction times required to enol acetylate an 11β-hydroxy-3-oxo 5β-steroid (2.5 hr) compared to a 3-oxo 5β-steroid (1.5 hr) it would seem that the altered enol acetate ratio is due to a slower formation of Δ^3-enol acetate. Glpc analysis of the reaction mixtures indicated that the 11β-hydroxyl group is acetylated rapidly (30 min) and is not the primary cause of the retarding effect.

Mechanistic studies by Jeffery and Satchell[34] of the isopropenyl acetate–sulfuric acid catalyzed acetylation reaction have shown that the reactive species is a mixed anhydride of acetone sulfonic acid and acetic acid. Moffett and Weisblatt[35] found that the reaction was sensitive to steric effects. It is difficult, however, to visualize how the C-11-acetoxyl group could directly hinder the approach of the anhydride to the C-3–C-4 region of the steroid. As solvation effects do not seem to play a significant role, since removal of the C-17 polar substituent had no effect on the product composition, it must be assumed that insertion of the C-11 substituent and the resulting β-face nonbonded interactions between C-19, C-11, and C-18 probably causes a slight "arching" of the steroid ring system which in turn causes the C-4 hydrogens to be more shielded by the C-7 and C-9 α hydrogens. The steric environment of the C-2 hydrogens would remain essentially unaffected by such a distortion.

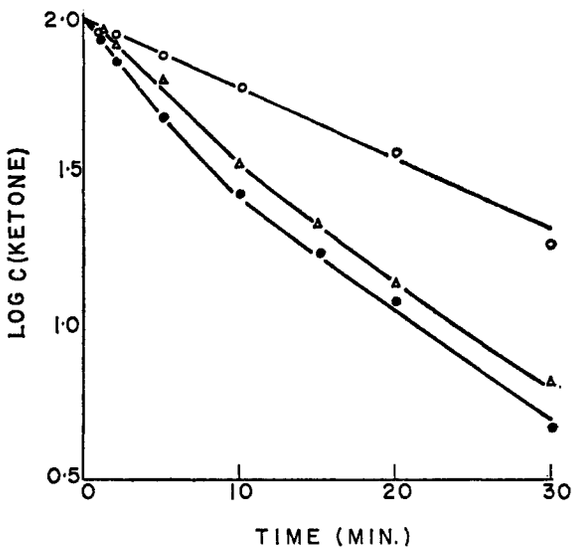

Figure 1.—Rates of enol acetylation using acetic anhydride–perchloric acid catalyst for 11β-hydroxy-5β-androstan-3-one (○), 17β-acetoxy-11β-hydroxy-5β-androstan-3-one (△), and 17β-acetoxy-5β-androstan-3-one (●).

(34) E. A. Jeffery and D. P. N. Satchell, *J. Chem. Soc.*, 1906 (1962).

(35) R. B. Moffett and D. I. Weisblatt, *J. Am. Chem. Soc.*, **74**, 2183 (1952).

Based on the relationship $\Delta F^\circ = -RT \ln K$, it is possible to determine the difference in free energy between isomeric pairs of enol acetates, but comparisons cannot be made concerning the ease of enol acetate formation in going from 3-oxo 5β-steroids to 11β-hydroxy-3-oxo 5β-steroids. To obtain such information the rates of enol acetylation using the acetic anhydride–perchloric acid catalyst method were measured for ketones **10a**, **10b**, and **10c**. The catalyst concentration was adjusted so that 11β-hydroxyl group acetylations were instantaneous (less than 45 sec), the enol acetylations required approximately 1.0 hr, and the equilibrations required over 24 hr. The enol acetylations all followed pseudo-first-order reaction rates in the presence of excess acetic anhydride and the equilibration effects were considered negligible during the first half of the reaction (10 min).

Examination of the rate constants listed in Table IV indicates that the Δ^2-enol acetate rates essentially are constant for the compounds investigated. Substitution on the β face of the C or D ring of the 3-oxo 5β-steroids affects only the rate of formation of Δ^3-enol acetate. This indicates that the energy required to form the less stable Δ^2-enol acetate is constant and that the 11β-hydroxyl group causes a distortion which makes Δ^3-enol acetate formation more difficult.

The equilibrium mixtures of enol acetates recorded in Table III indicate that the introduction of the 11β-acetoxyl group shifts the equilibrium point between enol acetates in favor of the Δ^2-enol acetate. The free-energy difference which corresponds to 94% 3,17β-diacetoxy-5β-androst-3-ene (**11c**) and 6% 3,17β-diacetoxy-5β-androst-2-ene (**12c**) is $\Delta F^\circ_{25} = 1.65$ kcal/mole. The equilibrium mixture of 75% 3,11β,17β-triacetoxy-5β-androst-3-ene (**11a**) and 25% 3,11β 17β-triacetoxy-5β-androst-2-ene (**12a**) corresponds to a ΔF°_{25} of 0.65 kcal/mole. Thus, in 3-oxo 5β-steroids, the 11β-acetoxyl group diminishes the preferential formation of Δ^3-enol acetate by $\Delta F^\circ_{25} = 1.0$ kcal/mole. The steric requirements of the 11β-acetoxyl group in these compounds are identical with those of the 11β-hydroxyl group since the second substituent on the oxygen atom makes relatively little difference to the 1,3-diaxial interaction value.[36]

The equilibrium mixture of 82% 3,11β-diacetoxy-5β-androst-3-ene (**11b**) and 18% 3,11β-diacetoxy-5β-androst-2-ene (**12b**) which corresponds to $\Delta F^\circ_{25} = 0.90$ kcal/mole suggests that the 17β-acetoxyl group also has an influence on the enolization of the carbonyl group at C-3, probably by buttressing the C-18 angular methyl group. The difference in ΔF°_{25} between the 17β-acetoxy- and 17-deoxy-11β-hydroxy-3-oxo 5β-steroids would make the 17β-acetoxy group contribution about $\Delta F^\circ_{25} = 0.25$ kcal/mole.

Since previous work has shown that the thermodynamically controlled enol acetylation reaction parallels the enolization properties of carbonyl compounds,[11,13] it is possible to conclude that the 11β-hydroxyl group effect in the 3-oxo 5β-steroids favors Δ^2 enolization by $\Delta F^\circ_{25} = 1.0$ kcal/mole for steroids possessing a 17β substituent. In the absence of a C-17 substituent the value drops to $\Delta F^\circ_{25} = 0.75$ kcal/mole.

(36) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, N. Y., 1965, p 45.

Mechanistic studies of steroid reaction catalyzed by enzymes have shown repeatedly that enolization plays a major role in various transformations.[37-40] It is therefore significant that the 11β-hydroxyl group which imparts glucocorticoid activity can alter the enolization pattern of the carbonyl group at C-3. Further studies are underway to determine the 11β-hydroxyl group effect with Δ^4-3-ketones.

Experimental Section

General.—Melting points were determined on an Electrothermal apparatus by the capillary method and are corrected. Rotations were measured in chloroform solution. The infrared spectra were recorded on a Perkin-Elmer Model 221 double-beam spectrophotometer. The ultraviolet spectra were determined in 95% ethanol solution using a Bausch and Lomb Spectronic 502 recording spectrophotometer. The nmr spectra were determined on a Varian A-60A spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. The absorbant for thin layer chromatography (tlc) was Merck silica gel G and the solvent was benzene–ethanol (8:1). The absorbant for column chromatography was methanol-washed, neutral Florisil activated at 125°. Gas chromatography (glpc) was carried out on a Model 810 F & M gas chromatograph equipped with dual flame detectors. The columns were 5% Fluro Silicone FS-1265 (QF-1) on 60–80 mesh Diatoport S, 8 ft × 4 mm o.d. The carrier gas was helium at a flow rate of 60 ml/min and the column temperature was 210° for C-17 deoxy steroids and 230° for C-17-acetoxy steroids. Quantitative estimation of mixtures was made by triangulation of the signals.

3,3-Ethylenedioxy-21-acetoxy-17α-hydroxypregn-5-ene-11,20-dione (**2**).—The title compound [2, mp 265–267° (lit.[14] mp 268–271°), $[\alpha]^{25}D$ +59° (*c* 1.04) (lit.[41] $[\alpha]D$ +46°)] was prepared from cortisone acetate (**1**, 10 g) in 88% yield by the procedure of Allen, Bernstein, and Littell.[14]

3,3-Ethylenedioxypregn-5-ene-11β,17α,20,21-tetrol (**3**).—The crude 3,3-ethylenedioxy-21-acetoxy-17α-hydroxypregn-5-ene-11,-20-dione (**2**, 10.1 g) was suspended in absolute ethanol (500 ml) and treated with sodium borohydride (10.0 g) at room temperature for 1 hr. A solution of sodium hydroxide (30 g) in water (50 ml) was added to the steroid suspension and an additional portion of sodium borohydride (7.0 g) was added. The suspended material dissolved and the solution was refluxed for 4.5 hr after which the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (500 ml), washed with salt solution (three 500-ml portions), dried over sodium sulfate, and filtered, and the solvent was removed under reduced pressure. The residue [9.9 g; ν_{max}^{Nujol} 3460 (OH), 1020, and 1090 cm^{-1} (ketal)], a mixture of C-20 epimeric compounds, was not purified but used directly in the subsequent reaction.

3,3-Ethylenedioxy-11β-hydroxyandrost-5-en-17-one (**4**).—A solution of sodium periodate (11.3 g) in water (75 ml) was added dropwise with stirring to a chilled (0°) solution of 3,3-ethylenedioxypregn-5-ene-11β,17α,20,21-tetrol (**3**, 9.9 g) in ethanol (200 ml). After the addition was complete the bath was removed and the mixture was stirred at room temperature (4.5 hr). The mixture was poured into ice–water (1.5 l.) containing a trace of pyridine and the product was collected by filtration. The crude 3,3-ethylenedioxy-11β-hydroxyandrost-5-en-17-one (**4**, 4.9 g, mp 208–209°) was crystallized from acetone–hexane: mp 208–210°; $[\alpha]^{26}D$ +5° (*c* 1.1); $\nu_{max}^{CCl_4}$ 3480 (OH), 1740 (>C=O) and 1095 cm^{-1} (ketal) (lit. mp 213–218°,[15] $[\alpha]D$ −100°).[16] The purity of the compound was verified by glpc.

3,3-Ethylenedioxyandrost-5-ene-11β,17β-diol (**5**).—Sodium borohydride (2.5 g) was added to a stirred solution of 3,3-ethylenedioxy-11β-hydroxyandrost-5-en-17-one (**4**, 2.44 g) in ethanol (200 ml). The reaction mixture was refluxed (2.5 hr) and the solvent was removed under reduced pressure. The residue was partitioned between dichloromethane (100 ml) and water (100

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ml). The organic layer was separated, the aqueous portion was extracted with dichloromethane (two 50-ml portions) and the combined dichloromethane extracts were washed with brine (three 100-ml portions). The solution was dried over magnesium sulfate and the solvent was distilled under reduced pressure. The crude 3,3-ethylenedioxyandrost-5-ene-11β,17β-diol (**5**) was crystallized from ethanol (2.06 g): mp 189–190.5°; $[\alpha]^{24}D$ +139.6° (*c* 1.0); ν_{max}^{KBr} 3430 (OH), 1625 (>C=C<), and 1090 cm^{-1} (ketal). The compound was homogeneous by tlc and glpc.

Anal.[42] Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 71.93; H, 9.38.

17β-Acetoxy-3,3-ethylenedioxyandrost-5-en-11β-ol (**6**).—3,3-Ethylenedioxyandrost-5-ene-11β,17β-diol (2.4 g) was acetylated by the usual method using acetic anhydride (8 ml) and pyridine (5 ml). The 17β-acetoxy-3,3-ethylenedioxyandrost-5-en-11β-ol (**6**, 2.0 g) was crystallized from ethanol containing 1% pyridine: mp 183.5–185.5°; $[\alpha]^{25}D$ +211° (*c* 1.0); ν_{max}^{Nujol} 3540 (OH), 1720 ($OCOCH_3$), and 1095 cm^{-1} (ketal). The compound was homogeneous by tlc and glpc.

Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.58; H, 8.66.

17β-Acetoxy-11β-hydroxyandrost-4-en-3-one (**8a**).—A solution of 17β-acetoxy-3,3-ethylenedioxyandrost-5-en-11β-ol (**6**, 1.66 g) in 50% aqueous acetic acid (50 ml) was heated on a steam bath (20 min) to effect hydrolysis of the ketal.[19] The solution was cooled and the solvent was removed under reduced pressure (40°). The residue was dissolved in dichloromethane (100 ml), washed with 5% sodium bicarbonate solution (two 50-ml portions), then with salt solution (two 50-ml portions), and dried over sodium sulfate. The solvent was distilled under reduced pressure and the residue, 17β-acetoxy-11β-hydroxyandrost-4-en-3-one (**8a**) was crystallized from acetone–hexane (1.37 g): mp 151°; $\nu_{max}^{CCl_4}$ 1735 ($OCOCH_3$), 1680 (>C=O), and 1615 cm^{-1} (>C=C<); λ_{max}^{EtOH} 242 mμ (ε 19,830); $[\alpha]^{24}D$ +122° (*c* 0.5) (lit.[43] mp 149.5–151.5°, $[\alpha]D$ +121°).

3,3-Ethylenedioxyandrost-5-en-11β-ol (**7**).—A mixture of 3,3-ethylenedioxy-11β-hydroxyandrost-5-en-17-one (**4**, 2.6 g), ethylene glycol (120 ml), potassium hydroxide (10 g), and hydrazine hydrate (20 ml) was refluxed (1 hr) then the temperature was raised until the excess hydrazine was slowly distilled (2 hr) from the reaction mixture. Refluxing was continued (bath temperature 220–230°) until glpc on an aliquot of crude reaction mixture indicated that all of the intermediate hydrazone had reacted (8 hr). On cooling the steroid crystallized and was filtered. The crude 3,3-ethylenedioxyandrost-5-en-11β-ol (**7**, 1.36 g) was washed successively with ethylene glycol (50 ml) and water (50 ml) and air dried, mp 134–136°. Recrystallization from acetone–hexane afforded pure 3,3-ethylenedioxyandrost-5-en-11β-ol (1.12 g): mp 134–136°, $\nu_{max}^{CCl_4}$ 3620 (OH) and 1096 cm^{-1} (ketal), $[\alpha]^{26}D$ 38° (*c* 1.1).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 76.3; H, 9.15. Found: C, 76.4; H, 9.34.

11β-Hydroxyandrost-4-en-3-one (**8b**).—The ketal (**7**, 1.0 g) was treated with aqueous acetic acid as described for the preparation of **8a**. After evaporation of the solvent the residue (0.92 g) was crystallized from acetone–hexane. The crystalline 11β-hydroxyandrost-4-en-3-one (**8b**, 700 mg, mp 169–171°) was homogeneous by glpc: $\nu_{max}^{CCl_4}$ 3620 (OH), 1660 (>C=O), and 1617 cm^{-1} (>C=C<); λ_{max}^{EtOH} 242 mμ (ε 14,800); $[\alpha]^{25}D$ +154° (*c* 1.0).

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.1; H, 9.8. Found: C, 79.1; H, 9.9.

17β-Acetoxy-11β-hydroxy-5α-androstan-3-one (**9b**).—A solution of 17β-acetoxy-11β-hydroxyandrost-4-en-3-one (**8a**, 100 mg) in ether–dioxane (6 ml, 1:1, v/v) was added to a vigorously stirred solution of metallic lithium (35 mg) in liquid ammonia (30 ml). The mixture was stirred (5 min) and the reaction was quenched by the addition of solid ammonium chloride (5 g). The ammonia was evaporated and the residue was partitioned between chloroform (50 ml) and water (50 ml). The aqueous layer was washed with additional chloroform (50 ml) and the combined chloroform extracts were washed with brine (three 50-ml portions) until neutral. The solution was dried over sodium sulfate and filtered and the solvent was removed under reduced pressure. Tlc analysis indicated that the product was a binary mixture (R_f 0.6 and 0.43). The infrared [$\nu_{max}^{CCl_4}$ 3450 (OH) and 1698 cm^{-1} (>C=O)] indicated complete reduction of the 17β-acetoxyl group while the conjugated ketone had been reduced to a mixture of saturated ketone **9a** and saturated alcohol. The mixture was acetylated by the usual method using acetic anhydride pyridine. The solvents were removed *in vacuo* and the residue (46 mg) was chromatographed over Florisil (20 g) using benzene as eluent. The 17β-acetoxy-11β-hydroxy-5α-androstan-3-one (**9b**, 33 mg) was crystallized from acetone–hexane: mp 192–196°; $[\alpha]^{26}D$ +21° (*c* 0.7); $\nu_{max}^{CCl_4}$ 3620 (OH), 1736 ($OCOCH_3$), and 1712 cm^{-1} (>C=O). Glpc analysis indicated that the compound was homogeneous.

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.59; H, 8.99. Found: C, 72.53; H, 9.09.

11β-Hydroxy-5α-androstan-3-one (**9c**).—A solution of 11β-hydroxyandrost-4-en-3-one (**8b**, 100 mg) in ether–dioxane (10 ml, 1:1, v/v) was added to a vigorously stirred solution of metallic lithium (247 mg) in liquid ammonia (30 ml) over a period of 30 sec. The mixture was stirred (60 sec) at reflux temperature and the reaction was quenched by the addition of solid ammonium chloride (5 g). The product, 11β-hydroxy-5α-androstan-3-one (**9c**, 39.4 mg) was isolated as described in the preparation of **9b**, and crystallized from acetone–hexane: mp 190–193°, $[\alpha]^{26}D$ +41° (*c* 1.0), $\nu_{max}^{CCl_4}$ 3616 (OH) and 1713 cm^{-1} (>C=O). Glpc analysis indicated that the compound was homogeneous.

Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.8; H, 10.3.

17β-Acetoxy-11β-hydroxy-5β-androstan-3-one (**10a**).—A mixture of 17β-acetoxy-11β-hydroxyandrost-4-en-3-one (**8a**, 5 g) in ethanol (74 ml) containing 3 *N* hydrochloric acid (7.4 ml) and 10% palladium on charcoal catalyst (440 mg) was hydrogenated at ambient pressure and temperature by shaking in an atmosphere of hydrogen. After the stoichiometric uptake of hydrogen (45 min) the catalyst was removed by filtration and washed with acetone. The combined washings and ethanolic solution were diluted with water (100 ml) and concentrated to half-volume (100 ml) under reduced pressure. The suspension was extracted with ether (two 100-ml portions) and the organic layer was washed with bicarbonate and salt solutions, dried over sodium sulfate, and filtered, and the solvent was evaporated. The residue (4.9 g) was analyzed by glpc and was shown to consist of 62% 17β-acetoxy-11β-hydroxy-5β-androstan-3-one (**10a**, retention time 21.5 min) and 38% 17β-acetoxy-11β-hydroxy-5α-androstan-3-one (**9b**, retention time 23.5 min). The mixture of 5β and 5α isomers was identified by glpc analysis using peak enhancement of the 5α isomer by the 17β-acetoxy-11β-hydroxy-5α-androstan-3-one (**9b**) previously prepared.

The mixture of **9b** and **10a** (4.5 g) was separated by column chromatography using Florisil (800 g) and eluting the column with benzene–ether (9:1). The 5β isomer was eluted prior to the 5α isomer. Pure 17β-acetoxy-11β-hydroxy-5β-androstan-3-one (**10a**, 1.46 g), recrystallized from acetone–hexane, gave mp 126.5–127°; $[\alpha]^{26}D$ −86° (*c* 0.5); $\nu_{max}^{CCl_4}$ 3615 (OH), 1735 ($OCOCH_3$), 1712 (>C=O), and 1249 cm^{-1} ($OCOCH_3$). Glpc analysis demonstrated a single peak.

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.59; H, 8.99. Found: C, 72.71; H, 9.08.

Further elution of the column gave 17β-acetoxy-11β-hydroxy-5α-androstan-3-one (**9b**, 856 mg) which was crystallized from acetone–hexane, mp 196°; mixture melting point with authentic material was undepressed.

The configurational assignments at C-5 were verified by nmr spectroscopy. The angular methyl line widths at half-height are recorded in Table I and are an average of two measurements.

11β-Hydroxy-5β-androstan-3-one (**10b**).—A mixture of 11β-hydroxyandrost-4-en-3-one (**8b**, 1.5 g) in ethanol (25 ml) containing 3 *N* hydrochloric acid (2 ml) and 10% palladium on charcoal catalyst (150 mg) was hydrogenated as described above in the preparation of **10a**. The mixture of 5β and 5α isomers (1.43 g) was identified by glpc analysis using peak enhancement of the 5α isomer by authentic 11β-hydroxy-5α-androstan-3-one (**9c**) previously prepared.

A mixture (4.0 g) of **9c** and **10b** was separated by column chromatography using Florisil (250 g) and eluting the column with hexane–ether (24:1). The pure 11β-hydroxy-5β-androstan-3-one (**10b**, 1.56 g) was triturated with hexane and crystallized from acetone–hexane: mp 148–152°, $[\alpha]^{26}D$ +43° (*c* 1.0), $\nu_{max}^{CCl_4}$ 3640 (OH) and 1714 cm^{-1} (>C=O). Glpc analysis demonstrated a single peak.

(42) Microanalyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

(43) The preparation and enol acetylation of 17β-acetoxy-5β-androstan-3-one has previously been reported.[11] The glpc retention times of the enol acetates are known and required no further identification.

Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.7; H, 10.3.

Further elution of the column with hexane–ether (19:1) gave 11β-hydroxy-5α-androstan-3-one (**9c**, 1,1 g) which was crystallized from acetone–hexane, mp 190–193°; mixture melting point with authentic material was undepressed. The nmr spectrum is recorded in Table I.

Isopropenyl Acetate Enol Acetylation of 17β-Acetoxy-11β-hydroxy-5β-androstan-3-one (10a).—A solution of **10a** (1.0 g) in isopropenyl acetate (25 ml) containing sulfuric acid catalyst (0.01 ml) was refluxed (1 hr) under nitrogen, then the condenser was turned down, the pressure was reduced, and the solvent was slowly distilled. Samples of the solution were removed at regular intervals, treated with sodium bicarbonate solution and ether, and analyzed by glpc. After 8 ml of solvent had been collected over a period of 2.5 hr glpc indicated reaction to be complete. The reaction mixture was cooled, diluted with ether (200 ml), and washed with sodium bicarbonate (two 100-ml portions) and salt solution (two 100-ml portions). The solution was dried over sodium sulfate, filtered, and evaporated under reduced pressure. The residue (1.18 g) was analyzed by glpc and two compounds were detected at retention times of 14.1 and 17.1 min which represented 53% 3,11β,17β-triacetoxy-5β-androst-3-ene (**11a**) and 47% 3,11β,17β-triacetoxy-5β-androst-2-ene (**12a**), respectively.

Fractional crystallization from acetone–hexane gave pure Δ^2-enol acetate **12a** (175.3 mg): mp 153–155°; $\nu_{max}^{CCl_4}$ 1753 (>C=COCOCH$_3$), 1736 (OCOCH$_3$) and 1698 cm^{-1} (>C=C<); glpc showed a single peak at retention time 17.1 min; $[\alpha]^{24}D$ +54° (*c* 0.9). The nmr spectrum of the compound showed 1.2 vinyl H, unresolved multiplet centered at 5.21 ppm ($W_{h/2}$, 8 cps).

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.55; H, 8.41.

The mother liquors from the crystallizations of the Δ^2-enol acetate (**12a**) were combined and separated by preparative glpc on an 8 ft × 0.5 in. column of 5% QF-1 on 60–80 mesh Diatoport S. The major constituent of the mixture, 3,11β,17β-triacetoxy-5β-androst-3-ene (**11a**, 64 mg) failed to crystallize from the usual solvents. The compound was homogeneous (glpc and tlc): $\nu_{max}^{CCl_4}$ 1755 (>C=COCOCH$_3$), 1735 (OCOCH$_3$), and 1698 cm^{-1} (>C=C<). The nmr spectrum of the compound showed 1 vinyl H, singlet at 5.05 ppm ($W_{h/2}$ = 3 cps).

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.41; H, 8.39. Found: C, 69.81; H, 8.22.

Isopropenyl Acetate Enol Acetylation of 11β-Hydroxy-5β-androstan-3-one (10b).—A solution of **10b** (202 mg) in isopropenyl acetate (10 ml) containing *p*-toluenesulfonic acid catalyst (12 mg) was refluxed (2.5 hr) under nitrogen then the pressure was reduced and the crude product was isolated as previously described: $\nu_{max}^{CCl_4}$ 1754 (>C=COCOCH$_3$), 1733 (OCOCH$_3$), and 1700 cm^{-1} (>C=C<). Glpc demonstrated peaks at 9.5 and 11.2 min which represented 54.2% 3,11β-diacetoxy-5β-androst-3-ene (**11b**) and 45.8% 3,11β-diacetoxy-5β-androst-2-ene (**12b**), respectively. The mixture of enol acetates was separated by glpc as previously described; however, the individual enol acetates failed to crystallize from the usual solvents. The nmr spectrum of the major constituent (glpc retention time 9.5 min) showed 1.1 vinyl H, singlet at 5.05 ppm ($W_{h/2}$ = 3.5 cps). The nmr spectrum of the second compound (glpc retention time 11.2 min) showed 0.9 vinyl H, unresolved multiplet centered at 5.21 ppm ($W_{h/2}$ = 8 cps).

Thermodynamically Controlled Enol Acetylation of 17β-Acetoxy-11β-hydroxy-5β-androstan-3-one (10a).—A mixture of acetic anhydride (1.2 ml) and 70% perchloric acid (0.02 ml) was added to a stirred solution of 17β-acetoxy-11β-hydroxy-5β-androstan-3-one (**10a**, 49.1 mg) in benzene (8 ml) and carbon tetrachloride (3 ml). Glpc analysis of aliquots of reaction mixture removed at 1-hr intervals indicated that the equilibrium was reached after 7 hr. The reaction mixture was diluted with carbon tetrachloride (10 ml) and washed with 5% sodium bicarbonate and salt solutions, dried over sodium sulfate, and filtered, and the solvent was evaporated leaving an oil (47 mg). Glpc analysis of the product detected two compounds at retention times of 14.1 and 17.1 min which were present in a ratio of 74.5% 3,11β,17β-triacetoxy-5β-androst-3-ene (**11a**) to 25.5% 3,11β,17β-triacetoxy-5β-androst-2-ene (**12a**). The compounds were identified by infrared analysis and glpc (peak enhancement by pure compounds **11a** and **12a** prepared by the isopropenyl acetate method).

The equilibrium mixture of enol acetates (74.5% **11a** and 25.5% **12a**) was also generated by subjecting the mixture of enol acetates from the isopropenyl acetate method (53% **11a** and 47% **12a**) to the enol-acetylating conditions herein.

Thermodynamically Controlled Enol Acetylation of 11β-Hydroxy-5β-androstan-3-one (10b).—A solution of 11β-hydroxy-5β-androstan-3-one (18.3 mg) in benzene (3 ml) and carbon tetrachloride (1.2 ml) was treated with an acetic anhydride (0.5 ml)–70% perchloric acid (0.001 ml) mixture as previously described. Glpc analysis indicated that the equilibrium mixture consisted of 82% 3,11β-diacetoxy-5β-androst-3-ene (**11b**, retention time 8.3 min) and 18% 3,11β-diacetoxy-5β-androst-2-ene (**12b**, retention time 10.0 min). The enol acetates were identified by infrared [$\nu_{max}^{CCl_4}$ 1754 (>C=COCOCH$_3$), 1733 (OCOCH$_3$), and 1700 cm^{-1} (>C=C<)] and by superposition of the glpc peaks of the enol acetates (**11b** and **12b**) previously prepared by the isopropenyl acetate method. Identical equilibrated mixtures could be obtained by submitting the mixture of enol acetates from the isopropenyl acetate method (54.2% **11b** and 45.8% **12b**) to these conditions.

Kinetics of Acetic Anhydride–Perchloric Acid Enol Acetylations.—The rates of enol acetylation of **10a**, **10b**, and **10c**[43] were determined by dissolving the steroid (0.03 mmole) in benzene (3.0 ml) and carbon tetrachloride (1.2 ml). A stock solution of acetic anhydride (250 ml) and 70% perchloric acid (0.025 ml) was prepared and aliquots (0.25 ml) were added to the steroid solutions which wre stirred at 25°. The reactions were carried out simultaneously with freshly prepared acetic anhydride–perchloric acid solution to avoid variation in the stock solution because of the darkening which occurred on standing. Samples of the reaction mixtures (10 drops) were taken, diluted with ether (1 ml), and mechanically shaken in a test tube containing sodium bicarbonate solution (1 ml). The organic layer was drawn off and dried with sodium sulfate, filtered, and analyzed by glpc.

The 11β-hydroxyl group of compounds **10a** and **10b** underwent rapid acetylation since samples taken after a reaction time of 45 sec and analyzed by glpc were devoid of starting ketones **10a** and **10b** but contained two new compounds (**10c** and **10d**) which were prepared and characterized below. The results of glpc analysis are recorded in Table IV. The reaction rates for the enol acetylation of **10a**, **10b**, and **10c** were calculated from the slope of the lines plotted in Figure 1. The ratios of enol acetates which were formed during 50% of the reaction were constant indicating that equilibration was not significant in the first half of the reaction. The average content of enol acetates is recorded in Table IV and reflects the relative rates of formation of Δ^2- and Δ^3-enol acetate. These rates were then used to calculate the absolute rate constants for Δ^2- and Δ^3-enol acetate formation. Prolonging the reaction times to approximately 30 hr led to equilibrated mixtures which were identical with those found in Table III.

3,3-Ethylenedioxy-11β,17β-diacetoxyandrost-5-ene (17a).—A sample of *p*-toluenesulfonic acid (85 mg) in isopropenyl acetate (20 ml) was stirred under nitrogen at 45° until dissolution was complete (20 min). A solution of 3,3-ethylenedioxyandrost-5-ene-11β,17β-diol (**5**, 835 mg) in isopropenyl acetate (50 ml) was added slowly (10 min) and the reaction mixture was refluxed (2.5 hr). The mixture was diluted with ether (200 ml) and washed with sodium bicarbonate solution (two 100-ml portions) and brine until the wash water was neutral. The solution was dried over sodium sulfate and filtered, and the solvent was evaporated. The 3,3-ethylenedioxy-11β,17β-diacetoxyandrost-5-ene (**17a**) was crystallized from ethanol containing 1% pyridine (377 mg): mp 167–170°; $[\alpha]^{25}D$ −17° (*c* 0.8); $\nu_{max}^{CCl_4}$ 1735 (OCOCH$_3$), 1670 (>C=C<), and 1090 cm^{-1} (ketal). The compound was homogeneous by glpc analysis.

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.28; H, 8.53.

11β,17β-Diacetoxyandrost-4-en-3-one (15a).—A solution of 3,3-ethylenedioxy-11β,17β-diacetoxyandrost-5-ene (**17a**, 202 mg) in 75% aqueous acetic acid (10 ml) was heated on a steam bath (10 min), cooled, diluted with water (40 ml), and neutralized with 5% sodium hydroxide solution (pH 8). The solution was extracted with dichloromethane (two 50-ml portions), the organic layer was washed with water until neutral, dried over magnesium sulfate, and filtered, and the solvent was evaporated. The 11β,17β-diacetoxyandrost-4-en-3-one (**15a**) was crystallized from hexane (175 mg): mp 139–141.5°, λ_{max}^{EtOH} 238 mμ (ε 15,800), $[\alpha]^{25}D$ +111° (*c* 1.4) (lit.[28] mp 141–142.5°, $[\alpha]D$ +118°). Glpc analysis demonstrated a single peak at retention time 37.4 min.

11β-Acetoxyandrost-4-en-3-one (15b).—A solution of 3,3-ethylenedioxyandrost-5-en-11β-ol (**7**, 272 mg) in isopropenyl acetate (10 ml) was treated with a solution of *p*-toluenesulfonic acid (33 mg) in isopropenyl acetate (5 ml) as described above. The crude 3,3-ethylenedioxy-11β-acetoxyandrost-5-ene [**17b**, 358 mg, $\nu_{max}^{CCl_4}$ 1729 ($OCOCH_3$) and 1090 cm^{-1} (ketal)] failed to crystallize from the usual solvents. Glpc analysis demonstrated one major component at retention time 16 min.

The crude product was hydrolyzed with 75% acetic acid as described above. The hydrolysate (289 mg) was analyzed by glpc and one major component (retention time 16 min) of 95% purity was detected. The 11β-acetoxyandrost-4-en-3-one (275 mg) failed to crystallize from the usual solvents. The compound was purified by column chromatography over Florisil and eluted with benzene. Preparative glpc was used to obtain an analytical sample, which was homogeneous by glpc: $\nu_{max}^{CCl_4}$ 1732 ($OCOCH_3$), 1673 (>C=C—C=O), and 1617 cm^{-1} (>C=C<); λ_{max}^{EtOH} 239 mμ (ε 15,600); $[\alpha]^{26.5}D$ +172° (*c* 0.7).

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.3; H, 9.15. Found: C, 76.0; H, 9.08.

11β,17β-Diacetoxy-5β-androstan-3-one (10e).—A solution of acetic anhydride (2.5 ml) and 70% perchloric acid (0.0025 ml) was added to a stirred solution of 17β-acetoxy-11β-hydroxy-5β-androstan-3-one (110 mg) dissolved in benzene (30 ml) and carbon tetrachloride (12 ml). After a reaction time of 45 sec, the reaction was quenched by the addition of 5% sodium bicarbonate (100 ml). The organic layer was diluted with ether (100 ml), washed with salt solution (100 ml), dried over sodium sulfate, and filtered, and the solvent was evaporated. Glpc analysis of the crude product (114 mg) detected a single compound at retention time 32 min. The 11β,17β-diacetoxy-5β-androstan-3-one (**10e**) was crystallized from acetone–hexane; mp 234.5–235.5°; $\nu_{max}^{CCl_4}$ 1736, 1732 ($OCOCH_3$), and 1715 cm^{-1} (>C=O); $[\alpha]^{26}D$ +37° (*c* 0.7).

Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.62; H, 8.69

11β,17β-Diacetoxy-5β-androst-1-en-3-one (16a).—A stirred solution of 3,11β,17β-triacetoxy-5β-androst-2-ene (64.3 mg) in carbon tetrachloride (3 ml) containing epichlorohydrin (0.1 ml) was treated with bromine in carbon tetrachloride solution (0.71 ml of 0.21 *M* Br_2). The reaction mixture was stirred at room temperature until the color of bromine disappeared. The solvents were evaporated under reduced pressure and the residual oil was analyzed by tlc. A single compound was detected at R_f 0.89. Infrared analysis [$\nu_{max}^{CCl_4}$ 1250 ($OCOCH_3$) and 1729 cm^{-1} (>C=O and $OCOCH_3$)] suggested the 2β-bromo-11β,17β-diacetoxy-5β-androstan-3-one (**14a**) structure. The compound failed to crystallize from the usual solvents.

The bromo ketone (**14a**, 75 mg) was dehydrobrominated by dissolving in dimethylformamide (4 ml) containing lithium chloride (75 mg) and lithium carbonate (120 mg). The suspension was stirred under nitrogen and refluxed (1.75 hr). The solution was cooled, diluted with ether (100 ml), washed with 3 *N* HCl and then with salt solution until neutral. The solution was dried over sodium sulfate and filtered, and the solvent was evaporated. The crude dehydrobromination product on glpc analysis was composed of 97% 11β,17β-diacetoxy-5β-androst-1-en-3-one (**16a**) at retention time of 29.3 min, 1.5% 11β,17β-diacetoxy-5β-androstan-3-one (**10e**) at retention time of 24.5 min, and 1.5% 11β,17β-diacetoxyandrost-4-en-3-one (**15a**) at a retention time of 37.4 min. The compounds at 24.5 and 37.4 min were identified by peak enhancement with authentic material. The residue was crystallized from acetone–hexane: mp 216–217° (55 mg), $\nu_{max}^{CCl_4}$ 1735 ($OCOCH_3$), 1662 (>C=C—C=O), and 1698 cm^{-1} (>C=C<); λ_{max}^{EtOH} 229 mμ (ε 8260); $[\alpha]^{28}D$ +111° (*c* 1.0).

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.29; H, 8.06. Found: C, 71.07; H, 8.24.

Bromination–Dehydrobromination of 3,11β,17β-Triacetoxy-5β-androst-3-ene (11a).—A stirred solution of 3,11β,17β-triacetoxy-5β-androst-3-ene (52 mg) in carbon tetrachloride (2 ml) containing epichlorohydrin (0.1 ml) was treated with a solution of bromine (18 mg) in carbon tetrachloride (1 ml) as described above. The residual oil (57 mg) after evaporation of the solvents was analyzed by tlc. One major component was detected at R_f 0.47 with minor spots at R_f 0.6 (starting material **11a**) and R_f 0.4 [11β,17β-diacetoxy-5β-androstan-3-one (**10e**)].

The infrared spectrum of the crude product ($\nu_{max}^{CCl_4}$ 1730 cm^{-1}) was consistent with the 4β-bromo-11β,17β-diacetoxy-5β-androstan-3-one (**13a**) structure. Column chromatography over Florisil (30 g) and elution with benzene–hexane (3:1) afforded homogeneous material (20 mg, R_f 0.47) which failed to crystallize from the usual solvents.

The bromo ketone (**13a**) was dehydrobrominated as described above using lithium chloride (36.1 mg) and lithium carbonate (42 mg) in dimethylformamide (3 ml). The crude dehydrobromination product was analyzed by glpc and two major constituents were detected at retention times of 37.4 min [11β,17β-diacetoxyandrost-4-en-3-one (**15a**)] and 32 min [11β,17β-diacetoxy-5β-androstan-3-one (**10e**)]. The compounds were identified by peak enhancement with authentic material. The compounds were separated by preparative tlc and the infrared and ultraviolet spectra of the 11β,17β-diacetoxyandrost-4-en-3-one were identical with those of authentic material previously prepared.

Registry No.—**3**, 7784-93-2; **4**, 3552-67-8; **5**, 4758-60-5; **6**, 7778-21-4; **7**, 7778-23-6; **8a**, 7778-22-5; **8b**, 7778-24-7; **9b**, 7778-25-8; **9c**, 7778-26-9; **10a**, 10026-40-1; **10b**, 7778-27-0; **11a**, 10026-41-2; **12a**, 7778-28-1; **11b**, 7778-29-2; **12b**, 7784-94-3; **15a**, 7784-95-4; **15b**, 10026-42-3; **10e**, 7778-30-5; **16a**, 7778-31-6; **14a**, 7778-32-7; **13a**, 7778-33-8; **12c**, 7199-33-9; **11c**, 4968-08-5; **10c**, 1164-92-7; **17a**, 7778-37-2.

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