$[\alpha]_D$ −281.5°. The n.m.r. of the total crystalline product had only signals associated with the epimer **8b**.

Ketonic Cleavage of 6β-Acetyltestosterone (8b).—A solution of 0.05 g. of **8b** in 20 cc. of methanolic sodium hydroxide solution (3%) was refluxed for 24 hr. under nitrogen. Water was added and the product was isolated from ether. Crystallization from ether–pentane gave 0.018 g. (45%) of crystals, m.p. 145–148°, identified as testosterone by comparison with an authentic sample.

6β-Acetyl-5α-androstan-3-on-17β-ol Acetate (10).—A solution of 0.8 g. of 6β-acetyltestosterone acetate **8** in 20 cc. of ethanol was hydrogenated over 0.4 g. of palladium-on-charcoal (10%). After 1 mole equiv. of hydrogen was absorbed, further uptake ceased. Filtration and evaporation gave residue which was crystallized from ether–pentane to give 0.45 g. (56%) of **10**, m.p. 140–141°, $[\alpha]_D$ −13°; λ^{KBr} 5.77 and 5.85 μ; λ_{max}^{EtOH} 285 mμ (ε 96).

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.61; H, 9.13.

6α-Acetyl-5α-androstan-3-on-17β-ol Acetate (11).—A solution of 0.15 g. of the β-isomer **10** in 70 cc. of methanol and 3 cc. of 10% sodium hydroxide solution was refluxed for 1.5 hr. The isolated product from ether was reacetylated with pyridine and acetic anhydride (3 cc. each) overnight at room temperature. The isolated product was crystallized from ether–pentane to give 0.10 g. (68%) of 6α-isomer **11**, m.p. 168–170°, $[\alpha]_D$ +40°; λ^{KBr} 5.77 and 5.85 μ; λ_{max}^{EtOH} 284 mμ (ε 151).

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.74; H, 9.09.

6α-Ethyl-5α-androstan-17β-ol (12).—6α-Acetyl-5α-androstan-3-on-17β-ol (**11**, 0.3 g.) was added to a solution of 0.3 g. of sodium and 1.5 cc. of hydrazine (anhydrous) in 15 cc. of diethylene glycol. The mixture was boiled under reflux for 3 hr. and then the temperature was gradually increased and the excess of hydrazine distilled off. When the temperature of the reaction mixture reached 215°, it was boiled under reflux for another 2 hr. The isolated product was recrystallized from ether–pentane to give 0.1 g. of 6α-ethyl-5α-androstan-17β-ol (**12**), m.p. 179–180°, $[\alpha]_D$ +26°; λ^{KBr} 5.75 μ.

Anal. Calcd. for $C_{21}H_{36}O$: C, 82.83; H, 11.92. Found: C, 82.68; H, 11.47.

Irradiation of 4-Methylandrosta-3,5-diene-3,17β-diol Diacetate (13).—A solution of 1 g. of 4-methyldienol diacetate **13**[14] in 80 cc. of cyclohexane was irradiated for 3 hr. The absorbance of the solution was determined during the irradiation, and after 3 hr. the ε reached a constant value of 4700. The solvent was evaporated to dryness and the residue was chromatographed on alumina (40 g.). Elution with pentane–benzene (3:1) gave 0.14 g. of the starting material **13**, m.p. 174–175°.

The second fraction eluted with pentane–benzene (1:4), 0.15 g. (17%), was identified as 4-methyltestosterone acetate, m.p. 156–158°.

The third fraction eluted with the same solvents yielded 0.17 g. (17%) of crystals recrystallized from methylene chloride–hexane; m.p. 176–178°, $[\alpha]_D$ −48.5°; λ^{KBr} 5.77, 5.83, and 5.87 μ; $\lambda_{max}^{cyclohexane}$ 291 mμ (ε 145). The structure **14** was assigned to this compound.

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.55; H, 8.96.

The fourth fraction eluted with benzene gave 0.13 g. (13%) of 6β-acetyl-4-methyltestosterone acetate, m.p. 187–190°, $[\alpha]_D$ −210°; λ^{KBr} 5.75, 5.80, 5.95, and 6.27 μ; λ_{max}^{EtOH} 252 mμ (ε 13,500); in 4% methanolic sodium hydroxide, λ_{max} 410 mμ (ε 9100).

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.48; H, 8.87.

Methylation of 4-Acetylandrost-5-en-3-on-17β-ol Acetate (2).—A solution of 0.49 g. of the enol **2** in 40 cc. of *t*-butyl alcohol containing 0.12 g. of potassium was treated at room temperature with 5 cc. of methyl iodide. After standing overnight at room temperature under nitrogen, the solution was filtered and evaporated to dryness. The residue, after acetylation with acetic anhydride and pyridine, was crystallized from methylene chloride–hexane and gave 0.27 g. (53%) of 4β-acetyl-4α-methyl derivative **14**, m.p. 176–178°, identical with the compound obtained by irradiation.

Attempted Isomerization of 6β-Acetyl-4-methyltestosterone Acetate (15).—A solution of 0.1 g. of **15** in 20 cc. of ethanol containing 0.2 cc. of sulfuric acid (20%) was boiled under reflux for 6 hr. The product was isolated from ether, m.p. 187–190°, and was identical in all respects with the starting material.

Acknowledgment.—We wish to thank Dr. Youval Shvo for the n.m.r. determinations. This work was supported by a grant (AM 05327-028) from the National Institutes of Health.

[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE, WEIZMANN INSTITUTE OF SCIENCE, REHOVOTH, ISRAEL]

Stereochemical Studies of Unsaturated Acetyl Steroids

BY MALKA GORODETSKY, DAN AMAR, AND YEHUDA MAZUR

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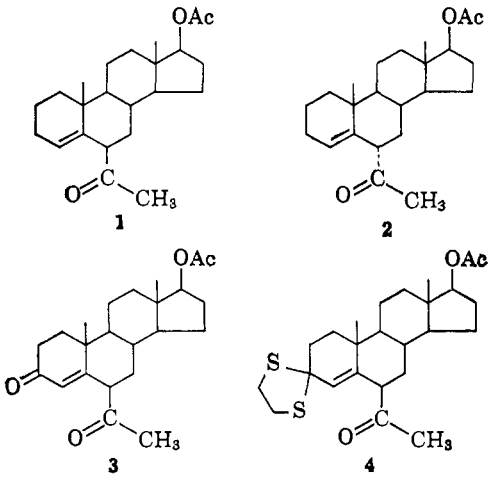
The configuration and rotameric conformation of a number of β,γ-unsaturated acetyl steroids were established using ultraviolet absorption and circular dichroism data. It was found that the 4β-acetyl-5-ene system (in **6**) and the 6β-acetyl-4-ene system (in **1** and **3**) can be regarded as inherently disymmetric chromophores. On the other hand, the analogous β,γ-unsaturated acetyl group in 6α-acetyl-4-ene derivatives (**2** and **9**), 4β-acetyl-4α-methylandrost-5-en-3-on-17β-ol acetate (**5**), and also in 2β-acetyl-2α-methylandrost-5-en-17β-ol acetate (**8**), does not possess this characteristic. This conclusion facilitates the assignment of the configuration and conformation to the acetyl group and rings A and B in these compounds. The stereochemistry of alkylation of Δ^4-3-keto steroids was determined using as a basis the configuration at C-4 of 4β-acetyl-4α-methylandrost-5-en-17β-ol (**6**).

Ultraviolet absorption spectra and optical rotational data of β,γ-unsaturated ketones can be used for the assignment of the relative spatial configuration of the two chromophores in a molecule.[1] In systems where more than one conformation can be envisaged, and in particular when one of the chromophores can undergo free rotation, these physical data are invaluable in determining the conformations.[1] It was therefore of interest to compare the ultraviolet and optical properties of epimeric β,γ-unsaturated acetyl derivatives possessing the double bond in a fused ring system.

The two compounds chosen were 6β-acetylandrost-4-en-17β-ol acetate (**1**) and its 6α-acetyl epimer **2**. The 6β-acetyl derivative **1** was obtained from the previously described 6β-acetyltestosterone acetate (**3**)[2] by a two-step sequence. Treatment of **3** with ethanedithiol under mild conditions (*p*-toluenesulfonic acid in acetic acid) yielded the 3-thioketal **4**. Desulfurization with Raney nickel resulted in the desired 6β-acetyl isomer **1** (m.p. 177–179°). Isomerization of **1** with base, and subsequent reacetylation, gave a mixture of **1** and the 6α-acetyl epimer **2** in roughly equal proportions, from which the latter (m.p. 117–119°)

(1) (a) A. Moscowitz, K. Mislow, M. A. W. Glass, and C. Djerassi, *J. Am. Chem. Soc.*, **84**, 1945 (1962); (b) R. C. Cookson and J. Hudec, *J. Chem. Soc.*, 429 (1962), and earlier references cited therein.

(2) M. Gorodetsky and Y. Mazur, *J. Am. Chem. Soc.*, **86**, 5213 (1964).



could be separated by chromatography. Both compounds could be converted to the same equilibrium mixture by base treatment.

The equatorial α-epimer **2** displays ultraviolet absorption data characteristic of the two separate chromophores.[3] This spectrum consists of long wave length carbonyl transitions (n $\rightarrow$ π^*) recorded in Fig. 1, as well as short wave length bands (Fig. 2). The latter

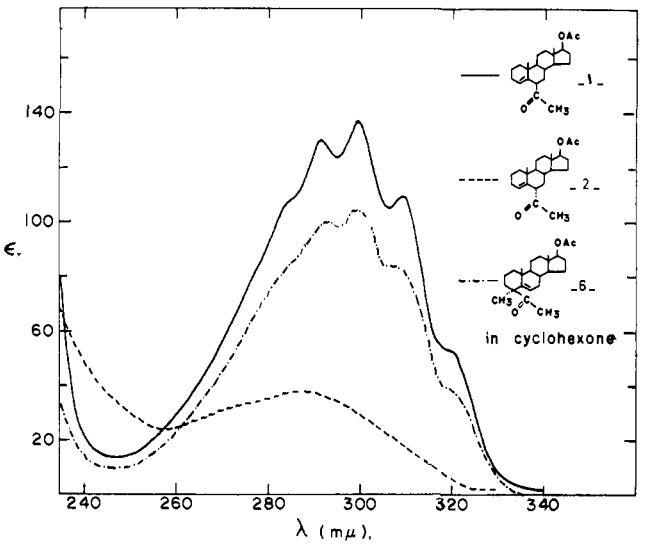


Fig. 1.—Ultraviolet spectra of β,γ-unsaturated acetyl steroids (high wave length region).

comprises the n $\rightarrow$ σ^* transition of the carbonyl group and $\pi \rightarrow \pi^*$ of the double bond, both of which appear as end absorption (Fig. 2). On the other hand, the β-epimer **1** displays an ultraviolet spectrum characteristic of a coupled carbonyl and double bond system, namely a red shift, enhancement of the absorption intensity, and pronounced vibrational fine structure of the n $\rightarrow$ π^* transitions (Fig. 1).[1,3,4] In the low wave length region, a shoulder is observed at *ca.* 210 mμ. The latter is assigned to a $\pi \rightarrow \pi^*$ charge-transfer band within the β,γ-unsaturated system,[4,5] which is superimposed on a higher intensity band of the two separate chromophores

(3) S. F. Mason, *Quart. Rev.* (London), **15**, 287 (1961).

(4) H. Labhart and G. Wagniere, *Helv. Chim. Acta*, **42**, 2219 (1959).

(5) (a) S. Winstein, L. de Vries, and R. Orlosky, *J. Am. Chem. Soc.*, **83**, 2020 (1961); (b) E. M. Kosower, W. D. Closson, H. L. Goering, and J. C. Gross, *ibid.*, **83**, 2013 (1961).

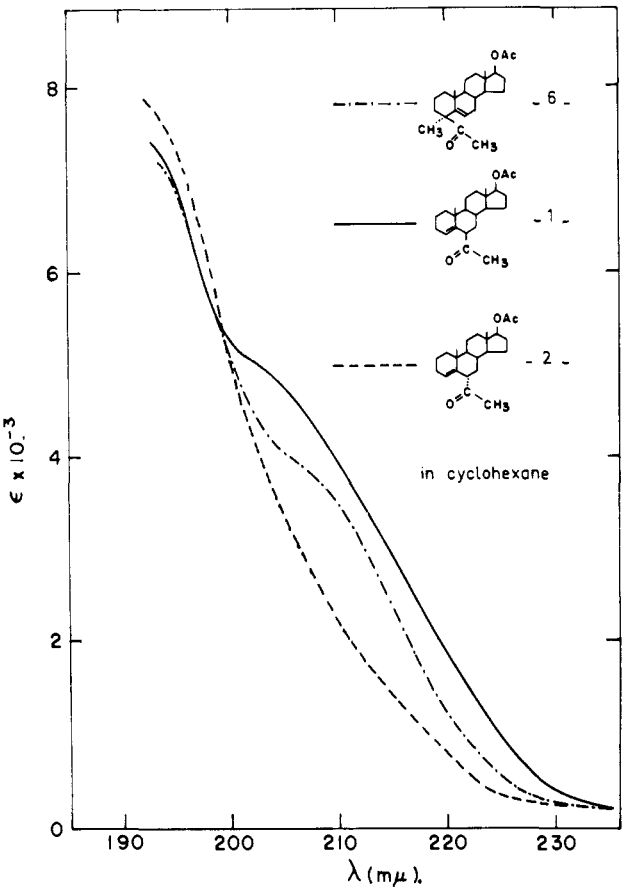


Fig. 2.—Ultraviolet spectra of β,γ-unsaturated acetyl steroids (low wave length region).

The coupling of the double bond and carbonyl orbitals results usually in the enhancement of the rotatory power of the n $\rightarrow$ π^* transition.[1,6] Thus the epimer **1** shows a high circular dichroism,[7] negative maximum of $\Delta\epsilon$ -11.71, and the epimer **2** a low positive one ($\Delta\epsilon$ $+1.68$) (Fig. 3). The magnitude of the latter is of the same order as expected for ketonic transitions, unperturbed by an additional chromophore.[8]

The negative sign of the circular dichroism maximum of the β-isomer **1** defines the chirality[1a] of the β,γ-unsaturated ketone system, and allows the assignment of the rotameric conformation to the acetyl group as represented in Fig. 4.[9]

The absence of an intensified n $\rightarrow$ π^* transition and the apparent lack of a charge-transfer transition in **2** suggest the conformation shown in Fig. 5 (or the

(6) S. F. Mason, *Quart. Rev.* (London), **17**, 20 (1963).

(7) The circular dichroism determinations were carried out by courtesy of Prof. G. Ourisson (unless otherwise stated) for which we are greatly indebted. The ordinate values in the c.d. curves are given in $\Delta\epsilon = \epsilon_L - \epsilon_R$. The latter value is related to the molecular ellipticity by the equation: $\Delta\epsilon = 0.303\Theta$.

(8) (a) L. Velluz and M. Legrand, *Angew. Chem.*, **73**, 603 (1961); (b) P. Witz, H. Herrmann, J.-M. Lehn, and G. Ourisson, *Bull. soc. chim. France*, 1101 (1963); (c) K. Wellman, R. Records, E. Bunnenberg, and C. Djerassi, *J. Am. Chem. Soc.*, **86**, 492 (1964).

(9) (a) The n.m.r. spectrum of **1** shows a signal attributed to the C-4 proton at 350 c.p.s., appearing as a triplet (J = 4.5 c.p.s.). This indicates coupling with the C-3 protons only, pointing to the β-axial configuration of the acetyl group. The proton at C-6 (183 c.p.s.) has a doublet-like pattern (J = 5 c.p.s.), indicative of distortion of ring B in **1**. A similar distortion of ring B was found by us previously to occur in 6β-acetyltestosterone acetate (**3**) by n.m.r. spectroscopy (see ref. 2). (b) The n.m.r. spectra were taken in deuteriochloroform on an A-60 Varian spectrometer, tetramethylsilane serving as internal reference. Peak positions are reported downfield from tetramethylsilane. We are indebted to Dr. Y. Shvo of this Institute for the n.m.r. determinations.

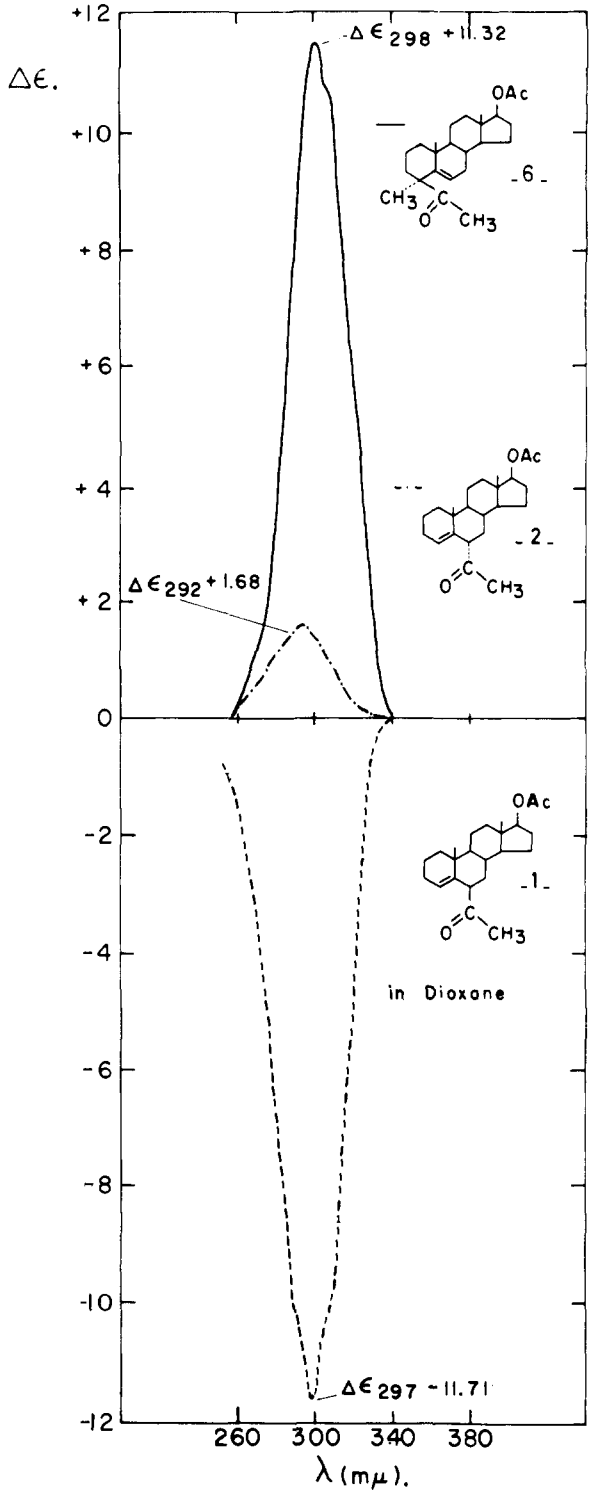


Fig. 3.—Circular dichroism of β,γ-unsaturated acetyl steroids.

alternative derived by rotation of the C=O bond by 180°).[10]

Partial conjugation of the carbonyl and the double bond in **1** may contribute also to its relative thermodynamic stability as compared to its 6-acetyl epimer **2**, in which this conjugation is absent. This is seen from the above-described equilibration data, which indicated equal proportion of the two epimers instead of the usual preponderance of the equatorial isomer.[11]

(10) The signal of the C-4 proton, which appears at 306 c.p.s. (multiplet), is shifted upfield by 14 c.p.s. as compared to the signal of the C-4 proton in Δ^4-androsten-17β-ol acetate (320 c.p.s.). This shift is attributed to the diamagnetic shielding caused by the carbonyl group when oriented as in Fig. 5 (see ref. 9b).

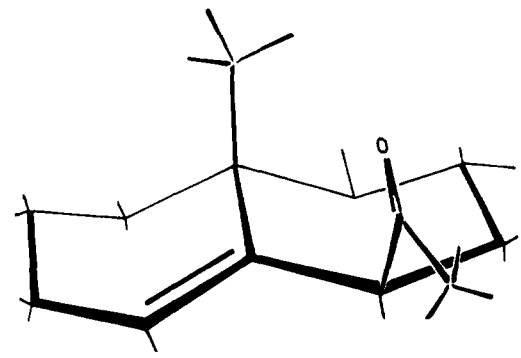


Fig. 4.—Conformation of 6β-acetylandrost-4-en-17β-ol acetate (1)

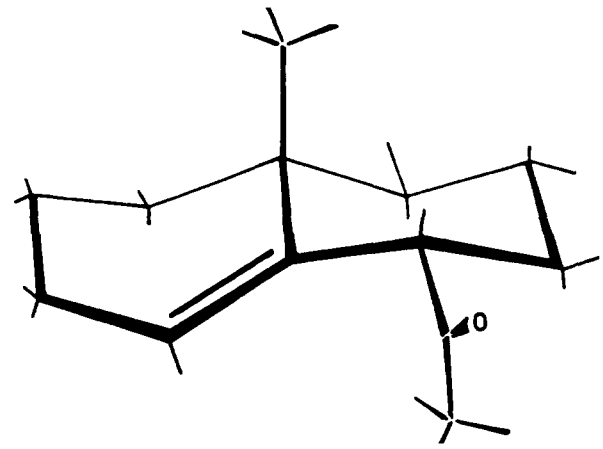
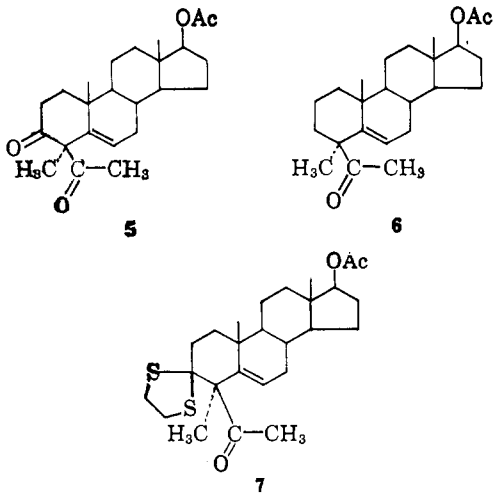


Fig. 5.—Conformation of 6α-acetylandrost-4-en-17β-ol acetate (2).

The major differences in the ultraviolet and rotatory data of the epimeric 6-acetyl-Δ^4 derivatives **1** and **2** could serve as a basis for the assignment of conformation in analogous systems, such as steroidal 4-acetyl-Δ^5 derivatives. The diketone **5**, possessing a 4-acetyl group and a double bond in the Δ^5-position, was recently synthesized by us[2] and assigned the α-methyl, β-acetyl configuration at C-4 although rigorous proof for this stereochemistry was missing.[2] The diketone **5** was converted to the desired 4β-acetyl-4α-methyl olefin **6** by treatment of **5** with ethanedithiol and boron trifluoride, followed by desulfurization of the resulting thioketal **7** with Raney nickel.

Comparison of the ultraviolet spectrum of the 4β-acetyl-4α-methyl derivative **6** (Fig. 1 and 2) with those of the epimeric pair **1** and **2** shows clearly that the stereochemistry at C-4 in **6** is similar to the isomer **1**. The circular dichroism curve of the 4β-acetyl-4α-methyl olefin **6** (Fig. 3) displays a pronounced positive maximum of the same magnitude but opposite sign compared to that of **1**. This behavior points to an enantiomeric chirality[1a] of the β,γ-unsaturated carbonyl system in **6** as compared to that in **1**. We conclude therefore that the acetyl group in **6** is β-oriented and its carbonyl dipole directed toward C-1, as seen in Fig. 6. The nonbonded interaction between the 4β-acetyl substituent and the methyl at C-19 in **6** should distort ring A as in **1**. The similarity of the absolute values of the two circular dichroism curves of **1** and **6** indicates that this distortion in fact exists.

(11) Similar equilibration data were found previously by us for the C-6 epimeric pair **3** and **9**.[2]



In the case of 2β-acetyl-2α-methyl-5α-androst-3-en-17β-ol acetate (**8**),[12] no enhancement of the n $\rightarrow$ π^* absorption and no charge-transfer band could be seen. The mutual orientation of the two chromophores in **8**, therefore, does not permit their coupling. The most likely conformation for **8** is one in which the acetyl group is in a quasi-axial position, with the carbonyl dipole in a plane parallel to that containing the C_{10}- and C_{19}-atoms.

It is of importance to emphasize that coupling of the orbitals within the β,γ-unsaturated ketone chromophore should result in both ultraviolet and rotatory effects. Other factors not involving intensity transfer in the ultraviolet from the double bond to the carbonyl transitions might also enhance the n $\rightarrow$ π^* bands.[13]

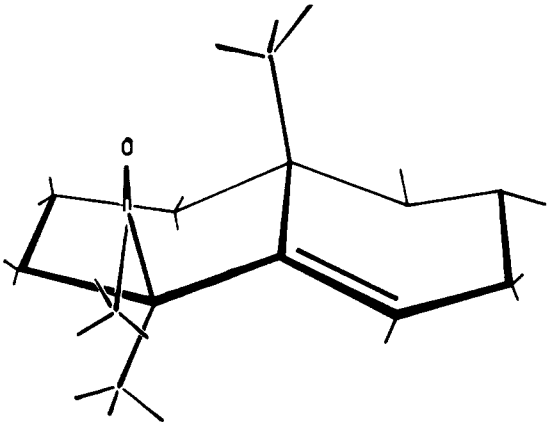
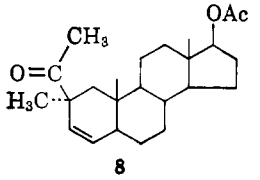


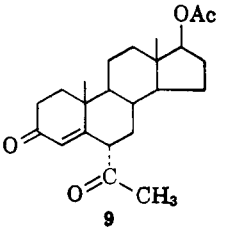
Fig. 6.—Conformation of 4β-acetyl-4α-methyl-5-en-17β-ol acetate (**6**)

In such an event the rotatory power of these transitions would not necessarily be increased. Thus, the high intensity values of the n $\rightarrow$ π^* transition in the unsaturated diketone **5** (ϵ 149 at $\lambda_{max}^{C_6H_{12}}$ 291 mμ; Fig. 7) do not imply coupling of the carbonyl and double bond orbitals, because of the comparatively low maximum of its circular dichroism curve ($\Delta\epsilon$ +3.31 at 306 mμ; Fig. 7). It follows, therefore, that in **5** the relative position of the acetyl group at C-4 and the Δ^5-double bond is different from that in **1**. A reasonable suggestion would be a quasi-boat conformation of ring A in **5**, analogous to that postulated by us previously for 4,4-dimethyl-Δ^5-steroids possessing the C_{19}-methyl group.[14]

(12) For preparation of this compound see Experimental.

(13) For different examples see: ref. 1b, footnote on p. 432; D. J. Cram and H. Steinberg, *J. Am. Chem. Soc.*, **76**, 2753 (1954).





The enhancement of the n $\rightarrow$ π^* transitions can be further augmented when the carbonyl function is homoconjugated to an β,γ-unsaturated carbonyl system.[14,15] In such instances, the ultraviolet absorption and the rotatory maxima of the n $\rightarrow$ π^* transition of the isolated carbonyl group may reach extreme values. The ultraviolet spectra of the epimeric 6-acetyltestosterone acetates **3** and **9** possessing such a 1,5-diketo-2-ene system were investigated.

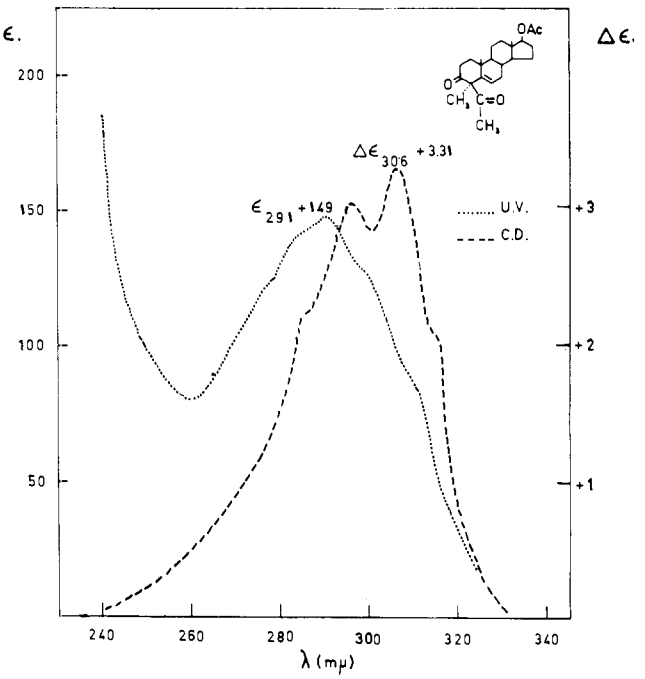


Fig. 7.—Circular dichroism (in dioxane) and ultraviolet spectrum (in cyclohexane) of 4β-acetyl-4α-methylandrost-5-en-3-on-17β-ol acetate (**5**).

In the higher wave length region, the two epimers **3** and **9** have low intensity bands between *ca.* 320–360 mμ (Fig. 8). These bands are associated with the n $\rightarrow$ π^* transitions of the 3-ketone chromophore.[3,16] The bathochromic shift observed in the band position of both **3** and **9** as compared with testosterone[17] results probably from the inductive effect exerted by the carbonyl dipole through the carbon chain. A similar red shift was observed previously in 6β- and 6α-bromocholest-4-en-3-one.[16] The main peaks in the n $\rightarrow$ π^* region (Fig. 8) belong to the transitions of the carbonyl function at C-6. The much higher extinction values of **3** as compared to those of **1** are mainly attributed to a smaller energy separation between the

(14) M. Gorodetsky and Y. Mazur, *Tetrahedron Letters*, 227 (1964).

(15) Similarly, R. C. Cookson and S. MacKenzie [*Proc. Chem. Soc.*, 423 (1961)] observed a pronounced increase in the n $\rightarrow$ π^* transition and rotatory power when a styrene chromophore was substituted for a double bond in a system possessing β,γ-homoconjugated carbonyl chromophore.

(16) C. W. Bird, R. C. Cookson, and S. H. Dandegaonker, *J. Chem. Soc.*, 3675 (1956).

(17) The respective positions of the three highest wave length peaks are: testosterone, 338, 352, and 368 mμ; **9**, 342, 357, and 372 mμ; **3**, 346, 362, and 378 mμ.

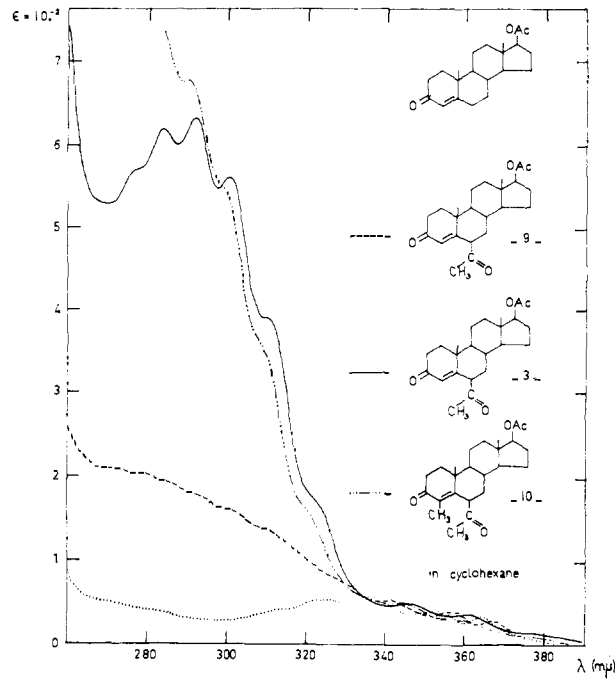


Fig. 8.—Ultraviolet spectra of Δ^4-3-keto steroids (high wave length region).

two interacting chromophores in the former.[1b,6] The ϵ-values in 6α-acetyltestosterone acetate (**9**) are much smaller than in its 6β-epimer **3**, but still have comparatively high values. This increase does not originate from coupling of the appropriate carbonyl and α,β-unsaturated ketone orbitals, as seen from the "normal" circular dichroism curve of **9** (see later), and resembles therefore the similar enhancement occurring in the diketone **5**.

The spectra of 6α-acetyltestosterone acetate (**9**) in the low wave length region (λ_{max} 229.5 mμ in cyclohexane, λ_{max} 238 mμ in ethanol) resemble that of testosterone acetate (λ_{max} 231.5 mμ in cyclohexane, λ_{max} 241 mμ in ethanol), the only difference being a small hypsochromic shift. On the other hand, the spectrum of 6β-acetyltestosterone acetate (**3**; λ_{max} 246 mμ in ethanol) exhibited a bathochromic shift as compared to testosterone acetate.[18] This red shift in **3** can be explained by the reduction of the ionization potential of the charge-transfer transition caused by the tautomeric effect, and neighboring group participation, of the 6β-acetyl substituent suitably oriented in space.[19] On the other hand, the small blue shift observed in **9** results from the inductive effect of the 6α-acetyl substituent on this transition in the Δ^4-3-ketone.[19]

In cyclohexane (Fig. 9) the ultraviolet band of substance **3** in the 240 mμ region appears as a multiplet of three peaks (one is a shoulder), the main one (at 239 mμ) again being shifted appreciably to higher wave length as compared to testosterone acetate. This multiplet in cyclohexane is common to other 1,5-diketo-2-ene chromophores having intensified n $\rightarrow$ π^* transitions.[2] The cause of the multiplet in cyclohexane is not at present clear. It is of interest to note that the intensity of n $\rightarrow$ π^* bands in the 300 mμ region of **3** was increased further when cyclohexane was

(18) A red shift in the high intensity band was observed previously in Δ^4-3-ketones substituted at C-10 with a formyl or acetyl group [P. N. Rao and C. L. Axelrod, *J. Org. Chem.*, **27**, 4694 (1962)].

(19) H. J. Ringold and A. Bowers, *Experientia*, **17**, 65 (1961).

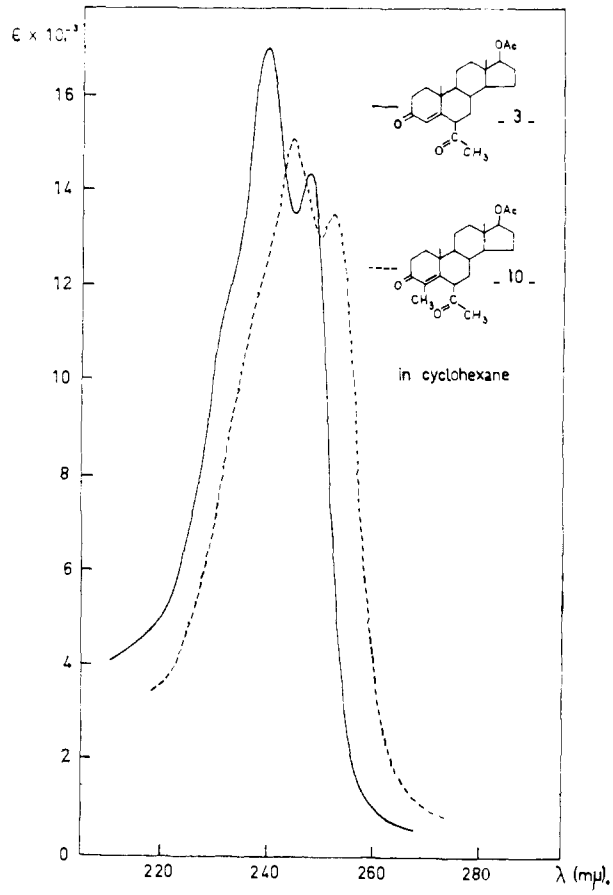


Fig. 9.—Ultraviolet spectra of Δ^4-3-keto steroids (230–250 mμ region).

substituted for ethanol. This increase is at the expense of the $\pi \rightarrow \pi^*$ band in the 240 mμ region, the intensity of which is decreased (ϵ_{246} mμ 16,400 in cyclohexane, ϵ_{239} mμ 13,100 in ethanol). This behavior is characteristic of β,γ-unsaturated ketones possessing coupled carbonyl and double bond transitions.[1b,6]

In the low wave length region, the spectrum of the 6β-acetyl compound **3** reveals an additional band (shoulder) at λ *ca.* 210 mμ (ϵ *ca.* 4500) superimposed on the high intensity transition. This shoulder (observed in cyclohexane) points to an additional $\pi \rightarrow \pi^*$ charge transfer from the π-orbital of the α,β-unsaturated carbonyl group to the π^*-orbital of the isolated ketone at C-6. As expected, this transition is missing in the 6α-acetyl isomer **9**.

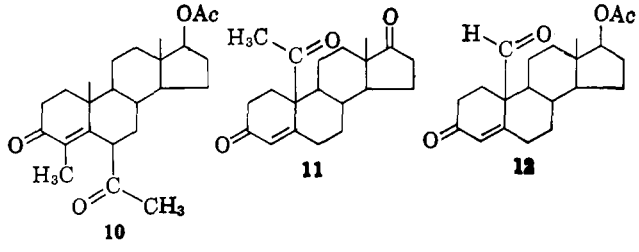
The circular dichroism curves of the two isomers **3** and **9**, as well as of testosterone acetate,[8a] are reproduced in Fig. 10.[20] In the 300 mμ region, the 6α-acetyl derivative **9** shows a positive curve with a normal value. The exceptionally high negative maximum of the circular dichroism curve of the 6β-isomer **3** points to a very high rotatory power of the enhanced n $\rightarrow$ π^* transition, the chirality of this β,γ-unsaturated carbonyl group being similar to that of compound **1** previously described. In the 340 mμ region, the 6α-isomer **9** has a negative circular dichroism curve similar to that of testosterone acetate.[7a] In isomer **3**, on the other hand, the sign of the curve in this region is reversed. This reversal was previously observed in 6β-bromo-Δ^4-3-ketones and was explained by postulating a distorted conformation of ring B. An analogous

(20) These c.d. curves were done in the laboratories of Roussel-Uclaf, Romainville, France. We are indebted to Dr. Poirier for these determinations.

distortion was also proposed by use for the 6β-acetyl compound **3** on the basis of n.m.r. results.[2]

The ultraviolet spectra of some other compounds possessing the 1,5-diketo-2-ene system was also investigated. The above-described typical ultraviolet features were observed in all the compounds having an orientation of the isolated carbonyl group relative to the α,β-unsaturated ketone chromophore suitable for orbital coupling. Thus, 4-methyl-6β-acetyltestosterone acetate (**10**),[2] which possesses a stereochemistry analogous to that of the nonmethylated analog **3**, shows a similar ultraviolet spectrum (Fig. 9) and circular dichroism. The circular dichroism curve of **10**[20] (in methanol) exhibits two maxima, a very intense negative one at 290 mμ ($\Delta\epsilon$ −27) and a positive one at 337 mμ ($\Delta\epsilon$ +0.6).

The ultraviolet spectra of the Δ^4-3-ketones **11** and **12**,[21] possessing a carbonyl function at C-10 in cyclohexane, also show the typical multiplet of the high intensity $\pi \rightarrow \pi^*$ transitions in addition to the enhanced 300 mμ $n \rightarrow \pi^*$ absorptions.[22]



The establishment of the stereochemistry of acetyl groups in Δ^4- and Δ^5-unsaturated steroids permits further the assignment of the configuration to derived compounds. For instance, it was possible to use 4β-acetyl-4α-methylandrost-5-en-17β-ol acetate (**6**) as a basis for the determination of the configuration at C-4 in 4,4-dialkyl-Δ^5-steroids. This determination is of some importance, since it will enable us to decide on the direction of alkylation in compounds possessing Δ^4-3-keto systems.

Methylation of 4-ethyltestosterone acetate (**13**)[23] with methyl iodide in the presence of potassium *t*-butoxide in *t*-butyl alcohol gave mainly 4β-ethyl-4α-methylandrost-5-en-3-on-17β-ol acetate (**14**) (m.p. 150–152°, $[\alpha]_D$ −42°), which on modified Wolff–Kishner reduction of the ketone group and reacetylation was transformed to 4β-ethyl-4α-methylandrost-5-en-17β-ol acetate (**15**), (m.p. 144–145°, $[\alpha]_D$ −89°). The latter substance proved to be identical with the compound obtained by Wolff–Kishner reduction of 4β-acetyl-4α-methylandrost-5-en-17β-ol acetate (**6**), thus establishing the stereochemistry of C-4 of **14**. On the other hand, ethylation of 4-methyltestosterone acetate (**16**)[24] with ethyl iodide yielded mainly 4α-ethyl-4β-methylandrost-5-en-17β-ol acetate (**17**), (m.p. 168–170°, $[\alpha]_D$ −27°), which on removal of the 3-keto

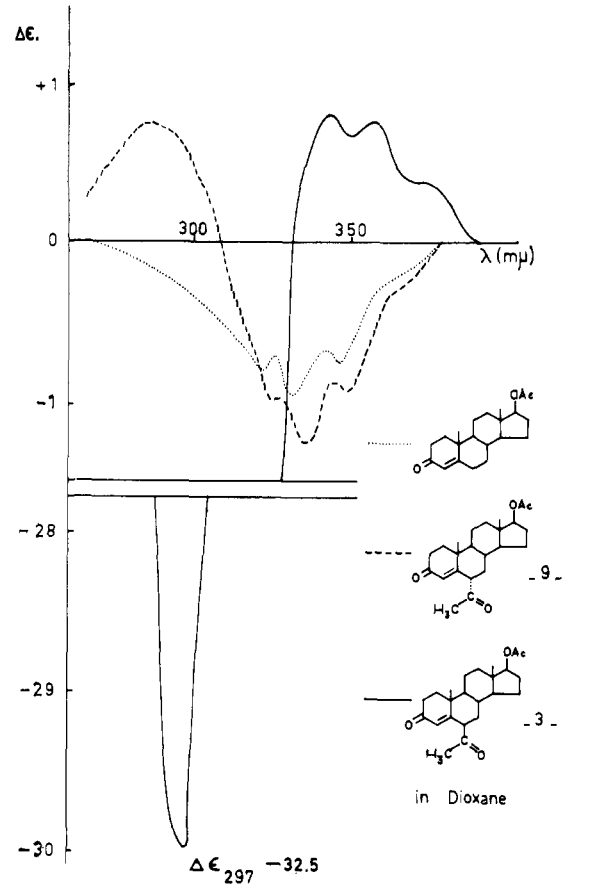
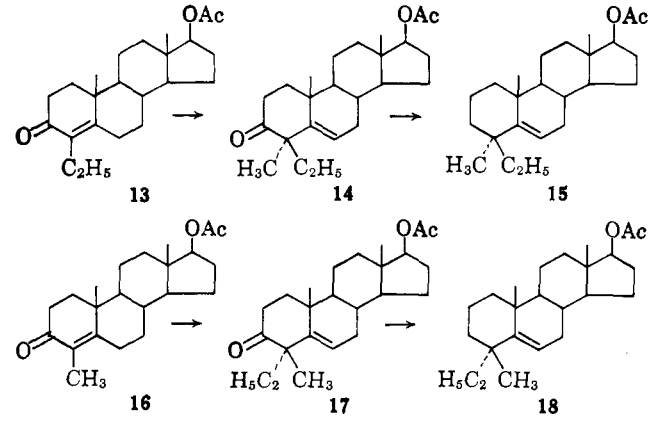


Fig. 10.—Circular dichroism of Δ^4-3-keto steroids.

group was converted to the C-4 epimeric 4α-ethyl-4β-methylandrost-5-en-17β-ol acetate (**18**), (m.p. 92–93°, $[\alpha]_D$ −84°).



Accordingly, the alkylation of 4-alkyl-3-keto-Δ^4-steroids at C-4 results in α-substitution. Very recently Just and Richardson[25] arrived at the same conclusion through experiments performed in the cholestane series, using a different approach. α-Alkylation occurs also in other 3-keto-Δ^4-steroids and similar systems possessing alkyl, carbomethoxy, or acetyl substituents at C-4.[2,26] In order to accommodate both α-side and axial attack of the alkyl halide, it was postulated that ring A exists as a boat in the transition state.[25] Recently a similar conformation was found in the result-

(21) We are indebted to Dr. K. Schaffner for the samples of the two compounds. For compound **12** see P. N. Rao and L. R. Axelrod, *J. Org. Chem.*, **27**, 4694 (1962).

(22) The ultraviolet spectrum of **11** in cyclohexane reveals bands at: λ 236 (sh), 240.5, and 246 (sh) mμ (ε 10,800, 12,800, and 11,700) and at λ 284, 292, 297, 305(sh), and 317(sh) mμ (ε 312, 312, 303, 285, and 202). The ultraviolet spectrum of **12** in the same solvent shows bands at: λ 234, 238.5(sh), and 243(sh) mμ (ε 11,500, 12,700, and 11,700) and at λ 294(sh), 302.5, 312, 323, and 336(sh) mμ (ε 260, 253, 250, 239, and 157).

(23) N. W. Atwater, *J. Am. Chem. Soc.*, **82**, 2847 (1960).

(24) F. Sondheimer and Y. Mazur, *ibid.*, **79**, 2906 (1957).

(25) G. Just and K. St. C. Richardson, *Can. J. Chem.*, **42**, 464 (1964).

(26) *Cf.* G. Stork and J. W. Schulenberg, *J. Am. Chem. Soc.*, **78**, 250 (1956); E. Wenkert, A. Afonso, J. B. Bredenberg, C. Kaneko, and A. Tahara, *ibid.*, **86**, 2038 (1964).

ing 4,4-dialkyl-Δ^5-3-keto steroids.[14] On the other hand, it is still conceivable that the alkylation involves only steric factors, in view of the specific behavior of the Δ^4-3-keto system. Further work is in progress to clarify this point.

Experimental

All melting points were taken in capillaries and were uncorrected. Ultraviolet spectra were determined on a Cary 14 spectrophotometer and the infrared spectra on a Perkin–Elmer Infracord. The rotations were done in chloroform.

6β-Acetylandrost-4-en-17β-ol Acetate (1).—A solution of 6β-acetyltestosterone acetate (0.6 g.)[2] in 3 cc. of acetic acid and 1 cc. of ethanedithiol was treated with 0.7 g. of *p*-toluenesulfonic acid. After standing for 1 hr. at room temperature the reaction mixture was filtered off and the crystals thus obtained were recrystallized twice from ether. The thioketal **4** (0.45 g.) melted at 230–231°, $[\alpha]_D$ −202°; λ_{max}^{KBr} 5.75, 5.85 μ.

Anal. Calcd. for $C_{25}H_{36}O_3S_2$: C, 66.94; H, 8.12; S, 14.27. Found: C, 67.11; H, 8.20; S, 14.38.

A solution of 0.44 g. of thioketal **4** in 70 cc. of ethanol was treated with a suspension of Raney nickel in ethanol (3 spoonsful) and boiled under reflux overnight. The filtered solution was evaporated *in vacuo* and the resulting crystalline material was chromatographed on silica (24 g.). Elution with pentane–ether (7:1) gave 0.29 g. of 6β-acetylandrost-4-en-17β-ol acetate (1) which melted after recrystallization from ether–hexane at 177–179°, $[\alpha]_D$ −201.5°; λ_{max}^{KBr} 5.76, 5.84 μ.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.10; H, 9.30.

6α-Acetylandrost-4-en-17β-ol Acetate (2).—A solution of 0.1 g. of 6β-acetylandrost-4-en-17β-ol acetate (1) in 10 cc. of methanol was treated with 0.5 cc. of 10% sodium hydroxide solution. After boiling under reflux for 3 hr. the solution was left at room temperature overnight. The material was isolated with ether and was reacetylated with acetic anhydride and pyridine at room temperature. Isolation with ether gave crystalline material, $[\alpha]_D$ −48°. It was then chromatographed on alumina (10 g.). Elution with pentane–ether (25:1) gave the starting material (0.043 g.) 1, m.p. 178–179°. The next fraction eluted with the same solvent gave 0.038 g. of **2**, m.p. 110–113° (after recrystallization from ether–pentane), $[\alpha]_D$ +74°; λ_{max}^{KBr} 5.76, 5.85 μ.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.69; H, 9.59.

Similar treatment of 0.05 g. of **2** with 10% sodium hydroxide solution in methanol gave after reacetylation a mixture of the two epimers 1 and **2** in the same ratio, as found from the optical rotation value of the total mixture ($[\alpha]_D$ −48°). Chromatography of this material on alumina yielded 0.02 g. of 1 and 0.017 g. of **2**.

4β-Acetyl-4α-methylandrost-5-en-17β-ol Acetate (6).—A solution of 0.16 g. of 4β-acetyl-4α-methylandrost-5-en-3-on-17β-ol acetate (**5**)[2] in 2 cc. of ethanedithiol was treated with 1 cc. of boron trifluoroetherate for 3 hr. at room temperature. The product was isolated with ether, washed with cold sodium hydroxide solution, and recrystallized from ether–pentane. The thioketal **7** thus obtained (0.13 g.) had m.p. 173–174°, $[\alpha]_D$ +105°; λ_{max}^{KBr} 5.76, 5.85 μ.

Anal. Calcd. for $C_{26}H_{38}O_3S_2$: C, 67.51; H, 8.28. Found: C, 67.43; H, 8.36.

A solution of 0.1 g. of the thioketal **7** in 50 cc. of ethanol was treated with a Raney nickel suspension in ethanol (2 spoonsful) and boiled under reflux overnight. Evaporation of the filtered solution gave, after recrystallization from ether–pentane, 0.065 g. of 4β-acetyl-4α-methylandrost-5-en-17β-ol acetate (**6**), m.p. 187–188°, $[\alpha]_D$ +110°; λ_{max}^{KBr} 5.72, 5.84 μ.

Anal. Calcd. for $C_{24}H_{36}O_3$: C, 77.37; H, 9.75. Found: C, 77.54; H, 9.74.

2β-Acetyl-2α-methylandrost-3-en-17β-ol Acetate (8).—A solution of 0.2 g. of 2α-acetyl-2α-methylandrostan-3-on-17β-ol acetate, m.p. 189–190°,[27] was dissolved in 20 cc. of acetone and heated under reflux with Raney nickel (1 spoonful) which was previously refluxed for 3 hr. with acetone. The solvent was then evaporated from the filtered solution and the residue recrystallized from ether–hexane to give 0.08 g. of 2β-acetyl-2α-methylandrost-3-en-17β-ol acetate (**8**), m.p. 218–220°; λ_{max}^{KBr} 5.76, 5.87, 13.32, 13.74 μ.

Anal. Calcd. for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74. Found: C, 77.21; H, 9.62.

Methylation of 4-Ethyltestosterone (13).—A solution of 0.5 g. of 4-ethyltestosterone (**13**)[23] in 25 cc. of *t*-butyl alcohol was treated with a solution of 0.5 g. of potassium in 25 cc. of *t*-butyl alcohol, and then with 5 cc. of methyl iodide. The reaction mixture was heated under reflux for 3 hr., filtered, and the obtained solution evaporated to dryness. It was then reacetylated with acetic anhydride and pyridine, and the crystalline residue chromatographed on alumina (20 g.). The material was eluted with pentane–ether (10:1) and was recrystallized from ether–pentane to give 0.35 g. of 4β-ethyl-4α-methylandrost-5-en-3-on-17β-ol acetate (**14**), m.p. 150–152°, $[\alpha]_D$ −42°; λ_{max}^{KBr} 5.78, 5.88 μ.

Anal. Calcd. for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74. Found: C, 77.21; H, 9.85.

Ethylation of 4-Methyltestosterone (16).—A solution of 1 g. of 4-methyltestosterone (**16**)[24] in 50 cc. of *t*-butyl alcohol was treated with a solution of 1 g. of potassium in 50 cc. of *t*-butyl alcohol, and then with 10 cc. of ethyl iodide. The reaction mixture was heated under reflux for 3 hr., filtered, and the solution evaporated to dryness. The residue was reacetylated with acetic anhydride and pyridine for 0.5 hr. on steam bath; the material isolated from ether was chromatographed on alumina (30 g.). Elution with pentane–ether (10:1) gave 4α-ethyl-4β-methylandrost-5-en-3-on-17β-ol acetate (**17**), 0.63 g., m.p. 168–170°, $[\alpha]_D$ −27°; λ_{max}^{KBr} 5.78, 5.86 μ.

Anal. Calcd. for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74. Found: C, 77.25; H, 9.81.

4β-Ethyl-4α-methylandrost-5-en-17β-ol Acetate (15).—(a) 4β-acetyl-4α-methylandrost-5-en-17β-ol acetate (**6**, 0.02 g.) was added to a solution of 0.1 g. of sodium and 0.5 cc. of hydrazine in 5 cc. of diethylene glycol. The solution was heated under reflux for 3 hr. (180°) and then the temperature was slowly increased while the reflux was discontinued until it reached 215°. Additional reflux for 2 hr., extraction with ether, and reacetylation gave residue which was chromatographed on alumina. Elution with pentane–ether (97:3) gave 0.018 g. of 4β-ethyl-4α-methylandrost-5-en-17β-ol acetate (**15**), m.p. 144–145°, $[\alpha]_D$ −89°.

Anal. Calcd. for $C_{24}H_{38}O_2$: C, 80.39; H, 10.68. Found: C, 80.45; H, 10.68.

(b) 4β-Ethyl-4α-methylandrost-5-en-3-on-17β-ol acetate (**14**, 0.06 g.) was added to a solution of 0.1 g. of sodium and 0.5 cc. of hydrazine in 5 cc. of diethylene glycol. Similar treatment as in (a) gave a residue which was chromatographed on 10 g. of alumina. Elution with pentane–ether (97:3) gave 0.047 g. of 4β-ethyl-4α-methylandrost-5-en-17β-ol acetate (**15**), m.p. 144–145°, identical with the product obtained in the previous experiment.

4α-Ethyl-4β-methylandrost-5-en-17β-ol Acetate (18).—4α-Ethyl-4β-methylandrost-5-en-3-on-17β-ol acetate (**17**, 0.1 g.) was added to a solution of 0.2 g. of sodium and 1 cc. of hydrazine in 10 cc. of diethylene glycol. Treatment as described above gave crystalline residue which was chromatographed on 10 g. of alumina. Elution with pentane–ether (20:1) gave 0.08 g. of 4α-ethyl-4β-methylandrost-5-en-17β-ol acetate (**18**); after recrystallization from ether–methanol, m.p. 92–93°, $[\alpha]_D$ −83°.

Anal. Calcd. for $C_{24}H_{38}O_2$: C, 80.39; H, 10.68. Found: C, 80.31; H, 10.68.

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(27) A. Yogev, M. Gorodetsky, and Y. Mazur, in publication.