androstane-3β,17β-diol (Ie, 1.43 g), acetic acid (28.3 ml), acetic anhydride (5.66 ml), and *p*-toluenesulfonic acid (283 mg) was stirred under a nitrogen atmosphere for 3 hr at 20°. Water was slowly added until the steroid had precipitated completely. Filtration afforded the crude diacetate Ig (mp *ca.* 200° subl), which was recrystallized from methylene chloride–hexane to give the analytical sample of Ig, mp 199–204° subl, $[\alpha]_D$ −42°.

Anal. Calcd for $C_{25}H_{33}BrO_6$: C, 60.85; H, 6.74; Br, 16.20; O, 16.21. Found: C, 61.39; H, 6.67; Br, 15.71; O, 16.05.

5α-Bromo-6β,19-oxido-17α-ethinylandrostane-3β,17β-diol 17-Acetate (Ih).—To a suspension of 5α-bromo-6β,19-oxido-17α-ethinylandrostane-3β,17β-diol diacetate (Ig, 4 g) in absolute methanol (100 ml) was added a solution of pure sodium hydroxide (62.5 mg of 97% purity) in dry methanol (4 ml). After stirring at 20° under a nitrogen atmosphere for 80 min, the solution became homogeneous. Stirring was continued for a further 40 min, then the solution was neutralized with a few drops of concentrated hydrochloric acid and concentrated to low volume. This was poured into water and the formed precipitate was filtered off, washed, and dried. The crude Ih (3.6 g, mp 190–192°) was crystallized from acetone–hexane to furnish the analytical sample, mp 193–195°, $[\alpha]_D$ −38°.

Anal. Calcd for $C_{23}H_{31}BrO_4$: C, 61.19; H, 6.92; Br, 17.71; O, 14.18. Found: C, 61.93; H, 7.46; Br, 17.65; O, 14.12.

17α-Ethinylandrost-5-ene-3β,17β,19-triol 17-Acetate (IIv).—A mixture of 5α-bromo-6β,19-oxido-17α-ethinylandrostane-3β,17β-diol 17-acetate (Ih, 1 g), zinc powder (2 g), and ethanol (20 ml) was heated under reflux for 4 hr, filtered, and evaporated. The residue was crystallized from methanol–water to afford IIv (0.72 g, mp 225–229°). The analytical sample showed mp 230–232°, $[\alpha]_D$ −116°.

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66; O, 17.18. Found: C, 74.28; H, 8.68; O, 17.29.

17β,19-Dihydroxy-17α-ethinylandrost-4-en-3-one 17-Acetate (IIIi).—A solution of 17α-ethinylandrost-5-ene-3β,17β,19-triol 17-acetate (IIv, 1.5 g) in toluene (90 ml) was heated until a few milliliters of solvent had distilled off. To the hot solution were added cyclohexanone (6 ml) and aluminum isopropoxide (300 mg), and the mixture was then heated under reflux for 10 min. The cooled suspension was neutralized with acetic acid (0.3 ml) and steam distilled. The aqueous residue was extracted with chloroform, and the extracts were dried and then percolated over a column of washed alumina (20 g), washing with chloroform. The combined eluates were evaporated, giving the desired IIIi (mp 140–146°, 600 mg). Crystallizations from acetone–hexane afforded the pure compound, mp 158–162° $[\alpha]_D$ +28°, λ_{max} 242–244 mμ (log ε 4.20).

Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16; O, 17.28. Found: C, 74.67; H, 8.28; O, 17.35.

17β-Hydroxy-17α-ethinylandrost-4-en-3-on-19-oic Acid 17-Acetate (IIIj).—A solution of 17β,19-dihydroxy-17α-ethinylandrost-4-en-3-one 17-acetate (IIIi, 100 mg) in acetone (10 ml) was cooled to 0–5° and oxidized with 8 *N* chromic acid in aqueous sulfuric acid during 1 hr. The excess of reagent was destroyed by the addition of sodium bisulfite solution; the mixture was poured into water and extracted with methylene chloride. The extracts were washed three times with 10 ml of 2% aqueous sodium hydroxide solution, and the combined basic extracts were then carefully acidified with concentrated hydrochloric acid and reextracted with methylene chloride. After being dried and concentrated to a small volume in a stream of air, the extracts were diluted with hexane and concentration was continued in an air stream until abundant precipitation occurred. The crude material was filtered off (635 mg, mp 143–149°) and crystallized several times as above to furnish the analytical sample of IIIj, mp 150–153°, $[\alpha]_D$ +76°, λ_{max} 242 mμ (log ε 4.07).

Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34; O, 20.81. Found: C, 71.37; H, 7.67; O, 20.73.

17β-Hydroxy-17α-ethinyl-19-norandrost-4-en-3-one 17-Acetate (IIIk).—A solution of 17β-hydroxy-17α-ethinylandrost-4-en-3-on-19-oic acid 17-acetate (IIIj, 100 mg) in methanol (15 ml) containing concentrated hydrochloric acid (4 drops) was heated under reflux for 1 hr, neutralized with aqueous sodium hydroxide solution, concentrated to small bulk, and poured into water. The formed precipitate was filtered off, washed with water, and dried. The crude material (65 mg, mp 148–154°) was crystallized from acetone–hexane to give pure IIIk, mp 160–162°, identical in all respects with an authentic sample.

Stereochemical Studies. II.[1] Conformational Analysis of Δ^5-3-Keto Steroids[2]

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Received August 9, 1965

The conformation of ring A in Δ^5-3-keto steroids was determined through ultraviolet absorption, circular dichroism, and optical rotatory dispersion data. In most of the Δ^5-3-keto steroids investigated, a coupling of the two chromophores was observed as indicated by increased $n \rightarrow \pi^*$ transitions and the appearance of $\pi \rightarrow \pi^*$ transitions of the β,γ-unsaturated carbonyl group. Introduction of a C-7 keto function to a "coupled" Δ^5-3-keto system caused additional enhancement of the $n \rightarrow \pi^*$ transitions of the isolated C-3 carbonyl group and changed markedly the normal ultraviolet pattern of the α,β-unsaturated carbonyl chromophore. An absence of the interaction characteristics in 4,4-dialkyl Δ^5-3-ketones indicates a quasi-boat conformation for its ring A. Supporting evidence for the latter was found in the nmr data.

Recent literature contains ample and detailed information on the conformational studies of cyclic saturated ketones.[3] The method most widely used for conformational analysis involves studies of the rotatory properties of the carbonyl chromophor of unsymmetrical molecules. This method allows determination of the position of the carbonyl group in relation to other bonds in the molecule, and thereby enables elucidation of the conformation of the ring containing the carbonyl group.[4] This rather simple situation becomes more involved when the cyclic ketone contains a double bond in the neighborhood of the carbonyl group. In some of the latter instances an interaction occurs between the two chromophores causing, among others, changes in the rotatory properties of the carbonyl group, thereby invalidating deductive analogies with the saturated compounds.[4] On the other hand, this very interaction of the carbonyl and double-bond chromophores can be used to establish their relative

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(1) Part I: M. Gorodetsky, D. Amar, and Y. Mazur, *J. Am. Chem. Soc.*, **86**, 5218 (1964).

(2) Part of this material was published in a preliminary form: M. Gorodetsky and Y. Mazur, *Tetrahedron Letters*, 227 (1964).

(3) M. Balasubramanian, *Chem. Rev.*, **62**, 591 (1962); G. R. Chaudhry, T. G. Halsall, and E. R. H. Jones, *J. Chem. Soc.*, 2725 (1961); A. Lablache-Combier, J. Levisalles, J. P. Pete, and H. Rudler, *Bull. Soc. Chim. France*, 1689 (1963).

(4) (a) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960; (b) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 4013 (1961); (c) for recent examples, see K. M. Wellamn, P. H. A. Laur, W. S. Briggs, A. Moscowitz, and C. Djerassi, *ibid.*, **87**, 66 (1965), and previous publications.

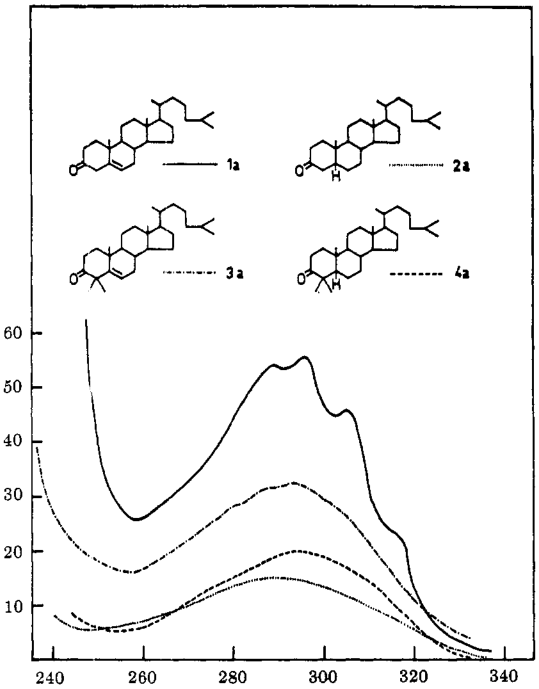
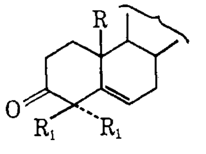


Figure 1.—Ultraviolet spectra of saturated-3-keto steroids and Δ^5-3-keto steroids in cyclohexane.

positions in the molecule.[5] Recently, we have taken an advantage of this method and used it for establishing the rotameric conformation in β,γ-unsaturated acetyl steroids.[1] It seemed to us that this conformational analysis could be also applied to β,γ-unsaturated ketones, in which both functions are part of a bicyclic system. The compounds chosen for this study were Δ^5-3-keto steroids of the following structure.



$R = H, CH_3$
$R_1 = H, CH_3, C_2H_5$

In analogy to the saturated compounds we have reason to believe that the conformation of the ring A in Δ^5-3-keto steroids will be strongly influenced by the substitution in the positions 4 and 10. Recent observations on the nonchair conformation in ring A in 2α-bromo-4,4-dimethylcholest-5-en-3-one[6] substantiate this view.

Only a few data are available in the literature on the ultraviolet spectra of β,γ-unsaturated six-membered ring ketones.[7] These compounds were reported to have a rather smaller n → π^* absorption maximum (ϵ 20–50). These extinction values are of comparative magnitudes to those of the saturated analogs and are therefore much smaller than those found in the bridged β,γ-unsaturated carbonyl compounds[7] (*e.g.*, bicyclo[2.2.1]hept-5-en-2-one). In the latter the ϵ values are in the range of 100–300. In these bridged ketones the two chromophores are close enough in space and not orthogonally related for a participation of the double bond in the n → π^* transition of the carbonyl bond.[4a,5,8]

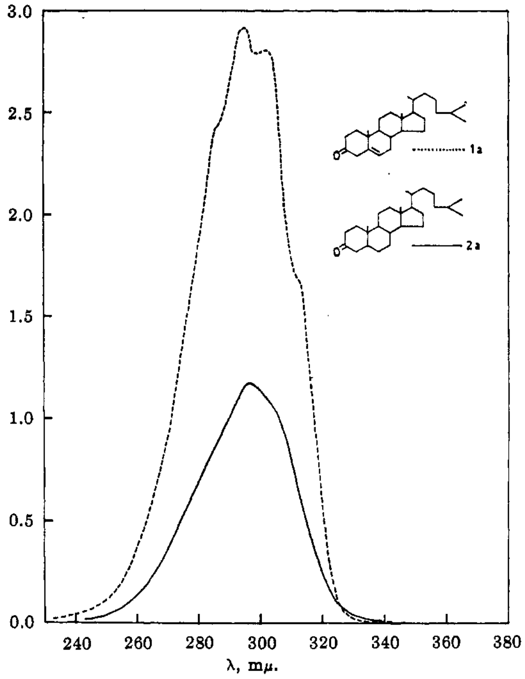


Figure 2.—Circular dichroism curves of cholest-5-en-3-one (**1a**) and cholestan-3-one (**2a**).

More information is available on the optical rotatory dispersion and circular dichroism of the β,γ-unsaturated six-membered ring ketones.[9] The amplitude of the Cotton curve and the ellipticity maxima in these compounds do not permit classification of these ketones as possessing dissymetric chromophores,[10] and therefore no special attention has been attached to them.

The ultraviolet absorption spectra of cholest-5-en-3-one (**1a**)[11] and cholestan-3-one (**2a**) (see Chart I) were compared (Figure 1). The n → π^* absorption of the enone **1a** shows a definite increase of its intensity when compared with the saturated ketone **2a**. In addition, a bathochromic shift and vibrational fine structure is seen in the spectrum of **1a**. These ultraviolet characteristics point to a participation of the double bond in the transition of the carbonyl chromophore. On the other hand, the increase in the carbonyl absorption in 4,4-dimethylcholest-5-en-3-one (**3a**), relative to its saturated analog, 4,4-dimethylcholestan-3-one (**4a**), is much smaller (Figure 1).[12] Also, almost no bathochromic shift and no vibrational fine struc-

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(5) (a) *Inter alia*, A. Moscowitz, K. Mislow, M. A. W. Glass, and C. Djerassi, *J. Am. Chem. Soc.*, **84**, 1945 (1962); (b) G. Snatzke, B. Zeeh, and E. Müller, *Tetrahedron*, **20**, 2937 (1964).

(6) D. T. Cropp, B. B. Dewhurst, and J. S. E. Holker, *Chem. Ind.* (London), 209 (1961); B. B. Dewhurst, J. S. E. Holker, A. Lablache-Combier, and J. Levisalles, *ibid.*, 1667 (1961); R. J. Abraham and J. S. E. Holker, *J. Chem. Soc.*, 806 (1963).

(7) (a) R. C. Cookson and N. S. Wariyar, *ibid.*, 2302 (1956); (b) H. Labhart and G. Wagniere., *Helv. Chim. Acta*, **42**, 2219 (1959). It is to be noted that the value of ϵ 100 indicated by Labhart and Wagniere for the transition of cyclohex-3-en-one is higher than the one found by us for this compound (ϵ 36 at λ_{max} 278 mμ in cyclohexane.)

(8) S. F. Mason, *Quart. Rev.* (London), **15**, 287 (1961); R. C. Cookson and J. Hudec, *J. Chem. Soc.*, 429 (1962).

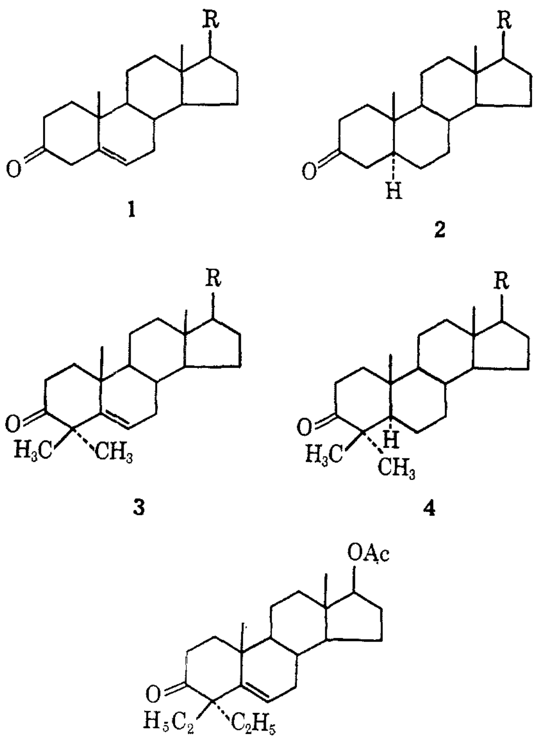
(9) (a) C. Djerassi, O. Halpern, V. Halpern, and B. Riniker, *J. Am. Chem. Soc.*, **80**, 4001 (1958); (b) P. Witz, H. Herrman, J. M. Lehn, and G. Ourisson, *Bull. Soc. Chim. France*, 1101 (1963).

(10) For the definition of dissymmetric chromophores, see ref 5a.

(11) The ultraviolet spectra were taken on a Cary 14 spectrophotometer with cells of 0.1-cm width, in cyclohexane solution.

(12) A small bathochromic shift in the ultraviolet maximum and an increase of the ϵ values of the n → π^* transition are seen when the spectra of the dimethyl ketone **4a** is compared with that of the unsubstituted ketone **2a**. An analogous substitution effect was observed by us in the ultraviolet maxima of cyclohexanone and 2-methylcyclohexanone. See also C. N. Rao, G. K. Goldman, and J. Ramachandran, *J. Indian Inst. Sci.*, **43**, 10 (1961).

CHART I



5a, R = C_8H_{16}
b, R = OAc

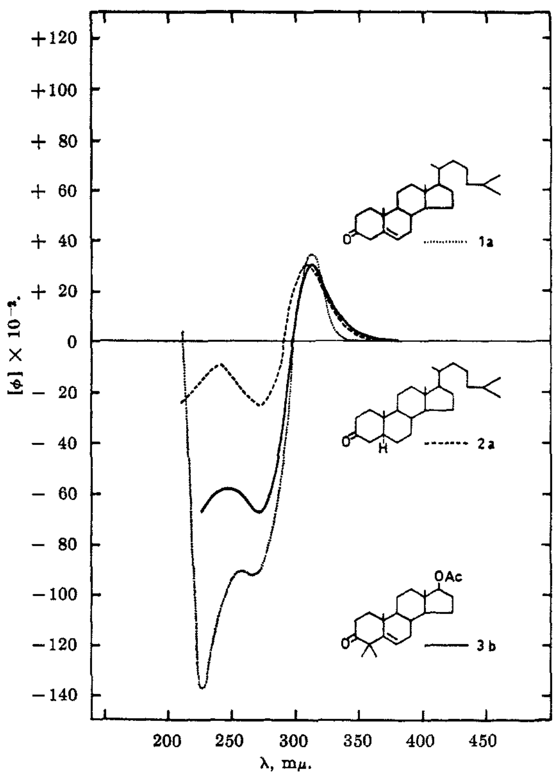


Figure 3.—Optical rotatory dispersion curves of cholest-5-en-3-one (**1a**), cholestan-3-one (**2a**), and 4,4-dimethylandrost-5-en-17β-ol-3-one acetate (**3b**).

ture could be observed in the spectrum of **3a** (Figure 1). The difference between the intensity of the n → π* transition in cholest-5-en-3-one (**1a**) and its 4,4-dimethyl homolog **3a** points to a different steric relation of the two chromophores in **1a** and **3a**. Assuming a normal chair conformation for ring A in an unsubstituted Δ⁵-3-keto steroid, we must assign to this ring in the 4,4-dimethyl-Δ⁵-3-keto compounds a nonchair conformation. Almost identical ultraviolet spectra were obtained for the respective compounds in the androstan-17β-ol series. The 4,4-diethylandrost-5-en-17β-ol-3-one acetate (**5**) exhibited an ultraviolet absorption spectrum similar to that of 4,4-dimethyl homolog **3b** in its shape and absorption maximum values (ϵ 36 at $\lambda_{\max}^{C_6H_{12}}$ 296 mμ).

The increase of the n → π* transition observed in the ultraviolet spectrum of cholest-5-en-3-one (**1a**) due to the overlap of the orbitals of the two chromophores in the molecule should also be seen in the optical rotatory properties of this compound. The circular dichroism curve of **1a** (Figure 2)[13] shows a definite increase in the $\Delta\epsilon$ values compared with the curve of the saturated analog **2a**.[9b] The increase in the circular dichroism values of the unsaturated analog **3a** is much smaller ($\Delta\epsilon$ 1.56 at $\lambda_{\max}$ 294 mμ)[9b] and the shape of this curve is similar to that of the saturated ketone **2a**. This result confirms the assumption that in the dimethyl derivatives **3a** the double bond and the carbonyl group do not interact appreciably. The comparison of the optical rotatory dispersion curves[14] of the saturated and β,γ-unsaturated 3-keto steroids (Figure 3) revealed additional remarkable features. Cholest-5-en-3-one (**1a**) shows an increased Cotton-effect amplitude, [*a*] +127°, compared with that of the saturated ketone **2a**, [*a*] +55°,[15] and in addition another negative extremum at 228 mμ, [φ] −12700°, absent in **2a**. This extremum arises from a second negative Cotton effect of zero rotation value at 212 mμ. It seems that this second negative Cotton effect is due to a π → π* transition of the Δ⁵-3-keto chromophore in **1**. Such a π → π* transition can be expected in a β,γ-unsaturated carbonyl system, wherever an increase of the absorption and the rotatory power of the n → π* transition is observed. The optical rotatory dispersion curve of 4,4-dimethylandrost-5-en-17β-ol-3-one acetate (**3b**) (Figure 3) does not show this characteristic of the nonmethylated analog **1**; The Cotton effect amplitude of **3b** is of smaller magnitude, [*a*] +98°,[16] and at the lower wavelength the second (negative) extremum is not observed.

We also want to comment on the sign of Cotton effect in the described compounds. It is obvious that the contribution of the double bond to the Cotton effect is in accord with the octant rule,[4,5] when applied to the n → π* transition. The stereochemical model indicates clearly that the double bond in unsubstituted Δ⁵-3-keto steroids lies in the upper left, *i.e.*, positive octant, relative to the carbonyl group. The Cotton effect of the π → π* transition in **1a** has negative sign, opposite to that of n → π* transition.

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[13] Part of the circular dichroism determinations were carried out by the courtesy of Professor G. Ourisson of University of Strasbourg and part by the courtesy of Dr. G. Snatzke, University of Bonn, for which we are greatly indebted. These determinations were taken in dioxane solution on a Jouan dichrograph; the ordinate values in the CD curves are given in $\Delta\epsilon = \epsilon_L - \epsilon_R$.

(14) The optical rotatory dispersion measurements were carried out on a Japanese Spectroscopic Co. apparatus. The ordinate values are given in molecular rotation units, [φ].

(15) The amplitude, [*a*], and the rotational extreme values recorded for these compounds on our instrument were lower than those reported in the literature: C. Djerassi, W. Closson, and A. E. Lippmann, *J. Am. Chem. Soc.*, **78**, 3163 (1956); N. Allinger and M. A. Darooge, *ibid.*, **84**, 4561 (1962).

(16) The reported values for these compounds are of lower magnitude.[9]

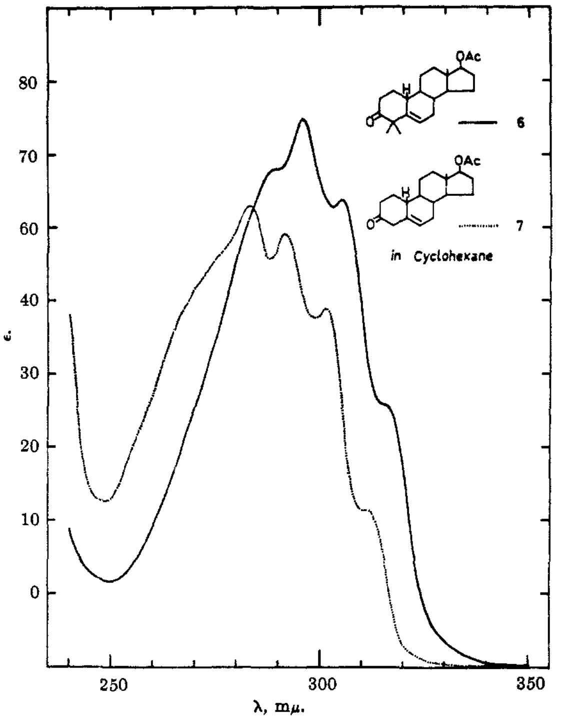


Figure 4.—Ultraviolet spectrum of estr-5-en-17β-ol-3-one acetate (7) and 4,4-dimethylestr-5-en-17β-ol-3-one acetate (6) (region of the n → π* transitions).

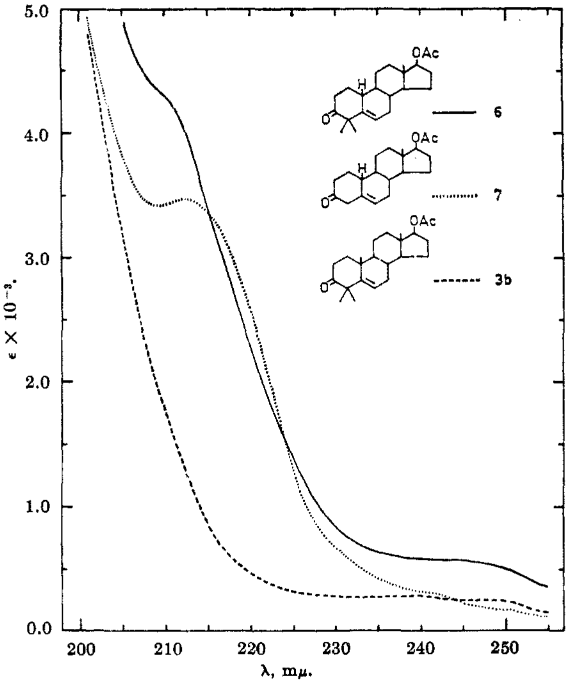
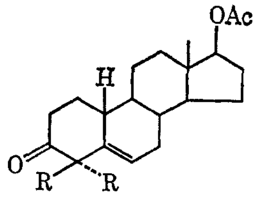


Figure 5.—Ultraviolet spectrum of estr-5-en-17β-ol-3-one acetate (7), 4,4-dimethylestr-5-en-17β-ol-3-one acetate (6), and 4,4-dimethylandrost-5-en-17β-ol-3-one acetate (3b) (region π → π* transitions) in cyclohexane.

It seems to us that, if the octant rule were to be applied to the π → π* transitions, a new set of octant coordinates would be referred to the systems possessing this β,γ-unsaturated carbonyl chromophore.

The change in the conformation of ring A in dimethyl-Δ^5-3-keto steroids **3** is due mainly to the nonbonded interaction between the C-19 methyl group and the β-methyl at C-4. It was therefore expected that in systems lacking the C-19 methyl, *e.g.*, 4,4-dimethyl-19-norandrost-5-en-3-one (estr-5-en-3-one) derivatives, the conformation of ring A would be the normal one.

In Figure 4 the ultraviolet spectrum of 4,4-dimethyl estr-5-en-17β-ol-3-one acetate (**6**) is compared with the spectrum of estr-5-en-17β-ol-3-one acetate (**7**). Both ketones show increased extinction values in the 300-mμ region, the shape of their absorption curves has all the features of a coupled β,γ-unsaturated carbonyl system. These characteristics are in agreement with a normal chair conformation in the 19-nor Δ^5-3-ketone **7** and in its 4,4-dimethyl homolog **6**. Similarly, the circular dichroism curve of **6** [λ_{max} 307 mμ ($\Delta\epsilon$ 3.2)][16] possess enhanced $\Delta\epsilon$ values and also resembles in its shape that of cholest-5-en-3-one (**1a**). This corroborates the similarity of ring A conformation in both compounds.



6, R = CH_3
7, R = H

In the lower wavelength region of the ultraviolet spectrum, both the 19-nor Δ^5-ketone **7** and its 4,4-dimethyl derivative **6** show absorption bands at about λ_{max} 210 mμ (Figure 5). These absorption bands are assigned to the π → π* transitions of the β,γ-unsaturated chromophore. As expected this π → π* transition is not observed in the 4,4-dimethyl Δ^5-3-ketone **3b** (Figure 5).

Recently, Dewhurst, *et al.*,[17] also indicated the presence of the π → π* transitions, in cholest-5-en-3-one (**1**) and in 4,4-dimethyl-19-nor ketone **6**. The conclusion reached by these authors from this evidence regarding the ring-A conformation in Δ^5-3-keto steroids were similar to ours.

Furthermore, the optical rotatory dispersion curve of 19-nor derivative **6** in ethanol (Figure 6) has both an increased amplitude of its n → π* transition ([*a*] +128°) with a zero rotation value at 305 mμ and a second negative extremum at 228 mμ ([φ] −25000°) assigned to a π → π* transition, with a zero rotation value at 218 mμ. As expected when ethanol is replaced by cyclohexane (Figure 6), the maximum for n → π* transition is shifted to higher wavelength (zero value at 310 mμ) and the maximum of the one assigned to the π → π* transition to lower wavelength (zero value at 212 mμ).

A yet larger enhancement of the ultraviolet interaction between the carbonyl at C-3 and the 5,6-double bond could be expected when an additional carbonyl function is introduced at C-7. This additional carbonyl at C-7 is not expected to change the conformation of ring A. On the other hand, the ultraviolet interaction should be more pronounced in the 1,5-diketo-2-ene system than in the keto-3-ene system. The replacement of the double-bond chromophore by an α,β-unsaturated carbonyl chromophore should result

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(17) B. B Dewhurst, J. S. E. Holker, A. Lablache-Combier, M. R. G. Leeming, J. Levisalles, and J. P. Pete, *Bull. Soc. Chim. France*, 3259 (1964).

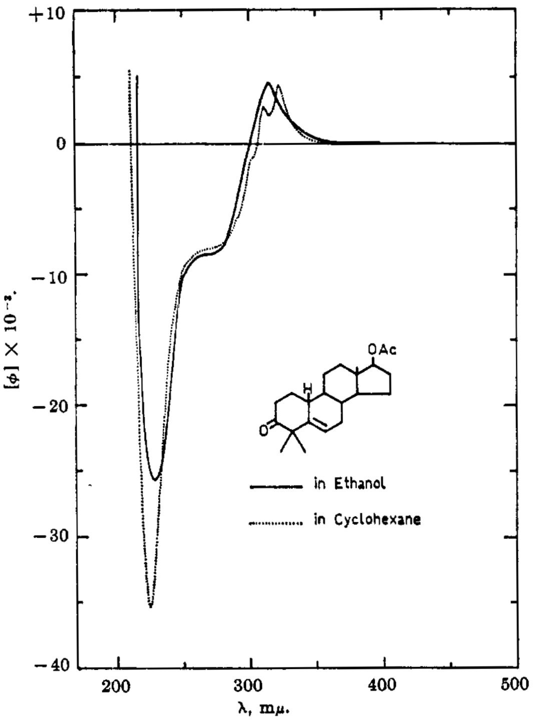
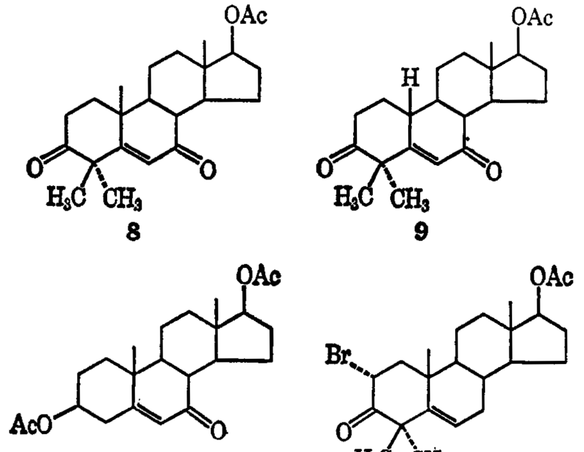


Figure 6.—Optical rotatory dispersion curves of 4,4-dimethylestr-5-en-17β-ol-3-one acetate (6) in cyclohexane and in ethanol.

mainly in a decrease of the energy separation between the two interacting transitions.

The two compounds possessing this 1,5-diketoene system, 4,4-dimethylandrost-5-en-17β-ol-3,7-dione acetate (8) and its 19-nor analog 9 (see Chart II), were thus compared. In Figure 7 the ultraviolet spectra of the two ketones are reproduced. The spectrum of 8 shows the features expected of the two separate noninteracting chromophores: the n → π* transition of the carbonyl at C-7 (at *ca.* 340 mμ), the n → π* transition of the carbonyl at C-3 (at *ca.* 300 mμ), and the π → π* transition of Δ^5-7-keto group (at λ_{max} 230 mμ). On the other hand, in the spectrum of the 19-nor derivative 9, a pronounced change is observed. The n → π* transition in the 300-mμ region assigned to the carbonyl at C-3 is remarkably enhanced; the π → π* charge-transfer band of the Δ^5-7-ketone is shifted to higher wavelength and shows a multiplicity. In addition, a new band appeared at λ_{max} 212 mμ. The later band is assigned to an additional π → π* charge-transfer transition. The direction of this charge transfer is from the π orbital of Δ^5-7-ketone to the n orbital of the ketone at C-3. This ultraviolet pattern is characteristic for compounds possessing 1,5-diketo-2-ene systems, in which coupling between the orbitals of the isolated carbonyl and α,β-unsaturated system is possible.[1]

CHART II



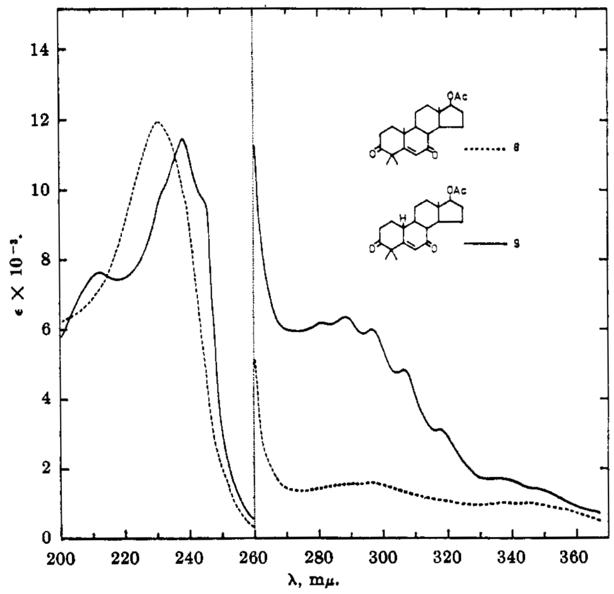


Figure 7.—Ultraviolet spectrum of Δ^5-7-keto steroids in cyclohexane.

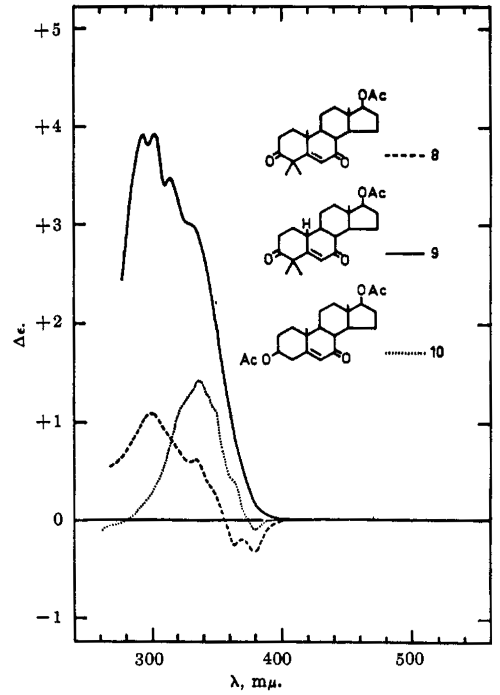


Figure 8.—Circular dichroism curves of Δ^5-7-keto steroids.

The rotatory power of the carbonyl at C-3 is also more pronounced when it is homoconjugated to Δ^5-7-ketone, provided that ring A possesses the normal chair conformation. The circular dichroism curve of the diketone 8 (Figure 8), where the ring A is out of the normal conformation, shows peaks owing to the isolated ketone at C-3 at about 300 mμ and owing to the conjugated ketone at about 340 mμ. The former are absent in the circular dichroism curve of the compound **10**, possessing only the Δ^5-7-ketone chromophore. In the 4,4-dimethyl-19-nor diketone **9**, the peaks due to the carbonyl at C-3 are considerably enhanced as expected.

The conformational changes in the Δ^5-3 keto steroids were further investigated with the help of nmr data. It is well known that a carbonyl group can have a large long-range effect on a chemical shift of protons when the latter have a definite steric relation with the former.[18] Thus, introduction of a carbonyl group at C-3 in 5α-H steroids causes a large deshielding of the methyl protons at C-10.[19] Also a C-5–C-6 double bond has a similar deshielding effect on the C-10 methyl protons. When both chromophores are present in the molecule and no change in the conformation of the A/B rings are envisaged, these deshielding effects should be additive.[19] Comparison of the chemical shift of the C-10 methyl protons in the 17β-ol acetates of androstane, androstan-3-one (**2b**), androst-5-ene, and androst-5-en-3-one (**1**) (Table I) illustrates this additivity rule.[19,20] Thus, the introduction of a carbonyl at C-3 to a Δ^5-steroid results in a paramagnetic shift of the C-10 methyl protons by *ca.* 14 cps. On the other hand, the introduction of the same function (C-3 carbonyl) to the 4,4-dimethyl Δ^5-steroid shifts this signal diamagnetically by *ca.* 11 cps. The assignment of the signals in the dimethyl derivative (Table I) was done by comparison with 4,4-dimethyl-d_6-androst-5-en-17β-ol-3-one acetate, prepared by methylation of testosterone with methyl-d_3 iodide. The d_6 derivative of the 4,4-dimethyl ketone **3b** showed methyl signals at 52 and 48 cps, the former assigned to the methyl protons at C-10,[21] while the latter is the C-13 methyl signal whose position remains unaffected by the functionality of ring A. A comparably high-field signal, assigned to C-10 methyl protons was also found in 4,4-diethylandrost-5-en-17β-ol-3-one acetate (**5**) and in 2α-bromo-4,4-dimethylandrost-5-en-17β-ol-3-one acetate (**11**).[22] Similar diamagnetic shift of the C-10 methyl protons of *ca.* 9 cps were observed when the corresponding signals in androst-5-ene-3,17-diol-7-one diacetate (**10**) and in the 4,4-dimethyl Δ^5-3,7-diketone **8** acetate were compared.

TABLE I

CHEMICAL SHIFTS OF THE C-10 METHYL PROTONS IN DERIVATIVES OF ANDROSTAN-17β-OL ACETATE[a]

Compound	Cps
Androstan-17β-ol acetate	47[b]
Δ^5-	62[b]
3-Oxo-(**2b**)	62[b]
Δ^5-3-Oxo-(**1b**)	76
4,4-Dimethyl-Δ^5-	63
4,4-Dimethyl-Δ^5-3-oxo-(**3b**)	52
4,4-Diethyl-Δ^5-3-oxo-(**5**)	52
2α-Bromo-4,4-dimethyl-Δ^5-3-oxo-(**11**)	56
Δ^5-3β-Acetoxy-7-oxo-(**10**)	72[b]
4,4-Dimethyl-Δ^5-3,7-dioxo-(**8**)	62.5

[a] See ref 20. [b] See also ref 19.

Since the introduction of a C-3 carbonyl is not expected to change the spatial relationship of the C-10 methyl and the C-5–C-6 double bond much, we may assume that the carbonyl group is the main factor[23] for this diamagnetic shift of the C-10 methyl protons. This shielding effect by the carbonyl dipole could be exerted when the conformation of ring A becomes boatlike. In this conformation the carbonyl dipole is almost parallel to the direction of the C-10–C-19 bond. We could also assume that in a "quasi-boat" conformation the carbonyl group would still exert a certain shielding effect on the methyl protons at C-10.

In their recent publication, Dewhurst, *et al.*,[17] found the same effect of the carbonyl chromophore on the chemical shift of the methyl protons at C-10 in Δ^5-3-keto steroids. In addition these authors observed temperature variation of the position of the signal due to C-10 protons in 4,4-dimethylcholest-5-en-3-one (**3a**), indicating a temperature-dependent conformation of the latter compound. It is noteworthy that no solvent dependence of the signal due to the methyl protons at C-10 in the 4,4-dimethyl Δ^5-3-ketones **3a** and **3b** could be observed by us.

It is of interest to add that also in another 3-keto steroid, postulated to have a boat conformation, *e.g.*, in the 2α-bromo-2β-methylandrostan-17β-ol-3-one acetate,[24] the signal assigned to the methyl protons at C-10 appeared in comparative high field (44.5 cps).

The results of the ultraviolet, optical rotatory dispersion, and nmr measurements clearly show that the introduction of alkyl groups into the C-4 positions in Δ^5-3-ketones changes the conformation of ring A. When the C-10 methyl group is absent, no change of ring-A conformation is envisaged. It is noteworthy that our previous observations[1] on the alkylation of steroidal Δ^4-3 ketones can be well explained by assuming a boat conformation for a transition state of these reactions.

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(18) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Ltd., London, 1959, p 124.

(19) R. F. Zürcher, *Helv. Chim. Acta*, **44**, 1380 (1961); **46**, 2054 (1963).

(20) The nmr spectra were taken in deuteriochloroform on Varian A-60 spectrometer, tetramethylsilane serving as internal reference. Peak positions are reported in cycles per second downfield from tetramethylsilane.

(21) A different assignment was reported for the methyl protons in this compound: G. Slomp and F. McKellar, *J. Am. Chem. Soc.*, **82**, 999 (1960).

(22) This signal in **11** was assigned by comparison with 2α-bromo-4,4-dimethyl-d_6-androst-5-en-17β-ol-3-one acetate.

(23) The diamagnetic susceptibility of single C–C bonds which are in a different steric relation to the C-10 protons when the conformation of the ring A changes and small variation in the double-bond position can also influence the chemical shift of these protons.

(24) R. Mauli, H. J. Ringold, and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 5494 (1960).