122 (C-17 acetoxy), and 132 c.p.s. (C-2 acetyl), all with integration area of three protons. In addition, a multiplet at 190 c.p.s. was observed and assigned to the hydrogens of the thioketal group.

Anal. Calcd. for $C_{26}H_{40}O_3S_2$: C, 67.21; H, 8.68. Found: C, 67.34; H, 8.72.

A solution of 1.2 g. of the thioketal **19** in 100 cc. of ethanol was treated with Raney nickel (5 spoonfuls of ethanolic suspension) and refluxed overnight. Filtration and evaporation of the solvent gave a crystalline residue which after recrystallization from ether–hexane gave 0.55 g. of **20**, m.p. 155–156°, $[\alpha]_D$ −0.6°, $\lambda^{KB'}$ 5.75 μ. In the n.m.r. spectrum signals were observed at 38 (C-19 methyl), 47 (C-18 methyl), 52 (C-2 methyl), 122 (C-17 acetoxy), and 128 c.p.s. (C-2 acetyl).

Anal. Calcd. for $C_{24}H_{38}O_3$: C, 76.96; H, 10.28. Found: C, 76.82; H, 10.19.

Pyrolysis of the Dimeric Ketone 21.—The diketone **21** (0.05 g.) was heated in an evacuated tube (25 mm.) at 250° for 5 min. Then the tube was evacuated further under high vacuum (0.1 mm.) and the products were sublimed at the same temperature. The sublimed material had m.p. 130–150°, λ_{max}^{EtOH} 241 mμ (ϵ 5100), and in the n.m.r. peaks were observed attributed to both products **16** and **17**. The signals of 2-methyl ketone **16** were found at 48.5 (C-18 methyl), 61 (doublet, J = 8 c.p.s., C-2 methyl), 65 (C-19 methyl), and 124 c.p.s. (C-17 acetate). Those assigned to the Δ^1-3-ketone **17** are at 50 (C-18 methyl), 60 (C-19 methyl), 107 [C-2 methyl, doublet (J = 1.5 c.p.s.)], and 124 c.p.s. (C-17 acetate). The integration of the main peaks gave the ratio of the two isomers as 1:1.

5α-Androst-2-ene-3,17β-diol d_6-Diacetate (22).—5α-Androstan-3-on-17β-ol (3 g.) was treated with d_6-acetic anhydride (4 cc.) and a few crystals of *p*-toluenesulfonic acid. The mixture was heated for 3 hr. at 110° and then for 2 hr. at 140°. The resulting solution was cooled and the produced crystals filtered and washed with pentane and recrystallized twice from ether–pentane. The d_6-diacetate **22** obtained (2 g.) had m.p. 175–176°. Its n.m.r. was similar to that of diacetate **11** in which the two peaks at 123 and 132 c.p.s. (attributed to the acetoxy and acetyl hydrogens at C-17 and C-3) were absent.

Photolysis of Enol Acetates Mixtures.—(a) A solution of 1.5 g. of cholest-2-en-3-ol acetate (**11**) and 0.5 g. of 5α-androst-2-ene-3,17β-diol d_6-diacetate (**22**) in 170 cc. of cyclohexane was irradiated until its ultraviolet absorption at 283 mμ reached a constant value (ϵ 1300 in 20 hr.). The solvent was evaporated and the residue chromatographed on silica gel (60 g.).

The first fraction eluted with pentane gave, after two recrystallizations from ether–methanol, cholest-2-en-3-ol acetate (**11**, 0.15 g., m.p. 93–94°). In its n.m.r. spectrum the signal at 123 c.p.s. attributed to the acetoxy group had the same integration area as the starting material **11**, indicating that no observable deuteration occurred.

The next fraction eluted with the same solvent (0.75 g.) consisted of a mixture of the diacetate **11** and 2-acetylcholestan-3-one (**12**, ultraviolet and infrared spectrum).

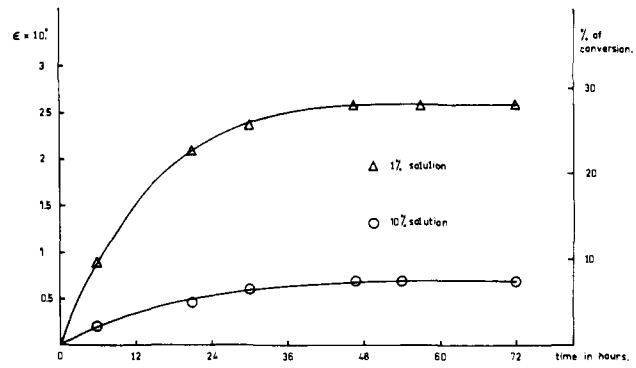

Fig. 4. —The rate of formation of acetylacetone (**2**) from isopropenyl acetate (**1**).

The third fraction eluted with the same solvent gave, after recrystallization from methanol, 2-acetylcholestan-3-one (**12**), 0.075 g., m.p. 98–100°.

The fourth fraction eluted with pentane–ether (98:2), recrystallized from ether–pentane, yielded 0.36 g. of crystals, m.p. 175–176°, of 5α-androst-2-ene-3,17β-diol d_6-diacetate (**22**). Its n.m.r. spectrum was identical with that of the starting material **22** (no signals at 123 and 132 c.p.s. attributed to the nondeuterated acetoxy groups could be observed; Fig. 2 and 3).

The fifth fraction eluted with the same solvent mixture gave, after crystallization from ether–pentane, 0.2 g. of crystals which were rechromatographed on 10 g. of silica gel. The fraction eluted with pentane–ether (98:2) was recrystallized twice from ether–pentane to give 0.075 g. of 2-d_3-acetyl-5α-androstan-3-on-17β-ol d_3-acetate (**23**), m.p. 177–178°, which did not give a melting point depression when admixed with the diketone **10**.

(b) A solution of 0.35 g. of cholest-2-en-3-ol acetate (**11**) and 1.04 g. of 5α-androst-2-ene-3,17β-diol d_6-diacetate (**22**) in 170 cc. of cyclohexane was irradiated for 18 hr. (the irradiation was stopped when the maximum absorption of the solution in the ultraviolet reached a constant value). Chromatography on silica gel resulted in the same four compounds isolated in the experiment a. The second compound (40 mg.) eluted from the column with pentane (positive ferric chloride test) was rechromatographed on 30 g. of silica. Elution with pentane and two recrystallizations from ether–methanol gave 0.025 g. of 2-acetylcholestan-3-one (**12**), m.p. 98–100°. Its n.m.r. spectrum was identical in all the details with that of the authentic diketone **12**.

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

Photochemistry of Enolic Systems. II. Irradiation of Dienol Acetates[1]

BY MALKA GORODETSKY AND YEHUDA MAZUR

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Irradiation of dienol acetates derived from testosterone and 4-methyltestosterone with a low pressure mercury lamp is described. The irradiation involves acetyl rearrangement from oxygen at C-3 to the carbon at C-4 and C-6. Thus androsta-3,5-diene-3,17β-diol diacetate (**1**) resulted in **2** and **8**; 4α-methylandrosta-3,5-diene-3,17β-diol diacetate (**13**) yielded the corresponding 4-methyl homologs **14** and **15**. The chemistry and stereochemistry of the isolated products support the previously postulated cage mechanism and stereoelectronic control for this photochemical reaction.[1b] The stability relations of the 6-acetyltestosterone epimers are discussed and compared with those of the corresponding epimeric saturated derivatives. The unusual stability of the 6β-acetyltestosterone is explained by electronic factors.

In the previous publication we described the irradiation of some enol acetates.[1b] We would now like to discuss the action of ultraviolet light on conjugated enol acetates. The systems chosen were the dienol acetates derived from Δ^4-3-keto steroids. These enol acetates have an extended conjugation and therefore show a strong ultraviolet absorption in the 200–260 mμ region. The light source used was again the low

(1) (a) Presented in part: 1, at 2nd International Symposium on the Chemistry of Natural Products, Prague, 1962; Abstracts of Communications, p. 115; 2, at 19th International Congress of Pure and Applied Chemistry, London, 1962; Abstracts A, p. 341; (b) Part I, A. Yogev, M. Gorodetsky, and Y. Mazur, *J. Am. Chem. Soc.*, **86**, 5208 (1964).

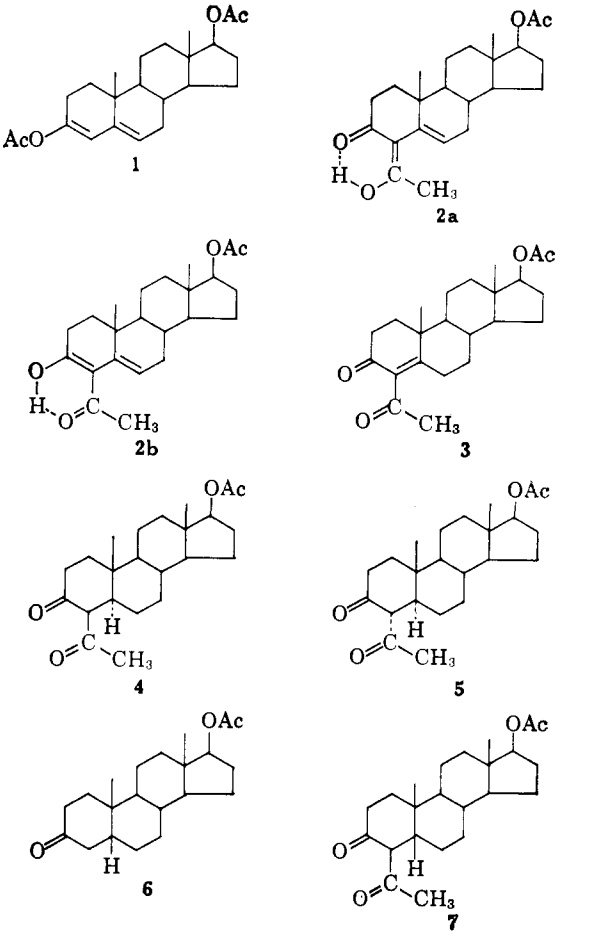
pressure mercury immersion lamp (Hanau NT/6) emitting mainly at 253.7 mμ, and the solvent was cyclohexane. The first compound irradiated was androsta-3,5-diene-3,17β-diol diacetate (**1**),[2] which in cyclohexane exhibits an ultraviolet maximum at 238 (ε 20,500) and at 253.7 mμ possesses absorption intensity of ε 4500.

The progress of the irradiation was followed by the determination of the absorbance of the solution at 238 mμ. This decreased gradually until it reached the value of ε 7500, in 7 hr. (the maximum having shifted to 230 mμ), and further irradiation did not change this ultraviolet pattern. Direct crystallization then yielded a substance, m.p. 150–152° (26% yield), which had a coloration with ferric chloride.

This substance was identified as 4-acetylandrost-5-en-3-on-17β-ol acetate existing in one or both enolic forms **2a** and **2b**, as evidenced by the elemental analysis, the infrared and the ultraviolet spectrum [λ_{max}^{MeOH} 227, 297, and 324 mμ (ε 16,900, 4800, and 5200)]. In methanolic sodium hydroxide solution the enol **2** gives an enolate [λ_{max} 249 and 316 mμ (ε 12,000 and 10,300)]. On the other hand, boiling with ethanolic hydrochloric acid isomerizes **2** to the nonenolic 4-acetyltestosterone acetate (**3**), m.p. 127–128°. This endione exhibits an ultraviolet maximum at 241 mμ (ε 15,000) and in the infrared shows absorption expected for a saturated carbonyl group in addition to the peaks of the acetate and α,β-unsaturated carbonyl group. These spectral data of **3** indicate that the 4-acetyl group is not conjugated with the Δ^4-3-keto chromophore. Therefore the carbonyl dipole of the acetyl group is in a plane which is probably perpendicular to that containing the Δ^4-3-keto function.

Hydrogenation of 4-acetyltestosterone acetate (**3**) in ethanol over palladium–charcoal resulted in smooth uptake of 1 equiv. of hydrogen. The crude product gave a strong coloration with ferric chloride. However, direct chromatography on alumina yielded a crystalline product which now no longer showed enolic properties. This is explained by assuming initially a *cis* addition of hydrogen to **3** leading to 4β-acetyl-5α-androstan-3-on-17β-ol acetate (**4**) which enolizes readily. Chromatography of **4** on alumina results in epimerization and yields the thermodynamically more stable 4α-acetyl derivative (m.p. 183–185°).[3] The latter shows an ultraviolet and infrared spectrum of saturated nonenolic diketone. The ultraviolet spectrum of **5** in ethanolic sodium hydroxide (λ_{max} 315.5 mμ, ε 12,000), on the other hand, indicates that the enolate ion can be formed.

An additional indication of the α-equatorial configuration of the acetyl group in **5** is obtained from the n.m.r. spectrum.[4] The hydrogen at C-4 is flanked by two carbonyl groups, and therefore appears at low field (200 c.p.s.) as a doublet (J = 12.5 c.p.s.). This high coupling constant indicates clearly that the hydrogen at C-4 is *trans*-diaxially situated with respect to the hydrogen at C-5, and therefore β-axial.



Proof for the stereochemistry of the β-diketone **5** at C-5, and hence for the α-hydrogenation of the acetyl derivative **3**, was obtained by the synthesis of its isomer, the 4β-acetyl-5β-androstan-3-on-17β-ol acetate, m.p. 180–182°, which was different from the diketone **5**. This compound was obtained by the action of acetic anhydride and boron trifluoride etherate on 5β-androstan-3-on-17β-ol acetate (**6**) and subsequent hydrolysis of the boron difluoro chelate.[5]

The β-equatorial configuration of the 4-acetyl group is indicated by the stability of **7** in basic solution and its ketonic structure is again confirmed by the infrared and the ultraviolet spectra. In the latter only a saturated ketonic absorption maximum is observed in neutral solution, and on addition of base to the alcoholic spectrum solution, a maximum appears at 313 mμ (ε 12,000).[5]

The reason for the ketonic structure of compound **7** is mainly the steric hindrance of the axial hydrogen at C-4, which therefore cannot be easily removed. In the diketone **7** the axial hydrogen at C-4 is strongly shielded by the two axial hydrogens at C-7 and C-9. The axial 4-acetyl ketone, on the other hand, has an equatorial hydrogen at C-4 which can be removed with facility to give the corresponding enol. The epimerization of this enol is therefore not reversible.

It is of interest to note that 2-acetyl-5α-androstan-3-on-17β-ol acetate[1] in contrast is completely enolic.[6]

(2) U. Westphal, *Chem. Ber.*, **70**, 2128 (1937).

(3) Similar behavior was observed previously when 4-carbomethoxy-10-methyloctahydrophenanthren-3-one was hydrogenated; E. Wenkert and B. G. Jackson, *J. Am. Chem. Soc.*, **81**, 5601 (1959).

(4) The n.m.r. spectra were taken in deuteriochloroform on an A-60 Varian spectrometer, tetramethylsilane serving as internal reference. Peak positions are reported in c.p.s. downfield from tetramethylsilane.

(5) To be published at a later date.

(6) One of the enol forms of the 2-acetylandrostan-3-on-17β-ol acetate and its 4-acetyl analog probably possesses a structure with a double bond in the position 2,3 and 3,4, respectively. It is well known that the 2,3-position of the double bond is energetically more favored than the 3,4-position. This factor adds to the stability of the enolic form of the 2-acetyl derivative

The chromatographic separation of the irradiated products revealed in addition to the enol **2** (3% yield) the starting material **1** (7% yield), testosterone acetate (4% yield), and another α,β-unsaturated ketone **8** (6.6% yield), m.p. 165–166°.[5,7] The structure and the stereochemistry of this compound was indicated by its elemental analysis and spectral data. In the infrared, bands of acetate, carbonyl, and α,β-unsaturated carbonyl chromophore were observed and in the ultraviolet a maximum was found at λ_{max}^{EtOH} 246 mμ (ϵ 13,100).[8] In the n.m.r. spectrum of **8** (Table I),

TABLE I

NUCLEAR MAGNETIC RESONANCE DATA OF 6- AND 4-SUBSTITUTED TESTOSTERONE ACETATE[4]

Compound	H at C-18	H at C-19	H at C-6	H at C-4
Testosterone acetate	51	72		345 broad singlet[a]
6β-Acetyl **8a**	51	65[b]	203	372 singlet
6α-Acetyl **9a**	51	76[c]	208 octet	327 doublet (J = 2 c.p.s.)
4-Methyltestosterone acetate	51	72		107 broad singlet[d]
4-Methyl-6β-acetyl **15**	50.5	63[b]	227 doublet (J = 5.5 c.p.s.)	120 singlet[d]

[a] *Cf.* ref. 9b. [b] The distorted conformation of rings A and B and the effect of the carbonyl dipole at C-6 in **8a** and **9a** results in a different chemical shift of C_{19}-methyl hydrogens when compared with the analogous one in testosterone and 4-methyltestosterone acetate. [c] This comparatively higher field value is attributed mainly to the effect of the carbonyl dipole at C-6 which has a suitable geometry (see text) for a diamagnetic shielding of C_{19}-methyl group. [d] A sharp singlet appears only when a homoallylic splitting of methyl hydrogens at C-4 with the axial proton at C-6 is possible. *Cf.* T. H. Pinhey and S. Sternhell, *Tetrahedron Letters*, 275 (1963).

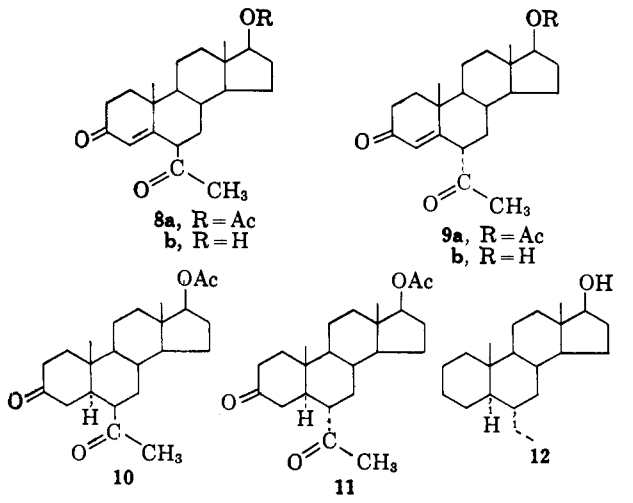
the vinylic proton at C-4 appeared at 372 c.p.s. as a singlet; this suggests that the allylic hydrogen at C-6 has an α-configuration in which the dihedral angle between C_4–H and C_6–H bonds should be very small and not sufficient to cause an allylic spin–spin coupling of the C-4 proton.[9] The signal attributed to the proton at C-6 in the substance **8** appears as a doublet-like band at 203 c.p.s. (J = 5 c.p.s.), the two vicinal carbonyl groups and the double bond being responsible for the low chemical shift. This pattern can be related to the dihedral angles in the H_α–C_6–C_7<$^{H_\alpha}_{H_\beta}$ part of the molecule.

This doublet-like signal indicates that the respective dihedral angles between the α-hydrogen at C-6 and both hydrogens at C-7 are different from those expected for an undistorted cyclohexane ring.[10] The nonbonded 1,3-diaxial interaction between the C-19 methyl and the bulky C-6 acetyl group could well be responsible for the postulated distortion of the chair conformation of ring B (and possibly also of ring A). Similar conformations have recently been suggested for other Δ^4-3-keto steroids having bulky substituents at C-6 in the β-position.[9]

Compound **8** is a vinylogous β-diketone and therefore gives, after prolonged boiling with alcoholic sodium hydroxide solution, ketonic cleavage and yields testosterone.

Boiling of 6β-acetyltestosterone acetate (**8a**) with ethanolic hydrochloric acid, however, resulted in partial epimerization at C-6 (as well as in saponification at C-17). Chromatographic separation on alumina yielded, in addition to 6β-acetyltestosterone (**8b**), m.p. 191–193°, stereoisomeric 6α-acetyltestosterone (**9b**), m.p. 160–161°. In the infrared, **9** showed peaks attributed to carbonyl and α,β-unsaturated carbonyl groups; in the ultraviolet the maximum was shifted to a shorter wave length (λ_{max}^{EtOH} 238 mμ, ϵ 14,000)[8] as compared with the β-acetyl derivative **8** (λ_{max}^{EtOH} 246 mμ).

The n.m.r. spectrum of **9** (Table I) indicated the equatorial configuration of the 6-acetyl group. The signal attributed to the C-4 vinylic proton appeared at 327 c.p.s. as a doublet (J = 2 c.p.s.). This pattern indicates an allylic splitting of this proton with the axial 6β-proton as expected for a dihedral angle between the C_4–H and C_6–H bonds of near 90°. The



signal attributed to the β-hydrogen at C-6 appears as an octet due to coupling with the two protons at C-7 as well as the one at C-4.[9b,c]

The chemical shift of the C-4 proton and the C-19 methyl protons in 6α-acetyltestosterone (**9**) provided information regarding the geometry of the α-acetyl group. A 6α-substituent in Δ^4-3-keto steroids usually lowers the position of the C-4 signal, this paramagnetic effect being associated partly with 1,3-interactions.[9c] In 6α-acetyltestosterone (**9**) the position of the C-4 signal is shifted, but diamagnetically [327 compared to 345 c.p.s. in testosterone acetate (Table I)]. The shift to the lower field is undoubtedly caused by the carbonyl dipole at C-6 which can exert

and the ketonic form of the 4-acetyl ketone **5**. *Cf.* R. B. Turner, W. R. Meador, and R. E. Winkler, *J. Am. Chem. Soc.*, **79**, 4122 (1957); N. A. Nelson and R. N. Schut, *ibid.*, **80**, 6630 (1958).

(7) It is pertinent to note that a 6β-acetyl-Δ^4-3-ketone was previously obtained by a different route in progesterone series; J. A. Zderic and D. C. Limon, *ibid.*, **82**, 2304 (1960).

(8) A bathochromic shift is observed in the ultraviolet absorption maximum of Δ^4-3-ketone axially substituted in the γ-position by a carbonyl-bearing substituent; analogous equatorial substitution results in a hypsochromic shift: P. N. Rao and C. L. Axelrod, *J. Org. Chem.*, **27**, 4694 (1962); K. Schaffner, personal communication. Similar ultraviolet effect is known to occur in 6-bromo-Δ^4-3-ketones: C. W. Bird, R. C. Cookson, and S. H. Dandegaonker, *J. Chem. Soc.*, 3675 (1956).

(9) (a) D. J. Collins and J. J. Hobbs, *Tetrahedron Letters*, 197 (1963); (b) T. A. Wittstruck, S. K. Malhotra, and H. J. Ringold, *J. Am. Chem. Soc.*, **85**, 1699 (1963); (c) K. Tori and K. Kuriyama, *Chem. Ind.* (London), 1525 (1963).

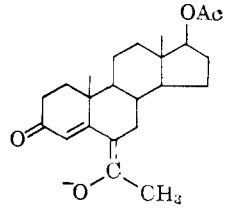
(10) Deviations from the normal coupling constants expected for adjacent protons in the ring A and B of steroids were previously observed and suggested to indicate a distortion in those rings. *Cf.* K. L. Williamson and W. S. Johnson, *J. Am. Chem. Soc.*, **83**, 4623 (1961); R. J. Abraham and J. S. E. Holker, *J. Chem. Soc.*, 806 (1963); A. Lablache-Combier, J. Levisalles, J. P. Pete, and H. Rudler, *Bull. soc. chim. France*, 1689 (1963).

it only when oriented perpendicularly to the plane of rings A and B.

Acid treatment of either **8** or **9** gave an equilibrium mixture which consisted of the two compounds in about equal amounts. This follows from the optical rotation data and also from the ultraviolet and n.m.r. measurements performed on the equilibrated mixture.

These results were surprising because of the much larger preponderance of the axial isomer than expected.[11] An additional factor should therefore be taken into consideration, which changes the usual stability relationship. We assume that this factor is electronic in nature, which contributes to the stability of the β-isomer **8** and arises possibly from partial conjugation of the carbonyl group at C-6 with the Δ^4-3-keto chromophore. This conjugation is not possible in the 6α-acetyl isomer, where the π-orbitals of the two functions are orthogonal to each other. On the other hand, the geometry of 6β-acetyl isomer **8** could allow for such an overlap of the two ground state π-orbitals to take place contributing to its relative thermodynamic stability.[12]

Both isomers **8** and **9** were soluble in dilute alcoholic sodium hydroxide solutions, giving the same enolate ($\lambda_{max}^{EtOH-NaOH}$ 422 mμ, ϵ 22,300). Acidification of this enolate led to the β-isomer **8** only. On this basis we assigned to the enolate the structure



Protonation of such an enolate would be expected to occur at C-6 from the less hindered α-side, giving the kinetically controlled product having an axial substituent at C-6.[13]

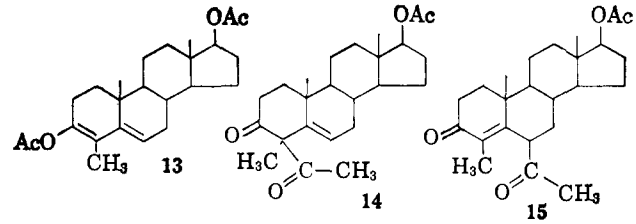
Hydrogenation of **8** in ethanol over palladium–charcoal resulted in the uptake of 1 equiv. of hydrogen, yielding the saturated 6β-acetyl ketone **10**, m.p. 140–141°. This diketone could be isomerized in acid or base to give exclusively the more stable 6α-acetyl derivative **11**, m.p. 168–170° This normal behavior[11] confirms the stereochemistry at C-6 of the saturated diketones **10** and **11**.

The stereochemistry at C-5 in the 6α-acetyl ketone **11** was deduced from the n.m.r. spectrum. It has been reported that the chemical shift of C_{19}-methyl protons in compounds possessing A/B *cis* configuration occurs at lower field than in the corresponding A/B *trans* epimers, the difference being about 8 c.p.s.[14] This generalization can be applied to various ring A substituted steroids, but cannot be used in 3-keto steroids[14] (in the latter, the paramagnetic deshielding attributed to the carbonyl group affects the C-19 methyl hydrogen more in A/B *trans* compounds than in the A/B *cis* ones). Therefore the 6α-acetyl ketone **11** was reduced by a modified Wolff–Kishner procedure to give 6α-ethyl-5α-androstan-17β-ol (**12**), m.p. 179–180°.

The chemical shift of the C_{19}-methyl group in this compound was found to be 48 c.p.s., which is similar to the reported values for A/B *trans* compounds. This result indicates the α-configuration at C-5, and shows that hydrogenation of 6β-acetyltestosterone acetate (**8**) has proceeded from the α-side.

The second compound irradiated was the 4-methylandrosta-3,5-diene-3,17β-diol diacetate (**13**).[15]

After irradiation for 3 hr., most of the starting material had reacted as indicated by the absorption intensity of the solution. Two compounds were isolated by chromatography on alumina. The structure assigned to the first one (m.p. 176–178°) is 4β-acetyl-4α-methylandrost-5-en-3-on-17β-ol acetate (**14**, 17%) and to the second (m.p. 187–190°), 6β-acetyl-4-methyltestosterone acetate (**15**, 13%).



The 4-acetyl ketone **14** showed infrared and n.m.r. spectra in accord with the assigned structure. In the ultraviolet only a weak absorption in the 300 mμ region was observed.

The identical diketone **14** was also obtained by methylation of the enol **2** with methyl iodide and potassium *t*-butoxide in *t*-butyl alcohol. It is assumed that in this reaction the electrophilic methyl iodide attacks the enolate ion at C-4 from the α-side. The α-side attack would be explained by assuming steric factors only being responsible in this methylation. The other possibility is a transition state in which ring A has a boat conformation and an α-axial approach of methyl iodide.[16]

The second irradiation product **15** exhibited an infrared spectrum in accord with the assigned structure. In the ultraviolet a maximum was observed at 252 mμ (ϵ 13,500).[8] The signal of the hydrogen at C-6 appeared in the n.m.r. spectrum (Table I) as a doublet at 227 c.p.s. (J = 5.5 c.p.s.). The pattern of the latter was similar to that observed in the 6β-acetyl analog **8** and again indicated a 6α-equatorial proton in a distorted chair conformation of the ring B.[9c] The chemical shift of the C_6-proton when compared with the analogous one in the 4-unmethylated compound **8** (203 c.p.s.) indicates a paramagnetic effect, caused possibly by the 1:3 interaction between the C_6-hydrogen and 4-methyl group.[17]

The 6β-acetyl compound **15** in ethanolic sodium hydroxide solution gives the enolate ion (λ_{max} 4100,

(11) Cyclohexane derivatives possessing an equatorial acetyl group are thermodynamically much more stable than their axial epimers. *Cf.* E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp. 239–247.

(12) The overlap of the π-orbitals of the 6β-acetyl group and the Δ^4-3-keto chromophore in **8** is evident also from its ultraviolet spectrum in the low wave length (λ_{max} 212, ϵ 4500, in cyclohexane); to be published later in detail.

(13) H. E. Zimmerman and T. W. Cutshall, *J. Am. Chem. Soc.*, **81**, 4305 (1959); P. T. Herzig and M. Ehrenstein, *J. Org. Chem.*, **16**, 1050 (1951).

(14) R. F. Zürcher, *Helv. Chim. Acta.*, **44**, 1380 (1961); **44**, 1755 (1961); **46**, 2054 (1963).

(15) D. N. Kirk, V. Petrov, and M. H. Williamson, *J. Chem. Soc.*, 3872 (1960).

(16) *Cf.* G. Stork and J. W. Schulenberg, *J. Am. Chem. Soc.*, **84**, 284 (1962).

(17) *Cf.* G. Slamp and B. R. McGarvey, *ibid.*, **81**, 2200 (1959); J. C. Jacquessy, J. C. Lehn, and J. M. Levisalles, *Bull. soc. chim. France*, 2444 (1961).

ϵ 9100) which, when acidified, regenerates the starting material. On the other hand, no isomerization was observed when **15** was boiled in acid solution; this behavior can be explained by the difficulty of removing the 6α-hydrogen, which is sterically hindered by the 4-methyl group. This nonbonded 1:3 interaction must also be responsible for the incomplete enolization of **15** in basic media, as seen from the low ϵ-value (9200 as compared to 23,000 in **8**).

We have suggested previously[1] that the photolysis of enol acetates involves formation of acetyl radicals, which are enclosed in a solvent cage. Furthermore, we assumed that the acetyl recombination with α-carbon atom involves a transition state in which stereoelectronic factors play some role. The results of the irradiations of **1** and **13** can well be explained by the suggested mechanism. The fact that acetyl migrates from oxygen at C-3 to the carbon at C-6 excludes a four-centered mechanism and indicates formation of acetyl radicals. Both the 6-acetyl derivatives **8** and **15** obtained from the photolyses have β-configurations and their formation should involve an attack of the acetyl radical from the more hindered β-side of the molecule. This is rationalized by assuming a transition state, in which the π-orbitals of the Δ^4-3-keto chromophore overlap with the "axially" oriented lone electron orbital. In the same fashion the formation of the 4β-acetyl-4α-methyl compound **14** can be explained, although a rigorous proof for its stereochemistry at C-4 is still missing.

Photolysis of dienol acetates of Δ^4-3-ketone may be useful for the synthesis of steroids and triterpenoids possessing an oxygenated substituent at C-4. The advantage of this procedure is the stereospecifity of the introduction of such substituents into Δ^4-3-keto systems and should therefore be suitable for the synthesis of some natural compounds.

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. All the irradiations were performed with an immersion Hanau low pressure NT 6/20 ultraviolet mercury lamp in an externally cooled tube of 40-mm. diameter and *ca.* 150-cc. volume.

Irradiation of Androsta-3,5-diene-3,17β-diol Diacetate (1).—A solution of 1.5 g. of dienol acetate 1[2] in 80 cc. of cyclohexane was irradiated for 7 hr. Aliquots were taken out every hour and their absorbance at 230 mμ established. After 7 hr. the ϵ reached a constant value of 7500 and the irradiation was stopped. The solvent was then evaporated under reduced pressure and the oily residue treated with 15 cc. of methanol to give 0.4 g. of 4-acetyl-androst-5-en-3-on-17β-ol acetate (**2**), m.p. 150–152° (26%). The product gives a strong coloration with ferric chloride solution; λ^{KBr} 5.74, 6.28, and 8.03 μ; λ_{max}^{MeOH} 227, 297, and 324 mμ (ϵ 16,009, 4800, and 5200); $[\alpha]_D$ −79° [$\lambda_{max}^{MeOH-OH}$ 249 and 316 mμ (ϵ 12,000 and 10,300)].

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.05; H, 8.56.

The mother liquor from the crystallization was evaporated to dryness and chromatographed on alumina (Merck acid washed). The fraction eluted with pentane–benzene (3:1) gave 0.11 g. (7%) of the starting material **1**, m.p. 154–155°.

The second crystalline fraction, 0.05 g., m.p. 148–150°, was identified as the enol **2** (3%).

The third crystalline fraction eluted with benzene gave 0.06 g. (4%) of crystals of testosterone acetate, m.p. 143–145°.

The fourth crystalline fraction eluted with benzene–ether (19:1) gave 100 mg. (6.6%) of crystals which were recrystallized from ether; m.p. 165–166°, $[\alpha]_D$ −306°; λ^{KBr} 5.76, 5.83, 5.98, and 6.21 μ; λ_{max}^{EtOH} 246.5 mμ (ϵ 13,100).

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.20; H, 8.75.

The structure of 6β-acetyltestosterone acetate (**8a**) was assigned to this compound.

4-Acetyltestosterone Acetate (3).—A solution of 0.4 g. of enol **2** in 30 cc. of methanol was treated with 0.3 cc. of 20% sulfuric acid. It was then heated on a steam bath for 1.5 hr., extracted with ether, washed, and dried. The crystalline residue was acetylated with acetic anhydride and pyridine (3 cc. each) overnight at room temperature. The product isolated from ether was purified by chromatography on silica gel (12 g.). Elution with benzene–ether (9:1) gave 0.295 g. (74%) of 4β-acetyltestosterone acetate (**3**) which after recrystallization from ether–hexane had m.p. 127–128°, $[\alpha]_D$ −50°; λ^{KBr} 5.74, 5.84, 6.0, and 6.20 μ; λ_{max}^{EtOH} 241 mμ (ϵ 15,000).

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.14; H, 8.43.

4α-Acetyl-5α-androstan-3-on-17β-ol Acetate (4).—A solution of 0.075 g. of 4-acetyltestosterone acetate (**3**) was hydrogenated in 15 cc. of ethanol with 0.075 g. of palladium on charcoal (10%). After 1 mole equiv. of hydrogen was absorbed, the further uptake ceased and the solution was filtered and evaporated to dryness. It gave a strong coloration with ferric chloride solution. This residue was dissolved in 10 cc. of pentane–benzene mixture (1:1) and chromatographed on a column of alumina. Elution with benzene gave 0.046 g. (61%) of crystals which after recrystallization from ether–methanol melted at 183–185°, $[\alpha]_D$ +36°, λ^{KBr} 5.77 and 5.85 μ; $\lambda_{max}^{cyclohexane}$ 288 mμ (ϵ 176); $\lambda_{max}^{MeOH-NaOH}$ 315.5 mμ (ϵ 12,000).

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 74.22; H, 9.24.

Acid Treatment of 6β-Acetyltestosterone Acetate (8a).—A solution of 0.62 g. of **8a** in 30 cc. of methanol containing 5 cc. of hydrochloric acid (10%) was refluxed for 2.5 hr. Water was added and the product extracted with ether. The residue was dissolved in benzene and chromatographed on 13 g. of alumina. Elution with benzene–ether (9:1) gave 0.2 g. of crystals (36%) of **8b** which after recrystallization from ether had m.p. 191–193°, $[\alpha]_D$ −281.5°; λ^{KBr} 5.82, 6.01, and 6.22 μ; λ_{max}^{EtOH} 246.5 mμ (ϵ 13,600).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.37; H, 9.15.

The second fraction (0.35 g.) eluted with the same solvents and with benzene–ether (4:1) proved to be a mixture of the two epimers **8b** and **9b**. The last fraction eluted with benzene–ether (4:1) gave 0.044 g. (9%) of crystals of **9b** which melted after recrystallization from ether at 160–161°, $[\alpha]_D$ +94°; λ^{KBr} 5.83, 6.0, and 6.21 μ; λ_{max}^{EtOH} 238 mμ (ϵ 14,200).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.42; H, 9.30.

Acetylation of the alcohol **9b** with pyridine and acetic anhydride gave the acetate **9a**, m.p. 150–152°, $[\alpha]_D$ +66°; λ^{KBr} 5.83, 5.94, and 6.18 μ; λ_{max}^{EtOH} 238 mμ (ϵ 14,000).

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 73.90; H, 8.63.

Isomerization of the Epimers 8b and 9b with Acids.—A solution of **8b** (0.01 g.) in 10 cc. of methanol and 0.2 cc. of sulfuric acid (20%) was refluxed for 3 hr. under nitrogen and left overnight at room temperature. Isolation from ether gave a crystalline mixture, m.p. 140–155°, $[\alpha]_D$ −74.5°, λ_{max}^{EtOH} 242 mμ (ϵ 12,000). Its composition was found from the n.m.r. spectra which shows the signals attributed to both epimers. Comparison of the integrated area of the corresponding main peaks gave the ratio of **8b** to **9b** as 45:55. The same ratio of the two isomers was attained from $[\alpha]_D$ and λ_{max} values of the mixture of isomers. When the epimer **9b** was treated under similar conditions, an identical mixture of **8b** and **9b** was obtained as found from the n.m.r., $[\alpha]_D$, and ultraviolet data.

Treatment of the Epimers 8b and 9b with Base.—A solution of 0.1 g. of **8b** in 100 cc. of ether was extracted 5 times with 100 cc. each of a solution of water–methanol (4:1) containing 4% sodium hydroxide. Most of the material dissolved in the basic solution. In the ultraviolet the basic solution had absorption maximum at 422 mμ (ϵ 22,300). The same value was obtained when **8b** was dissolved in 4% methanolic sodium hydroxide solution.

Similarly, **9b** could be extracted from ether by basic aqueous methanol to give the enolate with identical ultraviolet spectrum.

Acidification of the Enolate of 8 or 9.—The basic solution from before was cooled to 0° and acidified with cold hydrochloric acid (10%). Extraction with ether gave **8b**, m.p. 191–193°,

$[\alpha]_D$ −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.

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

Stereochemical Studies of Unsaturated Acetyl Steroids

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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°)

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