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CONFORMATIONAL ANALYSIS OF Δ^5-3-KETO-STEROIDS AND THEIR 4,4-DIMETHYL DERIVATIVES

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It is well-known that homoconjugation of a carbonyl group may result in an increase of its absorption intensity in the 300 mμ region of the ultraviolet (ascribed to the $n \longrightarrow \pi^*$ transitions), provided its two chromophores possess a certain spatial relationship. This arrangement must allow the overlap of the extended $2p_\pi$ orbital ($\pi \longrightarrow \pi^*$ transition orbital) with the two mutually orthogonal $2p_y$ and $2p_x$ orbitals of the oxygen (the $n \longrightarrow \pi^*$ transition orbital).[1]

This enhancement of the $n \longrightarrow \pi^*$ absorption in homoconjugated ketones can be used for determining the relative positions of the two chromophores in systems for which different conformations can be envisaged.[1c,e] Such a system is ring A in Δ^5-3-keto-steroids. It is evident from Fig. 1 that the double bond at C_5-C_6 increases appreciably the intensity of the carbonyl absorption in the 4,4-dimethyl-19-nor-ketone I and the C_4-unmethylated Δ^5-3-ketone II as compared with the saturated ketone IV. This is expected for a "chair" conformation of ring A, where the two chromophores are positioned so

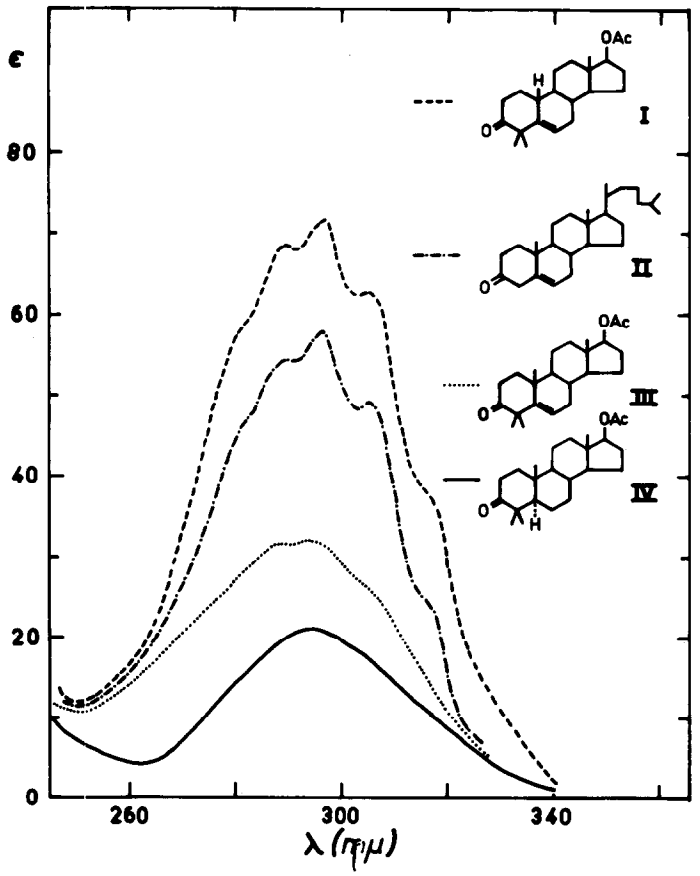

FIG. 1. - Ultraviolet spectra in cyclohexane

as to permit the mixing of the appropriate orbitals. The much smaller enhancement in the 4,4,19-trimethyl compound III points to a different conformation of its ring A. This is reflected more vividly by the u.v. spectra of 3,7-diketo-Δ^5 steroids (fig. 2). The addition of a conjugated carbonyl

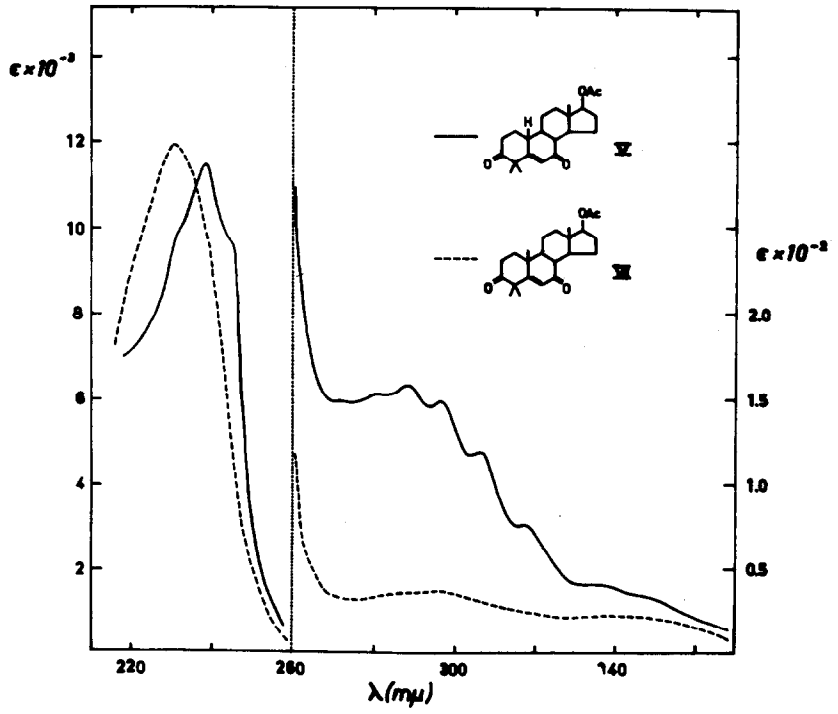

FIG. 2 - Ultraviolet spectra in cyclohexane

function at C_7 results in further intensification of the n transitions allocated to the carbonyl at C_3 in the 4,4-dimethyl-19-nor diketone V, but not in its 19-methyl homolog VI.[2] Furthermore the low wavelength absorption ($\pi \longrightarrow \pi^*$ transitions) of the Δ^5-7-keto system in V is influenced in its turn by the $n \longrightarrow \pi^*$ transition of the carbonyl at C_3; this results in a bathochromic shift of 8 mμ as compared with Δ^5-7-keto steroids lacking the carbonyl at C_3,[3] and in a multiplicity of the peak

(the latter in non-polar solvents), both of which are absent in the u.v. spectrum of VI. This u.v. effect is also shared by other compounds possessing a 1,5-diketo-2-ene chromophore, in which an increase of $n \longrightarrow \pi^*$ absorption of the isolated 5-carbonyl is observed.[4] It is to be noted that, as expected, I, II and VI show an increase of intensity of the $n \longrightarrow \pi^*$ transitions and a decrease of the $\pi \longrightarrow \pi^*$ transitions with the rise in the polarity of the solvent.[1a,d]

The optical rotational strength of these ketones should also be influenced by the homoconjugated double bond, whenever the u.v. enhancement is observed.[1] This is evident by comparison of the reported optical rotatory dispersion (o.r.d.) amplitude values of 19-nor-androstan-3-one-17-ol (VII) [a+54][5] and of its 4,4-dimethyl-Δ^5-derivative (I, 17β-OH) [a+147].[6] The rotatory power of the carbonyl at C_3 is also more pronounced when it is homoconjugated to a Δ^5-7-ketone, as indicated by the circular dichroism (c.d.) curve of the 4,4-dimethyl-19-nor-diketone V, which shows peaks with Δε 3.88, 3.87 and 3.43 (at 296, 305 and 315 mμ);[7] the comparative Δε value for I (17β-OH) is 1.84 (at 296 mμ).[8] On the other hand, the lack of enhancement of the o.r.d. amplitude of the 4,4,19-trimethyl-ketone III (17β-OH) [a+42.5] and of the c.d. values of its 7-keto analog VI [Δε 1.07 at 300 mμ][7] point to a different steric arrangement of the carbonyl at C_3 and the double bond at C_5-C_6.

The relative position of the C_{19}-methyl in respect to the carbonyl and the double bond is indicated by its chemical shift in the n.m.r. spectrum. It is known that carbonyl groups at C_3 and C_7, as well as the 5,6-double bond, exert a long range deshielding effect on the C_{19}-methyl group.[9] The approximate

values reported for these paramagnetic displacements, which are roughly additive, are 14, 17 and 12 c.p.s. (at 60 Mc.) respectively (the standard chosen is the C_{19}-methyl of androstan-17-ol acetate at 47 c.p.s.). In accordance, the C_{19}-methyl signal of II appeared at 74 c.p.s.[10] On the other hand, this signal in III appeared at 52 c.p.s.[11] A similar change in the chemical shift was observed in VI (C_{19}-methyl signal at 62.5) as compared to androst-5-en-7-on-17β-ol (C_{19}-methyl at 71 c.p.s.). It is assumed that it is mainly the change in the relative position of the carbonyl group at C_3 which is responsible for this shielding of the C_{19}-methyl group in III and VI although changes in the position of other groups could also contribute to some extent. Hence a quasi boat conformation of ring A in III and VI could well explain both the u.v. and n.m.r. data.[12] A similar conformation has been previously suggested for 2α-bromo-4,4-dimethyl-cholest-5-en-3-one.[13] The C_{19}-methyl signal of this latter compound and of its androsten-17β-ol analog, has been found by us to be 56 c.p.s. (assigned by comparison with 2α-bromo-4,4-di-CD_3-androsten-3-on-17β-ol), and therefore is in accord with this assumption.[14]

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2. This enhancement seems to result mainly from the reduction of energy separation between $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transition when passing from I to V (ref. 1e, footnote, p. 432).

3. Androst-5-en-7-on-17β-ol acetate has in cyclohexane λ_{max} 229 mμ (ε 13,000).

4. Such compounds also include 6β-acetyl-testosterone and 10-acetyl, estr-5-en-3,17-dione (to be published later).

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7. The c.d. curve was taken in dioxane; it shows also additional peaks at longer wavelength, associated with $n \rightarrow \pi^*$ transition of the Δ^5-7-keto system.

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10. The n.m.r. spectra were taken in $CDCl_3$ on an A-60 Varian spectrometer (60 Mc./sec.), tetramethylsilane serving as the internal reference.

11. This signal was allocated to the C_{19}-methyl group by comparison with the n.m.r. spectrum of III in which the 4,4-CH_3 groups were replaced by CD_3 groups (prepared by methylation of testosterone with CD_3I); the 19-methyl signal of the 4,4-di-C_2H_5 homolog appeared also at 52 c.p.s.

12. It is to be noted that the relative positions of the n.m.r. signals in the compounds discussed do not change when passing from polar ($CDCl_3$) to non-polar (CCl_4) solvents, pointing to the solvent independence of the conformation postulated.

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14. The comparative values for the C_{19}-methyl signal in 2α-bromo-2β-methyl-androstan-3-on-17β-ol (also postulated to have ring A in a boat conformation; K. Mauli, H.J. Ringold and C. Djerassi, J. Am. Chem. Soc. 82, 5494 (1960)] and 2α-methyl-androstan-3-on-17β-ol are 44.5 and 65 c.p.s. For other examples, see J.M. Lehn and G. Ourisson, Bull. Soc. Chim. France. 1113 (1963).