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# CIRCULAR DICHROISM, PROTON MAGNETIC RESONANCE AND CONFORMATION OF STEROID 4-EN-3-ONES, 4, 9-DIEN-3-ONES AND 4, 9, 11-TRIEN-3-ONES

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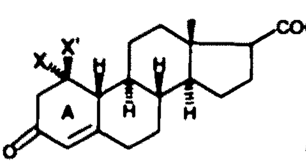
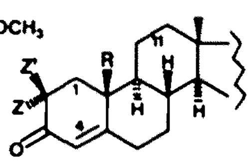
**Abstract**—Room and low-temperature CD of the title dienones and trienones (**3** to **9**) clearly show that a conformational equilibrium occurs between two ring A half-chair conformers. The relative stability of the two conformers depends on substitution of ring A. These results may be extended to other series of steroids and in particular to 4-en-3-ones. CD of these enones (**14** to **28**) is consistent with a conformational equilibrium between the known quasi-*cis*-quasi-*trans* conformers. The controversial conformational behaviour of 2 β-substituted 19-nor-4-en-3-ones is explained by a dynamic equilibrium in solution between the two afore-mentioned conformers rather than by single twist or deformed boat conformer.

More than 15 years ago, Cotton effects in the $\pi \rightarrow \pi^*$ transition region of conjugated dienes and enones were claimed to reflect the chirality of the inherently dissymmetric conjugated chromophore. Further conformational analysis was limited due to the possible occurrence of less populous strongly active conformers and because low-wavelength ORD backgrounds were difficult to analyse in terms of contributions from separate transitions. Nevertheless, inversion of the $\pi \rightarrow \pi^*$ Cotton effect in $C_1$ isomeric 1-methyl-19-nor-progesterones **1a** and **1b** could be related to opposite chiralities of the enone chromophore[1] and accordingly the conformation of ring A of the 1β isomer **1b** was assumed to be different from that of the unsubstituted **1** or 1 α-substituted **1a** derivative.

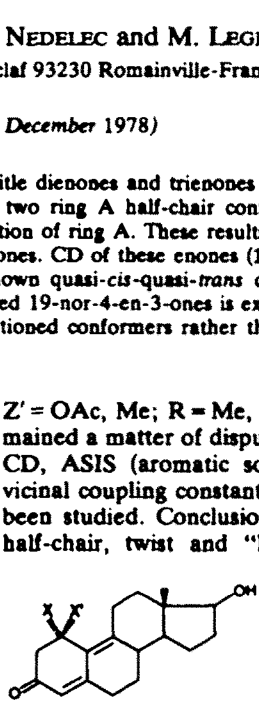
Depending on substitution, ring A of steroid 4-en-3-ones† has been assigned normal half-chair, inverted half-chair and other conformations (Fig. 1).[2] In the solid state, ring A of unsubstituted (**2** Z = Z′ = H) or 2α-substituted 4-en-3-ones (**2**, R = Z = $CH_3$, Z′ = H) takes up conformations close to normal half-chair, as shown by X-ray analysis[3,4], and the same situation prevails in solution at least for the major conformer, as shown by CD, NMR and energy calculations.[2, 5-7] Conformations in solution of 2, 2 dimethyl derivatives (**2** Z = Z′ = $CH_3$) suggested in the literature[5] do not fundamentally disagree with X-Ray measurements,[8] but those of 2β-monosubstituted 4-en-3-ones **2** (R = Z = H, Z′ = OAc, Me; R = Me, Z = H, Z′ = OAc) have remained a matter of dispute for several years. ORD, CD, ASIS (aromatic solvent induced shifts) and vicinal coupling constants of the proton at $C_2$ have been studied. Conclusions were variable: inverted half-chair, twist and "half-boat"* conformations



**1a** X=$CH_3$, X′=H
**1b** X=H, X′=$CH_3$



**2** R=H or $CH_3$



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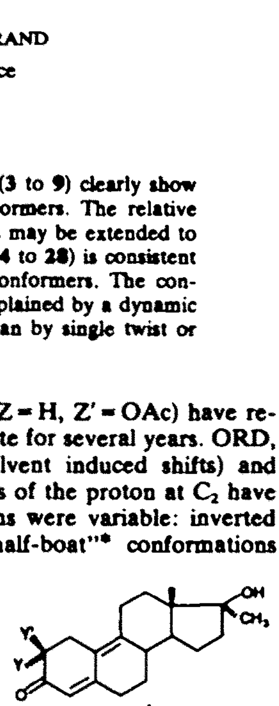

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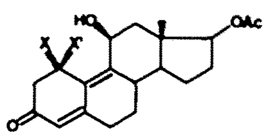

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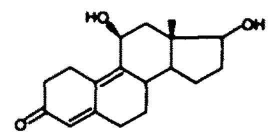

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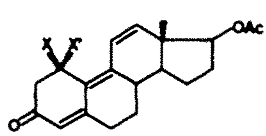
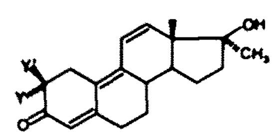


**7**



**8**

Letters following the structure number:

- none: unsubstituted X = X′ = Y = Y′ = H
- *a*: α-substituted X, Y = $CH_3$ X′, Y′ = H
- *b*: β-substituted X, Y′ = $CH_3$ X, Y = H
- *c*: 2,2-disubstituted Y = Y′ = $CH_3$

†Only steroids of natural configuration 8 β, 9 α, 10 β, 13 β, 14 α will be considered.

*The "half-boat" terminology is misleading. This conformer, redrawn in Fig. 1 from **2** is actually a deformed or distorted boat. In half-chair conformers, the 1–2 dihedral angle is close to ± 50°; accordingly, 1α,2β- substituents are axial in the normal conformer and equatorial in the inverted one, the equatorial substituent at $C_2$ being in both cases roughly eclipsed by the 3 ketone group.

Signs of torsion angles are given according to Bucourt.[12]

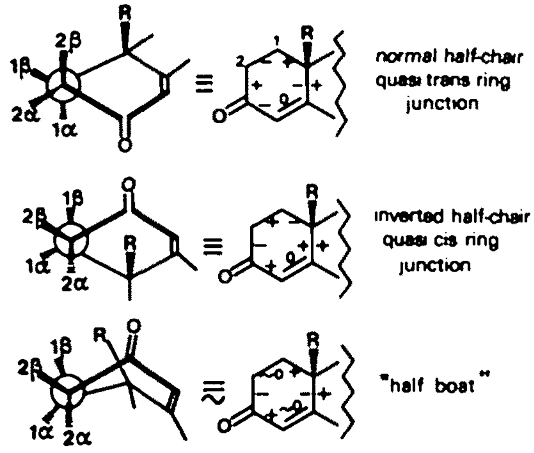



Fig. 1 Conformations of ring A in steroid 4-en-3-ones

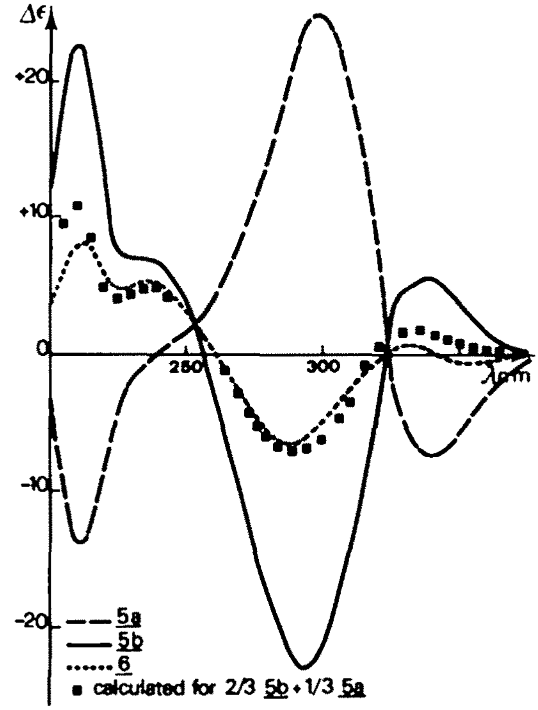



Fig. 3 CD of 11β-hydroxydienones (ethanol, room temperature)

have been assigned to ring A of these compounds[2, 5, 6] Significantly enough, only conformations close to normal or inverted half-chair could be found in the solid state.[9-11]

CD of the $\pi \rightarrow \pi^*$ transition of steroid 4-en-3-ones is expected to give valuable information on the conformation of the enone chromophore; unfortunately, this wavelength-region is complicated due to the presence of two bands, one of which corresponds to the isotropic $\pi \rightarrow \pi^*$ UV absorption and the other is of unknown origin.[13] This complication does not exist for 4, 9-dien-3-ones as **3** to **6** and 4, 9, 11-trien-3-ones as **7** or **8**. Their $\pi \rightarrow \pi^*$ transitions are located respectively about 290-300 and 340 nm and offer more favourable conditions for measurements.[14] As will be shown later in this paper, these enones, dienones and trienones all fall nicely into place in the same general scheme of ring A conformational behaviour. This scheme is best established by first considering the dichroism of the trienones and dienones.

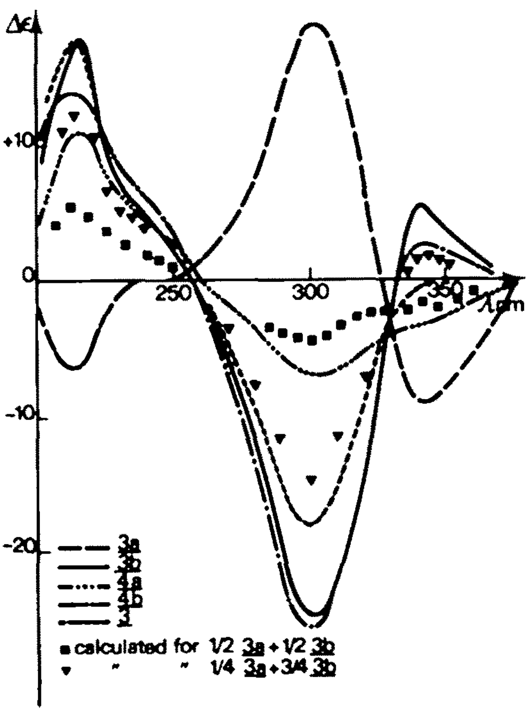



Fig. 2 CD of dienones (ethanol, room temperature)

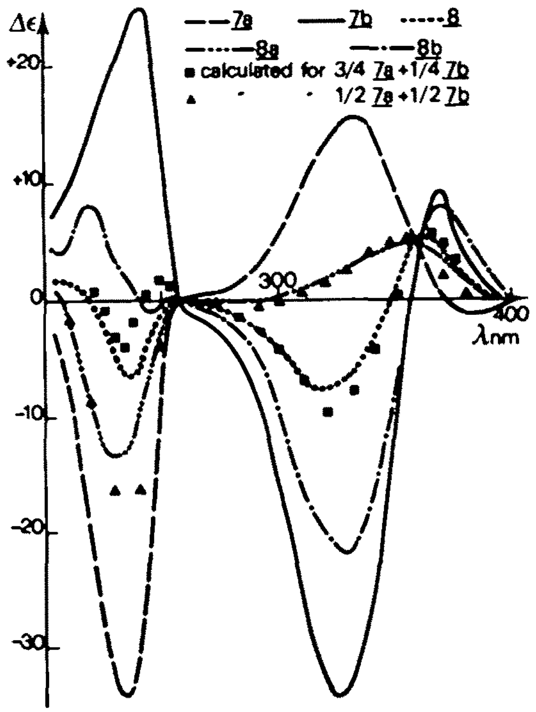



Fig. 4 CD of trienones (ethanol, room temperature)

*Circular dichroism of* 4, 9-*dien*-3-*ones and* 4, 9, 11-*trien*-3-*ones*

When carbon 1 bears an equatorial substituent, steric interference may occur between this substituent and the 11 methine or methylene group. This interference may be relieved by a conformational change of ring A and this in turn should be clearly noticeable on the CD of the $\pi \rightarrow \pi^*$ transition. Thus, a 1$\beta$-substituent (**3b**, **5b**, **7b**) should favour the inverted half-chair conformation for ring A and accordingly 1$\alpha$-substitution (**3a**, **5a**, **7a**) should stabilise the normal half-chair. We feel that boat and other conformers must have higher energy and may to a first approximation be neglected. In the absence of conformational changes, Me substitution on $C_1$ or $C_2$ should have a negligible effect on the dichroism of the $\pi \rightarrow \pi^*$ transition. Actually, the dichrograms (400 to 210 nm) of 1$\beta$-methyl-dienones or trienones **3b**, **5b**, **7b** are found to be roughly antipodal to those of the corresponding 1$\alpha$ isomers **3a**, **5a**, **7a**. The dichroism of ring A unsubstituted compounds **3**, **6**, **8** or 2 Me substituted analogs[15] **8a**, **b**, **c**, **4a**, **b**, **c** are intermediate between those of the 1$\alpha$ and 1$\beta$ derivatives[16] **3a**, **5a**, **7a** and **3b**, **5b**, **7b** (Figs. 2–4)*.

Taking dichrograms of the 1$\alpha$ and 1$\beta$ methylated compounds as representative of ring A in the normal and inverted half-chair conformations, one may roughly estimate the proportions of the two conformers for solutions of unsubstituted or 2 methylsubstituted dienones or trienones. Matches between experimental and calculated spectra are surprisingly good (Figs 2–4). Thus, the qualitative picture is that of a conformational equilibrium between the normal and inverted half-chairs. The stability of the normal half chair decreases in the following order:

$$1\alpha\text{Me} > 2\alpha\text{Me} > \underset{\approx 2,2\text{-di Me}}{\text{unsubstituted}} > 2\beta\text{Me} > 1\beta\text{Me}$$

and for a given type of substitution

trienone > 11$\beta$-hydroxydienone > dienone
as **8** as **6** as **3**

The predominant conformations are normal half chair for the 2$\alpha$-methyl-trienone **8a** and inverted half chair for unsubstituted or 2$\beta$-methyl-substituted dienones **3**, **4b**, **4c**, **6** and trienone **8b**. In agreement with these conclusions, inverted half-chair conformations have been found by X-Ray analysis for the closely related dienones **11**,[17] **12**,[18] **13**[19]† and by energy calculations[20] for an unsubstituted 4, 9-dien-3-one as **3**.

Conformational equilibria in solution could in several cases be confirmed by variable temperature CD measurements: 1$\beta$- methylhydroxydienone **5b** and 1$\alpha$-methyltrienone **7a** were assumed to be pure conformers and their dichroïsm (in EPA)‡

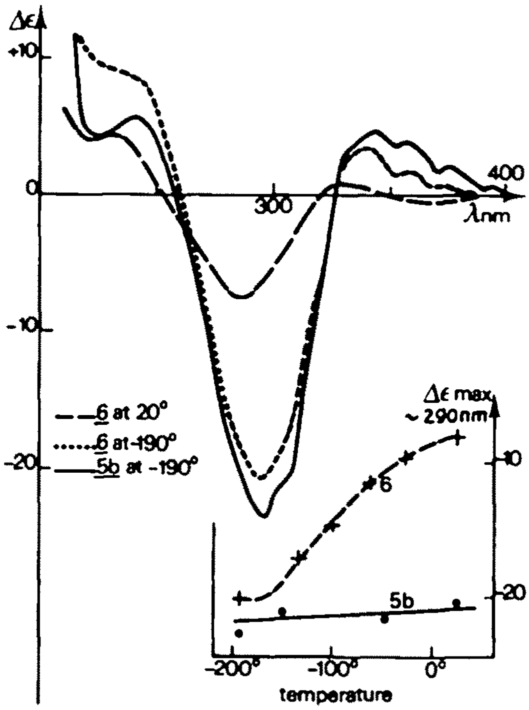



Fig. 5 CD of unsubstituted and 1$\beta$-methyl-11$\beta$-hydroxy-dienones in EPA at room and low temperature

virtually does not change between room and liquid nitrogen temperature. On the contrary, drastic changes are found for the unsubstituted hydroxydienone **6** and 2$\alpha$-methyltrienone **8a**. As expected, the low temperature CD of both compounds matches quite well the CD of the conformationally pure model compound (Figs 5 and 6).

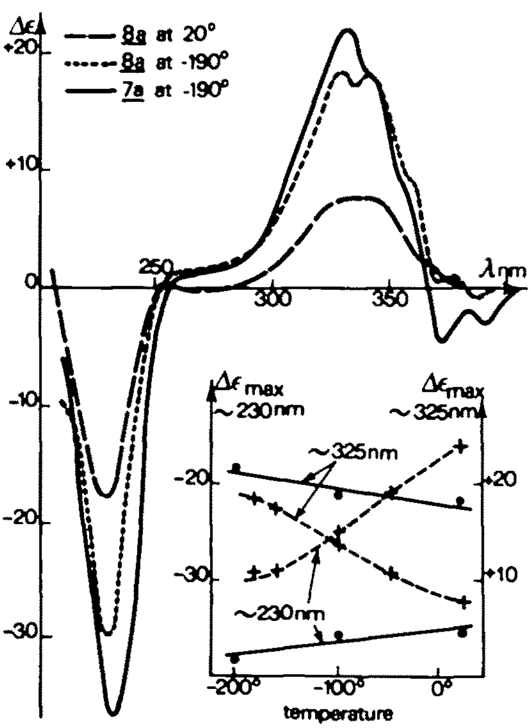



Fig. 6 CD of 1$\alpha$- and 2$\alpha$-methyltrienones in EPA and variation with temperature

*2, 2 dimethyl compounds **4c**, **8c** not shown on Figs 2–4 have CD similar to those of the unsubstituted analogs: **4c** $\lambda_{max}$ 214, 300, 345 nm $\Delta\epsilon$ = +11.6; −17.8; +1.1, **8c** $\lambda_{max}$ 235, 320, 367 nm $\Delta\epsilon$ = −7.4; −7.3; +5.9.

†Signs of the torsion angles, Fig. 5, ref.,[17] should actually be reversed[20]

‡5-5-2 v/v mixture of ether, isopentane and absolute ethanol

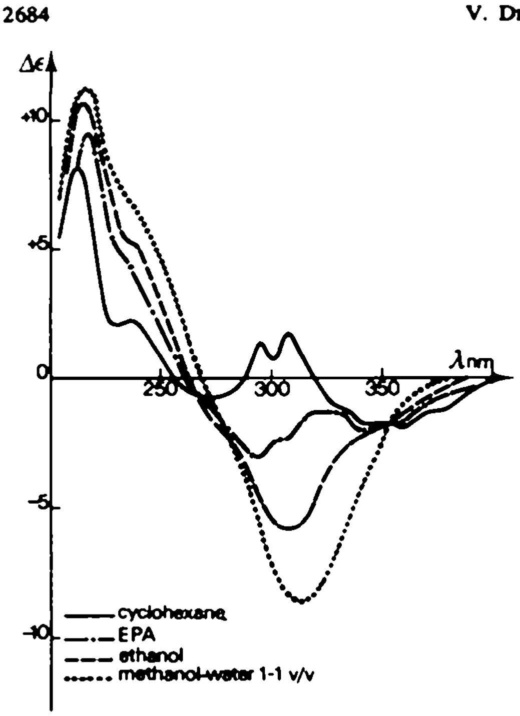



Fig. 7 Room-temperature CD of 2α-methyldienone 4a in different solvents

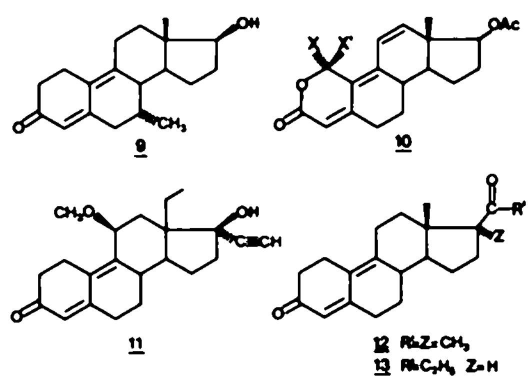
1β-methyltrienone **7b** was unavailable for variable temperature measurement, but 2β-methyltrienone **8b** showed at 320-322 nm the expected trend ($\Delta\epsilon_{max}$ $\pi\rightarrow\pi^*$ = −27 at 20° and −37 at −190° in EPA) and displacement of the equilibrium towards the more stable inverted half-chair conformer. Conversely, heating the ring A unsubstituted dienone **3** increases the proportion of the less stable normal half chair ($\Delta\epsilon_{max}$ at 300 nm in n-hexanol rises progressively from −21.8 at −40° to −13.5 at +110°)

However, no definite conclusions could be drawn from low temperature CD measurements on the "unsubstituted" trienone **8** nor the 2α-methyldienone **4a**. At room temperature, in ethanol, both compounds appear to be mixtures of the two half-chair conformers in about equal amounts. The dichroism of **8** does not change significantly with temperature suggesting a very small energy difference between the two half chairs. The dichroism of **4a** varies slightly with temperature but in a way inconsistent with a simple displacement of the conformational equilibrium. This is because CD of **4a** is very solvent sensitive (Fig. 7). Room temperature spectra suggest a solvent dependent tautomeric or conformational equilibrium (pseudo-isosbestic points around 270 and 350 nm). The effect appears surprisingly strong for a solvent displacement of conformational equilibrium, however this cannot be ruled out and no better explanation is presently available. Anyway, strong solvent effects in conjunction with conformational equilibria are expected to lead to unpredictable CD results at variable temperatures, especially in mixed solvents as EPA and accordingly the peculiar behaviour of **4a** is not inconsistent with our general conformational scheme.

Introduction of 9-10 unsaturation in 4-en-3-ones confers new flexibility to steroid ring B. Dreiding models show that in the ring A inverted half-chair conformer steric 1-11 interference might be released if ring B were also in an inverted conformation (Fig. 8).

If this were the case, the inverted half-chair conformer would be significantly destabilized for the 7α-methyldienone **9** compared with the unsubstituted analog **3**. In the inverted ring B conformer, the 7α-position is equatorial and 7α-substitution would lead to steric hindrance between the 7α-substituent and the 15 methylene group. That such interaction does not occur is clearly shown by the close similarity of CD spectra of **3** and **9**, both at room and low temperature (in EPA, **3** has $\Delta\epsilon_{max}$ at 293 nm = −21 at 20° and −26 at −100°; **9** shows $\Delta\epsilon_{max}$ = −20 at 20° and −28 at −150°). Thus, ring-A inversion proceeds without a concomitant inversion of ring B and ring-B conformations in solution are not fundamentally different from those found in the solid state for similar structures (**11, 12, 13**).

Conformational equilibria similar to those described above have also been found in steroid




9 10 11

12 R=Z=CH₃
13 R=C₂H₅ Z=H

a,b same meaning as before

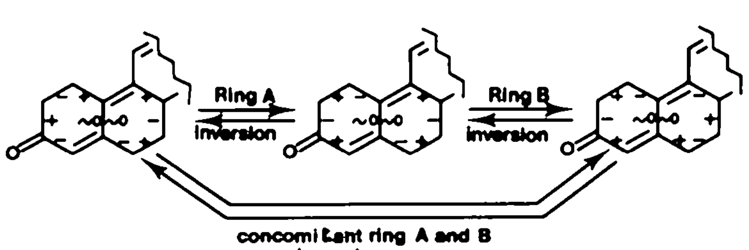



Fig. 8 Conformations of rings A and B in dienones and trienones

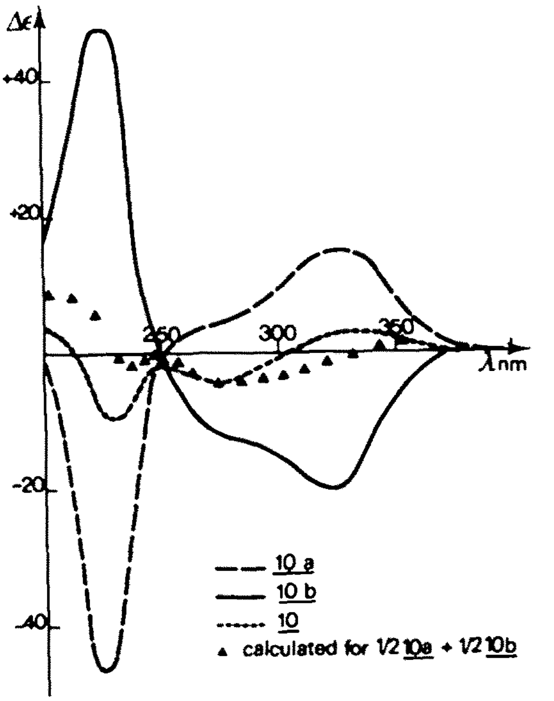
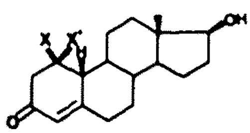



Fig. 9 CD of trienic lactones (ethanol, room temperature)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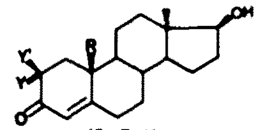
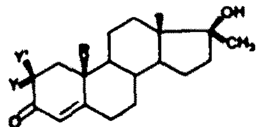
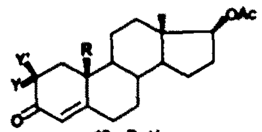
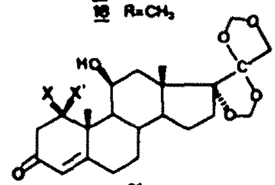

15 R=H
16 R=CH₃


17 R=H
18 R=CH₃


19 R=H
20 R=CH₃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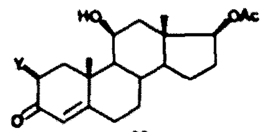
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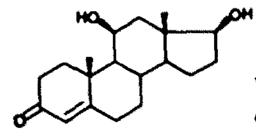
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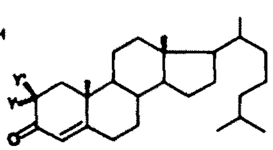
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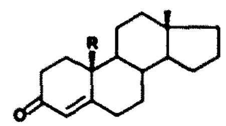
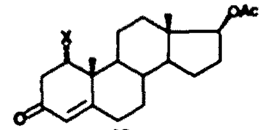

25 R=H
26 R=CH₃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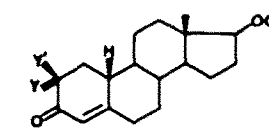
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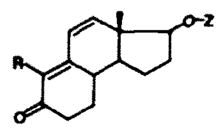
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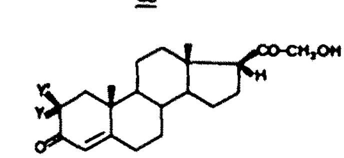
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a,b,c same meaning as before

2-oxatrienones **10**, **10a**, **10b** (Fig. 9). Again CD of the $C_1$ methylated isomeric compounds are roughly antipodal. They also bear some crude resemblance to those of 1 methyltrienones **7a**, **7b**. Room-temperature CD of the unsubstituted lactone **10** is intermediate and consistent with the presence of two conformers in roughly equal amounts.

Though the true half-chair geometry certainly differs to some extent between the trienic ketones as **7** and **8** and lactones as **10** it appears that conformational equilibria are quite general for steroids with a partial 4-en-3-carbonyle structure.

Despite the expected difficulties, this prompted us to reexamine steroid 4-en-3-ones for the occurrence of similar equilibria.

*Circular dichroism of steroid 4-en-3-ones*

$\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions are well separated, but the first is somewhat obscured by the occurrence of a low-wavelength band usually appearing as a maximum or inflexion. Sometimes this band is too weak or has merged with the "isotropic" $\pi \rightarrow \pi^*$ band around 240 nm. As already noticed for 19-nor-progesterones **1a** and **1b**, $C_1$ isomeric 1-methyl-4-en-3-ones **14a**-**14b** and **21a**-**21b** give rise to opposite Cotton effects in both $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ regions. Except perhaps for the high-frequency component (usually in the 210–220 nm range), dichrograms of the unsubstituted or 2 methyl substituted enones show intermediate CD intensities. According to their room-temperature CD, 4-en-3-ones may be roughly classified in the following order (Table 1):

$$1\alpha-\text{Me}, 2\alpha-\text{Me}, \frac{(\text{unsubstituted})}{(2,2\text{-di Me})}, 2\beta-\text{Me}, 1\beta-\text{Me}$$

This is identical to the relative stability sequence of the two half chairs found in the dienone or trienone series and suggests that a similar type of equilibrium may operate for enones. Contrary to dienones and trienones, the proportions of the two conformers cannot be quantitatively deduced from the dichrograms of enones, because none of these dichrograms can be taken as truly representative of a pure half chair. Substitution effects are expected to occur for $n \rightarrow \pi^*$ transitions, even without conformational change. The $\pi \rightarrow \pi^*$ transition may be thought to be independent of substitution as such and to reflect exclusively conformational changes. Unfortunately, the shape and the intensity of the composite $\pi \rightarrow \pi^*$ band depends on the wavelength separation, sign and intensity of the high-frequency component, and this component seems to be quite

Table I Room-temperature CD and UV of steroid 4-en-3-ones in ethanol

| Structure | | $\lambda_{max}^{nm}$ ($\Delta\epsilon$ or $10^{-3}$, $\epsilon$) | | | |
|---|---|---|---|---|---|
| N° | Me | CD : $\pi\rightarrow\pi^*$ | | CD : $n\rightarrow\pi^*$ | UV : $\pi\rightarrow\pi^*$ |
| **oestrenones** | | | | | |
| 14a | 1α | | 243 (+14.0) | 320 (-3.1) | 242 (15.4) |
| 17a | 2α | 225i (+14.5) | 239 (+12.2) | 320 (-3.0) | 240 (16.1) |
| 14 | - | 220i (+6) | 238 (+ 7.3) | 320 (-1.8) | 241 (16.9) |
| 17 | - | 220 (+7.2) | 235i (+ 6.6) | 317 (-1.9) | 240 (17.2) |
| 17c | 2.2 | 215 (+6.6) | 240 (+ 6.1) | 322 (-2.3) | |
| 17b | 2β | 213 (+5.5) | 245 (-5.2) | 322 (-1.0) | 241 (16.0) |
| 19b | 2β | 204 (+4.3) | 241 (-5.5) | 322 (-0.9) | 240 (16.8) |
| 14b | 1β | | 245 (-21.5) | 325 (+1.3) | 244 (14.7) |
| **androstenones** | | | | | |
| 20a | 2α | 218 (+ 8.3) | 238 (+ 10) | 322 (-2.3) | 240 (16.3) |
| 16 | - | 217 (+11.5) | 235i (+8.3) | 320 (-1.6) | 240 (16.3) |
| 18c | 2.2 | 210 (+ 9.5) | | 335 (-2.0) | 241 (15.9) |
| 16b | 2β | 210 (+ 12) | 243 (-21.7) | 322 (+1.3) | 243 (14.5) |
| **11-β-hydroxy-enones** | | | | | |
| 21a | 1α | | 243 (+23.6) | 322 (-3.1) | 245 (14.4) |
| 22a | 2α | 228 (+13.5) | | 317 (-2.4) | 241 (15.0) |
| 23 | - | 228 (+13.3) | 240i (+10.7) | 317 (-1.6) | 242 (15.6) |
| 21b | 1β | 212 (+10.8) | 250 (-19.2) | 321 (+1.5) | 248 (12.6) |
| **cholestenones** | | | | | |
| 24a | 2α | 215 (+11.7) | 235i (+8.9) | 321 (-2.45) | 241 (16.1) |
| 24b | 2β | ~205 (+11) | 244 (-26.7) | 322 (+1.43) | 244 (15.3) |

i : inflexion

sensitive to substitution and solvent effects. Measurements are also adversely affected by instrumental noise (±1 to 1.5Δε units peak to peak in most cases), which rises sharply towards low wavelength. Despite these difficulties, results are consistent with the conformational equilibrium hypothesis.

Recent calculations on 19-nor-testosterone **14** have shown that the energy differences between the two half chairs is small enough so that both conformers (corresponding to quasi-*cis* and quasi-*trans* fusions between rings A and B) should be present at room temperature.[7] Both conformers have also been found in the crystalline cell.[21] Room and low-temperature CD of 19 nor testosterone **14** in EPA is shown in Fig. 10. By going from +20° to −190°, the 230 nm maximum is bathochromically shifted and rises in intensity: at 240 nm, Δε increases by about 6–7 units. This increase originates in the displacement of the conformational equilibrium towards the more stable normal half-chair (quasi-*trans*) conformer. Similar results are obtained for the closely related **17** in EPA or **25** in MI* (Table II). The shape of the $\pi\rightarrow\pi^*$ absorptions is somewhat modified in the 19-methyl enones **16**, **26**. The high-frequency component raises in intensity with respect to the low frequency one. The overall change with temperature (about 3Δε units) is definitely smaller than for the 19-nor analogs **14**, **25**. This would be in agreement with an increased stability of the normal half-chair (quasi-*trans*) conformer in **16**, **26** as compared to **14**, **25** and is consistent with earlier findings.[7] The behaviour of the 11β-hydroxy compound **23** in EPA more closely parallels that of the 19-nor compounds **14**, **17** though $\Delta\epsilon_{max}$ and variation of Δε with temperature (~10 units at 240 nm from +20° to −170°) are somewhat higher here.

As expected, 1α-methyl-enones **21a**, **27a** show little change with temperature in the $\pi\rightarrow\pi^*$ region both in EPA and MI; a single maximum without any inflexions is found and it occurs at a wavelength close to that of the isotropic UV maximum. In other 4-en-3-ones studied here, separation of the component bands in the $\pi\rightarrow\pi^*$ region usually increases in apolar solvents. No separation is found for 1α-Me derivatives and this suggests

*1-3 v/v mixture of methylcyclohexane and isopentane

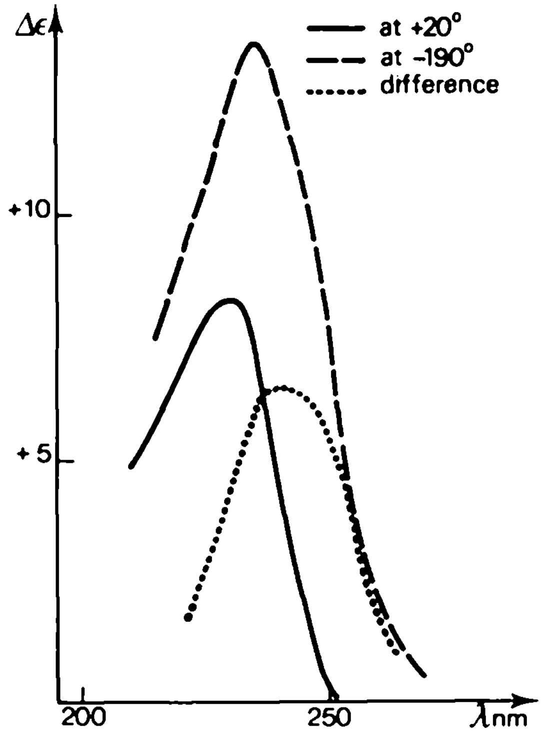


Fig. 10 CD of 19-nor-testosterone *14* in EPA and difference between +20° and −190°

that the high frequency component is very weak or absent. The whole $\pi \rightarrow \pi^*$ band of **27a** shifts bathochromically at low temperature in both MI and EPA; this occurs without any significant change in $\Delta\epsilon_{max}$, band shape or area and thus should not originate from a conformational equilibrium displacement. The 19-nor compound **14a** (in ethanol) shows a $\Delta\epsilon_{max}$ definitely weaker than **27a** (in EPA or MI) or **21a** (in ethanol or EPA). Unfortunately, neither **27a** nor **22a** were available for further study of this difference. 1β-methyl-enones **14b** and **21b** show also a single $\pi \rightarrow \pi^*$ band, which varies to some extent in intensity with temperature becoming more negative as temperature is lowered. In these compounds, the inverted half-chair (quasi-*cis*) conformer is predominant but some normal half chair (quasi-*trans*) should be present at room temperature. These conclusions are in qualitative agreement with theoretical calculations.[20]

2α-methyl-enones **15a**, **20a**, **22a** show only a slight increase of the $\pi \rightarrow \pi^*$ dichroism as temperature is lowered and are mostly normal half chairs. A single $\pi \rightarrow \pi^*$ maximum is found in EPA, but this is certainly a composite band as judged by secondary inflexions or maxima in ethanol or MI (Tables I and II). 2β-methyl enones show a very different behaviour depending on the presence or not of the 19-Me group. 2β substitution introduces 1:3-diaxial interaction between the 2β-and 19-Me groups and strongly destabilises the normal half-chair conformer in the 19-Me compound **16b**. The strong negative $\pi \rightarrow \pi^*$ dichroism of **16b** is similar to that of 1β-methyl-4-en-3-ones and in agreement with an inverted half-chair conformation. The proportion of normal half chair should be increased in the 19-nor analogs **17b**, **19b** and accordingly the $\pi \rightarrow \pi^*$ maximum is less negative ($\Delta\epsilon \sim -6$) in these compounds and consistent with roughly equal proportions of the two half chairs (taking for instance +20 and −30 as representative for normal and inverted half chair). Also no significant change of the $\pi \rightarrow \pi^*$ absorption occurs in the temperature range studied and this indicates that the energy difference between the two conformers is close to nil.

The $\pi \rightarrow \pi^*$ CD of 2, 2-dimethyl-enones does not allow unquestionable conformational conclusions, especially for the 19-Me compound **18c**. In the 19-nor series (**17c**, **28c**), a pure or nearly pure normal half chair is most probable. The $\pi \rightarrow \pi^*$ dichroism does not change with temperature; it is comparable to that found for the normal half chair of testosternone **16** but very different from that of an inverted half chair (as **16b**) or a 1–1 mixture of the two conformers (as in **17b** or **19b**). The $n \rightarrow \pi^*$ dichroism (see below) is also consistent with this conclusion. In the dienone of trienone series studied above, 2, 2-dimethyl derivatives are conformationally very close to their 2 unsubstituted analogs. This should be also true for the 19-nor-4-en-3-one series, provided the 10 hydrogen does not strongly interfere with other groups (especially the 2β Me) Actually, the conformations of the 2-methyl-19-nor-enones or polyenones studied here result apparently from only two factors:

(a) the overall structure of the ring system (compared with trienones, the normal half chair is stabilised in enones and destabilised in dienones);

(b) the preference of the 2-Me to more or less eclipse the adjacent ketone CO. This factor cancels in 2, 2-dimethyl compounds.

The situation is less clear for the 2, 2-dimethylandrostenones as **18c**. Again the $\pi \rightarrow \pi^*$ CD does not vary with temperature but the overall shape of the dichrogram does not allow any definite conclusions. Unpublished X-ray results[a] and energy calculations[20] show that in the solid state ring A takes a distorted 1, 2 diplanar (sofa) conformation, which may also prevail in solution, but it is not clear why an inverted half chair is not preferred.

*$n \rightarrow \pi^*$ dichroism of enones*

In the early studies of CD, the $\pi \rightarrow \pi^*$ transition was unaccessible to measurement and most structural and conformational studies were based on the $n \rightarrow \pi^*$ dichroism. Table III shows present results which are in general qualitative agreement with the foregoing conclusions.

For conjugated cyclohexenones, the sign of the $n \rightarrow \pi^*$ dichroism had been correlated with the enone chirality or SNATZKE's first chiral sphere[22] and a theoretical calculation[23] of the isolated C=C−C=O chromophore predicted that for transoid enones the contribution of this chirality would lead to opposite signs for the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ dichroisms. CD of 2β-methylestrenones **17b**, **19b** (Tables I, II, III) first appeared to be in contradiction with this rule. Actually conformational equilibria may result in variable relative CD signs for the two transitions depending on the CD amplitude of the pure conformers and on their ratio at equilibrium.

**Table II** $\pi \rightarrow \pi^*$ CD of steroid 4-en-3-ones ($\Delta\varepsilon$) at variable temperature[a)]

| Structure[k] | | $\lambda_{max}$[b] | +20° | −50° | −100° | −150° | −170° or −190° | Solvent |
|---|---|---|---|---|---|---|---|---|
| **14** | nor | 230–235 | +8.1 | – | +12.7 | +13.4 | +13.5[c] | EPA |
| **17** | " | 230–237 | +7.5 | – | +11.1 | +12.8 | +14.0[c] | EPA |
| **25** | " | 230–235 | +8.4 | +10.9[e] | +11.8 | +13.1 | +16.3[c] | MI |
| **16** | – | 235[j] | +9.3 | +10.0 | +11.5 | +12.6 | – | EPA |
| | | 216 | +13.0 | +13.5 | +14.5 | +14.7 | | EPA |
| **26** | – | 230 | +7.2 | +8.4[e] | – | +9.2[f] | +10.3[c] | MI |
| | | 210–218[g] | +6.8 | +8.0[e] | – | +8.7[f] | +9.9[c] | MI |
| **23** | – | 228–232 | +13.7 | +18.0 | +19.3 | +20.5 | +20.6[d] | EPA |
| **27a** | 1α | 237–242 | +22.8 | +24.6 | +23.2 | +23.7 | +23.8[c] | EPA |
| | | 232–237 | +22 | +23.6 | +23.6 | +22.5 | +21.3[d] | MI |
| **21a** | " | 242 | +22.0 | +24.8 | +25.1 | +25.2 | +24.6[d] | EPA |
| **14b** | nor,1β | 239–242 | −20.8 | −23.1 | −23.9 | −24.6 | −25.0[c] | EPA |
| **21b** | 1β | 246–248 | −20.0 | −22.5 | −26.3 | −29.5 | −30.9[d] | EPA |
| **15a** | nor,2α | 232–237 | +13 | – | +14.5 | +15.4 | +16[c] | EPA |
| **20a** | 2α | 233–234 | +15.0 | +15.8 | +15.8 | +14.8 | +15.6[d] | EPA |
| **24a** | " | 232–235 | +7.3 | +9.3 | +9.6 | +10.4 | +9.2[d] | MI |
| | | ~205[h] | +8.8 | +11.7 | +11.6 | +12.6 | +11.6 | |
| **22a** | " | ~225[h] | +14.5 | +14.3 | +15.0 | +15.0 | +14.7[d] | EPA |
| **17b** | nor,2β | ~239[h] | −5.1 | – | −5.2 | −4.8 | – | EPA |
| **19b** | " | 237–240 | −6.9 | −6.8 | −6.6 | −6.5 | −6.3[c] | EPA |
| **16b** | 2β | 237–240 | −25.5 | −27.4 | −29.5 | −30.7 | −31.6[c] | EPA |
| **24b** | " | 238–240 | −31.7 | – | −31.9 | −32.1 | – | MI |
| **17c** | nor,2.2 | 230–238[i] | +7.5 | – | +8.0 | +8.0 | – | EPA |
| **28c** | " | ~235 | +6.4 | +7.5 | +7.9 | +8.3 | +8.6[d] | EPA |
| | | ~215[h] | +5 | +6 | +6 | +7 | +7[d] | |
| **18c** | 2.2 | 240[j] | +1.3 | +1.3 | +3.1 | +3.3 | +3.5[d] | EPA |
| | | ~210 | +13.8 | +13.7 | +14.6 | +14.6 | +14.9 | |

a) – peak to peak noise $\leqslant \pm 1.2\ \Delta\varepsilon$ units unless otherwise stated ;
b) – respectively at +20° and at the lowest temperature mentioned ;
c) – at −190° ; d) – at −170° ; e) – at −70° ; f) – at −130° ;
g) – maximum or inflexion ; h) – peak to peak noise $\leqslant \sim\pm 2\ \Delta\varepsilon$ units ;
i) – very broad maximum ; j) – inflexion ; k) – N° ; "nor" refering to 19 position, Me location

The possible occurrence of such equilibria should thus be carefully examined and caution should be exercised when drawing conformational conclusions solely from the $n \rightarrow \pi^*$ region of conjugated enones. $n \rightarrow \pi^*$ transitions are expected to be more sensitive to vicinal substitution as such and to temperature (fine structure). Solvent effects may also be very important: a particularly striking case is again that of the 2β-methyl-estrenones **17b**, **19b** to be compared with the 2β-methyl-androstenone **16b** (Table IV, Fig. 11). This behaviour is not exceptional. Several other conjugated steroid ketones show important changes in the $n \rightarrow \pi^*$ region whereas changes in the $\pi \rightarrow \pi^*$ region are much less pronounced. No completely satisfactory explanation can be offered at the present time but clearly EPA spectra at variable temperatures are bound in such cases to show a much more complex behaviour than that originating from a simple conformational equilibrium.

*Proton magnetic resonance*

Vicinal coupling constants and aromatic solvent induced shifts (ASIS) have been used to assign conformations to ring A of steroid-4-en-3-ones.[2,5,6]

When the 2 substituent is an OH or an OAc group, vicinal coupling constants $J_{cis}$ and $J_{trans}$ are readily measured and dihedral angles deduced from Karplus type relations. Half-boat[2] and twist[5] conformations have been assigned to 2β-acetoxy-19-nor-4-en-3-ones (**2** R = Z = H, Z′ = OAc) where $J_{cis} = J_{trans} = 7.9$[2] or $J_{cis} = 6.9$, $J_{trans} = 9.3$[5] in $CDCl_3$.

Table III n → π* dichroism of steroid 4-en-3-ones at variable temperature

| | Structure, solvent and $\lambda^{max}$ b) | $\Delta\varepsilon_{max}$ : $\int \Delta\varepsilon \frac{d\lambda}{\lambda}$ a) | | | | |
|---|---|---|---|---|---|---|
| | | +20° | -50° | -100° | -150° | -170° or -190° |
| 14 | 322, 333 | -1.51 | - | -1.87 [k] | -2.06 [k] | -2.12 [c][k] |
| EPA | 318, 330, 344, 362 | -0.22 | - | -0.26 | -0.28 | -0.28 |
| 17 | 322, 333 | -1.46 | - | -1.85 | -2.03 [k] | -2.22 [c][k] |
| EPA | 318, 330, 345, 361 | -0.21 | - | -0.26 | -0.28 | -0.29 |
| 25 | 312, 322, 336, 351, 366 | -1.42 | -1.68 [g] | -2.00 | -2.20 | - |
| MI | 312, 322, 336, 351, 366 | -0.17 | -0.20 | -0.21 | -0.24 | - |
| 16 | 320, 332 | -1.49 | -1.64 | -1.72 | -1.82 [k] | - |
| EPA | 317, 330, 346, 362 | -0.19 | -0.23 | -0.25 | -0.25 | - |
| 26 | 312, 324, 337, 352, 368 | -1.46 | -1.72 | - | -1.93 [f] | - |
| MI | 312, 323, 337, 352, 367 | -0.17 | -0.19 | - | -0.21 | - |
| 23 | 321, 333 | -1.47 | -1.67 | -1.84 | -2.01 [k] | -2.14 [c][k] |
| EPA | 318, 331, 346, 363 | -0.21 | -0.23 | -0.26 | -0.27 | -0.28 |
| 27a | 325, 336 | -2.50 | -2.65 | -2.89 | -3.06 | -3.25 [c] |
| EPA | 321, 333, 348, 366 | -0.38 | -0.38 | -0.41 | -0.41 | -0.42 |
| 27a | - 327, 340, 355 | -2.23 | -2.45 | -2.62 | j) | j) |
| MI | 315, 327, 340, 355, 372 | -0.29 | -0.31 | -0.32 | -0.35 | -0.35 |
| 21a | - 324 | -1.99 | -2.16 | -2.20 | -2.23 | - |
| EPA | 318, 332, 347, 365 | -0.28 | -0.30 | -0.31 | -0.31 | - |
| 14b | - 322, 335, 347 | +1.25 | +1.39 | +1.49 | +1.58 | +1.67 [c] |
| EPA | 308, 319, 333, 347, 363 | +0.18 | +0.19 | +0.20 | +0.21 | +0.20 |
| 21b | 325, 334 | +1.18 | +1.57 | +1.87 | +2.30 | +2.47 [d] |
| EPA | 319, 331, 346, 364 | +0.18 | +0.23 | +0.28 | +0.32 | +0.34 |
| 15a | - 329 - - | -2.27 | -2.50 | -2.67 | -2.88 | -3.02 [c] |
| EPA | 316, 328, 342, 357 | -0.31 | -0.33 | -0.34 | -0.35 | -0.35 |
| 20a | 323, 331 | -2.48 | -2.70 | -2.94 | -3.08 | -3.15 [d] |
| EPA | 317, 328, 343, 359 | -0.35 | -0.36 | -0.38 | -0.39 | -0.39 |
| 24a | - 323, 335, 349, 363 | -2.34 | -2.47 | -2.66 | -2.87 | -2.85 [d] |
| MI | 310, 321, 333, 347, 363 | -0.30 | -0.30 | -0.32 | -0.33 | -0.33 |
| 22a | 322, 331 | -2.02 | -2.21 | -2.36 | -2.49 | -2.50 [d] |
| EPA | 317, 329, 343, 359 | -0.28 | -0.30 | -0.31 | -0.31 | -0.30 |
| 17b | 313, 325, 336, 350, 367 | -0.49 | -0.52 [h] | -0.72 | -1.03 [e] | - |
| EPA | 309, 321, 334, 349, 365 | -0.07 | -0.06 | -0.08 | -0.11 | - |
| 19b | 312, 324, 337, 350, 367 | -0.48 | -0.64 | -0.76 | -0.93 | -1.13 [c] |
| EPA | 308, 320, 333, 348, 365 | -0.07 | -0.08 | -0.09 | -0.11 | -0.12 |
| 16b | 320, 330 | +1.23 | +1.49 | +1.69 | +1.86 | +1.96 [c] |
| EPA | 316, 329, 342, 358 | +0.17 | +0.19 | +0.21 | +0.22 | +0.22 |
| 24b | - 322, 333, 347 | +1.59 | +1.85 | +2.09 | +2.12 | - |
| MI | 309, 320, 332, 343, 363 | +0.20 | +0.22 | +0.24 | +0.25 | - |

Table III

| Structure, solvent and $\lambda^{max}$ b) | | $\Delta\varepsilon_{max}$ ; $\int\Delta\varepsilon \frac{d\lambda}{\lambda}$ a) | | | | |
|---|---|---|---|---|---|---|
| | | +20° | -50° | -100° | -150° | -170° or -190° |
| 17c | 325, 333 | -1.94 | -2.20 | -2.40 | -2.67 | -2.80 c) |
| EPA | 318, 331, 345, 362 | -0.26 | -0.28 | -0.31 | -0.32 | -0.32 |
| 28c | 324, 333 | -1.90 | -2.15 | -2.32 | -2.50 | -2.67 c) |
| EPA | 318, 331, 345, 362 | -0.26 | -0.28 | -0.29 | -0.30 | -0.31 |
| 18c | - 333 | -1.97 | -2.31 | -2.57 | -2.82 | -2.90 d) |
| EPA | 319, 332, 345, 362 | -0.28 | -0.31 | -0.35 | -0.36 | -0.36 |

a) for each compound and temperature, the figure in the first line is $\Delta\varepsilon$ at the main maximum ; the figure in the second is $\int\Delta\varepsilon \frac{d\lambda}{\lambda}$ . b) first line $\lambda^{max}$ at 20° ; second line $\lambda^{max}$ at the lowest temperature measured ; the main maximum is underlined, inflexions are not shown. c) at - 190° d) at -170° e) at -160° f) at -130° g) at -40° h) at -30° j) at -150°, the fine structure is washed out. At -190°, a novel fine structure appears max. at 332, 345nm infl. at 322 and 360nm. This change is reversible and reproducible and may originate from crystallization or aggregation. The $\pi\rightarrow\pi^*$ dichroism was measured on 20 times more diluted solutions and crystallization or aggregation effects, if any, are within the measurement error in this region of the spectrum. k) The inversion in the relative intensities of the maxima at ~320 and 330nm is seen at -100° for 14 and at -150° for 17, 16 and 23. At these and lower temperatures, figures refer to the ~330nm maximum.

Table IV $\pi\rightarrow\pi^*$ CD of steroid 2β-methyl-4-en-3-ones in different solvents

| Solvent | 19 Me : 16b | | 19 nor: 17b* | |
|---|---|---|---|---|
| Cyclohexane | 233(-25) | 200(+10) | 233(-8) | 210(+1) |
| Ethanol | 243(-20) | 208(+10) | 243(-5) | 213(+5) |
| $MeOH-H_2O$ v/v | not measured | | 246(-4) | ~210(+6) |

* peak to peak noise less than ± 1 $\Delta\varepsilon$ unit

Actually large errors on individual $J_{cis}$, $J_{trans}$ values may result from a first order approximation for X in an ABX spectrum,[24] especially when the X part approximates the deceptively simple case, whereas the sum $J_{cis}+J_{trans}$ can always be determined unambiguously. We suggest that the quoted individual values are not representative and that these compounds rather involve a dynamic equilibrium between the two ring A half-chairs. If this were the case, the sum $J_{cis}+J_{trans}$ should decrease as increases the proportion of the axial substituent. In agreement with this expectation, $J_{cis}+J_{trans}$ (~16 Hz for 2β-acetoxy-19-nor-4-en-3-ones) is below the range (17–20 Hz) found[2, 5, 6] for all other 2-hydroxy of 2-acetoxy-4-en-3-ones (2 R = H or Me, Z or Z′ = OH or OAc excluding R = Z = H, Z′ = OAc). Also in 2β-hydroxy-4-en-3-ones (2 R = Me Z = H Z′ = OH) $J_{trans}$ decreases from ~14 Hz in chloroform to ~11 Hz in pyridine[6] as the inverted half-chair conformer is destabilized by breakage of the ketone-OH hydrogen bond. These data are again in satisfactory agreement with the dynamic equilibrium hypothesis.

In 2-methyl-4-en-3-ones, the 2 proton coupling constants cannot be easily measured and ASIS have been used to assign equatorial-axial orientations to the Me group.[5] ASIS found here for representative 2α-and 2β-methyl and 2-2 dimethyl-enones,

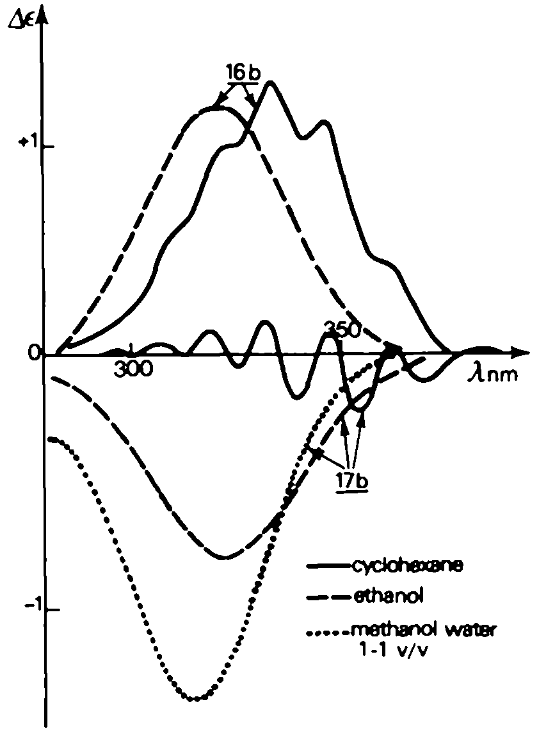


Fig. 11 n → π* CD of 2β-methyl-enones *16b* and *17b* in different solvents at room temperature

dienones or trienones (Experimental) may be explained in terms of dynamic equilibria but are much less conclusive than the CD measurements. Shifts are often weak and liable to significant errors on the 60–90 MHz PMR scale. Assignments may be ambiguous. In cases as **4a**, **19b**, very significant solvent effects are observed by CD and these should certainly be better understood before interpreting the ASIS values on a firm basis.

## CONCLUSIONS

A conformational equilibrium between two ring A half-chair conformers is found by CD for steroid 4–9-dien-3-ones and 4, 9, 11-trien-3-ones. CD of 4-en-3-ones is consistent with a similar equilibrium involving quasi-*cis* and quasi-*trans* ring junction conformers; however, no firm conclusions could be reached for the 2, 2-dimethyl-4-en-3-ones in the 10β-Me series. In special cases, very strong solvent effects have been found and these deserve further study. Literature and present PMR data (coupling and ASIS) may also be explained in terms of a dynamic equilibrium.

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## EXPERIMENTAL

CD, UV, IR and PMR measurements were performed on Roussel Jouan Dichrograph II or SA Instruments Dichrograph Mark III, Cary 14 or 15 UV spectrometers, Grubb and Parsons IR Spectromaster, Varian A60A or Bruker WH90 NMR spectrometers. For low-temperature CD measurements, a Roussel Jouan attachment was used.

Unless otherwise stated, CD and UV $\lambda_{max}^{nm}$ (ε or Δε are in 95% ethanol. IR frequencies in $cm^{-1}$ for $CHCl_3$ solutions, PMR chemical shifts δ in ppm with respect to internal TMS and coupling constants J in hertz for $CDCl_3$ solns. s, d, m refer to singlet, doublet, multiplet. EPA refers to a 5-5-2 v/v mixture of ether, isopentane and absolute ethanol and MI to a 1-3 v/v mixture of methylcyclohexane and isopentane.

Volumes were corrected for solvent contraction according to ref. 25.

$\int \Delta\varepsilon_{\lambda}^{\Delta\lambda}$ was computed by measuring Δε at 2.5 nm intervals.

Following compounds have been described previously: **3**[26], **3a**, **3b**[16], **4a**, **4b**[15], **4c**[27], **5a**, **5b**[16], **6**[28], **7a**, **7b**[16], **8**, **8a**, **8b**[15], **8c**[27], **9**[29], **10**[30], **14a**, **14b**[16], **15a**[31], **15b**[32], **17**[33], **17a**[32], **17b**, **17c**[27], **18**[34], **18c**[35], **20a**[36], **21a**, **21b**[37], **22a**[38], **23**[39], **25**[40], **26**[41], **27**[42] 19-nortestosterone **14** and testosterone **16** are trivial compounds.

1-*Methyl*-3-*oxo*-17β-*acetoxy*-2-*oxa*-*estra*-4, 9, 11-*trienes* (**10a**, **10b**) were obtained through the general route described for **10**.[30] The 17 benzoate of **29** (R = –CH = O; Z = $C_6H_5$—CO—) was first reacted at –70° with Me Mg Br to yield a mixture of alcohols (**29** R = –CHOH-Me Z = $C_6H_5$CO—) which could be separated as dinitrobenzoates. After saponification of the dinitrobenzoate, the configuration of the alcohols was determined by CD of the nitrites and Horeau's method of partial resolution.[43] Reformatsky reaction and lactonisation[30] followed by saponification of the 17-benzoate and acetylation yielded the two lactones.

Compound **10a** F = 166° $\alpha_D$ = +416° (0.5%, $CHCl_3$); IR: 1718–1730, 1694 (C = O)1597, 1560 (C = C); UV: 228 (6.300) 327 (29.200); CD: 225 (–46) 325 (+16); PMR: 0.95 (s. 18 $CH_3$) 1.45 (d, J = 7, 1 $CH_3$) 2.08 (s. $CH_3$ C = O) 4.8 (m, $H_{17}$) 5.6 (m, $H_4$, $H_{11}$) 6.13, 6.50 (d, J = 10, $H_{11}$, $H_{12}$).

Compound **10b**: F = 163° $\alpha_D$ = –546° (0.54%, $CHCl_3$); IR: 1740 sh, 1722, 1707, 1690–1682 (C = O) 1598, 1563 (C = C); UV: 229 (6.500) 323 (27.800); CD: 222 (+45) 320 (–20.4); PMR: 0.94 (s, 18 $CH_3$) 1.47 (d, J = 7, 1 $CH_3$) 2.08 (s, $CH_3$ C = O) 4.8 (m, $H_{17}$) 5.6 (m, $H_4$, $H_{11}$) 6.13, 6.42 (d, J = 10, $H_{11}$, $H_{12}$).

2β-*Methyltestosterone* **16b** was obtained by kinetic methylation[27] of 17-tetrahydropyranyltestosterone followed by hydrolysis of the tetrahydropyranyl ether.

Compound **16b**: F = 140° $\alpha_D$ = –85° (0.55%, $CHCl_3$); IR: 3610 (OH) 1670 (C = O) 1627 (C = C); PMR: 0.79 (s: 18 $CH_3$) 1.11 (d: J = 7, 2 $CH_3$); 1.17 (s: 19 $CH_3$) 3.7 (m, $H_{17}$) 5.77 ($H_4$).

17β-*Acetates of* 2β-*methyl testosterone and* 19-*nortestosterone* (**20b**, **19b**) were obtained by the standard acetylation procedure from the corresponding alcohols.

Compound **19b**: F = 125° $\alpha_D$ = –34° (0.8%, $CHCl_3$); IR: 1730 (acetate) 1666, 1633, 1626 (conjugated ketone); UV, CD, PMR (see text).

Compound **20b**: F = 180° $\alpha_D$ = –85° (0.5%, $CHCl_3$); IR: 1730 (acetate) 1670, 1626 (conjugated ketone); UV: 243 (15.800); CD: 242 (–27) 320 (+1.45); PMR: see text.

2-*Methylcholestenones* (**24a**, **24b**). Methylation of cholestenone as suggested[44, 45] led to a compound F = 110° $\alpha_D$ = +29° (2% $CHCl_3$) [F = 110–111° $\alpha_D$ = +33.7 $CHCl_3$[44]] which was not actually a pure 2β-methylcholestenone and could be resolved by HPLC (silica, isopropyl ether-essence B 1/7, v/v) into the pure $2\alpha$ − methyl and $2\beta$-methylcholestenones:

Compound **24a**: F = 124° $\alpha_D$ = +88°5 (2%, $CHCl_3$); IR: 1668, 1626 (4-en-3-one) 884 (= CH); UV, CD: see text; PMR: 0.72 (s: 18 $CH_3$) 1.22 (s: 19 $CH_3$) 1.12 (d: J = 7, 2 $CH_3$) 5.72 ($H_4$).

Compound **24b**: F = 90° then 112° $\alpha_D$ = −73° (2%, $CHCl_3$); IR: 1668, 1626 (4-en-3-one) 877 (= CH); UV, CD: see text; PMR: 0.71 (s: 18 $CH_3$) 1.15 (s: 19 $CH_3$) 1.10 (d: J = 7, 2 $CH_3$) 5.72 ($H_4$).

*17β − Methoxy 2, 2-dimethylestra 4-en-3-one.* **28c** was obtained through kinetic methylation[27] of 19 nortestosterone.

Compound **28c**: F = 83–84°; IR: 1650, 1612 (4-en-3-one); UV: 240 (15.600); PMR: 0.82 (s: 18 $CH_3$) 1.07, 1.10 (s: 2 $CH_3$); 3.3 (m.$H_{17}$) 3.37 (s: $OCH_3$) 5.75 ($H_4$).

*ASIS*:

Chemical shifts in $CDCl_3$ followed by ($\delta_{C_6D_6} - \delta_{CDCl_3}$).

For **4a**, **4b**, **8a**, $C_6H_6$ was used instead of $C_6D_6$ and ASIS could not be determined for $H_4$. Assignments for **4c** and **17c** were checked by progressive change in solvent composition. Assignment for the 2-methyls in **18c** are somewhat uncertain: alternative assignment: 1.12 + 0.00, 1.18 + 0.06.

*2-Methyls and $H_4$*: **3**: 5.67 + 0.15; **4a**: 1.10 + 0.01, 5.63; **4b**: 1.13 + 0.08, 5.63; **4c**: 1.07 + 0.02, 1.11 + 0.12, 5.53 + 0.20; **8**: 5.78 + 0.11; **8a**: 1.14 ± 0.00, 5.75; **8b**: 1.13 ± 0.00, 5.75 + 0.14; **8c**: 1.08 + 0.05, 1.08 + 0.05, 5.65 + 0.13; **14**: 5.81 + 0.07; **17a**: 1.10 + 0.12, 5.80 + 0.10; **17c**: 1.05–0.07, 1.09 + 0.15, 5.68 + 0.12; **18**: 5.76 + 0.09; **18c**: 1.18 − 0.06, 1.12 + 0.12, 5.67 + 0.13; **19b**: 1.11 − 0.01, 5.78 + 0.10; **20a**: 1.22 + 0.07, 5.75 + 0.10; **20b**: 1.12 + 0.06, 5.67 + 0.13.

*19-Methyl*: **18**: 1.22 − 0.42; **18c**: 1.31 − 0.34; **20a**: 1.23 − 0.42; **20b**: 1.17 − 0.38.

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