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CIRCULAR DICHROISM OF C-6 SUBSTITUTED Δ^4-3-KETOSTEROIDS

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In α,β-unsaturated ketones, the signs of the Cotton effects associated with n-π* and long-wavelength π-π* transition are known to reflect the chirality of the C=C-C=O chromophore (1-4). In our previous paper dealing with a proton magnetic resonance (PMR) study of C-6 substituted Δ^4-3-ketosteroids (5), we also described that the sign of the n-π* Cotton effects in the compounds examined depends upon the bulkiness of 6β-substituents. However, when the angle of skew is small in the α,β-unsaturated carbonyl chromophore, the chirality contribution may partially or completely be offset by electronic interaction of the type observed in asymmetrically perturbed, intrinsically symmetric chromophores. In the course of further studies of the optical rotatory dispersion (ORD) and circular dichroism (CD) spectra of C-6 substituted Δ^4-3-ketosteroids, we have found that hetero atoms substituted on C-6β affect not only the n-π* but also the π-π* Cotton effects. Here, we report that electronic interaction of substitutents is an important factor determining the signs and amplitudes of the Cotton effects in α,β-unsaturated ketones.

In the TABLE are listed the data on CD maxima associated with the n-π* and the π-π* transitions of several compounds examined, together with the UV data on the π-π* absorption band. Legrand, et al. (6, 7) have recently reported that two CD bands near 220 and 240 mμ were observed with amplitudes depending on the structure of α,β-unsaturated ketones. Although the origin of the two bands is not defined, in C-6 substituted Δ^4-3-ketosteroids the 240 mμ band is very sensitive to the 6β-substituents, whereas the sign of the 210 mμ band remains unchanged, as seen from the TABLE. Further, 6α-substituted derivatives exhibit the ORD and CD curves similar to those of their parent compounds in the region above 210 mμ, whereas 6β-substituted derivatives show the curves with substantially different features. In 6β-bromotestosterone acetate (III) and 6β-chlorocholest-4-en-3-one (V), the signs and magnitudes of the n-π* and the π-π* Cotton effects appear to be correlated only with the chirality of the C=C-C=O

TABLE
CD and UV Data on Δ^4-3-Ketosteroids[a]

Compound	Solvent	CD maxima n-π* λ(mμ)	CD maxima n-π* [θ]	CD maxima π-π* λ(mμ)	CD maxima π-π* [θ]	CD maxima π-π* λ(mμ)	CD maxima π-π* [θ]	UV maxima λ(mμ)	UV maxima ε
Testosterone acetate (I)	D	331	-3810	236^{sh}	+28900	215	+31600!	236	14100
6α-Bromotestosterone acetate (II)	D	335	-3540	225^{inf}	+39500	215	+46200!	232	13500
6β-Bromotestosterone acetate (III)	D	351	+7110	253	-59700	220	+31200!	243	15400
6β-Bromo-19-nor-testosterone acetate(IV)	D	341	+2640	246	-34500	215	+8800!	241	12500
6β-Chlorocholest-4-en-3-one (V)	D	351	+2450	245	-36300			239	15000
Cholest-4-en-3-one (VI)	M	315	-4690	235^{sh}	+25700	218	+31000	240	16000
6β,17α-Dimethyltestosterone (VII)	M	335	+2130	252	-14800	220	+21800	236	16700
6α-Acetoxycholest-4-en-3-one (VIII)	M	319	-4830	230^{sh}	+12300	205	+18000	240	15400
6β-Acetoxycholest-4-en-3-one (IX)	M	326	-4300	246	-9600	213	+44300	234	14000
6β,11β,21-Trihydroxy-pregn-4-ene-3,20-dione (X)	M	327	-1820	252	-13200	225	+48400	235	13100
6β-Hydroxy-19-nor-testosterone (XI)	M	323	-4850	242	-17000	210	+15400	236	14400
6β-Acetoxy-19-nor-testosterone (XII)	M	326	-5760	242	-11500	210	+28800	235	14300
6β,19-Epoxyandrost-4-ene-3,17-dione (XIII)	M	330	-5240	236	-51000	-	-	236	13000
10β-Hydroxy-19-nor-testosterone (XIV)	M	321	-5460	235^{inf}	+22300	210	+18100	235	13300
19-Nortestosterone (XV)	M	317	-6090	231-225	+26000			239	15600

[a] The CD and UV spectra were recorded on a JASCO ORD UV-5 spectropolarimeter.
D: dioxane; M: methanol; sh: shoulder; inf: inflexion; ! : last reading.

chromophore. However, the inversion of the Cotton effects of 6β-bromo-19-nortestosterone acetate (IV) can be ascribed to electronic interaction between the bromine atom and the Δ^4-3-keto chromophore because the PMR spectrum of IV has provided evidence for the presence of no distortion in its B-ring, as described in the preceding paper (8). Therefore, the increase in molecular ellipticity associated with the n-π* and the π-π* transitions from the 19-nor IV to the 19-methyl compound III would be attributed to the change in the chirality of the C=C-C=O system arising from the 1,3-diaxial interaction between the 10-methyl group and the 6β-bromine atom. On the assumption that the radius of a 6β-substituent is a sole factor governing distortion of the C=C-C=O system, the larger increment in molecular ellipticity from cholest-4-en-3-one (VI) to 6β,17α-dimethyltestosterone (VII) ($\Delta[\theta]_{n\rightarrow\pi^*}$ = +6820 and $\Delta[\theta]_{\pi\rightarrow\pi^*}$ = -40500) than that from IV to III ($\Delta[\theta]_{n\rightarrow\pi^*}$ = +4470 and $\Delta[\theta]_{\pi\rightarrow\pi^*}$ = -25200) can not be explained, because the skew angles of the C=C-C=O groupings in VII and III are considered to be almost the same. (The van der Waals radii of a methyl group and a bromine atom are 2.0 and 1.95 Å, respectively (9)). Therefore, the rotatory contribution of the 6β-methyl group, though much smaller than that of bromine, should be taken into account.

An introduction of a 6β-hydroxy- or a 6β-acetoxy group into both a Δ^4-3-ketosteroid and its 19-nor compound has virtually no effect on the CD curve in the R-band region but gives rise to a negative CD maximum at about 250 mμ, which may be associated with its K-band. Since the conformation of the C=C-C=O chromophore is not significantly different from that of their parent testosterone as supported by the preceding PMR study (8), this negative CD band associated with the K-band is probably attributed to electronic interaction between the oxygen atom in the 6β-substituent and the Δ^4-3-keto electrons. A similar situation occurs in 6β,19-epoxyandrost-4-ene-3,17-dione (XIII), which exhibits a negative CD maximum at 330 mμ (n-π* of Δ^4-3-ketone), a positive maximum at 294 mμ (17-ketone), and a very large negative maximum at 236 mμ corresponding to the K-band. Examination of Dreiding models indicates that the C=C-C=O grouping can not have a planar conformation. If the sign of the Cotton effect of the K-band would permit to determine a correct conformation, XIII should have a helicity of the C=C-C=O system opposite to that of testosterone. However, no adequate explanation for the negative sign of the n→π* Cotton effect of XIII seems possible. The electronic interaction of the lone-pair on oxygen is believed to contribute strongly to the rotatory power of the K-band; and therefore, the helicity of the C=C-C=O system in XIII is believed to be the same as that in testosterone. It is highly plausible that the helicity rule for α,β-unsaturated ketones becomes invalidated by the presence of a hetero atom homoconjugated with the C=C-C=O grouping such as in the present case, in view of the fact that the helicity rule for cisoid-dienes (10) is inapplicable in the case of Erythrina alkaloids (11, 12).

Finally, of considerable interest is the fact that 10β-hydroxy-19-nortestosterone (XIV) exhibits the

CD curve similar to that of 19-nortestosterone (XV). Moreover, the fact that 10β-chloro-19-nortestosterone shows a normal negative n-π* Cotton effect (13) demonstrates that the influence of such electronic interaction on the Cotton effect, as observed in 6β-bromo compounds, will be identified with the spatial direction in which an atom is located relative to the C=C-C=O chromophore by a reasoning analogous to the octant rule (14).

In conclusion, the sensitivity of the Cotton effects of α,β-unsaturated ketones to very subtle interaction strongly suggests that much caution should be exercised when correlating the Cotton effects of such substances with their structure.

We dedicate this paper to Dr. Ken'ichi Takeda, Director of this laboratory and Honorary Editorial Adviser of this Journal, in celebration of the 60th anniversary of his birth.

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