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CIRCULAR DICHROISM SPECTRA OF 5- AND 7-BROMO-6-KETOSTEROIDS

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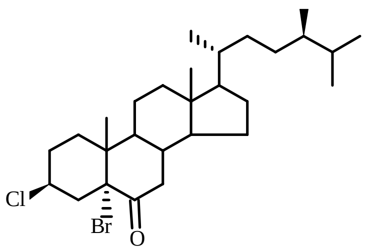
Circular dichroism spectra of 5α- and 7α-bromo-6-ketosteroids of the cholestane and stigmastane series were studied. A negative Cotton effect corresponding to the n—π-transition of the ketone was observed in the CD spectra of 5α-bromo-6-ketosteroids at 300 nm. The analogous Cotton effect was positive in CD spectra of 7α-bromo-6-ketosteroids.*

Key words: ecdysteroids, 5α- and 7α-bromo-6-ketosteroids, circular dichroism.

Steroidal 5α- and 7α-bromo-6-ketones are widely used as important intermediates in the chemical synthesis of ecdysteroid insect hormones and their structural analogs [1-3]. We synthesized previously a series of new compounds of this group from the corresponding α-bromo-6-ketosteroids [4-11]. It should also be noted that certain α-bromo-6-ketosteroids are interesting as biologically active compounds. In particular, rather active insect growth and development regulators are found among them [12, 13].



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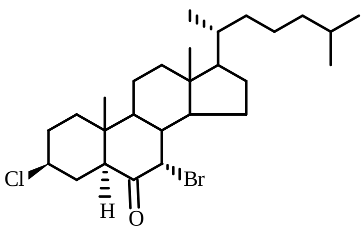
b: R = Et



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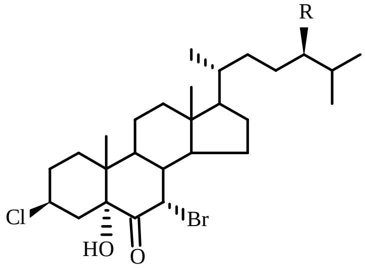

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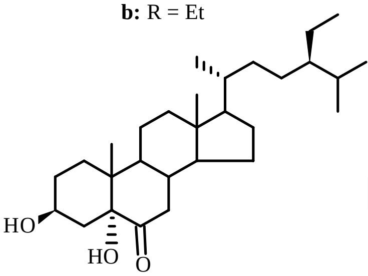

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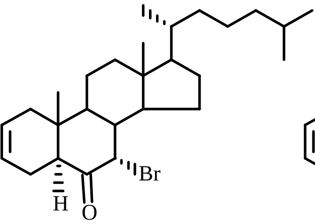

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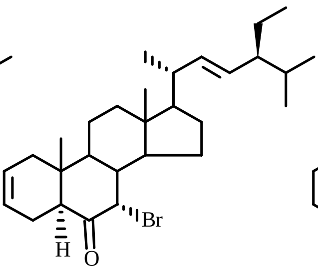

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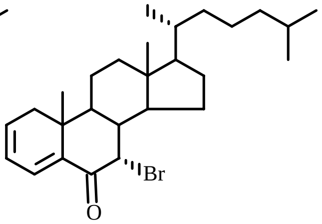

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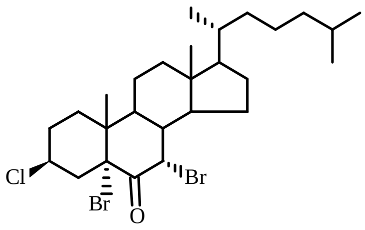

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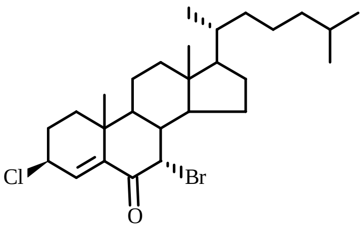

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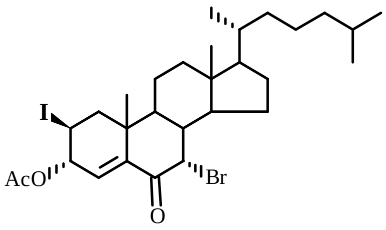

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TABLE 1. Band Parameters in UV and CD Spectra of 6-Ketosteroids **1-10**

Compound	UV spectrum		CD spectrum	
	λ, nm	ε, L/mol·cm	λ, nm	Sign and $[\theta]\cdot 10^4$, deg·cm^2/mol
1a	200-260*	-	200-260*	+
	307	130	306	-16.5
1b	200-260*	-	200-260*	+
	305	120	305	-17.0
2	200-250*	-	200-215*	+
	308	190	227	-1.5
			307	+12.5
3a	200-270*	-	200-250*	-
	335	100	332	+7.0
3b	200-270*	-	200-250*	-
	335	90	332	+7.5
4	200-230*	-	200-250*	+
	300	550	300	-11.8
5	200-250*	-	200-240*	+
	306	130	305	+3.0
6	200-250*	-	200-240*	+
	300	160	305	+3.0
7	236	7700	230	+32.0
	320	3500	312	+28.0
			362	-23.0
8	200-280*		200-250*	+
	335	110	335	-10.0
9			200-220*	+
			232	-9.0
	252	6800	260	+16.0
	339	180	328	+6.0
10	242	5500	225	+13.0
	330	140	338	-3.5

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*Band shoulder.

Owing to the great significance of 5- and 7-bromo-6-ketosteroids in ecdysteroid chemistry, we investigated specially the development of methods for establishing their structures, for example, using ^{13}C NMR spectra [14]. In the present article, we report results of a study of the CD spectra of previously synthesized α-bromo-6-ketosteroids of the cholestane and stigmastane series in order to elucidate the effect of the Br atom on the structurally dependent Cotton effect of the n—π^*-transition of the 6-ketone.

The presence in the steroids of axial Br atoms, which are in the α-position relative to the ketone, leads to characteristic changes in the CD spectra [15]. This provided hope that our investigations would develop a simple and reliable method for proving the structures of 5α- or 7α-bromo-6-ketosteroids. Table 1 presents data for the circular dichroism measurements of **1-10** and their UV spectra. Figure 1a illustrates CD spectra for certain representatives of the studied steroids with saturated and conjugated 6-ketones with a Br atom in the α-position.

The ketone in **1-6** and **8** is saturated. Therefore, it is noteworthy that the CD spectra of saturated *trans*-A/B-6-ketosteroids investigated by us previously [16], which have no substituents on C-5 or C-7, exhibit a Cotton effect near 292 nm that corresponds with the n—π^*-transition of the ketone. The negative sign of the Cotton effect is explained according to the well-known octant rule [17, 18] by the location of most of the molecule in the negative rear right upper octant. The strength of the Cotton effect depends little on the type of 3β-substituent. In particular, the molecular ellipticity of the band at 292 nm for (24*R*)-3β-hydroxy-5α-stigmastan-6-one was $-6.2\cdot10^3$ deg·cm^2/mol. However, the presence of an additional hydroxyl on the C$_5$-chiral center adjacent to the ketone in 3β,5α-dihydroxy-6-ketosteroid **4** increases by almost 20 times the strength of the

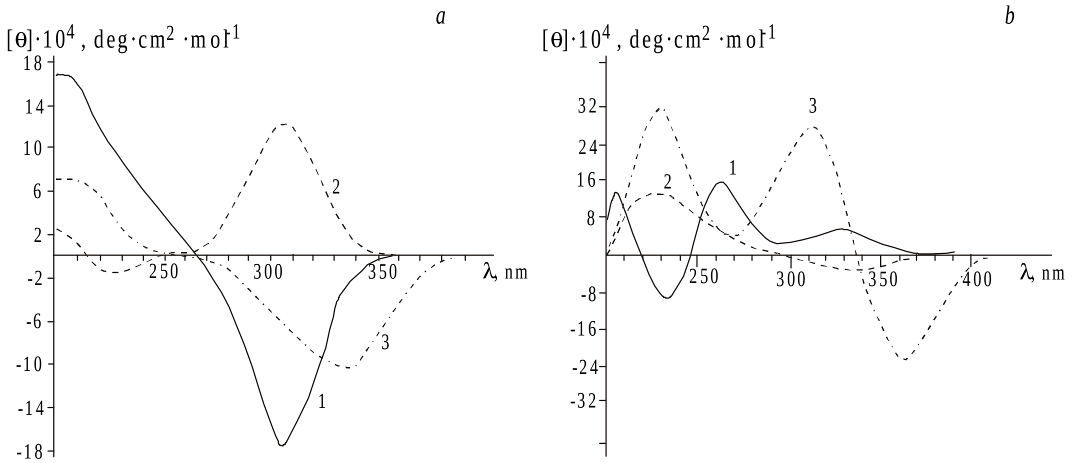

Fig. 1. CD spectra of α-bromo-6-ketosteroids **1a** (1), **2** (2), and **8** (3) (a) and CD of 7α-bromo-Δ^4-6-ketosteroids **9** (1), **10** (2), and **7** (3) (b).

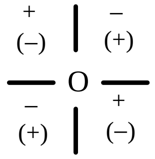

Fig. 2. Signs of rear octants in direct and inverse (in parentheses) rules.

Cotton effect and produces a long-wavelength shift of the n—π^*-transition of the ketone, which is characteristic of electronegative substituents (Table 1). The large increase in the strength of the Cotton effect in 5α-hydroxy-6-ketones is due to asymmetrical excitation of the ketone by the adjacent axial hydroxyl. Application of the octant rule to the carbonyl of steroidal ketone **4** indicates that the 5α-OH is located in the lower left octant (here and hereinafter, the rear octants are considered) and makes a negative contribution to the Cotton effect (Fig. 2). Replacing the 5α-OH by Br, as in 5α-bromo-6-ketosteroids **1a-b**, produces a further long-wavelength shift of the CD band and substantially increases its molecular ellipticity.

Analogously to the 5α-bromo substituent, an axial Br on the second C atom adjacent to the ketone, C-7, has a strong asymmetric effect on the ketone chromophore. Substituting the H by Br creates a chiral center. In fact, the 7α-bromo substituent in **2**, which falls in the lower right octant, makes a strong positive contribution according to the octant rule and reverses the sign of the Cotton effect for the n—π^*-transition (Fig. 1a).

We analyzed the CD spectra of steroidal derivatives **3a** and **b** and **8** with substituted C-5 and C-7 in order to evaluate the efficiency of axial substituents on adjacent C atoms to excite the ketone. A rather strong negative Cotton effect at the highest wavelength of 335 nm is observed in the spectrum of **8** although it is weaker than those in the spectra of **1a** and **b** (Fig. 1a, No. 3). This provides evidence that an angular Br on C-5 has a stronger influence on the ketone when two axial Br atoms are present simultaneously. However, the rather strong positive Cotton effect near 330 nm in the spectra of **3a** and **b** (Table 1) is consistent with more effective excitation of the ketone by the axial Br on C-7 than by the angular axial 5α-OH. In our opinion, this is due to the larger effective volume of the Br atom compared with O.

In examining the sensitivity of the Cotton effect for the n—π^*-transition of the 6-ketone chromophore to its nearest environment, the influence on it of the more distant environment should also be noted. This can be seen by comparing the strengths of the Cotton effect in spectra of **2** and Δ^2-7α-bromo-6-ketosteroid derivatives **5** and **6**. Dreiding molecular models show that the presence of a C=C bond in ring A in **5** and **6** and the change of geometry associated with it moves C-3 and C-4 from the positive upper left octant to the negative lower left one. The stereochemical features of compounds without a 3β-chloro substituent, which occupies the forward positive lower left octant, cause a large decrease in the strength of the positive Cotton effect of the 6-ketone in their CD spectra compared with the spectrum of **2** (Table 1).

Thus, Cotton effects corresponding to the n—π^*-transition in CD spectra of 5α- and 7α-bromo-6-ketosteroids have different signs. The CD spectra can be used rather simply and reliably to establish the site of the Br in these α-bromo-6-ketosteroids.

The UV absorption spectra of steroids with a saturated 6-ketone show the shoulder of a band in the short-wavelength region with a maximum below 200 nm (Table 1) that is due to π—π^*- and n—$\pi\sigma^*$-transitions of the ketone in addition to a very weak long-wavelength band for the n—π^*-transition. The CD spectra in the short-wavelength region also show the shoulder of a band with a sign opposite to that of the band for the n—π^*-transition of the ketone. The only exception is the CD spectrum of 7α-bromo-6-ketosteroid **2** (Fig. 1, No. 2). The weak negative band at 227 nm in it is apparently due to mutual overlap of two bands of opposite signs.

As expected, the conjugated ketosteroids **7**, **9**, and **10** that we studied differ from those examined above with saturated ketones by a large long-wavelength shift of the π—π^*-transition of the ketone both in the UV absorption spectra and the CD spectra. On the other hand, the band for the n—π^*-transition undergoes a less dramatic shift. Conjugation of the 6-ketone to one double bond has practically no effect on the strength of the n—π^*-transition whereas conjugation of it to two double bonds increases its strength by an order of magnitude. This feature of conjugated ketosteroid **7** is clearly visible in the CD spectrum, in which a large increase in the strength of the Cotton effect of the n—π^*-transition makes it comparable in strength with the Cotton effect of the π—π^*-transition (Fig. 1b, No. 3).

Table 1 and Fig. 1b show that the CD spectra of 7α-bromo-Δ^4-6-ketosteroids are highly characteristic for each individual compound. However, the signs of the Cotton effects cannot be predicted using the octant rule. In our opinion, this is explained by the conformational flexibility of ring A in the examined molecules since this ring can exist in two different half-chair conformations depending on the type and stereochemistry of the substituents on C-2 and C-3. The inverse octant rule for the n—π^*-transition that is usually used for stereochemical assignments in series of *trans*-α,β-unsaturated ketones [17, 18] (Fig. 2) is apparently not obeyed by the examined *cis*-enones **9** and **10**. Keeping in mind the negative long-wavelength Cotton effect in the CD spectrum of the *cis*-Δ^4-6-ketosteroid [18], the sign of the n—π^*-transition in the spectrum of **10** agrees with this empirical rule. However, the inversion of the signs of the Cotton effects of both electronic transitions in the spectrum of **9** is not likely due to the effect of the 3β-chloro substituent. The splitting of the n—π^*-transition into two bands of opposite signs at 312 and 362 nm in the spectrum of dienone **7** is also interesting (Fig. 1b). Nevertheless, the CD spectra can also be used to prove the structures of 7α-bromo-Δ^4-6-ketosteroids owing to their uniqueness. For example, analogous compounds of known structure can be compared.

EXPERIMENTAL

Syntheses of 1-3 and 5-10 were previously reported [4-11].

Circular dichroism spectra of **1-10** were recorded on a J-20 spectropolarimeter (Japan) in ethanol at concentrations of $4\cdot10^{-4}$-$1\cdot10^{-3}$ M in quartz cuvettes with 0.2- and 0.5-cm pathlengths. The instrument sensitivity was 0.005°/cm; time constant, 4; scan rate depending on spectral region, 0.5 and 1.0 nm/min. Molecular ellipticity was determined with a relative uncertainty <20%. UV absorption spectra were measured on a Specord M-400 spectrophotometer (Germany) at the same concentrations in quartz cuvettes with 0.2- and 1-cm pathlengths.

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