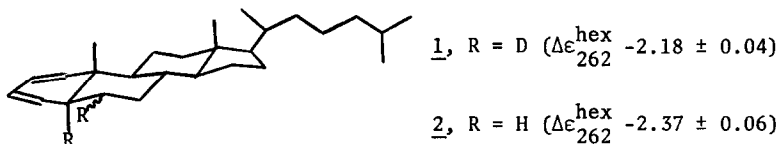


CIRCULAR DICHROISM OF 5 $\alpha$ -DEUTERIOCHOLESTA-1,3-DIENE

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*Summary:* Replacement of the 5 $\alpha$ -hydrogen by deuterium in 5 $\alpha$ -cholesta-1,3-diene decreased the  $\Delta\epsilon$  at 262 nm (in hexane) from  $-2.37 \pm 0.06$  to  $-2.18 \pm 0.04$ .

When an allylic axial alkyl (methyl) group in a chiral homoannular conjugated diene is replaced by hydrogen, the lowest-energy Cotton effect undergoes significant reduction in intensity or even reversal in sign.<sup>1</sup> To gain a better understanding of this change, we have prepared the 5 $\alpha$ -deuterio steroidal 1,3-diene 1 for comparison of its circular dichroism (CD) with that of the parent 5 $\alpha$ -hydrogen compound 2. Recent chiroptical studies of deuteriated cyclohexanones<sup>2</sup> suggest that substitution of deuterium for the allylic hydrogen in 2 should be detectable in the CD.



Bromination and dehydrobromination<sup>3</sup> of 5 $\alpha$ -deuteriocholestan-3-one<sup>4</sup> (prepared from cholesteryl acetate and reported<sup>4</sup> to contain 0.9 D at C-5, 1.25 D at C-6, and 0.4 D at C-7, but here referred to simply as the 5 $\alpha$ -deuterio derivative), mp 129-130°, furnished 5 $\alpha$ -deuteriocholest-1-en-3-one, which after separation from traces of cholest-4-en-3-one<sup>5</sup> by HPLC (EM Silica 60; gradient elution with CH<sub>2</sub>Cl<sub>2</sub>-EtOAc) had mp 99.5-100.5° (lit.<sup>3</sup> mp 99-101°). Treatment of the tosylhydrazone of the purified 1-en-3-one with MeLi (2.7 eq) in THF<sup>6</sup> at -78° (1 hr) and then at 25° (5 hr), followed by quenching with water, gave the desired 5 $\alpha$ -deuteriocholesta-1,3-diene (1). Chromatography on activated 25% silver nitrate-impregnated neutral alumina (elution with 3:2 ether-hexane) afforded pure 1 in 51% yield from the enone; mp 59.7-60.5°;  $[\alpha]_D$  (CHCl<sub>3</sub>) +74.2° (c 0.0104);  $\lambda_{\text{max}}$  (hexane) 262 nm ( $\epsilon$  3722); ms (18 e.v.) 2.64 D (from weighted average of M<sup>+</sup> peak intensities; cf. 2.55 D reported<sup>4</sup> for the starting 5 $\alpha$ -deuteriocholestan-3-one).

The same sequence from 5 $\alpha$ -cholestan-3-one gave pure 5 $\alpha$ -cholesta-1,3-diene (2) in comparable yield, mp 59.8-61.0°;  $[\alpha]_D$  (CHCl<sub>3</sub>) +72.8° (c 0.0110);  $\lambda_{\text{max}}$  (hexane) 262 nm ( $\epsilon$  3762); ms (M<sup>+</sup>) 368 (lit.<sup>6</sup> mp 64°;  $[\alpha]_D$  +75°;  $\lambda_{\text{max}}$  (EtOH) 262 nm ( $\epsilon$  5930)<sup>7</sup>).

The CD curves of dienes 1 and 2 are almost identical with the published curve of 5 $\alpha$ -androsta-1,3-dien-17 $\beta$ -ol.<sup>1</sup> In each case the negative  $\Delta\epsilon$  value shown by the formula above represents the mean of six determinations, three of which were measured independently by

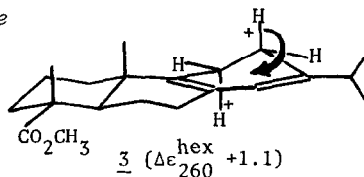
another laboratory.<sup>8</sup> The  $\Delta\epsilon$  of 1 is ca. 9% weaker than that of 2 ( $-2.37/-2.18 = 1.087$ ).<sup>9</sup> In this system, therefore, deuterium is dissignate compared with hydrogen, i.e. it makes a smaller allylic axial chirality contribution than hydrogen, in accord with the shorter effective C-D bond length.<sup>10</sup>

On the basis of these results, the positive 260-nm Cotton effect of 5 $\alpha$ -estra-1,3-dien-17 $\beta$ -ol ( $\Delta\epsilon +3.8$ ),<sup>1</sup> with essentially the same M(-) allylic axial and diene chirality as in 1 and 2, can be attributed to overriding positive allylic chirality contributions of the equatorial alkyl substituents at C-5 and C-10.<sup>11</sup> Accordingly, the 5 $\alpha$ ,10 $\beta$ -dideuterio derivative of the estradiene would be expected to exhibit an even stronger positive Cotton effect. Work is in progress to test this prediction.

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7. This higher  $\epsilon$  value reported for this diene suggests the possible presence of 2,4-cholestadiene; cf. UV data for steroidal 1,3-dienes in ref. 1 above.
8. We thank Prof. D. A. Lightner and Dr. J. K. Gawroński, The University of Nevada, Reno, for these measurements.
9. No adjustment is included for the isotopic composition or the influence of deuterium at C-6 and C-7. From the mass spectrum, 1 contains less than 7% of 2.
10. R. F. R. Dezentje and H. P. J. M. Dekkers, *Chem. Phys.*, **18**, 189 (1976); cf. S. F. Lee, G. Barth, and C. Djerassi, *J. Am. Chem. Soc.*, **100**, 8010 (1978). The lower atomic refractivity and slightly greater electronegativity of deuterium may also be involved (cf. ref. 2 above).
11. This interpretation is supported by the *positive* CD of methyl palustrate (3), with P(+) allylic axial chirality (cf. ref. 1 above), in which only hydrogens are attached to the homoannular allylic carbons. For further discussion, see J. S. Rosenfield, and E. Charney, *J. Am. Chem. Soc.*, **99**, 3209 (1977).



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