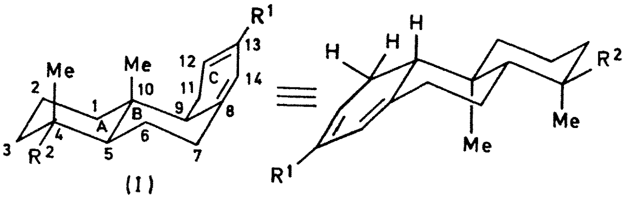
Comparative Cotton Effects of Steroidal 2,4-Dienes and Related Trienes: Origin of the Folded Conformation in Levopimaric Acid

By ALBERT W. BURGSTAHLER,* JACEK GAWRONSKI, THEODORE F. NIEMANN, and BENJAMIN A. FEINBERG
(*Department of Chemistry, The University of Kansas, Lawrence, Kansas* 66044)

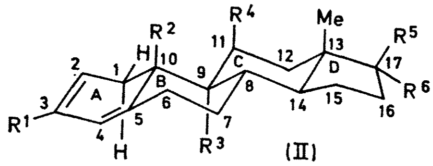
Summary The decreased intensity of the positive Cotton effects of a 9α-methyl- and a 19-nor-steroidal 2,4-diene compared to those of other steroidal 2,4-dienes suggests that the peculiar B/C folded conformation in levopimaric acid (negative Cotton effect) is caused by relief of a 1,3-diaxial repulsion between the C-10 angular methyl group and the 11β-hydrogen, probably enhanced by C-4 methyl buttressing, which the resulting eclipsing of the 9α- and 11α-hydrogens is not sufficient to override.

IT has been shown through o.r.d.,[1] n.m.r.,[1,2] and surface-film[3] measurements, as well as through its photochemical behaviour,[4] that levopimaric acid (Ia) exists in a peculiar B/C folded conformation with a nearly planar diene ring. The configurationally related cholesta-2,4-diene (IIa), on the other hand, prefers an extended conformation having a somewhat puckered or skewed diene moiety.[1,4]

To account for the folded conformation in (Ia), an attraction of some kind between the C-10 angular methyl group and the face of the diene system has been suggested.[1] An alternative explanation (first suggested to one of us by Professor R. B. Woodward) lies in relief of the 1,3-diaxial repulsion between the C-10 angular methyl group and the 11β-hydrogen that would be present in the extended, steroid-like conformation. On either basis, a 9α-methyl-steroidal 2,4-diene such as (IIc) might be expected to adopt an A/B folded conformation and hence exhibit spectral properties similar to those of (Ia).



(I)



(II)

TABLE 1

C.d. and u.v. maxima of levopimaric acid and steroidal 2,4-dienes[a]

Compound	R^1	R^2	R^3	R^4	R^5	R^6	λ, nm	Δε	ε
(Ia)	Pr^i	CO_2H	—	—	—	—	273	−12·2	6080
(Ib)	Pr^i	CO_2Me	—	—	—	—	273	−11·3	5900
(Ic)[b]	H	CMe_2OH	—	—	—	—	273	−10·9	6350
(IIa)	H	Me	H	H	C_8H_{17}	H	266	+12·4	6400
(IIb)[c]	Me	Me	H	H	C_8H_{17}	H	268	+11·1	6050
(IIc)	H	Me	Me	OH	BMD[d]		267	+ 3·9	6350
(IId)	H	Me	H	OH	BMD[d]		265	+ 9·4	6350
(IIe)	H	H	H	H	OH	H	265[e]	+ 2·1	4900
(IIf)[f]	H	Me	H	H	OH	H	265	+11·7	6450
(IIg)[f]	H	Me	H	H	OH	Me	265	+11·2	6400
(IIh)	H	Me	H	OH	OH	Me	265	+ 9·5	6400
(IIi)	H	Me	9(11)-ene		OH	Me	267	+ 7·1	5670
(IIj)	H	Me	9β,11β-oxide		OH	Me	268[e]	+ 1·3	6000

[a] Determined at 25° in methanol except for compounds (IIa) and (IIb), which were run in cyclohexane. [b] Prepard by the action of an excess of MeLi (ref. 6) on the tosylhydrazone of the partial ozonolysis product of methyl neoabietate (G. C. Harris and T. F. Sanderson, *J. Amer. Chem. Soc.*, 1948, **70**, 339; A. W. Burgstahler and L. R. Worden, *ibid.*, 1964, **86**, 96). [c] Prepared by use of MeI in place of water in quenching the tosylhydrazone elimination reaction (ref. 6). [d] Bismethylenedioxy-derivative of the hydrocortisone side-chain. [e] $\Delta\epsilon_{max}$ *ca.* 260 nm. [f] For alternative synthesis, see B. Berkoz, A. D. Cross, M. E. Adame, H. Carpio, and A. Bowers, *J. Org. Chem.*, 1963, **28**, 1976.

Like the other steroidal 2,4-dienes listed in Table 1, the desired 9α-methyl-2,4-diene (IIc)[†] was synthesized from the corresponding 4-en-3-one[5] by the tosylhydrazone-elimination method.[6] Although considerably weaker than that of the prototype (IId), the positive Cotton effect of (IIc) shows that the additional angular methyl group is not, in itself, able to alter the A/B conformation from type (II) to type (I). The relatively small Δε exhibited by (IIc) and the still smaller one displayed by the 19-nor-diene (IIe) indicate that these two dienes tend to approach the type (I) conformation more than do most other 2,4-dienes. The C-10 methyl group in (IIc), however, evidently encounters too strong an eclipsing interaction with the 1β-hydrogen to permit (IIc) to revert to the type (I) conformation. In addition, the C-4 methyl in (I) probably has a buttressing effect, which is absent in (IIc), that enhances the repulsion between the C-10 methyl group and the 11β-hydrogen *in (I)*. Relief of other repulsive interactions in (IIi) and (IIj) apparently also results in conformational changes in ring A and hence weaker Cotton effects in these two dienes as well.

That the conformation of (Ia) and (Ib) is not dependent

[†] All new compounds reported herein have been fully characterized by appropriate analytical and spectral data.

on the isopropyl group is shown by the comparable negative $\Delta\epsilon$ of the de-isopropyl derivative (Ic). Likewise, 3-methylcholesta-2,4-diene (IIb) has a λ_{max} and a positive $\Delta\epsilon$ that are very close to those of the parent diene (IIa). The distinctive bathochromic effect in the u.v. spectra of compounds of type (I) thus appears to depend primarily on the increased planarity of the chromophore.

Since the cisoid diene chirality rule[1,7] predicts only a weak Cotton effect for a nearly planar diene system, we conclude that the substantial negative Cotton effect exhibited by compounds of type (I) is better accounted for by the recently suggested[8] allylic axial bond chirality treatment [here 7α(−), 9,10(−), 11α(−)]. As seen in Table 2, this approach also correctly predicts the signs of the Cotton effects of various related steroidal conjugated trienes.

TABLE 2

Allylic axial chirality[8] and observed c.d. maxima[a] of steroidal trienes

Compound	Chirality of allylic axial bonds	λ, nm	$\Delta\epsilon$
Cholesta-2,4,6-triene[b]	1α(+), 10β(+), 8β(+)	304	+4·2
3-Acetoxycholesta-3,5,7-triene[c]	2β(−), 10β(−), 9α(−), 14α(+)	315	−16·2
Cholesta-4,6,8(14)-triene[d]	3α(+), 10β(+), 9α(+), 13β(+), 15β(−)	281	+22·3
9(11)-Dehydroergosterol acetate	4β(+), 10β(−), 12α(+), 14α(+)	323	+6·9

[a] Determined at 25° in cyclohexane. [b] Prepared from cholesta-4,6-dien-3-one by the method of ref. 6. [c] Enol acetate of cholesta-4,6-dien-3-one; *cf.* I. M. Heilbron, T. Kennedy, F. S. Spring, and G. Swain, *J. Chem. Soc.*, 1938, 869. [d] Acid-catalysed dehydration product of cholesta-4,7-dien-3β-ol.

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