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OPTICAL ROTATORY DISPERSION STUDIES—XII[1]

ABSOLUTE CONFIGURATIONS OF EPERUIC AND LABDANOLIC ACIDS

CARL DJERASSI and D. MARSHALL
Dept. of Chemistry, Wayne State University, Detroit 2, Mich., U.S.A.

Abstract—A comparison of the rotatory dispersion curves of appropriate nor-ketones of the eperuic acid and labdanolic acid series with those of derivatives of onocerin and manool establishes the absolute configurations of these diterpene acids.

KING and Jones[2] have recently presented evidence that the diterpene eperuic acid possesses structure (Ia). No stereochemistry was assigned but it was pointed out by these authors that one of their degradation products (m.p. 134–135°, $[\alpha]_D - 29{\cdot}9°$) appeared to be isomeric with an acid (m.p. 136–137°, $[\alpha]_D + 33°$) of the same structure (IIa) derived from ambrein.[3] The tentative inference could be drawn that these two compounds were in fact antipodes.

Shortly thereafter, Cocker and Halsall[4] established structure (IIIa) for the diterpene labdanolic acid and related it to the ambrein degradation acid (IIa). The identity of the two specimens, notably the sign of rotation, proved the absolute configuration of labdanolic acid as implied by expression (IIIa) since ambrein has been related to manool[5] and thence to the steroids and *D*-glyceraldehyde. Cocker and Halsall[4] have pointed out that there exists on the whole a remarkable similarity between the physical constants of various eperuic and labdanolic acid derivatives except for the fact that the rotations were invariably of opposite sign. The tentative conclusion was reached that these two acids are antipodes, in so far as rings A and B are concerned.

While there are a few examples known among the lower terpenes where both antipodes exist in nature, this has never been observed in the di- and tri-terpene series—all of them possessing the same absolute configuration (with respect to the C-10 angular methyl group) as the steroids. In view of the fact that rotatory dispersion measurements have led us to propose[6] that the diterpene cafestol may belong to the antipodal series, it was decided to apply our rotatory dispersion approach to the eperuic-labdanolic acid problem.

The rotatory dispersion curve of the keto ester (IIIb)[4] derived from labdanolic acid (IIIa) should be characterized by a strong negative single Cotton-effect curve[7]

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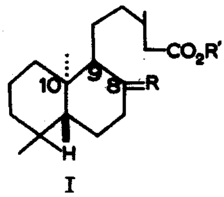
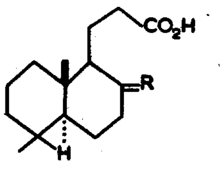
[1] Paper XI, C. Djerassi *Bull. Soc. Chim. Fr.* (1957) in press.
[2] F. E. King and G. Jones *J. Chem. Soc.* 658 (1955).
[3] L. Ruzicka and F. Lardon *Helv. Chim. Acta* **29**, 912 (1946).
[4] J. D. Cocker and T. G. Halsall *J. Chem. Soc.* 4262 (1956).
[5] L. Ruzicka, O. Dürst, and O. Jeger *Helv. Chim. Acta* **30**, 353 (1947).
[6] C. Djerassi, R. Riniker, and B. Riniker *J. Amer. Chem. Soc.* **78**, 6362 (1956).
[7] For nomenclature see C. Djerassi and W. Klyne *Proc. Chem. Soc.* 55 (1957).



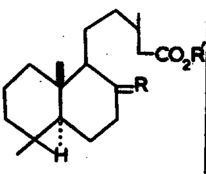
I

(a) $R=CH_2$ $R'=H$
(b) $R=O$ $R'=CH_3$



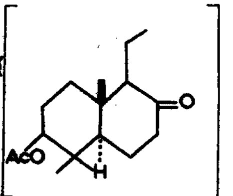
II

(a) $R=\overset{H}{\llcorner}CH_3$
(b) $R=O$



III

(a) $R=\overset{OH}{\llcorner}CH_3$ $R'=H$
(b) $R=O$ $R'=CH_3$



IV $_2$

similar to that exhibited by friedelin[6] and the mirror image of that of a 2-keto-5α-steroid.[8] That this is indeed the case is illustrated in Fig. 1 for the ester (IIIb)—R. D.[7] in dioxane (*c.* 0·094), 25°; $[\alpha]_{700}$ −18°, $[\alpha]_{589}$ −39°, $[\alpha]_{317\cdot5}$ −1440°, $[\alpha]_{277\cdot5}$ +1050°, $[\alpha]_{272\cdot5}$ +785°—and the validity of this approach is exemplified even further in

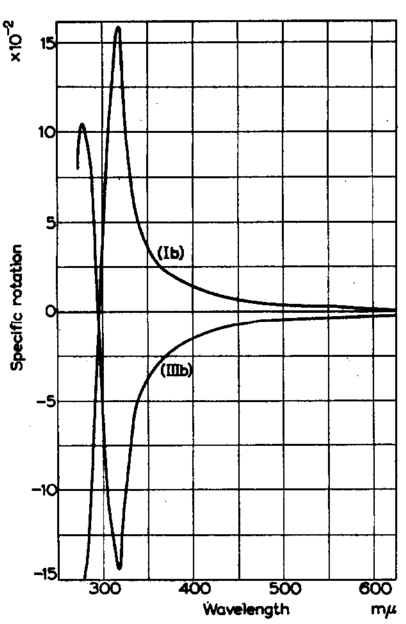


FIG. 1.

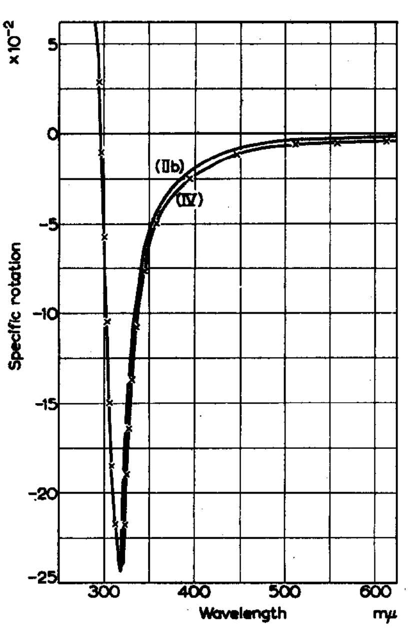


FIG. 2.

Fig. 2 where the rotatory dispersion curves of the keto acid (IIb)—R. D. in dioxane (*c.* 0·121), 25°; $[\alpha]_{700}$ −20°, $[\alpha]_{589}$ −21°, $[\alpha]_{317\cdot5}$ −2440°, $[\alpha]_{280}$ +2190°—derived[9] from manool and of bisnor-8, 13-dioxo-α-onocerane-3, 16-diol diacetate (IV)[10]—R. D. in dioxane (*c.* 0·054), 25°; $[\alpha]_{700}$ −26°, $[\alpha]_{589}$ −46°, $[\alpha]_{317\cdot5}$ −2392°, $[\alpha]_{275}$ +2472° —are reproduced. The absolute configurations of both manool and onocerin have already been established by classical chemical means[11,12] so that their rotatory dispersion curves can be used as even more precise models than those of steroids.

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[8] C. Djerassi, W. Closson, and A. E. Lippman *J. Amer. Chem. Soc.* **78**, 3163 (1956).

[9] B. Riniker, Thesis, E. T. H. Zurich, 1955, p. 33. cf. H. R. Schenk, H. Gurtmann, O. Jeger, and L. Ruzicka *Helv. Chim. Acta* **35**, 817 (1952).

[10] D. H. R. Barton and K. H. Overton *J. Chem. Soc.* 2639 (1955).

[11] E. Kyburz, B. Riniker H. R. Schenk, H. Heusser, and O. Jeger *Helv. Chim. Acta* **36**, 1891 (1953).

[12] D. Arigoni and O. Jeger *Ibid.* **39**, 174 (1956).

On the other hand, the rotatory dispersion curve (Fig. 1) of the keto ester (Ib)—R.D. in dioxane (*c.* 0·113), 25°; $[\alpha]_{700}$ +6°, $[\alpha]_{589}$ +17°, $[\alpha]_{317\cdot5}$ +1585°, $[\alpha]_{280}$ −1505°—obtained[2] from eperuic acid (Ia) is virtually the mirror image of that of the corresponding labdanolic acid derivative (IIIb). It should be noted that quantitatively, the curves are not exact mirror images—as is required of antipodes—and that a fairly large discrepancy exists in the melting points (m.p. 223° *vs.* 190°) of the oximes of the keto acids corresponding to (Ib) and (IIIb). We have had occasion to repeat the preparation of these oximes under identical conditions starting with the original diterpene samples and have fully confirmed the earlier constants.[2,4] * It would appear, therefore, that there exists a slight stereochemical difference between eperuic acid and labdanolic acid, possibly isomerism at C-9. This is supported by the observation of Cocker and Halsall[4] that identical infra-red curves and rotations (but opposite in sign) are observed in the common liquid Δ^8-unsaturated methyl esters.[9]

Aside from the minor difference mentioned above, we believe that the rotatory dispersion curves of Fig. 1 clearly justify the assumption that eperuic acid[2] is the first authentic case of a diterpene with the "wrong" absolute configuration. Current work in our laboratories based on rotatory dispersion analyses seems to suggest that such terpenoids are more common than has hitherto been assumed.

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* The keto esters (Ib) and (IIIb) exhibited identical infra-red spectra in chloroform solution, but the nujol (insol. in $CHCl_3$) spectra of the acid oximes were quite different.