

ENANTIOMERS OF LABDANOLIC ACID AND 13-EPI-LABDANOLIC ACID

C.A. Henrick, P.R. Jefferies and R.S. Rosich

Organic Chemistry Department, University of Western Australia,
Nedlands, Western Australia.

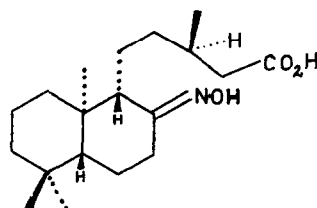
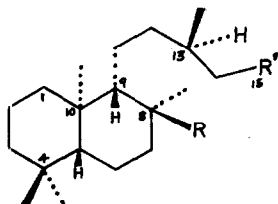
(Received 29 September 1964)

Cocker and Halsall (1a) compared the specific rotations of analogous derivatives of labdanolic acid (1) and eperuic acid (2,3) and suggested that their skeletons might be enantiomeric. Later, it was found that ORD curves of the norketo esters showed slight deviations from an antipodal relationship, and this was explained by assignment of the 9:10 syn stereochemistry to eperuic acid (4). It has been reported recently (5) that the C.D. curves of the norketo esters are antipodal, requiring that both series have 9:10 anti configurations. The differences between eperuic and labdanolic acid could be explained if they had the same configuration at C-13, and we wish to report results of parallel studies which support this view.

Separation of the methylated resin acids of Dodonaea lobulata F. Muell. has afforded a crystalline hydroxy ester (I). The physical constants of (I) and its derivatives (Table I) correspond accurately with those expected for the antipode of methyl labdanolate (1). The infrared spectrum (nujol) of (I) was identical with that published (6) for methyl labdanolate.

TABLE I
Enantio-Labdanolic Acid Derivatives

Compound	Formula [†]	Melting Point	$[\alpha]_D^*$
I	$C_{21}H_{38}O_3$	72-74°	+10°
II	$C_{20}H_{38}O_2$	81-83°	+ 8°
III	$C_{21}H_{38}O_2$	42-44°	-24°
IV	$C_{19}H_{33}O_3N$	188-190°	-78° (dioxan)



	R	R'
I	OH	CO ₂ Me**
II	OH	CH ₂ OH
III	H	CO ₂ Me

IV

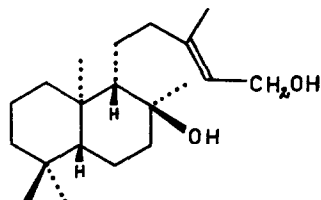
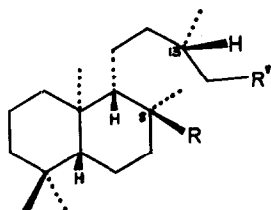
[†] Satisfactory analyses were obtained for all compounds described in this paper.

* Rotations were measured in CHCl₃ solution unless otherwise stated.

** For convenience the original assignment to the 13-configuration in labdanolic acid is taken to be correct (6,7), since the intramolecular hydrogen-bonding observed for methyl labdanolate (8) does not appear to invalidate this assignment (9).

Ricinocarpus muricatus Muell. Arg. has yielded a number of bicyclic diterpenes, one of which was the diol (V), $C_{20}H_{38}O_2$, m.p. 74-75°, $[\alpha]_D +3^\circ$ (c, 9). Oxidation of (V) with Jones reagent (10) gave the acid (VI), methyl ester (VII), $C_{21}H_{38}O_3$, m.p. 74-75°, $[\alpha]_D -3^\circ$ (c, 11). The infrared spectrum (nujol) of (VII) was identical with that of methyl 13-epi-labdanolate ($[\alpha]_D +2^\circ$) (6), thus indicating an enantiomeric relationship.

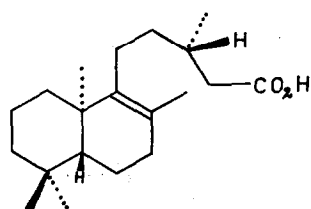
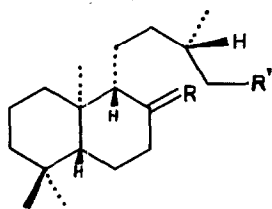
Authentic samples of the enantiomers of methyl labdanolate and 13-epi-labdanolate were prepared from the diol (VIII) (11), which has been related to 13-epi-(-)-manoyl oxide (12). Catalytic reduction $[Pt(H_2)/MeOH]$ of (VIII), oxidation with Jones reagent (10) and methylation gave a mixture of the 13-epimers which could be separated readily by chromatography on deactivated alumina as described for the enantiomeric mixture (7). The esters obtained were identical with (I) and (VII) obtained from Dodonaea lobulata and Ricinocarpus muricatus respectively.



	R	R'
V	OH	CH ₂ OH
VI	OH	CO ₂ H
VII	OH	CO ₂ Me
XIV	H	CO ₂ H

VIII

Methyl enanti-13-epi-labdanolate (VII) was dehydrated with phosphorus oxychloride in pyridine at 0° (1a) to give the expected mixture of double bond isomers (3,13) containing ca. 70% of the exocyclic olefin (IX) as determined from the N.M.R. spectrum of the mixture. Ozonolysis of (IX) and saponification gave the keto-acid (XI), characterized as its oxime (XII), $C_{19}H_{33}O_3N$, m.p. 224-226°, $[\alpha]_D -86^\circ$ (c, 1.0 in dioxan). The physical constants of this oxime (XII) correspond closely with those of the corresponding oxime [m.p. 223°, $[\alpha]_D -79.4^\circ$ (dioxan)] derived from eperuic acid (2). This suggests that eperuic acid is (X) and has a carbon skeleton which is antipodal with Labd-8(20)-en-15-oic acid (1) at all points except C-13.*



	R	R'
IX	CH ₂	CO ₂ Me
X	CH ₂	CO ₂ H
XI	O	CO ₂ H
XII	N·OH	CO ₂ H

XIII

Isomerisation of (IX) with refluxing 8% H₂SO₄/MeOH (1a) and saponification gave the acid (XIII), $C_{20}H_{34}O_2$, m.p. 70-71°, $[\alpha]_D -90^\circ$ (c, 4.0). Catalytic reduction [Pt(H₂)/HOAc] of (XIII) gave the acid (XIV), $C_{20}H_{36}O_2$, m.p. 62-63°.

* Dr. K.H. Overton (Glasgow) has informed us (25th September) that he has arrived at the same conclusion concerning the relationship of labdanolic and eperuic acids.

$[\alpha]_D -30^\circ(c, 2.6)$, formulated on the assumption that hydrogenation occurred at the less hindered β -face of the molecule (1). The *p*-bromophenacyl ester of (XIV), $C_{28}H_{41}O_3Br$, m.p. 72-73°, $[\alpha]_D -28^\circ(c, 4.5)$ corresponds to the derivative of dihydroperuic acid [lit. (2), m.p. 71-71.5°].

The chemical shifts (τ -values) (14)* of the methyl groups in the various derivatives are listed in Table II. It is noteworthy that the line positions of the 4-methyl groups ($\sim 9.13, 9.19$) are essentially the same as in kaurane, beyerane and phyllocladene compounds containing a 4-dimethyl grouping (15). The deshielding of the 10-methyl group by the 8α -CH₃ in compounds (V), (VII) and (XIV) is evident from a comparison of their spectra with that of (IX) (15).

TABLE II

Chemical Shifts (τ -values) of Methyl Groups.

Compound	4-Methyls	10-Methyl	8-Methyl	13-Methyl
V	9.13, 9.19	9.19	8.85	9.09 (d)
VII	9.13, 9.19	9.19	8.85	9.05 (d)
XIV	9.14, 9.17	9.14	9.12 (d)	9.03 (d)
IX	9.12, 9.19	9.32	-	9.06 (d)
XI	9.02, 9.14	9.28	-	9.03 (d)
XIII	9.11, 9.16	9.05	8.44	9.01 (d)

(d) = doublet (J, 6-7 cps).

* N.M.R. spectra were measured at 60 mc. for $CHCl_3$ or $CDCl_3$ solutions containing Me_4Si as internal standard.

REFERENCES.

1. (a) J.D. Cocker and T.G. Halsall, J. Chem. Soc., 4262 (1956);
(b) J.D. Cocker and T.G. Halsall, J. Chem. Soc., 4401 (1957).
2. F.E. King and G. Jones, J. Chem. Soc., 658 (1955).
3. T. Nakano and C. Djerassi, J. Org. Chem., 26, 167 (1961).
4. C. Djerassi and D. Marshall, Tetrahedron, 1, 238 (1957).
5. A.I. Scott, F. McCapra, F. Comer, S.A. Sutherland, D.W. Young, G.A. Sim and G. Ferguson, Tetrahedron, 20, 1339 (1964).
6. S. Bory and E. Lederer, Croat. Chem. Acta, 29, 157 (1957).
7. D.B. Sigley, N.A.J. Rogers and J.A. Barltrop, J. Chem. Soc., 4613 (1960).
8. A.J. Baker, G. Eglinton, A.G. Gonzalez, R.J. Hamilton and R.A. Raphael, J. Chem. Soc., 4705 (1962).
9. L. Mangoni and M. Belardini, Gazz. Chim. Ital., 92, 1379 (1962).
10. K. Bowden, I.M. Heilbron, E.R.H. Jones and B.C.L. Weedon, J. Chem. Soc., 39 (1946); see also C. Djerassi, R.R. Engle and A. Bowers, J. Org. Chem., 21, 1547 (1956).
11. P.R. Jefferies and T.G. Payne, Austral. J. Chem., in the press.
12. B.E. Cross, R.H.B. Galt, J.R. Hanson, P.J. Curtis, J.F. Grove and A. Morrison, J. Chem. Soc., 2937 (1963).
13. R. Hodges and R.I. Reed, Tetrahedron, 10, 71 (1960).
14. G.V.D. Tiers, J. Phys. Chem., 62, 1151 (1958).
15. C.A. Henrick and P.R. Jefferies, Austral. J. Chem., 17, 915 (1964).