21. *The Stereochemistry of Eperuic Acid.*

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The nor-keto-esters (II; R = O, R′ = Me) derived from eperuic and labdanolic acids are shown to possess the same configuration at C-13 whilst being otherwise antipodal. Comparison of the derived diol esters (IV) shows that the parent acids (II; R = CH_2, R′ = H) are themselves antipodal apart from C-13. The *trans-syn*-configuration previously assigned to eperuic acid can therefore be discounted and with it the last apparent exception among diterpenoids to the rule of A/B/C *trans-anti*-stereochemistry.

The structural relationships among the cyclic diterpenoids have only recently emerged from a state of relative confusion.[1] At the present time the great diversity of types found in this family of natural products is embraced by the biogenetic isoprene rule [2] in all constitutional, configurational, and (where the relevant information is available) biochemical details.[3]

In accordance with the rule, rings A, B, and C in the polycyclic diterpenoids are expected to exhibit *trans-anti*-stereochemistry, resulting from concerted trans-antiplanar cyclisation of a suitably oriented geranyl-geraniol precursor (I).[4] It was, however, until recently, accepted that there exists a small group of compounds apparently at variance with this widely exhibited steric situation and possessing a *trans-syn*-backbone. Of the compounds previously regarded as falling within this group, cafestol and kahweol,[5] gibberellic acid,[6] and, most recently, rosololactone and its congeners,[7] have been shown to follow the orthodox pattern, largely by the *X*-ray-crystallographic studies of Scott, Sim, and their colleagues. Isopimaric acid, likewise, has been acquitted as normal,[8] whilst even the constitution of rimuene is at present so insecure [9] as to render discussion of its stereochemistry meaningless.*

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* See footnote at end of Paper.

[1] See, for example, (*a*) de Mayo, " The Diterpenoids " in " The Chemistry of Natural Products," Vol. II, ed. Bentley, Interscience, New York, 1959; (*b*) Barltrop and Rogers, " The Chemistry of the Higher Terpenoids " in " Progress in Organic Chemistry," Vol. V, ed. Cook and Carruthers, Butterworths, London, 1961.

[2] Ruzicka, Faraday Lecture, " History of the Isoprene Rule," *Proc. Chem. Soc.*, 1959, 341; " Perspektiven der Biogenese und der Chemie der Terpene," *Pure Appl. Chem.*, 1963, **6**, 493.

[3] For a comprehensive survey see McCrindle and Overton, " The Chemistry of the Cyclic Diterpenoids " in " Advances in Organic Chemistry," Vol. V, ed. Raphael, Taylor, and Wynberg, Interscience, New York, in the press.

[4] For an elaboration of this thesis see Scott, McCapra, Comer, Sutherland, Young, Ferguson, and Sim, *Tetrahedron*, 1964, **20**, 1339.

[5] Scott, Sim, Ferguson, Young, and McCapra, *J. Amer. Chem. Soc.*, 1962, **84**, 3197.

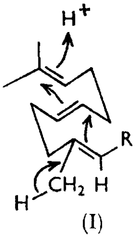
[6] McCapra, Scott, Sim, and Young, *Proc. Chem. Soc.*, 1962, 185.

[7] Scott, Sutherland, Young, Guglielmetti, Arigoni, and Sim, *Proc. Chem. Soc.*, 1964, 19.

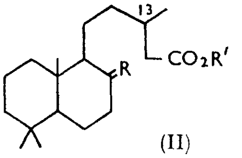
[8] Antkowiak, ApSimon, and Edwards, *J. Org. Chem.*, 1962, **27**, 1930; Ireland and Newbould, *ibid.*, 1963, **28**, 23.

[9] Carman, *Austral. J. Chem.*, 1963, **16**, 225.

There remained the sole apparent exception of eperuic acid. We now demonstrate that the previously proposed [10] and subsequently accepted [1b] stereochemistry of eperuic acid is inadmissible on the basis of both the recorded and additional evidence which we have obtained, and thereby remove this residual anomaly.



(I)



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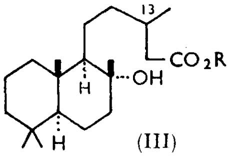

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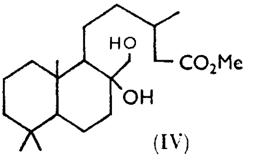

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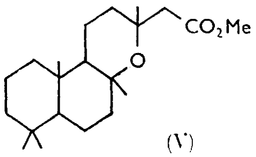

(V)

Eperuic acid (II; R = CH$_2$; R′ = H. 5β-H, 10α-Me) had been shown [10] to be essentially antipodal to labdanolic acid (III; R = H) (of established [11] configuration) by a comparison of the rotatory dispersions of the keto-esters (II; R = O, R′ = Me) derived from the two acids; these were found to be near, but not complete, mirror images. This minor discrepancy, and the much more serious divergence in the melting points (223° *vs.* 190°) of the oximes from the corresponding keto-acids (II; R = O, R′ = H), was attributed [10] to a possible difference in configuration at C-9. This would imply that the side-chain in the keto-ester from eperuic acid, and so presumably in eperuic acid itself, is axially (β) attached, thus resulting in an anomalous *trans-syn*-backbone.

Consideration of the conditions employed [11,12] to hydrolyse the two keto-esters prior to oximation (methanolic 2N-potassium hydroxide under reflux for 1 and 2 hr., respectively) convinced us that the side-chain in both oximes must have the stable equatorial configuration and that the stereochemical difference in these derivatives must therefore reside at C-13, the only other relevant asymmetric centre. A comparison [11] of the physical constants of the products arising from stepwise degradation of the side-chains in the labdanolic and eperuic series already suggests that the two become completely antipodal as soon as the asymmetry at C-13 is removed.

This has now been confirmed as follows. Sclareol was converted by the recorded procedure [13] into a mixture of methyl labdanolate and methyl 13-epilabdanolate (III; R = Me) which was separated by gradient elution chromatography over activated alumina. Dehydration [11] with phosphorus oxychloride in pyridine afforded in each case a mixture of methyl labd-8- and labd-8(20)-en-15-oates containing 58 and 72%, respectively, of the exocyclic olefin from the 13-normal- and 13-epi-esters (see Experimental section). Each olefin mixture was ozonised [11] and the required keto-ester (II; R = O; R′ = Me) separated by chromatography from unwanted ozonolysis products. The corresponding keto-ester from natural methyl eperuate (the specimen used was a similar mixture of double-bond isomers containing 32% of the exocyclic olefin) was similarly obtained.

Comparison of the three keto-esters showed, within experimental limits, no detectable difference (apart from sign) in their rotatory dispersion or circular dichroism; there were only minor divergences in the infrared (i.r.) solution spectrum of the ester

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[10] Djerassi and Marshall, *Tetrahedron*, 1957, **1**, 238.
[11] Cocker and Halsall, *J.*, 1956, 4262.
[12] King and Jones, *J.*, 1955, 658.
[13] Bory and Lederer, *Croat. Chem. Acta*, 1957, **29**, 157.

derived from methyl labdanolate as compared with the other two. On the other hand, comparison of the three acid oximes (II; R = NOH, R′ = H) proved decisive. Eperuic acid and 13-epilabdanolic acid gave, respectively, oximes of m. p. 224—226, 223—226°; $[\alpha]_D$ −82, +87° (±3°) (pyridine) whose i.r. (KCl disc) spectra and *X*-ray single crystal rotation photographs were indistinguishable, but differed from those of the oxime, m. p. 188—199°, $[\alpha]_D$ +53° (pyridine) from labdanolic acid. The keto-esters from labdanolic and eperuic acids are therefore antipodal except at C-13.*

However, there remained the possibility that in the formation of the keto-ester (or the oxime) from eperuic acid, inversion had occurred at C-9 and that therefore eperuic acid is epimeric with the antipode of dehydrolabdanolic acid, not only at C-13 but also at C-9. This was shown not to be the case as follows. Osmylation of the mixture of olefinic esters used for ozonolysis (see above) afforded in each of the three cases a mixture of products, from which the required diol ester (IV) could be separated by chromatography over activated alumina. Its constitution is supported by elemental analysis, i.r. solution spectrum, formation under mild conditions of an (oily) mono-acetate and mono-*p*-nitrobenzoate, and presence in the nuclear magnetic resonance (n.m.r.) spectrum of a 2-proton singlet at τ 6·5, arising from the methylene protons of the primary alcohol. Again, the diol esters, m. p. 88—90°, $[\alpha]_{546}^{21}$ +4° (pyridine) and m. p. 88—90°, $[\alpha]_{546}^{21}$ −5° (pyridine), respectively, from eperuic acid and 13-epilabdanolic acid had i.r. solution spectra and *X*-ray powder photographs that were indistinguishable, but differed from those of the diol ester, m. p. 77—79°, $[\alpha]_{546}^{21}$ −20° (pyridine) from labdanolic acid.

Thus it is established that eperuic acid has the normal *trans-anti*-configuration exhibited by all the recorded diterpenoids of established structure and that there are at present no known exceptions (the special cases of columbin [14] and thelepogine [15] apart) to this rule.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus. I.r. solution and KCl disc spectra were recorded by Mrs. F. Lawrie with a Unicam S.P. 100 double-beam spectrometer, n.m.r. spectra with a Perkin-Elmer 60 Mc. spectrometer. Woelm alumina, deactivated to the appropriate Brockman grade was used for column chromatography. Chromatoplates for thin-layer chromatography (t.l.c.) were prepared according to Stahl,[16] using Kieselgel G (Merck). Rotations are in chloroform, except where specified. Gas–liquid chromotography (g.l.c.) experiments were carried out on a Pye-Argon Chromatograph. Microanalyses are by Mr. J. M. L. Cameron, B.Sc., and his staff.

Methyl Labdanolate and Methyl 13-*Epilabdanolate*.—Sclareol was oxidised with sodium dichromate according to the method of Bory and Lederer.[13] The aldehydic product (58%) was further oxidised with silver oxide,[13] the total acid product (98%) esterified with diazomethane, and hydrogenated in ethanolic solution in presence of platinum oxide.

The mixture of saturated esters (24·5 g.) was adsorbed on activated alumina (neutral, Grade III; 1·8 kg.) and displaced by gradient elution [benzene–light petroleum (2 : 3) (2 l.), (1 : 9) (4 l.), (3 : 2) (3 l.), and (3 : 1) (3 l.)], fractions of 60 ml. being collected. Fractions 9 to 60 (10·63 g.) gave the ester (V), m. p. 107—108° (from methanol) $[\alpha]_D$ +18° (*c* 2·05) (lit.,[13] m. p. 101—111°, $[\alpha]_D$ +18°), fractions 140—184 (6·35 g.) gave methyl 13-epilabdanolate, m. p. 71—74° (from light petroleum) $[\alpha]_D$ +3° (*c* 1·28) (lit.,[13] m. p. 74—75°, $[\alpha]_D$ +2°) [i.r. spectrum (KCl disc) identical with the recorded spectrum [13]]. Subsequent fractions gave methyl labdanolate contaminated with methyl 13-epilabdanolate (i.r. spectrum) (5·3 g.) which could not be satisfactorily separated by repeated chromatography to give the required quantity of methyl labdanolate. The methyl labdanolate used, m. p. 69—72°, $[\alpha]_D$ −7° (*c* 2·12) (lit.,[17] m. p. 72—74°, $[\alpha]_D$ −7°) was extracted [17] from gum labdanum.

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* The actual configuration at C-13 in labdanolic acid is in our view not securely established.

[14] Overton, Weir, and Wylie, *Proc. Chem. Soc.*, 1961, 211.
[15] Fridrichsons and Mathieson, *Acta Cryst.*, 1963, **16**, 206.
[16] Stahl, *Chem.-Ztg.*, 1958, **82**, 323.
[17] Cocker, Halsall, and Bowers, *J.*, 1956, 4259.

Dehydration of Methyl Labdanolate and Methyl 13-*Epilabdanolate.*—The two hydroxy-esters were dehydrated with phosphorus oxychloride in pyridine [11] at 20°; the products had $[\alpha]_D$ $+21°$ (c 2·09) (lit.,[12] $+27°$) from methyl labdanolate and $-22°$ (c 4·46) from methyl 13-epilabdanolate. G.l.c. [0·5%, A.P.L./80—100 Embacel; 175°; 40 ml. A/min.] showed the presence in both cases of two products, of retention times 8 and 9·5 min., respectively. Quantitative i.r. comparison of the band at 890 cm.$^{-1}$ (CS_2; *exo*-methylene) in each mixture with the corresponding band in 3-methylenecholestane gave its content at 72% (13-epi), 58% (13-normal).

Ozonolysis of the Dehydration Products.—The olefin mixtures obtained above were ozonised in ethyl acetate at $-70°$.[12] The ketonic product containing two major components (t.l.c.) was chromatographed over activated alumina (neutral, Grade III). The fractions containing the least-polar component (t.l.c.) were examined for homogeneity by g.l.c. (10% A.P.L.; 225°; 40 ml. A/Min.; retention time 24 min.). This component showed $\nu_{max.}$ $(CCl)_4$ 1712 (cyclohexanone), 1739 cm.$^{-1}$ (methyl ester). Hydrolysis [11] furnished 8-oxo-20-norlabdan-15-oic acid, and (+)-8-oxo-20-nor-13-epilabdan-15-oic acid, which were characterised as the oximes, that from labdanolic acid forming prisms, m. p. 188—190° (from ethanol), $[\alpha]_D$ $+52°$ (c 0·84 in pyridine), and from 13-epilabdanolic acid, needles, m. p. 223—226° (from ethanol), $[\alpha]_D$ $+87°$ (c 0·72 in pyridine).

Natural methyl eperuate, n_D^{25} 1·4960, $[\alpha]_D$ $-22°$, was shown by g.l.c. (0·5%, A.P.L.; 175°; 40 ml. A/min.] to consist of a mixture of two olefins whose retention times were identical with those of the previously described dehydration products. Quantitative i.r. estimation (see above) showed the presence of 32% exocyclic olefin. Ozonolysis, separation of the products as above (g.l.c., t.l.c. and i.r. comparisons match the product from methyl 13-epilabdanolate), and hydrolysis furnished the oily (−)-8-oxo-20-nor-13-epilabdan-15-oic acid, characterised as the oxime, needles, m. p. 224—226° (from ethanol), $[\alpha]_D$ $-82°$ (c 1·18 in pyridine).

Methyl 8ξ,20ξ-*Dihydroxylabdan*-15-*oate.*—The olefin mixture (499 mg.) (obtained from dehydration with phosphorus oxychloride and pyridine of methyl labdanolate; see above) in anhydrous ether (10 ml.) and pyridine (10 ml.) and osmium tetroxide (500 mg.) were kept in the dark for two days, and the mixture of osmates decomposed with hydrogen sulphide. The gummy mixture of diol esters (550 mg.; two components on t.l.c.) was separated by chromatography over activated alumina (grade II, neutral, deactivated with 7·5% of 10% acetic acid; 30 g.). Elution with benzene–light petroleum (1 : 1) afforded methyl 8,9-dihydroxylabdan-15-oate (108 mg.), $\nu_{max.}$ 3580, 1735 cm.$^{-1}$, which could not be induced to crystallise.

Benzene then eluted the second product, *methyl* 8ξ,20ξ-*dihydroxylabdan*-15-*oate* (270 mg.), prisms, m. p. 77—79° [from ice-cold light petroleum (b. p. 40—60°)], $[\alpha]_{546}^{21}$ $-20°$ (c 1·11 in pyridine) (Found: C, 71·0; H, 10·8. $C_{21}H_{38}O_4$ requires C, 71·15; H, 10·8%. $\nu_{max.}$ (CCl_4) 3644, 3615 (free OH); 3570 (bonded OH); 1740 cm.$^{-1}$ (ester), singlet (2H) at τ 6·5 (in $CDCl_3$ with tetramethylene as internal standard).

The diol was converted quantitatively (t.l.c.) at room temperature into an oily monoacetate [$\nu_{max.}$ (film) 1735, 1240, 2550 cm.$^{-1}$] and an oily mono-*p*-nitrobenzoate [$\nu_{max.}$ (film) 3600, 1720, 1280, and 1120 cm.$^{-1}$]. It formed an oily acetonide quantitatively (t.l.c.), $\nu_{max.}$ 1735 cm.$^{-1}$, with an excess of acetone in presence of anhydrous copper sulphate at 20°.

Methyl 8ξ,20ξ-*Dihydroxy*-13-*epilabdan*-15-*oate.*—Prepared from the dehydration product of methyl 13-epilabdanolate by osymylation as above, this afforded fine needles, m. p. 88—90° [from ice-cold light petroleum (b. p. 40—60°)], $[\alpha]_{546}^{21}$ $-5°$ (c 2·22 in pyridine) (Found: C, 71·45; H, 10·7. $C_{21}H_{38}O_4$ requires C, 71·15; H, 10·8%). I.r., t.l.c., and n.m.r. properties showed only very minor differences from the corresponding diol derived from methyl labdanolate.

Antipode of Methyl 8ξ,20ξ-*Dihydroxy*-13-*epilabdan*-15-*oate.*—Prepared from natural methyl eperuate by osymylation as above, this afforded fine needles, m. p. 88—90° [from ice-cold light petroleum (b. p. 40—60°)], $[\alpha]_{546}^{21}$ $+4°$ (c 1·80 in pyridine). Reduction of this diol with lithium aluminium hydride afforded an oily triol (one product by t.l.c.; absence of $\nu_{max.}$ 1700—1800 cm.$^{-1}$). The derived *p*-nitrobenzoate and α-naphthylurethane were likewise non-crystalline. The dihydroxy-acid, obtained by alkaline hydrolysis, and its cyclohexylamine salt could not be crystallised.

We are grateful to Dr. Gurnos Jones, Keele, Dr. T. G. Halsall, Oxford, and Messrs. Firmenich, Geneva, for generous gifts, respectively, of methyl eperuate, gum labdanum, and sclareol, to Professors W. Klyne and G. Ourisson for optical rotatory dispersion and circular dichroism measurements, and to Drs. G. Sim and G. Ferguson for the *X*-ray rotation photographs.

[*Added in proof*: The constitution [18,19] and stereochemistry [18] of rimuene have been firmly established since submission of this manuscript; both are in complete accordance with the biogenetic isoprene rule.]

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[18] Connolly, McCrindle, Murray, and Overton, *Tetrahedron Letters*, 1964, **29**, 1983.
[19] Corbett and Wyllie, *Tetrahedron Letters*, 1964, **29**, 1903.