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THE STRUCTURE AND SYNTHESIS OF OLEUROPEIC ACID

Raphael Mechoulam, Naftali Danieli and Yehuda Mazur
The Daniel Sieff Research Institute
The Weizmann Institute of Science, Rehovoth, Israel

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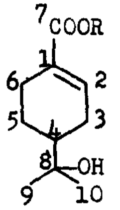
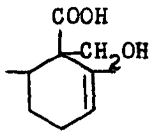
WE wish to report that oleuropeic acid[1] possesses structure Ia (p-ment-1-ene-7-oic acid).

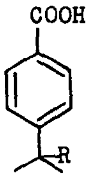
Oleuropeic acid was isolated by Shasha and Leibowitz[1] from the hydrolysate of a bitter principle[2] present in the leaves, unripe fruit and root bark of the olive tree (Olea europaea var. soori). Oleuropeic acid was assigned[1] structure II, mainly on the basis of a sulphur dehydrogenation which reportedly gave 2,6-dimethyl-benzoic acid, although no direct comparison with an authentic sample was mentioned.



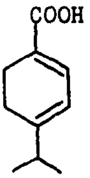
Ia, R = H
Ib, R = CH_3



II



IIIa, R = H
IIIb, R = OH



IV

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[1] B. Shasha and Y. Leibowitz, J. Org. Chem. 26, 1948 (1961); B. Shasha and Y. Leibowitz, Nature, Lond. 184, 2019 (1959).

[2] The bitter principle called oleuropein by these authors is undoubtedly different from the oleuropein, the structure of which was recently elucidated: L. Panizzi, M.L. Scarpati and G. Oriente, Gazz. Chim. Ital. 90, 1449 (1960); H.C. Beyerman, L.A. van Dijck, J. Levisalles, A. Melera and W.L.C. Veer, Bull. Soc. Chim. 1812 (1961).

We felt that structure II is not sufficiently corraborated, especially since its carbon skeleton is unusual for the monoterpenoid class and therefore a reinvestigation of the problem seemed justified.

Following the published extraction and purification procedure, we succeeded in obtaining oleuropeic acid, m.p. 155-158°, $[\alpha]_D$ -100°, identical with the published values. Further purification was achieved by converting the acid into its methyl ester, chromatography on alumina and hydrolysis back to the free acid, $C_{10}H_{16}O_3$, m.p. 164 - 166°, $[\alpha]_D$ -125°, ν_{max} (in KBr) 1695 cm^{-1} (unsaturated carboxylic acid), 1655 cm^{-1} (s) (conjugated double bond), λ_{max}^{EtOH} 218 mμ (ε 10.800), two active hydrogens (Zerewitinoff determination). Methyl oleuropate, $C_{11}H_{18}O_3$, Ib, was obtained as an oil, b.p. 112-114°/0.5 mm, $[\alpha]_D$ -104°, $n_D^{28^{\circ}}$ 1.5015, λ_{max}^{EtOH} 218 (ε 12.800), ν_{max} (in $CHCl_3$) 3580 cm^{-1} (hydroxyl group), 1705 cm^{-1} (α,β-unsaturated ester), 1655 cm^{-1} (s) (conjugated double bond). The NMR spectrum of Ib (in $CDCl_3$) showed the presence of one olefinic proton at 2.98 τ (split to an unresolved complex) and six protons of two methyl groups as a single peak at 8.80 τ, indicating that these two methyl groups are structurally similar. No protons of a vinylic methyl group could be observed. Neither was the presence of a proton α to a hydroxyl group indicated. The non-splitting of the common signal of the methyl groups shows that they possess no α hydrogen. In addition their rather low value could be attributed to the deshielding effect of an α hydroxyl group.

The hydroxyl group does not undergo acetylation with acetic anhydride in pyridine and is not oxidized with "Jones' reagent".[3] This supports the argument for its tertiary character. On catalytic hydrogenation (PtO_2/EtOH) Ia absorbs 1 mole of hydrogen, yielding an optically inactive product, m.p.

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[3] K. Bowden, I.M. Heilbron, E.R.H. Jones and B.C.L. Weedon, J. Chem. Soc. 39 (1946).

124-140°, probably a mixture of epimers.

Sulphur dehydrogenation yielded a crystalline mixture from which two compounds were isolated by chromatography. The less polar compound, m.p. 115-116°, is identical with cumic acid (IIIa) while the more polar one is identical with 1'-hydroxy-cumic acid (IIIb). Both compounds were compared directly with authentic samples.[4,5]

Boiling of Ia with 10 per cent sulphuric acid resulted in dehydration giving the dienoic acid IV, m.p. 130-132°, λ_{max}^{EtOH} 298 mμ (ε 7500).

These results are compatible with structure Ia only.

We have synthesized racemic oleuropeic acid by the sequence described in Fig. 1.

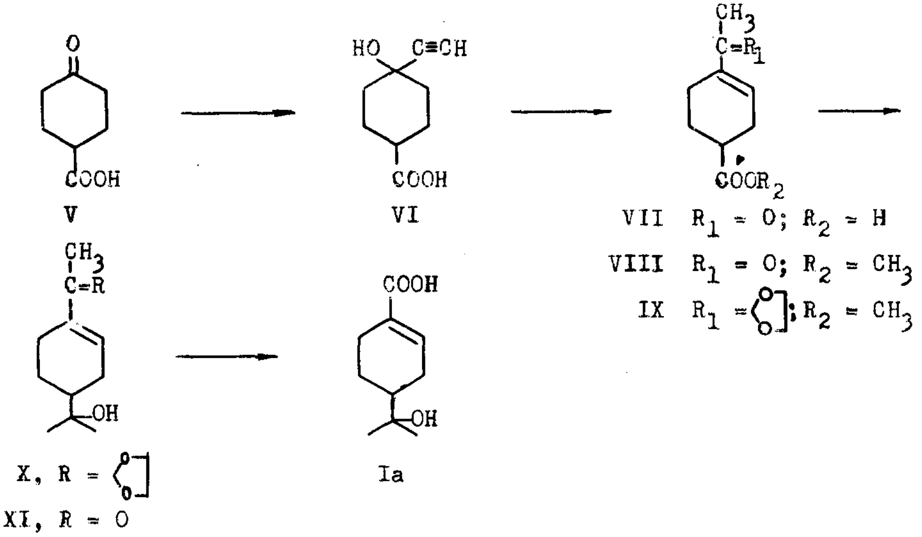

FIG. 1

Cyclohexanone-4-carboxylic acid (V) was condensed with potassium acetylide in t-butanol to give VI, m.p. 144-145°, $C_9H_{12}O_3$, which was rearranged to VII, $C_9H_{12}O_3$ m.p. 117-118°, λ_{max}^{EtOH} 237 mμ (ε 15,700) by refluxing

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[4] M.S. Newman and E.K. Easterbrook, J. Amer. Chem. Soc. 77, 3763 (1955).

[5] O. Widmann and J.A. Bladin, Ber. Dtsch. Chem. Ges. 19, 583 (1886).

in formic acid. Esterification gave the oily VIII, which ketalized with ethylene glycol and p-toluene-sulphonic acid in benzene to IX, $C_{12}H_{15}O_4$, b.p. 105-110°/1 mm, $n_D^{27^\circ}$ 1.4870. Reaction of IX with excess methyl magnesium iodide gave X, which on treatment with p-toluene-sulphonic acid in acetone-water was converted into the oily XI, λ_{max}^{EtOH} 233 mμ (ε 14,200). Oxidation with sodium hypoiodite in water gave Ia, m.p. 153-155°, identical with oleuropeic acid (comparison of the infra-red spectra). A mixture of the natural product (m.p. 164-166°) with the synthetic racemic acid melted at 159-162°.

While this manuscript was in preparation Herz and Wahlborg[6] published the conversion of β(-)pinene into Ia and IV. Professor Herz kindly supplied us with samples of these compounds. The identity of the dienoic acid (IV) was proved by direct comparison (m.m.p. and infra-red spectra). Ia (m.p. 154-156°) from β(-)pinene has a rotation of $[\alpha]_D$ -68.7°[7] and seems to be optically impure.[8] A mixture of it with natural oleuropeic acid melted at 159-162°, whereas a mixture with the racemic synthetic Ia melted at 153-155°. The infra-red spectra of Ia from β(-)pinene and that of oleuropeic acid were superimposable.

The absolute configuration of oleuropeic acid is determined as that of L-glyceraldehyde by its relationship to β(-)pinene.[6,9]

Acknowledgements - We are indebted to Prof. F. Sondheimer for his interest, to Prof. Herz for samples of Ia and IV and to Dr. Y. Shvo for the NMR determinations.

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[6] W. Herz and H.J. Wahlborg, J. Org. Chem. 27, 1032 (1962).

[7] Private communication by Professor Herz.

[8] The β(-)pinene used as starting material is reported as optically impure and further partial racemization might well have occurred in the course of the conversion.

[9] G. Austerweil, Bull. Soc. Chim. 39, 1643 (1926); A.J. Birch, Ann. Rep. Chem. Soc. 47, 192 (1950).