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DAVALLIC ACID, A TRITERPENE WITH A NOVEL SKELETON.

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DAVALLIC acid, $C_{30}H_{48}O_2$, m.p. 283°, is isolated from the rhizome of a Chinese fern, Davallia divaricata, which is widely used as a tonic and diuretic in Taiwan.

The present studies establish its structure as I. Davallic acid is a pentacyclic compound containing one carboxyl group and a tri-substituted double bond as revealed by the spectroscopic data of its derivatives; e.g., methyl davallate(II), $C_{31}H_{50}O_2$, m.p. 234°, M^+ 454, ν^{KBr} 1740 cm^{-1}, λ_{max}^{EtOH} 207 mμ (ε 5100), δ^{Chf} 5.32 (one olefinic proton, diffuse). Reduction of the ester II with lithium aluminum hydride gave davallol (III), m.p. 169-170°; acetate (IV), m.p. 191°, δ^{CCl_4} AB quartet at 3.9 and 4.2 ppm (J 11 cps) due to hindered $-CH_2OAc$. Treatment of davallol (III) with chromic trioxide in pyridine afforded the aldehyde davallal (V), m.p. 149°. The high-field region of its 100 mc NMR(1)

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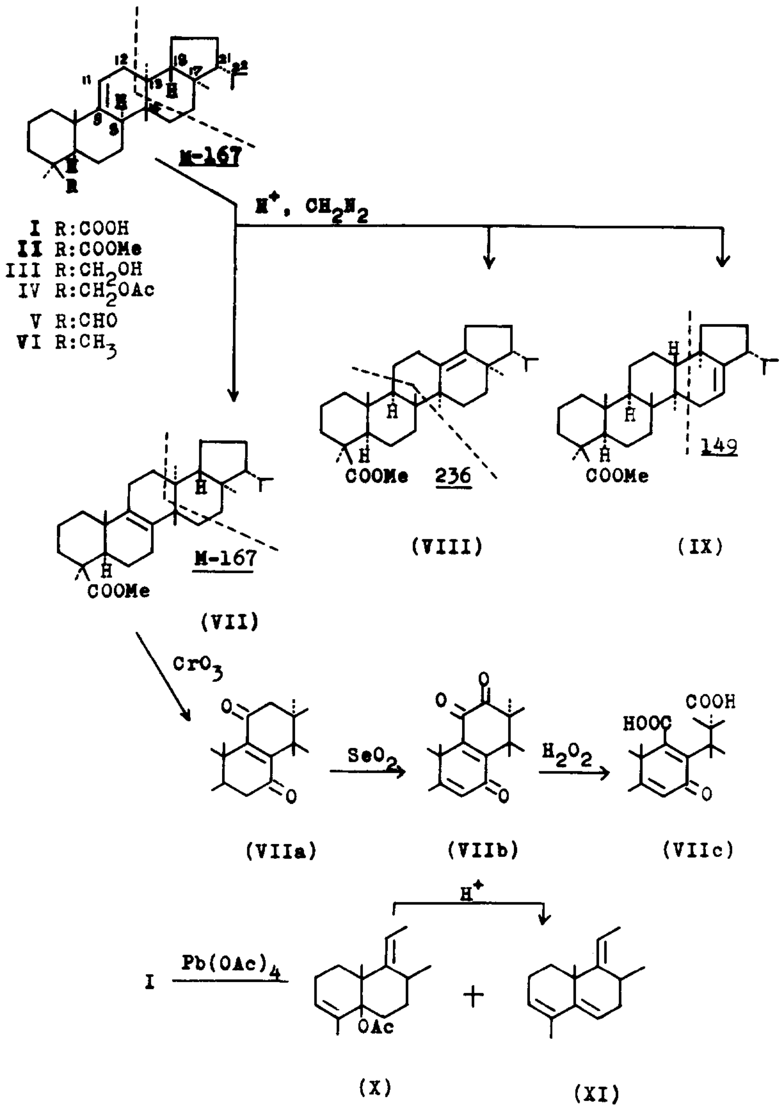
spectrum was revealing in that it disclosed the presence of five methyl singlets (0.75, 0.77, 0.83, 0.94, and 1.00 ppm), and a triplet at 0.80, 0.86, and 0.92 ppm with peak height ratios of ca. 1:2:1 that could be assigned either to an isopropyl(2) or two secondary methyl groups.

When davallic acid was refluxed with hydrochloric acid in acetic acid, followed by methylation, methyl isodavallate-1 (VII), $C_{31}H_{50}O_2$, m.p. 230°, was obtained in good yield together with minute amounts of two more isomers, methyl isodavallate-2 (VIII), m.p. 215°, and methyl isodavallate-3 (IX) m.p. 165°. The NMR spectra of isomers-1 and -2 lacked olefinic protons, whereas the spectrum of isomer-3 had a diffuse band around δ^{CDCl_3} 5.20.

Oxidation of isomer-1 with chromic trioxide in acetic acid first gave the trans-enedione(VIIa), m.p. 211°, $C_{31}H_{46}O_4$, λ_{max}^{KBr} 1740, 1680, 1615 cm^{-1}, λ_{max}^{EtOH} 271 mμ (e 7,500), which upon further oxidation with selenium dioxide gave the dienetrione (VIIb), $C_{31}H_{42}O_5$, m.p. 231°, λ_{max}^{KBr} 215 mμ (e 7,500), 283 mμ (e 7,900). Presence of the α-diketone group in the dienetrione was confirmed by its conversion with alkaline hydrogen peroxide into a seco-dicarboxylic acid (VIIc), λ_{max}^{KBr} 1740, 1700, 1690, 1660, 1630 cm^{-1}; λ_{max}^{EtOH} 252 mμ (e 8,800), 208 mμ (e 7,000). These series of oxidations and dehydrogenations are well-known in the field of tetracyclic terpenoids(3) and establish the C_8-C_9 location of the double bond in isomer-1 (VII).

Placement of the double bond at C_9-C_{11} rather at C_7-C_8 follows from the UV absorption of nordavallatriene (XI) and mass spectra of methyl davallate (II), davallol (III),


M-167
H+, CH2N2
I R:COOH
II R:COOMe
III R:CH2OH
IV R:CH2OAc
V R:CHO
VI R:CH3
COOMe
236
149
(VIII)
(IX)
M-167
(VII)
CrO3
SeO2
H2O2
HOOC
COOH
(VIIa)
(VIIb)
(VIIc)
H+
I
Pb(OAc)4
OAc
(X)
(XI)

davallal (V), davallene (VI) and methyl isodavallate-1 (VII)(4). They were all characterized by a strong M^+-15 peak due to cleavage of the C_{17}-methyl(5), and base peaks at m/e 287(II), 259(III), 257(V), 243(VI) and 287(VII), namely at M^+-167. This fragmentation constitutes the base peak of arborene(6) that carries a 9(11)-double bond, and has been assigned to cleavages at bonds 12-13, 13-14, and 15-16(6).

Oxidation of methyl isodavallate-1 (VII) with chromic trioxide in acetic acid gave the $\Delta^{7,9(11)}$-trans-diene, $C_{31}H_{48}O_2$, m.p. 207-208°, having a triplet in the UV at 233, 240, and 249 mμ (in EtOH). The 240 mμ maxium is typical for 13α, 14β-methyl compounds such as multiflorenol(7), bauerenol(8), and euphol(9); in contrast, the 13β, 14α-compounds (lanostane series(9) and arborene(6)) absorb at 236, 243, and 252 mμ. The formation of methyl isodavallate-2 (VIII) is similar to the euphenol-isoeuphenol rearrangement, the base peak at m/e 236 being tentatively assigned to the cleavage shown. The structure of the third isomer IX follows from the NMR spectrum and the base peak at m/e 149. These transformations require a 14β, 13α, 18β, 17α-configuration, and not a 14α, 13β-configuration of the lanosterol series, in which the rearrangement merely gives isolanosterol(10). Oxidation of methyl davallate with CrO_3-AcOH afforded 12-ketomethyl davallate, m.p. 252°, ν^{KBr} 1740, 1680, 1605 cm^{-1}, λ^{EtOH} 246 mμ (ε 9,500), with a positive Cotton effect ORD curve (peak: $[\Phi]^{MeOH}_{355}$ +5430; trough: $[\Phi]^{MeOH}_{305}$ -9920) of molecular amplitude (a) +15350. This is in contrast to the 13β,14α-arboren-12-one(6) having a negative Cotton effect curve.

Decarboxylation of davallic acid with lead tetraacetate yielded acetoxy nordavalladiene(X), m.p. 195°, ν^{KBr} 1740 cm^{-1}, δ^{CDCl_3} 1.54 (=C-Me), 1.97 (OAc), 5.33 ppm (diffuse), together with some triene XI, m.p. 165°, λ_{max}^{EtOH} 233, 241, 250 mμ (e 2,000, 2,200, 1,400), δ^{CDCl_3} 1.54(=C-Me), 5.36(diffuse). The triene was also produced by treatment of X with dry HCl in chloroform. The low λ_{max} intensity of the triene is caused by contamination (V.P.C.) but suffices to indicate the presence of a conjugated diene and not a triene system, and suggests that the original double bond is $\Delta^{9(11)}$ rather than Δ^7.

Evidence for ring E is as follow. In conjunction with structural studies on arborinol(6), the Wolff-Kishner reduction of davallal (V) to davallene (VI), m.p. 167° was carried out at Stanford, and it was found that davallene and fernene(12) were identical (m.p.,IR,V.P.C.)(13). Fernene has been related to hopene-2(14) and this also correlates davallic acid (I) with the hopane series(15). The stereochemistry at C-8, 14, 13, 18 and 17 required for the formation of isomers-1, -2 and -3 from davallic acid is in agreement with this correlation. Apparently, fernene and davallic acid belong to a new group of triterpenes derived biogenetically from hopane (the precursor could be something like hopene-a with an exocyclic C_{21}-C_{22} double bond). We suggest the name "fernane" for this rearranged hopane skeleton. Dreiding models show that ring B of davallic acid (I) is fixed in a boat form. The carboxyl group is assigned a β-axial configuration in view of the pK_{MCS} of isodavallic acid (Δ^8 isomer) at

8.60* (calcd. for a- and e-COOH, respectively, 8.41 and 7.91)(16), the IR doublet of methyl davallate at 1147 and 1160 cm^{-1} (CCl_4)(17), and the chemical shift of the $-CH_2OAc$ quartet centered at δ^{CCl_4} 4.05(18) in the NMR spectrum of davallol acetate (IV).

The mass spectra were measured at Stanford University and some at Hitachi Co., Naka Laboratories. The authors are grateful to Professor C. Djerassi and Dr. H. Vorbrüggen for discussions and identification of davallene. The studies were carried out in close contact with fernene(14), and we acknowledge this close cooperation.

REFERENCES

[1] The 100 mc measurement were kindly carried out by Dr. N. S. Bhacca, Varian Associates.

[2] J. M. Lehn and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1137 (1962).

[3] D. H. R. Barton, J. S. Fawcett and B. R. Thomas, *J. Chem. Soc.*, 3147 (1951); W. Voser, M. Montavon, H. H. Günthard, O. Jeger and L. Ruzicka, Helv. **33**, 1893 (1950); J. F. Cavalla and J. F. McGhie, *J. Chem. Soc.*, 744 (1951).

[4] The mass spectra of methyl davallate (II) and methyl isodavallate-1 (VII) were identical.

[5] C. Djerassi, H. Budzikiewicz and J.M. Wilson, *Tetrahedron Letters*, 263 (1962).

[6] H. Vorbrüggen, S. C. Pakrashi and C. Djerassi, *Ann.*, in press.

[7] P. Sengupta and H. N. Khastgir, *Tetrahedron* **19**, 123 (1963).

[8] F. N. Lahey and M. V. Leeding, *Proc. Chem. Soc.* (London), 342 (1958).

[9] G. Ourisson and P. Crabbé, *"Les triterpènes tétracycliques"*, p. 154, Hermann, Paris (1961).

[10] D. H. R. Barton, J. F. McGhie, M. K. Pradham and S. A. Knight, *J. Chem. Soc.*, 876 (1955).

[11] Measured with an automatic JASCO ORD/UV-5 spectropolarimeter.

[12] H. Ageta, K. Iwata and K. Yonezawa, *Chem. Pharm. Bull.* (Tokyo) **11**, 408 (1963).

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* Davallic acid itself was not soluble enough for pK measurements.

[13] Dr. H. Vorbrüggen, private communication.

[14] H. Ageta, K. Iwata and S. Natori, this journal, previous paper.

[15] G. V. Baddeley, T. G. Halsall and E. R. H. Jones, J. Chem. Soc., 3891 (1961).

[16] P. F. Sommer, V. P. Arya and W. Simon, Tetrahedron Letters 18 (1960); P. F. Sommer, C. Pascual, V. P. Arya and W. Simon, Helv. Chim. Acta, in press.

[17] Equatorial and axial COOMe groups of terpenes absorb at 1245 and 1155 cm^{-1} (sometimes doublet), respectively: Dr. M. Fetizon, private communication.

[18] E. Wenkert and P. Beak, Tetrahedron Letters, 358 (1961).