

THE EXACT NATURE OF MATATABILACTONE AND THE TERPENES OF NEPETA CATARIA

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Previously, T. Sakan and coworkers<sup>1</sup> reported that the active principle of the neutral fraction of Actinidia polygama for Felidae animals is matatabilactone which was identified as a mixture of iridomyrmecin (I) and isoiridomyrmecin (II).

In connection with a thorough investigation of the terpenes of Actinidia polygama, we have re-examined the lactone part of Actinidia polygama and the terpenes of Nepeta cataria.<sup>2</sup>

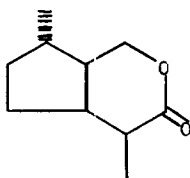
From the leaves and galls of Actinidia polygama we have isolated, in addition to iridomyrmecin and isoiridomyrmecin, three new lactones (dihydronepetalactone (III), isodihydronepetalactone (IV) and neonepetalactone (V)), which have been found to be quite attractive to cats. In addition, the absence of isomeric iridolactones<sup>3</sup> and dihydronepetalactones has been demonstrated by vapor phase chromatographic analysis. The isolation of these lactones was accomplished by repeated column chromatography on silicic acid of the lactone fraction, obtained by alkaline hydrolysis of the neutral

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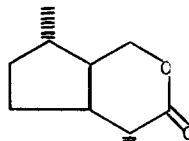
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fraction of Actinidia polygama, followed by acidification at room temperature.

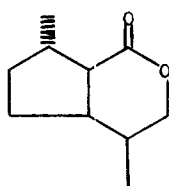
The final purification of each lactone was effected by VPC.



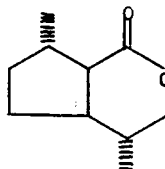
I



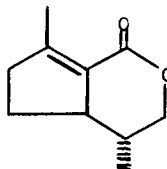
II



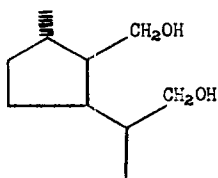
III



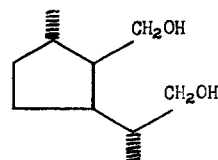
IV



V

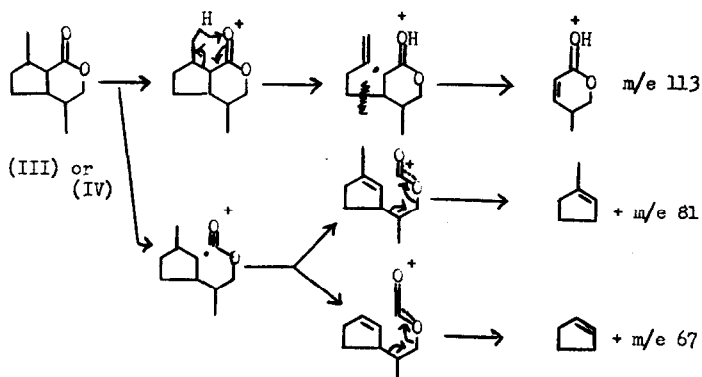


VI



VII

Lactones III,  $[\alpha]_D^{25} + 72^\circ$ , and IV,  $[\alpha]_D^{25} + 2.73^\circ$ , show an infrared absorption band at  $1725\text{ cm}^{-1}$  characteristic of a 6 membered lactone. The NMR spectrum of III exhibits two doublet methyl signals centered at  $9.12$  (3H,  $J$  6 c.p.s.) and  $8.85\tau$  (3H,  $J$  6 c.p.s.) and an ill-defined doublet at  $6.00\tau$  attributed to a  $-\text{CH}_2-\text{O}-$  group. The NMR spectrum of lactone IV also shows two doublet methyl signals at  $9.02$  ( $J$  6 c.p.s.) and  $8.90\tau$  ( $J$  6 c.p.s.), but the signals of the  $-\text{CH}_2-\text{O}$  protons at  $6.00\tau$  constitutes the AB part of an ABX pattern with  $J_{AX}$  4.5 c.p.s.,  $J_{BX}$  9 c.p.s. and  $J_{AB}$  11 c.p.s. The mass spectra of lactones III and IV show peaks at  $m/e$  168 (molecular ion), 153, 139, 113, 95, 81 (base peak) and 67. These fragments are best accounted for as shown below.

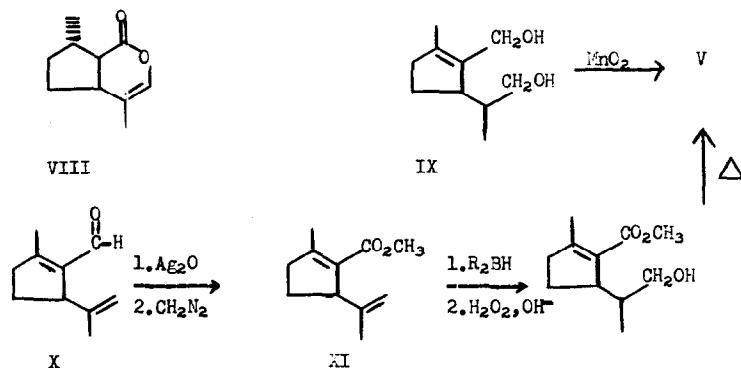


The stereochemistry of lactones III and IV were established by  $\text{LiAlH}_4$  reduction to  $\delta$ -iridodiol (VI) (bis-*p*-nitrobenzoate, m.p.  $138-139^\circ$ ) and  $\alpha$ -iridodiol (VII), m.p.  $79-80^\circ$ , respectively, whose properties and VPC retention times were identical with those of authentic samples.<sup>4</sup> In addition, catalytic hydrogenation of VPC pure nepetalactone (VIII) using platinum oxide and ethyl acetate afforded lactones III and IV in a ratio of approximately

20:1. The addition of hydrogen should occur from the least hindered  $\alpha$  side of nepetalactone and allows the assignment of structure III to the lactone produced in largest quantity, while the lactone produced in trace amount is assigned structure IV.

Neonepetalactone (V),  $C_{10}H_{14}O_2$ ,  $M^+$  166, exhibits infrared absorption at  $1710\text{ cm}^{-1}$  (C=O) and  $1645\text{ cm}^{-1}$  (C=C), and an ultraviolet maximum at  $241\text{ m}\mu$  ( $\log \epsilon$  4.0). The NMR spectrum of nonepetalactone shows the presence of a doublet methyl at  $9.05\tau$  (3H,  $J$  6 c.p.s.), a singlet methyl attached to a double bond at  $7.8\tau$ , and a  $-\text{CH}_2\text{O}$  group at  $5.8\tau$ .

From the spectral characteristics and biogenetic considerations<sup>5</sup> nonepetalactone was assigned structure V which was confirmed by its preparation by the  $\text{MnO}_2$  oxidation of the unsaturated diol IX<sup>6</sup> and by a total synthesis starting with limonene monooxide and proceeding through the unsaturated aldehyde X<sup>7</sup> and unsaturated ester XI as outlined below.<sup>8</sup>



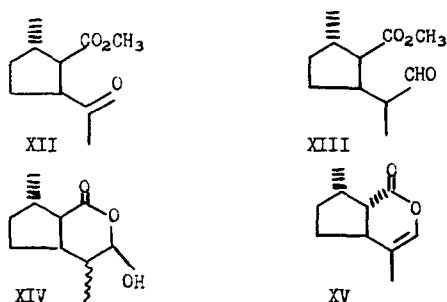
Catalytic hydrogenation of nonepetalactone (V), prepared from XI, using platinum oxide afforded lactones III and IV in a ratio of 1:4. This conversion suggests nonepetalactone is a mixture of isomers with the  $\alpha$ -methyl isomer predominating. Vapor phase chromatography of naturally occurring nonepetalactone demonstrated the presence of two poorly resolved components. The minor component had the same retention time as the  $\beta$ -methyl

isomer prepared by  $MnO_2$  oxidation of diol IX.

From the methanol extract of *Nepeta cataria* (cultivated in Japan) we have isolated two dihydronepetalactones whose identity with III and IV was confirmed by comparison of infrared spectra and VPC retention times. In addition, we have isolated methyl nepetonate (XII)<sup>2,9</sup> ( $C_{13}H_{16}O_3$ ,  $M^+$  184; IR, 1710 and 1725  $cm^{-1}$ ; NMR, 8.9 (3H, d), 7.9 (3H, s), 6.3 (3H, s), 6.6 (1H, m) and 7.4 $\tau$  (1H, m), an aldehyde ester (XIII) (IR, 1720, 2720, 1160 and 1195  $cm^{-1}$ ): and a hydroxy lactone (XIV) (IR, 1700 and 3380  $cm^{-1}$ ).

The structure of aldehyde ester XIII was established by sodium borohydride reduction and hydrolysis to dihydronepetalactone (III). Alkaline hydrolysis of the hydroxylactone XIV and sodium borohydride reduction afforded a mixture of lactones III and IV.

Examination of the neutral portion of three different samples of the oil of catnip (Fritzsche Brothers) by VPC demonstrated the presence of nepetalactone (VIII), isonepetalactone (XV),<sup>10</sup> eugenol and a trace of isodihyronepetalactone (IV). Eugenol and lactone IV have the same retention time on a carbowax 20 M column.



Isonepetalactone (XV), m.p. 27.5–29°, is converted to nepetalactone (VIII) by heating with potassium carbonate in xylene. This conversion<sup>10</sup> confirms the stereochemistry of XV suggested earlier by McElvain and Bates.

REFERENCES

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  5. The biogenetic considerations on the terpenes of Actinidia polyama will be discussed in a forthcoming publication (T.S.).
  6. Prepared from matatabiether (i) by treatment with 35% formic acid, followed by LiAlH<sub>4</sub> reduction. Matatabiether (i) is the major terpene of Actinidia polygama Miq. and its stereochemistry and synthesis has been established by Dr. S. Isce. A communication on matatabiether is forthcoming.
- The image shows the chemical structure of matatabiether (i), a bicyclic sesquiterpene. It consists of two fused five-membered rings. The right-hand ring is a lactone, with an oxygen atom at the top vertex and a carbonyl group (=O) at the bottom vertex. A methyl group is attached to the carbon atom at the bottom-right of the right-hand ring. The left-hand ring is a cyclopentane ring with a methyl group attached to the top-left carbon atom. The two rings are fused at the top-right and bottom-left carbons.
7. J. Wolinsky, M. Slabaugh and T. Gibson, J. Org. Chem. 29, 3740 (1964).
  8. Neonepetalactone obtained in this manner was contaminated with small amounts of lactones III and IV.
  9. G. Lukas, J. C. N. Ma, J. A. McCloskey and R. E. Wolff, Tetrahedron, 20, 1789 (1964).
  10. R. B. Bates and C. W. Sigel, Experientia, 19, 565 (1963).