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THE EXACT NATURE OF MATATABILACTONE AND THE TERPENES OF NEPETA CATARIA

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Previously, T. Sakan and coworkers[1] 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.[2]

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[3] 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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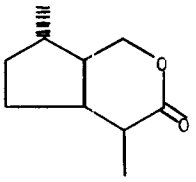
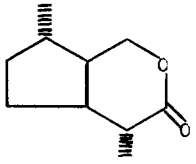
fraction of Actinidia polygama, followed by acidification at room temperature. The final purification of each lactone was effected by VPC.



I



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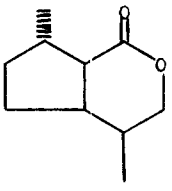
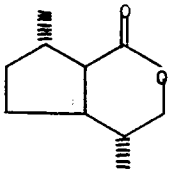


III



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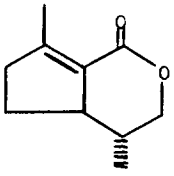
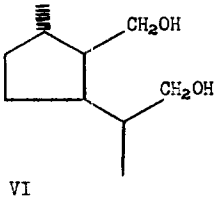
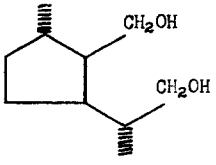


V

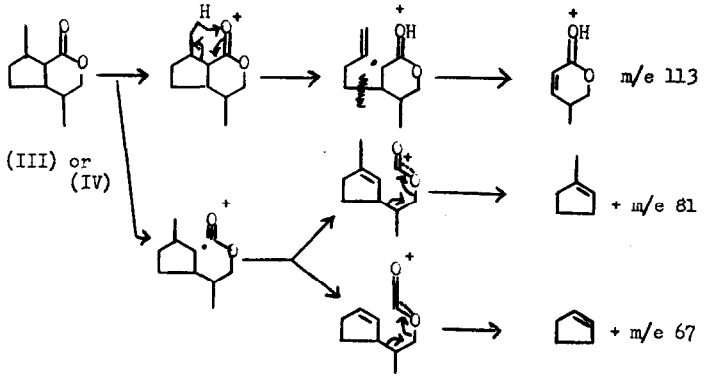


VI



VII

Lactones III, $[\alpha]_D^{25}$ + 72°, and IV, $[\alpha]_D^{25}$ + 2.73°, show an infrared absorption band at 1725 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 8.85τ(3H, J 6 c.p.s.) and an ill-defined doublet at 6.00τ attributed to a $-CH_2-O-$ group. The NMR spectrum of lactone IV also shows two doublet methyl signals at 9.02 (J 6 c.p.s.) and 8.90τ(J 6 c.p.s.), but the signals of the $-CH_2-O$ protons at 6.00τ 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.

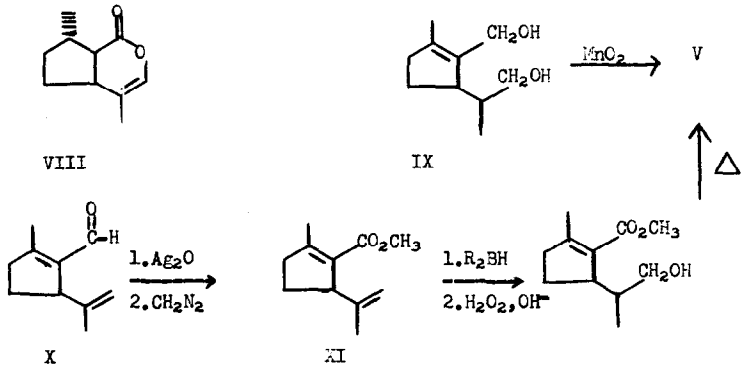


The stereochemistry of lactones III and IV were established by $LiAlH_4$ reduction to δ-iridodiol (VI) (bis-p-nitrobenzoate, m.p. 138-139°) and α-iridodiol (VII), m.p. 79-80°, respectively, whose properties and VPC retention times were identical with those of authentic samples.[4] In addition, catalytic 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 α 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 absorbtion at 1710 cm^{-1} (C=O) and 1645 cm^{-1} (C=C), and an ultraviolet maximum at 241 mμ (log ε 4.0). The NMR spectrum of neonepetalactone shows the presence of a doublet methyl at 9.05 τ (3H, J 6 c.p.s.), a singlet methyl attached to a double bond at 7.8 τ, and a $-CH_2-O$ group at 5.8 τ.

From the spectral characteristics and biogenetic considerations[5] neonepetalactone was assigned structure V which was confirmed by its preparation by the MnO_2 oxidation of the unsaturated diol IX[6] and by a total synthesis starting with limonene monooxide and proceeding through the unsaturated aldehyde X[7] and unsaturated ester XI as outlined below[8].



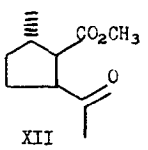
Catalytic hydrogenation of neonepetalactone (V), prepared from XI, using platinum oxide afforded lactones III and IV in a ratio of 1:4. This conversion suggests neonepetalactone is a mixture of isomers with the α-methyl isomer predominating. Vapor phase chromatography of naturally occurring neonepetalactone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

isomer prepared by MnO_2 oxidation of diol IX.

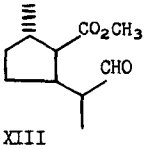
From the methanol extract of Nepeta cataria (cultivated in Japan) we have isolated two dihydronepetalactones whose identity with III and IV was confirmed by comparison of infrared spectra and VPC retention times. In addition, we have isolated methyl nepetonate (XII)[2,9] ($C_{13}H_{16}O_3$, M^+ 184; IR, 1710 and 1725 cm^{-1}; NMR, 8.9 (3H, d), 7.9 (3H, s), 6.3 (3H, s), 6.6 (1H, m) and 7.4τ(1 H, m), an aldehdye 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.

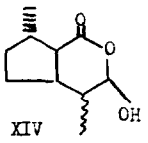
Examination of the neutral portion of three different samples of the oil of catnip (Fritzsche Brothers) by VPC demonstrated the presence of nepetalactone (VIII), isonepetalactone (XV),[10] eugenol and a trace of isodihydronepetalactone (IV). Eugenol and lactone IV have the same rention time on a carbowax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



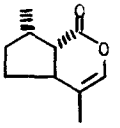
XII



XIII



XIV



XV

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

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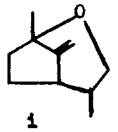
5. The biogenetic considerations on the terpenes of Actinidia polyama will be discussed in a forthcoming publication (T.S.).

6. Prepared from matatabiether (i) by treatment with 35% formic acid, followed by $LiAlH_4$ reduction. Matatabiether (i) is the major terpene of Actinidia polygama Miq. and its stereochemistry and synthesis has been established by Dr. S. Isoe. A communication on matatabiether is forthcoming.



i

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).