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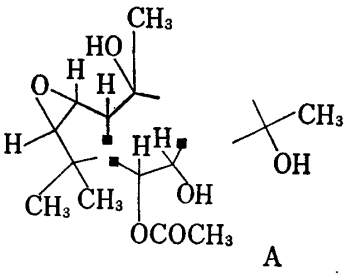
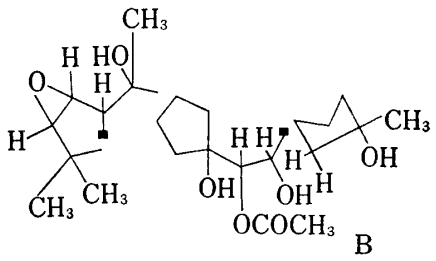
Stereostructure of Lyoniatoxin, Toxin of *Lyonia ovalifolia* var. *elliptica*

In 1960 Ikeda and Suzuki[1] announced the isolation of a toxin, lyoniatoxin, from the leaves of *Lyonia ovalifolia* DRUDE var. *elliptica* HANDEL-MAZZETTI (Ericaceae), a famous poisonous tree in Japan, the rational formula $C_{20}H_{27}O(OCOCH_3)(OH)_4$ being given for it. Immediately thereafter, Yasue, *et al.*[2] also reported the isolation of three toxins, lyoniol-A, B, and C, from the sprouts of the same plant. Later, it was found that lyoniol-A and B are identical with lyoniatoxin and desacetyllyoniatoxin, respectively.[3] However, the structures of these toxins remain unknown. We have recently investigated the structure of lyoniatoxin (L).

L, $C_{22}H_{34}O_7$, mp 250—253°, was shown by the infrared (IR) and nuclear magnetic resonance (NMR) spectra to possess two tertiary methyls (1.24, 1.54 ppm), two tertiary methyls on hydroxyl-bearing carbons (1.49, 1.85 ppm), one epoxide (3.25, 4.19 ppm (J=3.0 Hz)), one secondary acetoxyl (1702, 1264 cm^{-1}, 5.61 ppm), and hydroxyls (3510 cm^{-1}) one of which is secondary (3.86 ppm). Further, analysis of the NMR spectrum with the aid of double resonance experiments revealed the presence of the partial structure A.



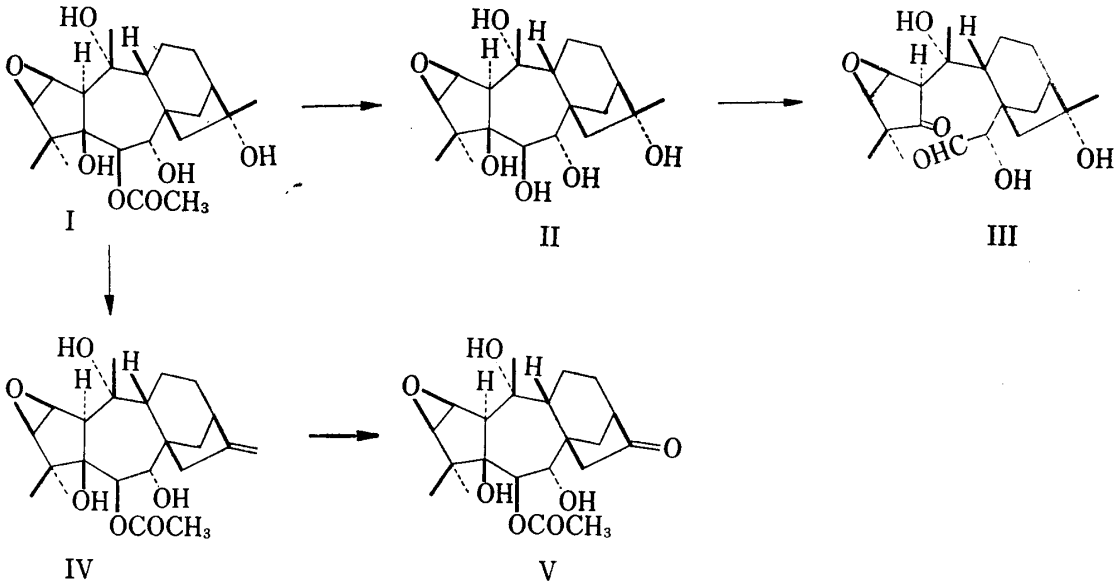
A



B

■ : denotes a quaternary carbon

While L is not reacted with periodate,[1] desacetyl L (II), mp 280—283°, derived from L by alkaline hydrolysis, on periodate oxidation afforded the dehydroderivative (III), mp



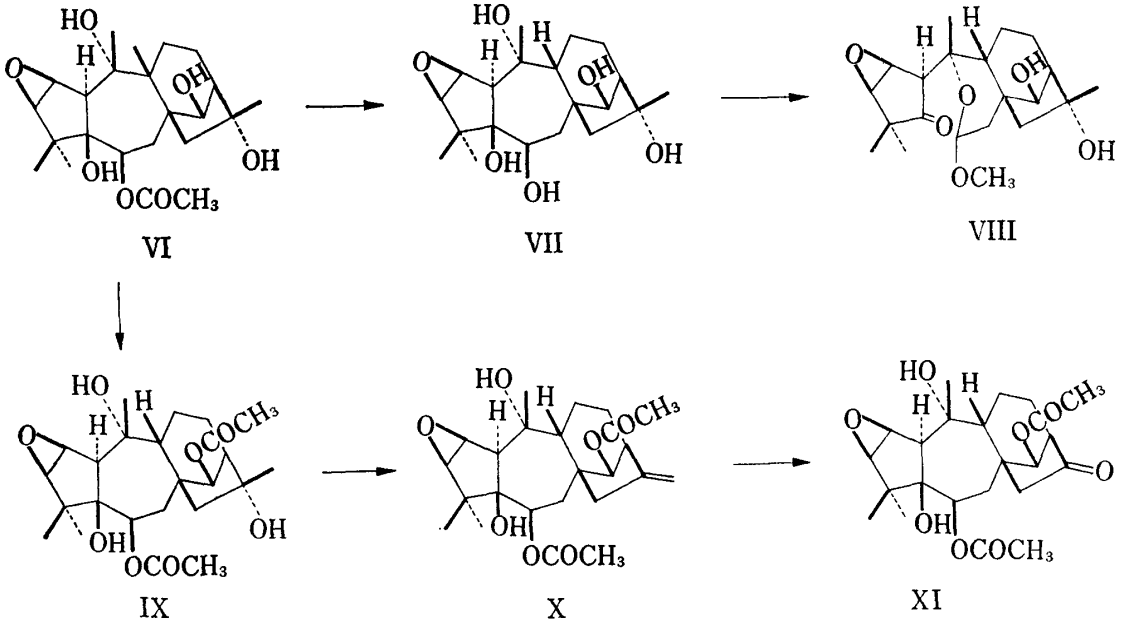
I II III

IV V

1) N. Ikeda and Y. Suzuki, *Shoyakugaku Zasshi*, **14**, 45 (1960).
2) M. Yasue, Y. Kato, T. Kishida, and H. Ota, *Chem. Pharm. Bull.* (Tokyo), **9**, 171 (1961).
3) M. Yasue, private communication.

150—157°, whose spectral properties indicate the formation of a cyclopentanone (1730 cm^{-1}) and an α-hydroxy-aldehyde group (9.55, 5.13 ppm) during the periodate oxidation. When L was treated with phosphorus oxychloride in pyridine, the dehydration product (IV), mp 215—216.5°, having a vinylidene group (4.65, 4.75 ppm) was obtained. Ozonolysis of the product (IV) yielded the norketone (V), mp 220—225°, whose spectral properties demonstrate the formation of a cyclopentanone (1731 cm^{-1}, $[\theta]_{306}+500$) and a methylene flanking a carbonyl (1404 cm^{-1}). These findings lead to the extension of the part-structure of L from A to B. Bearing in mind the tetracarbocyclic nature of L and the common occurrence of the grayanotoxins,[4,5] the asebotoxins,[5,6,7] and the rhodojaponins[5,7] possessing the andromedane skeleton in the same family, L may be assumed as having the same basic carbon skeleton. Hence, the accumulated data are interpreted to allow the assignment of structure I to L which is then an isomer of rhodojaponin II (R-II) (VI), a toxin of *Rhododendron japonicum* SURINGER (Ericaceae).

Under the validity of the expressed suppositions, the chemical shifts and splitting patterns of the signals in the NMR spectra of the derivatives of L (I, II, III, IV, and V) coincide with those of the corresponding derivatives of R-II (VI, VII, VIII, X, and XI) prepared by similar procedures, except for the differences caused by the replacement of the C-14 carbinyl hydrogens in the latter series by the C-7 carbinyl hydrogens in the former series. Furthermore, the ORD and CD curves of the cyclopentanone (V) are essentially identical with those of the cyclopentanone (XI). The facts that desacetyl L (II) consumes only one mole of periodate at a rapid rate and that the $J_{6,7}$ in the NMR spectrum of L is fairly large (9.6 Hz), indicate the *trans* relation ship of the C-6 and C-7 functions.



Based on the above evidence, we have concluded that L is represented by formula I.[8]

4) *cf.*, H. Kakisawa, T. Kozima, M. Yanai, and K. Nakanishi, *Tetrahedron*, **21**, 3091 (1965).
5) H. Hikino, M. Ogura, T. Ohta, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), in press.
6) H. Hikino, K. Ito, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **17**, 854 (1969).
7) H. Hikino, K. Ito, T. Ohta, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **17**, 1078 (1969).
8) The Nagoya City University group, in their independent investigation, has also arrived at a similar conclusion about the structure of L as our own. Both groups have agreed to present their respective results in separate communications simultaneously.

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Structure of Lyoniol-A (Lyoniatoxin)

Lyoniol-A (Lyoniatoxin)[1] $C_{20}H_{27}(OH)_4(OAc)(-O-)$ (I) is the main component of the toxic principles of *Lyonia ovalifolia* DRUDE (SIEB. et ZUCC.) var. *elliptica* HAND.-MAZZ. I was indicated to have four $\geqslant C-CH_3$ and an epoxide $-\overset{H}{\underset{\diagdown}{C}}-\overset{O}{\underset{\diagdown}{}}-\overset{H}{\underset{\diagdown}{C}}-$ from it's nuclear magnetic resonance (NMR) data: $\delta^{C_5H_5N}_{ppm}$ 1.26 (3H, singlet, $\geqslant C-CH_3$), 1.50 (3H, singlet, $\geqslant C-CH_3$), 1.57 (3H, singlet, $-C(OH)-\underline{CH_3}$), 1.88 (3H, broad singlet, $-C(OH)-\underline{CH_3}$), 2.17 (3H, singlet, $OCOCH_3$), 2.89 (1H, broad singlet, $\geqslant C(-C(OH)-H)-\underline{H}$), 3.27 (1H, doublet, J=3.0 cps, $-C(-O-)-\underline{H}$), 3.88 (1H, doublet, J=9.5 cps, $-C(OAc)-\underline{H}$), 4.21 (1H, doublet, J=3.0 cps, $-C(OH)-\underline{H}$), 5.64 (1H, doublet, J=9.5 cps, $-C(AcO)-\underline{H}$). Alkaline hydrolysis of I afforded deacetyl compound $C_{20}H_{27}(OH)_5$ (-O-) (II), NMR $\delta^{C_5D_5N\text{-}D_2O}_{ppm}$: 1.26 (3H, singlet), 1.55 (6H, singlet), 1.85 (3H, singlet), 2.86 (1H, broad singlet), 3.32 (1H, doublet, J=3.0 cps), 3.75, 3.98 (2H, AB quartet, J=9.3 cps), 4.30 (1H, doublet, J=3.0 cps). II was reversed to lyoniol-A with acetic anhydride and pyridine. The deacetyl derivative II consumed one mole of sodium periodate, but I did not, thus the acetoxyl group located vicinal to a hydroxyl group. The NMR data of I and II reveal that the glycolic part of the molecule is inserted between two tertiaryly substituted carbon atoms. The acetonide of II, formed in acetone with *p*-toluenesulfonic acid, is colorless needles from benzene and chloroform mixture (1:1), mp 241—249°. *Anal.* Calcd. for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88. Found: C, 67.79; H, 8.99. NMR $\delta^{C_5D_5N}_{ppm}$ 1.21, 1.44, 1.49, 1.51, 1.62, 1.83 (each 3H, singlet, $\geqslant C-CH_3 \times 6$), 2.85 (1H, broad singlet), 3.32 (1H, doublet, J=3.0 cps), 3.82 (1H, broad doublet, J=*ca.* 9.0 cps), 4.21 (1H, doublet, J=3.0 cps), 4.32 (1H, doublet, J=9.0 cps). This acetonide did not react with chromic acid in pyridine. Therefore three remaining hydroxyl groups are suggested to be tertiary alcohols.

1) N. Ikeda and Y. Suzuki, *Shoyakugaku Zasshi Japan*, **14**, 45 (1960); M. Yasue, Y. Kato, T. Kishida, and H. Ohta, *Chem. Pharm. Bull.* (Tokyo), **9**, 171 (1961).