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

In 1960 Ikeda and Suzuki¹⁾ 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.

■ : 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

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 cyclopenta-

none (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* relationship 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.

Pharmaceutical Institute,
Tohoku University,
Aoba-yama, Sendai

Central Research Laboratories,
Sankyo Co., Ltd.,
Hiromachi, Shinagawa, Tokyo

HIROSHI HIKINO
YASUKO HIKINO
TSUNEMATSU TAKEMOTO
SHUJI TAKAHASHI

Received December 20, 1969

[Chem. Pharm. Bull.]
18(4) 854-856 (1970)

UDC 581.19 : 547.597.02 : 615.31.011.5

Structure of Lyoniol-A (Lyoniatoxin)

Lyoniol-A (Lyoniatoxin)¹⁾ C₂₀H₂₇(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 $\geq\text{C}-\text{CH}_3$ and an epoxide $\begin{smallmatrix} \text{H} & \text{O} & \text{H} \\ & \diagdown & / \\ & \text{C} & - & \text{C} \\ & / & \diagdown \end{smallmatrix}$ from its nuclear magnetic resonance

(NMR) data: $\delta_{\text{ppm}}^{\text{C}_6\text{H}_5\text{N}}$ 1.26 (3H, singlet, $\geq\text{C}-\text{CH}_3$), 1.50 (3H, singlet, $\geq\text{C}-\text{CH}_3$), 1.57 (3H, singlet, $\text{OH}-\text{C}-\text{CH}_3$), 1.88 (3H, broad singlet, $\text{OH}-\text{C}-\text{CH}_3$), 2.17 (3H, singlet, OCOCH_3), 2.89 (1H, broad

singlet, $\geq\text{C}-\text{C}(\text{OH})-\text{C}(\text{H})-\text{O}-$), 3.27 (1H, doublet, $J=3.0$ cps, $\begin{smallmatrix} \text{O} \\ | \\ \text{C} & - & \text{C} & - & \text{C} < \\ | & & | \\ \text{H} & & \text{H} \end{smallmatrix}$), 3.88 (1H, doublet, $J=9.5$ cps, $\begin{smallmatrix} \text{OAc} & \text{H} \\ | & | \\ \text{C} & - & \text{C} & - & \text{C} < \\ | & & | \\ \text{H} & & \text{OH} \end{smallmatrix}$), 4.21 (1H, doublet, $J=3.0$ cps, $\begin{smallmatrix} \text{O} \\ | \\ \text{C} & - & \text{C} & - & \text{C} < \\ | & & | \\ \text{H} & & \text{H} \end{smallmatrix}$), 5.64 (1H, doublet, $J=9.5$ cps, $\begin{smallmatrix} \text{AcO} & \text{H} \\ | & | \\ \text{C} & - & \text{C} & - & \text{C} < \\ | & & | \\ \text{OH} & & \text{H} & & \text{OH} \end{smallmatrix}$). Alkaline hydrolysis of I afforded deacetyl compound C₂₀H₂₇(OH)₅

(-O-) (II), NMR $\delta_{\text{ppm}}^{\text{C}_6\text{H}_5\text{N}-\text{D}_2\text{O}}$: 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 tertiary 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 C₂₃H₃₆O₆: C, 67.62; H, 8.88. Found: C, 67.79; H, 8.99. NMR $\delta_{\text{ppm}}^{\text{C}_6\text{H}_5\text{N}}$ 1.21, 1.44, 1.49, 1.51, 1.62, 1.83 (each 3H, singlet, $\geq\text{C}-\text{CH}_3 \times 6$), 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).