

STEREOSTRUCTURE OF LEUCOTHOL B AND D, DITERPENOIDS OF *LEUCOTHOE GRAYANA*

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(Received in Japan 1 August 1972; received in UK for publication 8 August 1972)

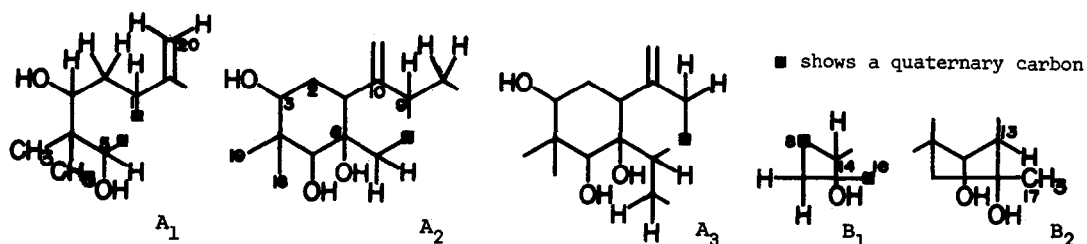
From the leaves of *Leucothoe grayana* Maximowicz (Ericaceae), a famous poisonous shrub in Japan, thirteen toxic diterpenoids of the andromedane skeleton, grayanotoxin I - XIII, have been isolated.¹⁾ Further survey has resulted in the isolation of three new diterpenoids having the novel carbon skeleton for which the terms leucothol A, B, and D (L-A, L-B, and L-D) are given.^{*1}

L-B, C₂₀H₃₂O₅, m.p. 257-258°, was demonstrated by the IR and ¹H NMR spectra^{*2} to contain three tertiary methyls (δ 1.40, 1.48, 1.50 ppm), a vinylidene (ν_{\max} 3100, 1642, 876 cm⁻¹, δ 4.96, 5.12 ppm), and hydroxyl (ν_{\max} 3380 cm⁻¹) three of which are secondary (δ 3.37, 3.94, 4.52 ppm). The ¹³C NMR spectrum^{*2} indicates the presence of three methyls (δ 23.8, 26.9, 26.9 ppm), five methylenes (δ 21.1, 26.0, 29.4, 38.8, 41.9 ppm), three methines (δ 38.2, 52.1, 55.3 ppm), two quaternary carbons (δ 50.9, 54.7 ppm), three secondary carbonyl carbons (δ 76.1, 80.7, 82.5 ppm), two tertiary carbonyl carbons (δ 78.2, 79.5 ppm), and a vinylidene (δ 106.4, 151.7 ppm).

L-B on acetylation gave the diacetate (II), m.p. 188-190°, the triacetate (III), and the tetraacetate (IV). The IR spectrum of the tetraacetate (IV) still shows the retention of a hydroxyl (ν_{\max} 3460 cm⁻¹), a fact which indicates L-B to be a penta-ol, all the oxygen atoms being accommodated. Since L-B has only one double bond, confirmed by catalytic hydrogenation of the triacetate (III) giving the saturated dihydro-derivative (V), L-B is a tetracarbo-cyclic compound.

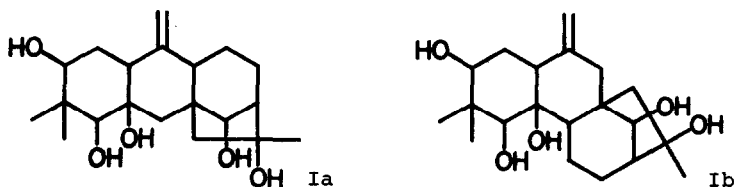
Analysis of the ¹H NMR spectrum of L-B clarified the environment of the A-ring as in formula A₁. Ozonolysis of L-B furnished the 20-norketone (VI), m.p. 230-231°, which on treatment with alkali gave the fully substituted enone (VII), m.p. 264-266° (λ_{\max} 247 nm, no vinyl hydrogen signal). In the ¹H NMR spectrum of the enone (VII), the C-1 methine hydrogen signal, observed in that of the norketone (VI), is missing and the C-5 carbonyl hydrogen signal is displaced downfield (-1.7 ppm) in comparison with that of the norketone (VI), indicating the formation of an ethylenic bond (C-1:C-6) α to C-5 during the dehydration of the norketone (VI). These results show that a tertiary hydroxyl is located at C-6 in L-B. The IR bands of the norketone (VI) and

the anhydro-norketone (VII) (ν_{\max} 1712 and 1648 cm^{-1} , respectively) demonstrate that the ring (B) containing the carbonyl is six- or larger-membered. These findings together with further analysis of the ^1H NMR spectrum of the enone (VII) lead to the extension of formula A₁ to A₂ or A₃.



Further NMR experiments of L-B showed that it has the partial structure B₁. Chromic acid oxidation of the diacetate (II) gave the cyclopentanone (VIII), m.p. 188-190° (ν_{\max} 1740 cm^{-1}). Treatment of the dihydro-triacetate (V) with cupric sulfate in dioxane yielded the vinylidene-derivative (IX), m.p. 248-249° (ν_{\max} 1653, 889 cm^{-1}), indicating that L-B has a methyl on a tertiary hydroxyl-bearing carbon. On ozonolysis the anhydro-derivative (IX) afforded the cyclopentanone (X) (ν_{\max} 1740 cm^{-1}). Since in L-B there are only four quaternary carbons, two of which have been assigned to those in the A-ring, one of the remaining two which carries both the methyl and the hydroxyl must be allotted to C-8 or C-16 in formula B₁. The C-14 carbonyl hydrogen signal in the spectrum of the anhydro-triacetate (IX) exhibits an upfield shift (+0.17 ppm) as compared with that of the triacetate (V), which excludes the formation of an allyl alcohol moiety during the dehydration of the triacetate (V). Therefore, the quaternary carbon bearing both the methyl and the hydroxyl is assigned to C-16. Formula B₁ is thus extended to B₂. The remaining quaternary carbon (C-8) is deduced to be identical with that in the B-ring.

The combined evidence leaves only two possible structures, Ia and Ib, for L-B. Provided that L-B is a diterpenoid biosynthesized from the common precursor geranyl geraniol, only the gross structure Ia is probable.



In the ^1H NMR spectrum of L-B, the coupling constants between the C-1 and C-2 hydrogens (J 2, 11 Hz) are attributed to axial-equatorial and axial-axial couplings, while those between the C-2 and C-3 hydrogens (J 2, 4 Hz) indicate the C-3 hydrogen to be equatorially oriented. A long

range coupling between the C-3 and C-5 hydrogens (J 1.5 Hz) shows that both the hydrogens are located in a *w*-arrangement, demonstrating the equatorial nature of the C-5 hydrogen. In agreement with the above assignment, intramolecular nuclear Overhauser effects were observed between the C-3 and C-18, C-3 and C-19, C-5 and C-18, and C-5 and C-19 hydrogens. The CD curve of 5-dehydro-L-B, L-D (XI) (*vide infra*), exhibits a negative Cotton effect ($[\Theta]_{313}$ -4250), like that of L-A (XII)² ($[\Theta]_{302}$ -12450), whereas that of the congener (XIII) which was derived from grayanotoxin II shows a positive Cotton effect ($[\Theta]_{303}$ +2050), a fact which indicates 1(*R*),6(*S*) or 1(*S*),6(*S*) configuration and consequently establishes the α -configuration of the C-6 hydroxyl in L-B. Comparison of the CD maximum of 5-dehydro-L-B (XI) with that of L-A (XII) reveals that a bathochromic shift of 11 nm and the decrease of the molecular ellipticity are observed, a fact which suggests that the C-6 hydroxyl is axially situated. No consumption of periodate by L-B supports the *trans*-diaxial relationship of the C-5 and C-6 hydroxyls. The CD curves of the 14-dehydro-diacetate (VIII) and the 17-norketone (X) exhibit negative and positive Cotton effects ($[\Theta]_{298}$ -350 and $[\Theta]_{299}$ +4750, respectively), establishing the absolute configuration of the bicyclo[3.2.1]octane moiety as 8(*S*),13(*R*). The fact that the coupling constant between the C-13 and C-14 hydrogens is very small is consistent with the α -configuration of the C-14 hydrogen. The C-14 carbonyl in the 14-dehydro-diacetate (VIII) acts to deshield the C-17 methyl hydrogens by 0.10 ppm relative to those in the 14-hydroxy-analog (II). This downfield shift is in accord with that (-0.11 ppm) between grayanotoxin II 3,6-diacetate and its 14-dehydro-derivative, showing the β -configuration of the C-17 methyl. The ORD and CD curves of the 20-norketone (VI) displaying positive Cotton effects (α +57, $[\Theta]_{298}$ +3700) are similar to those (α +30, $[\Theta]_{296}$ +2550) of the 20-norketone (XV) derived from L-A (XII) *via* the dihydro-derivative (XIV). This observation, which points to the like environment of the C-10 carbonyls in both the norketones (VI and XV), indicates that the C-1 and C-9 hydrogens are both β -oriented. After the establishment of the absolute stereochemistry at the A/B ring junction, both the C-3 and C-5 hydroxyls must be allocated the β -configurations.

From the accumulated data, it is concluded that L-B possesses the stereostructure I.

L-D, C₂₀H₃₀O₅, m.p. 259-260°, is a poly-hydroxy ketone (ν_{\max} 3460, 3360, 1707 cm⁻¹). Hydride reduction of L-D yielded two epimeric dihydro-derivatives, one of which was identified as L-B (I). Comparison of the ¹H NMR spectra of L-B and L-D revealed that the C-5 hydrogen signal in the former is absent in the latter, establishing that L-D is 5-dehydro-L-B (XI).

The leucotohols constitute a unique group of diterpenoids from the viewpoint of biosynthesis.

*1 Before the submission of this paper, we have learned that Hokkaido University group has also isolated similar substances, leucothol A,²⁾ B, and C,³⁾ from the same plant source, *L. grayana* leaves. The common substances, leucothol A and B, of both groups have been identified.

*2 The ¹H NMR spectra were determined using a Varian HA-100 and a Hitachi R-20 NMR spectrometer and the ¹³C NMR spectrum was recorded on a JEOL PS-100 pulsed-Fourier transform NMR spectrometer. Chemical shifts are expressed in ppm downfield from internal TMS.

1) *cf.*, H. Hikino, S. Koriyama, T. Ohta, and T. Takemoto, *Chem. Pharm. Bull.*, 20, 422 (1972).

2) N. Hamanaka, T. Okuno, H. Miyakoshi, A. Furusaki, and T. Matsumoto, *Abstract of the 25th Annual Meeting of the Chemical Society of Japan*, p. 1241, Hiratsuka, April 1972.

3) T. Matsumoto, private communication.

