Stereostructure of α -Dihydro-grayanotoxin-II

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Many Grayanotoxins have been isolated from the leaves of *Leucothoe grayana* Max. (*Ericaceae*). Grayanotoxin-I⁽¹⁾ (G-I), $C_{22}H_{36}O_7$, the main toxic constituent, has been assigned the structure⁽²⁾ shown. Grayanotoxin-II⁽¹⁾ (G-II), $C_{20}H_{32}O_5$, having one exocyclic methylene group between C_{10} and C_{20} , is hydrogenated to the epimeric dihydrocompounds,⁽³⁾ $C_{20}H_{34}O_5$, α -dihydro-G-II (mp 259~260°C) and β -dihydro-G-II (mp 217°C). G-I specifically increases sodium permeability of cytoplasmic membranes in skeletal muscles,⁽⁵⁾ squid axons⁽⁶⁾ and atria.⁽⁷⁾ α -Dihydro-G-II shows the same effect^(8,9) as G-I, whereas β -dihydro-G-II has little or no effect.⁽⁹⁾ α -Dihydro-G-II is used as a tool for studying membrane depolarization. It seems to be noteworthy to elucidate the configuration of 20-methyl group in α -dihydro-G-II. In this note we report that the 20-methyl group is in the β -configuration, which is in accord with the 20-methyl configuration of G-I.

G-I $R_1=OH$, $R_2=Ac$, $R_3=H$

α -Dihydro-G-II $R_1=R_2=R_3=H$

Tetraacetyl- α -dihydro-G-II $R_1=H$, $R_2=R_3=Ac$

On heating with acetic anhydride-pyridine, α - and β -dihydro-G-II yield the corresponding tetraacetates,⁽³⁾ $C_{28}H_{42}O_9$, in each of which C_6 -hydroxyl group⁽⁴⁾ in the 1,3-position to the 20-methyl group remains unchanged.⁽⁴⁾ A PMR signal due to a methyl group being at or near the 1,3-diaxial position to a hydroxyl group should suffer a remarkable downfield shift⁽¹⁰⁾ and protons of the methyl group should be further deshielded by the hydroxyl group on passing from deuteriochloroform to deuteriopyridine as solvent.⁽¹¹⁾

The PMR signals due to the 20-methyl groups in tetraacetyl- α -dihydro-G-II and tetraacetyl- β -dihydro-G-II determined in deuteriochloroform and deuteriopyridine solutions appeared as three-proton doublets at the following positions ($J=6\sim 7$ Hz).

	δ in $CDCl_3$	δ in pyridine- d_5
the α -isomer	1.10	1.30*
the β -isomer	0.90	0.82

The 20-methyl protons of the α -isomer absorbed at lower field than those of the β -isomer by 0.20 in deuteriochloroform and 0.48 in deuteriopyridine.

These results indicate that the 20-methyl group in α -dihydro-G-II is located at the pseudo-1,3-diaxial position to the $C_6\beta$ -hydroxyl group and therefore has the β -configuration.

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* In the doublet at 1.30, the lower field portion appeared at 1.35 and the higher one overlapped with a singlet methyl signal at 1.27, which was observed in both the 60 MHz and 100 MHz spectra of the α -isomer.