

REACTION OF GRAYANOTOXIN-II WITH MERCURIC ACETATE
AND THE A/B RING JUNCTION OF GRAYANOTOXINS

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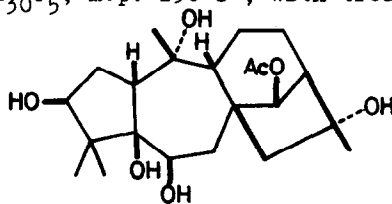
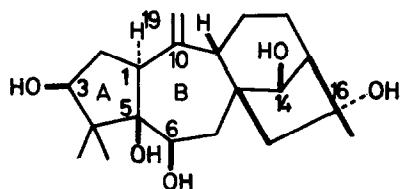
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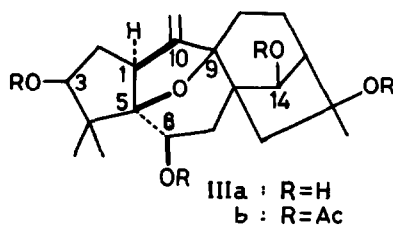
Grayanotoxin-I, Grayanotoxin-II and Grayanotoxin-III are obtained from the leaves of the various Ericaceae species¹⁾. The stereochemistry of Grayanotoxins was established except the A/B ring junction^{2,3)}. Kakisawa²⁾ compared the ORD curves of 3-keto grayanotoxin derivatives with those of several analogous ketones and supposed the A/B ring of Grayanotoxin-I to the cis-junction as indicated in II, but Kumazawa³⁾ assigned the other type of cis-junction (C₁-H and C₅-OH have both α -configuration). The authors obtained the chemical evidence that the configurations of the C₁-hydrogen and the C₅-hydroxyl were α and β , respectively, as shown in I.

Grayanotoxin-II (G-II) C₂₀H₃₂O₅, having one terminal methylene group, was converted to a dehydro compound (IIIa), C₂₀H₃₀O₅, m.p. 236-8°, with treatment



of mercuric acetate in tetrahydrofuran for about 30 hrs. followed with NaBH_4 -reduction⁴). This compound exhibited no α -glycol and was also obtained from 3,6,14,16-tetraacetyl G-II with the same treatment and then alkaline hydrolysis. The heating with acetic anhydride-pyridine gave the corresponding tetraacetate (IIIb), $\text{C}_{28}\text{H}_{38}\text{O}_9$, m.p. $171-2^\circ$, which showed no hydroxyl band in the infrared region. These results indicate that the C_5 -hydroxyl participates in a formation of transannular ether linkage.

The infrared bands of IIIa at 3100 , 1660 and 895 cm^{-1} and a two-proton singlet at $\delta\ 5.05$ ppm in the NMR spectrum prove that the terminal methylene group remain unchanged. Ozonolysis of IIIb and alkaline hydrolysis then gave a ketone $\text{C}_{19}\text{H}_{28}\text{O}_6$, m.p. $226.5-7.5^\circ$, which exhibited the infrared absorption characteristic of cyclopentanone at 1750 cm^{-1} . The hydrogenation of IIIa afforded a dihydro compound $\text{C}_{20}\text{H}_{32}\text{O}_5$, m.p. $206-7^\circ$, which on chromic acid-pyridine oxidation gave a triketone $\text{C}_{20}\text{H}_{26}\text{O}_5$, m.p. $173-4^\circ$. The NMR spectrum of the triketone showed two one-proton doublets at $\delta\ 2.07$ (J 17cps) and $\delta\ 3.26$ ppm (J 17cps) corresponding to the grouping $-\overset{|}{\underset{|}{\text{C}}}-\text{CO}-\text{CH}_2-\overset{|}{\underset{|}{\text{C}}}-$, which proved the presence of the C_6 -ketone. In addition to a strong cyclopentanone band due to the C_3 -ketone and the C_{14} -ketone, the infrared spectrum of the triketone



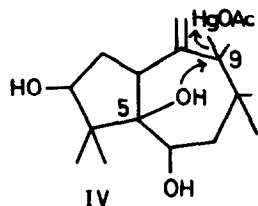
showed a weak cyclohexanone band at 1720 cm^{-1} based on the C_6 -ketone. These data indicate the formation of the ether compound as shown in IIIa.

When two five-membered rings are fused, the

cis-fusion is highly energetically favored. The formation of this ether indicates that the C₅-OH and the C₁-C₁₀ linkage in G-II must be in a cis relation with respect to A-ring and then this proves the trans relationship of A/B ring junction.

Reaction of α -dihydro G-II with 3,5-dinitro benzoylchloride and pyridine gave a monobenzoate C₂₇H₃₆O₁₀N₂, m.p. 229-30°. As the benzoate does not consume any lead tetraacetate, this is the C₆-monobenzoate. According to the benzoate rule⁵⁾, the benzoate would be more levorotatory if the C₆-OH had the β -configuration. This was found to be the case: 3,5-dinitro benzoate [M]_D²⁰ -146.3° vs. α -dihydro G-II [M]_D²⁰ +24.8°; it follows that the configuration of the C₆-OH is β in agreement with the conclusion of Kakisawa²⁾. As the cis relationship of the C₅- and C₆-hydroxyls has been proved, the configuration of the C₅-OH is also β , which consequently establishes that the configuration of the C₁-hydrogen must be α .

The preparation of this ether IIIa had been performed by the treatment with mercuric acetate and the subsequent NaBH₄-reduction, but afterwards it became evident that the ether could be obtained ever by omitting the reduction. The terminal double bond and mercuric acetate form a mercurinium ion. It is



supposed that the ion will rearrange to C₉-HgOAc (IV) which can yield the ether if the transannular attack of the C₅-OH occurs.

It was found that the C₅-OH of 3,6,14,16-tetraacetyl

G-II could be acetylated by treatment with isopropenyl acetate in the presence of p-toluene sulfonic acid. The obtained pentaacetate $C_{30}H_{42}O_{10}$, m.p. 184-5°, showed no hydroxyl band in the infrared region and gave G-II on alkaline hydrolysis. The acetate lost acetic acid when treated with mercuric acetate for about 100 hrs. giving a compound $C_{28}H_{38}O_8$, m.p. 160-60.5°, which also was obtained by dehydration with $SOCl_2$ -pyridine of tetraacetyl G-II. The compound showed bands in the ultraviolet region at 242 m μ (log ϵ 4.1) and in the infrared at 3100 and 1610 cm^{-1} . These spectral data lend support to the formation of the 1(5), 10(19)-diene. Since it is known that in the presence of acid an α -acetoxy mercuric acetate affords a double bond and a vic. diacetate⁶⁾, the formation of the diene will proceed via C_1 -HgOAc intermediate.

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