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STEREOCHEMISTRY OF GRAYANOTOXIN-II

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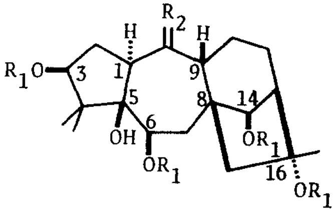
Grayanotoxin-II(abbreviated to G-II) has eight asymmetric centers as shown in I (1). The configurations shown there were assigned to those at C_8, C_9, C_{14} and C_{16} (2) and also to those at C_1 and C_3, while α-configuration was proposed for both C_5- and C_6-hydroxyl groups (3). Kakisawa (4), Tallent (5) and Matsumoto (6) presented independently the configurations shown in I except that all of them assigned β-configuration to C_1-hydrogen.

In this paper chemical evidences are reported that establish the stereochemistry of C_1, C_5 and C_6 leading to an entire structure(I) for G-II.

Tetraacetyl G-II(II) (7) was treated with one mole of N-bromosuccinimide in dry acetone (8) to give a bromo compound(III) in 80% yield, mp 129°(decomp.), $C_{28}H_{39}O_9Br$, and on catalytic hydrogenolysis, this afforded a debrominated compound(IV), mp 200.5°(decomp.), $C_{28}H_{40}O_9$; both III and IV exhibited no hydroxyl absorption in the IR spectra. An AB type quartet observed in the NMR spectrum

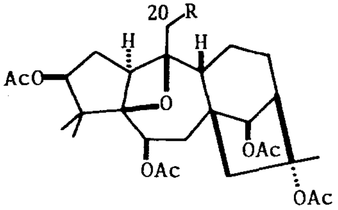


(I) R_1=H, R_2=CH_2

(II) R_1=Ac, R_2=CH_2

(V) R_1=Ac, R_2=$<^{OH}_{CH_3}$

(VI) R_1=H, R_2=$<^{OH}_{CH_3}$



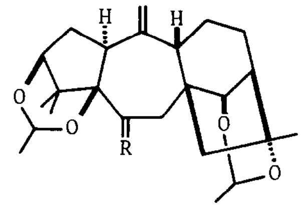
(III) R=Br

(IV) R=H

of the bromo compound(III) at δ($CDCl_3$) 3.32 and 4.40(J=11 cps) was attributed to the 20-bromomethyl group because the debrominated compound(IV) exhibited a three-proton singlet at δ($CDCl_3$) 1.32 instead of the AB type signal. The compound(IV) gave back tetraacetyl G-II(II) when exposed to a hot acetic acid solution of zinc acetate, and also tetraacetyl G-III(V) together with II in the presence of additional water. This implies the first successful conversion of G-II(I) into G-III(VI), a hydrolysate of V (7). The compound(IV), which thus retains stereochemistry consistent with G-II(I), can be concluded to have a four-membered ether ring fused to ring A. Since such a 4/5 ring system never exists in a trans type, the A/B ring juncture is determined as trans (9). This conclusion is in agreement with that reported by Iwasa who obtained 5,9-oxa compound (5/5 ring system) by the treatment of G-II(I) with mercuric acetate (10).

On treatment with diethylacetal, G-II(I) gave a diacetal(VII), mp 198°, $C_{24}H_{36}O_5$; this regenerated G-II(I) on hydrolysis with acetic acid-water. Sarett oxidation of the diacetal(VII) to a ketone(VIII), mp 183°, $C_{24}H_{34}O_5$, followed by hydrolysis with acetic acid-water to a ketol(IX), mp 206°, $C_{20}H_{30}O_5$, and by the ultimate acetylation, produced a triacetylketone(X), mp 163°, $C_{26}H_{36}O_8$. A specimen identical with X was also obtained from tetraacetyl G-II(II) by partial ammonolysis to give a triacetate(XI), mp 162.5°, $C_{26}H_{38}O_8$, followed by Sarett oxydation. Since the triacetate(XI) consumed one mole of lead tetraacetate, it retains a secondary hydroxyl group on C_6. From the data above, the diacetal(VII) should have a free hydroxyl group at C_6, accordingly one of the acetal groups between C_3 and C_5 and another between C_{14} and C_{16}. The C_5-hydroxyl group, thus being cis to 3β-hydroxyl group, can be determined as β-oriented and accordingly the C_1-hydrogen as α (9); the latter allotment is in accord with the previous one (3). The C_6-hydroxyl group is then settled as β-oriented since Dreiding models show that only cis type α-glycol can be transformed into ketals, e.g., XII and XIII (1), under such a stereochemical situation at C_1 and C_5 settled above.

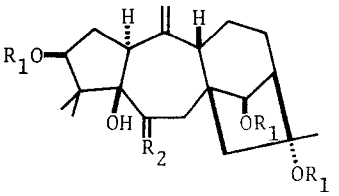
An earlier application of Prelog's asymmetric synthesis to phenylglyoxyl ester(XIV) had produced dextrorotatory atrolactic acid (Table 1), and consequently α-configuration was proposed for both C_6- and C_5-hydroxyl groups (3). Further examination of the same method revealed, however, that just a low optical yield



(VII) R=$<\begin{smallmatrix}H\\OH\end{smallmatrix}$

(VIII) R=O

(XIX) R=$<\begin{smallmatrix}H\\OH\end{smallmatrix}$

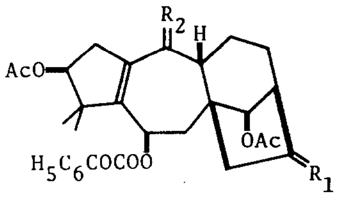


(IX) R_1=H, R_2=O

(X) R_1=Ac, R_2=O

(XI) R_1=Ac, R_2=$<\begin{smallmatrix}H\\OH\end{smallmatrix}$

(XX) R_1=H, R_2=$<\begin{smallmatrix}H\\OH\end{smallmatrix}$

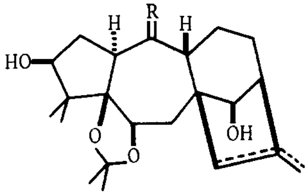


(XIV) R_1=$<\begin{smallmatrix}OAc\\CH_3\end{smallmatrix}$, R_2=CH_2

(XV) R_1=CH_2*, R_2=$<\begin{smallmatrix}H\\CH_3\end{smallmatrix}$(α)

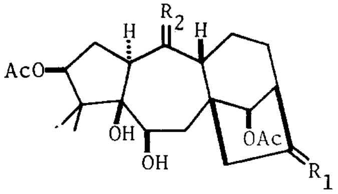
(XVI) R_1=$<\begin{smallmatrix}OAc\\CH_3\end{smallmatrix}$, R_2=$<\begin{smallmatrix}H\\CH_3\end{smallmatrix}$(α)

* mixed with endo-isomer



(XII) R=CH_2

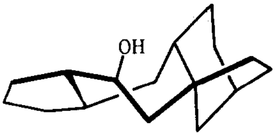
(XIII) R=$<\begin{smallmatrix}H\\CH_3\end{smallmatrix}$



(XVII) R_1=$<\begin{smallmatrix}OAc\\CH_3\end{smallmatrix}$, R_2=$<\begin{smallmatrix}H\\CH_3\end{smallmatrix}$(α)

(XVIII) R_1=CH_2*, R_2=$<\begin{smallmatrix}H\\CH_3\end{smallmatrix}$(β)

*mixed with endo-isomer



(XXI)

Table 1

Prelog's Method		
Compound	Yield[a]	Sign and Optical Yield[a]
XIV	69.5%	+7.9%
XV	71.0	+2.2
XVI	65.5	-1.6

Holeau's Method		
Compound	Yield[b]	Sign and Optical Yield[c]
VII	72.4% 81.9	0% 0
XI	86.4 83.4	+2.0 +2.1
XVII	83.9 91.0	+2.9 +3.6
XVIII	81.6	+2.5
XIX	66.1 65.3	-11.2 -12.1

a; of atrolactic acid
b; of esterification
c; of α-phenylbutyric acid

could be obtained from compound(XV), mp 118°(decomp.), $C_{32}H_{38}O_7$, and even the sign of rotation was inverted in case of compound(XVI), mp 139°, $C_{34}H_{42}O_9$ (Table 1). Similar ambiguity in the determination of the C_6-configuration resulted when

Horeau's method was applied to diacetal(VII), triacetyl G-II(XI), dihydro-XI (XVII), mp 193°, $C_{26}H_{40}O_8$, and anhydrodihydrodiacetyl G-II(XVIII), mp 149°, $C_{24}H_{36}O_6$. The optical yield of α-phenylbutyric acid was always low or zero as the case of VII (Table 1). Such an anomalous behavior of VII may be ascribable to the conformation of ring B. The C_6-proton of VII showed such small NMR coupling constants(J=2.4 and 4.8 cps) that it must lie inside the C_7-gem-protons (11). Since this demands that the B ring takes a boat form(XXI), both the C_9- and C_{15}-moieties come close to the 6β-hydroxyl group and counterbalance the atomic crowding of C_4-moiety. Supporting this point of view, 6-epi-diacetal(XIX) gave a proper sign of rotation in a higher optical yield (Table 1). The epimer (XIX) was prepared either by the reduction of the ketone(VIII) with lithium aluminum hydride or by the same reduction of the triacetylketone(X) to 6-epi-G-II (XX), mp 201°, $C_{20}H_{32}O_5$, followed by acetal formation, mp 152°, $C_{24}H_{36}O_5$.

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