

THE STEREOCHEMISTRY OF THE GRAYANOTOXINS

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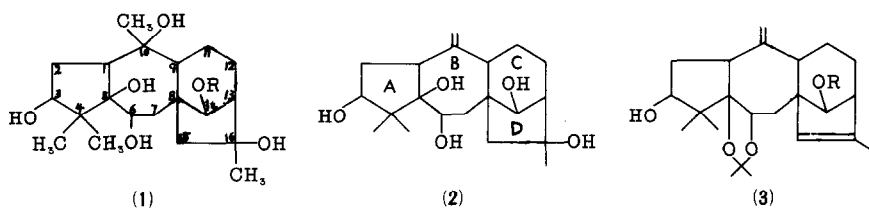
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It has already been shown that the toxic constituents of the Ericaceae, grayanotoxin-I (G-I) and grayanotoxin-III (G-III) can be expressed by 1 (R=Ac) and 1 (R=H), respectively;<sup>1,2</sup> on the other hand, Iwasa et al., showed independently that the third constituent, grayanotoxin-II could be represented by 2.<sup>3</sup>



Alkaline hydrolysis of G-I (1, R=Ac) afforded G-III (1, R=H), which could be dehydrated under mild conditions to yield G-II (2). Furthermore, treatment of G-II or G-III with anhydrous copper sulfate and acetone afforded the same isopropylidene derivative 3.<sup>4</sup> It follows that the

<sup>1</sup> H. Kakisawa, M. Kurono, S. Takahashi and Y. Hirata, Tetrahedron Letters 59 (1961).

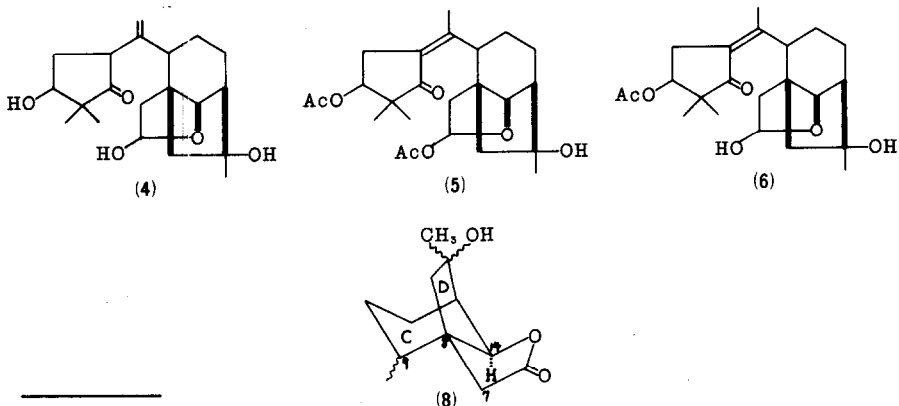
<sup>2</sup> H. Kakisawa, J. Chem. Soc. Japan, 82, 1096, 1216 (1961).

<sup>3</sup> J. Iwasa, Z. Kumazawa and M. Nakajima, Chem. & Ind. 511 (1961); Agr. Biol. Chem. 25, 782 (1961).

<sup>4</sup> H. Meguri, J. Pharm. Soc. Japan, 79, 1060 (1959).

optical centers of the three grayanotoxins belong to the same series, respectively.

Oxidation of G-II with sodium periodate gave dehydro-G-II,  $C_{20}H_{32}O_5$ , m.p.  $163^\circ$ , I.R. 3370, 1745 and  $1649\text{ cm}^{-1}$ .<sup>\*</sup> Since no aldehyde group was present, apparently a five-membered hemiacetal has been formed (4). Acetylation of this dehydro-G-II with pyridine-acetic anhydride was accompanied by a shift of the double bond to give the diacetyl  $\alpha,\beta$ -unsaturated carbonyl compound 5,  $C_{24}H_{36}O_7$ , m.p.  $180^\circ$ , I.R. 3600, 1740 and  $1700\text{ cm}^{-1}$ ,  $\lambda_{\text{max}} 255\text{ m}\mu$  ( $\epsilon 16,300$ ), and the monoacetyl  $\alpha,\beta$ -unsaturated compound 6,  $C_{22}H_{34}O_6$ , m.p.  $201^\circ$ , I.R. 3375, 3220, 1744, 1713 and  $1609\text{ cm}^{-1}$ . Chromic trioxide oxidation of the monoacetate 6 gave the keto- $\gamma$ -lactone 7,  $C_{22}H_{32}O_6$ , m.p.  $163^\circ$ , I.R. 3500, 1770, 1740, 1710 and  $1615\text{ cm}^{-1}$ ,  $\lambda_{\text{max}} 255\text{ m}\mu$  ( $\epsilon 14,600$ ). Since five-membered hemiacetal or lactone rings are fused to the five-membered D-ring in derivatives 4 to 7, and since these derivatives were formed under mild conditions, the two five-membered rings should be cis-fused (8).<sup>5</sup> Namely, the  $C^{14}$ -OR and the  $C^7$ - $C^8$  linkages in G-I, -II and -III are in a cis relation with respect to ring D.



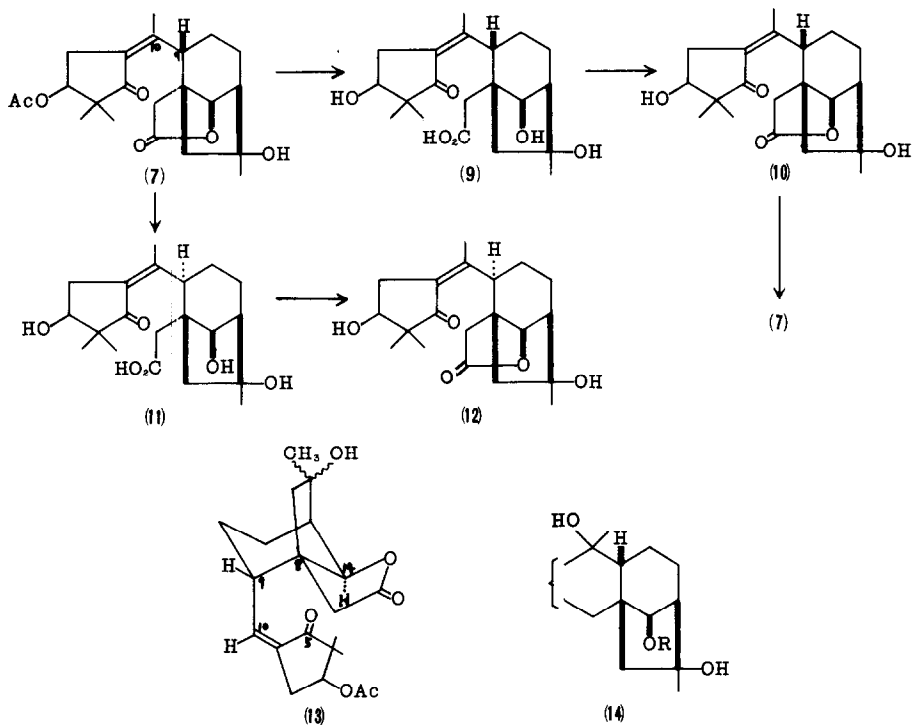
\* The I.R. spectra were measured in chloroform with a Nihon Bunko model 301 instrument. The U.V. spectra were measured in 95% ethanol with a Hitachi EPS-2 model.

<sup>5</sup> G. Stork and F.K. Clarke, J. Amer. Chem. Soc. **83**, 3114 (1961).

Mild alkaline hydrolysis of the monoacetyl- $\gamma$ -lactone 7 afforded the corresponding carboxylic acid 9,  $C_{20}H_{30}O_6$ , m.p.  $215^\circ$ , I.R. 3400, 1715, 1695 and  $1600\text{ cm}^{-1}$ ,  $\lambda_{\text{max}} 258\text{ m}\mu$  ( $\epsilon$  10,960), which when heated with acetic acid was easily converted into the  $\gamma$ -lactone 10,  $C_{20}H_{28}O_5$ , m.p.  $225^\circ$ , I.R. 3500, 1782, 1700 and  $1600\text{ cm}^{-1}$ ,  $\lambda_{\text{max}} 256\text{ m}\mu$  ( $\epsilon$  11,200). Acetylation of the lactone 10 gave back the original compound 7, and accordingly the conversions involve no change in the stereochemistry of the centers. Alkaline hydrolysis of the monoacetyl- $\gamma$ -lactone 7 under more vigorous conditions gave an isomeric carboxylic acid 11,  $C_{20}H_{30}O_6$ , m.p.  $162^\circ$ , I.R. 3370, 1715, 1700 and  $1598\text{ cm}^{-1}$ ,  $\lambda_{\text{max}} 260\text{ m}\mu$  ( $\epsilon$  12,000), which when heated with acetic acid yielded the corresponding  $\gamma$ -lactone 12,  $C_{20}H_{28}O_5$ , m.p.  $221^\circ$ , I.R. 3420, 1780, 1702 and  $1605\text{ cm}^{-1}$ ,  $\lambda_{\text{max}} 255\text{ m}\mu$  ( $\epsilon$  14,600). Spectroscopic properties of the two carboxylic acids 9 and 11, and the two  $\gamma$ -lactones 10 and 12, were respectively quite similar, excepting minor differences in the finger print region of the I.R. spectra. Hence it is apparent that these compounds represent two series of stereoisomers and that they are epimeric at  $C^9$ , which is conjugated to the  $C^5$ -carbonyl through the double bond and can be epimerized by base. Thus, the  $C^9-C^{10}$  bond in the  $\gamma$ -lactone 7 is axial with respect to ring C, and this is epimerized to the more stable equatorial conformation in carboxylic acid 11. These evidences indicate that the  $\gamma$ -lactone 7 can be represented by the conformational structure 13 and that the B/C ring junctions of the grayanotoxins are cis, i.e. 14 or its mirror image.

It has been reported that isopropylidene G-I (3) can be transformed into the monoketone 15<sup>1,2</sup> by catalytic hydrogenation, chromic trioxide oxidation, Wolff-Kishner reduction and subsequent chromic trioxide oxidation. This monoketone had a negative Cotton effect curve ( $[\alpha]_{312.5} -870^\circ$  (trough),  $[\alpha]_{280} +956^\circ$  (peak)), which in conjunction with the octant rule<sup>6</sup> leads to the absolute configuration 14 for the C/D rings.

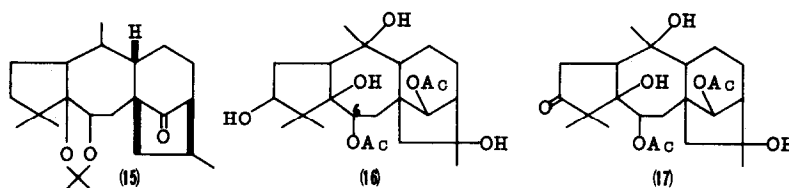
<sup>6</sup> W. Moffitt, R.B. Woodward, A. Moscovitz, W. Klyne and C. Djerassi, J. Amer. Chem. Soc. **83**, 4013 (1961).



Mild acetylation of G-I gave the diacetate 16,  $C_{24}H_{38}O_8$ , m.p.  $238^\circ$ , I.R.  $1738\text{ cm}^{-1}$ . The acetyl group is placed at  $C^6$  because although G-I was cleaved by sodium periodate the acetate 16 was stable to the reagent.

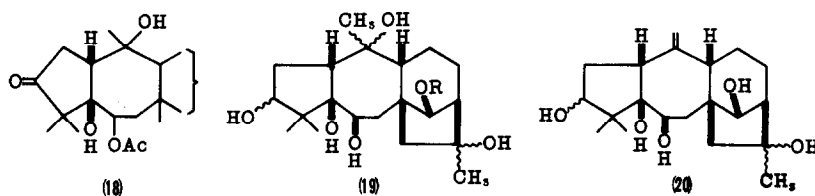
Chromic trioxide oxidation of this compound oxidized the secondary hydroxyl group to yield the ketone 17,  $C_{24}H_{36}O_8$ , m.p.  $201^\circ$ , I.R.  $1750$  and  $1735\text{ cm}^{-1}$ , which exhibited a weak negative Cotton effect curve ( $[\alpha]_{315} -524^\circ$  (trough),  $[\alpha]_{275} +838^\circ$  (peak)).

The  $10\beta$ , A/B trans guanolidic type 2-ketosesquiterpenoids<sup>7</sup> and A-nor-2-ketosteroids<sup>8</sup> exhibit positive Cotton effect curves having extremely large amplitudes, i.e.  $[\alpha] +15,000^{\circ}$  to  $[\alpha] +5000^{\circ}$ , whereas the A/B cis nor-2-ketosteroids merely exhibit weak negative Cotton effect curves.<sup>8</sup> Accordingly, the Cotton effect curve of ketone 17 indicates an A/B cis ring junction as well as the absolute configuration 18. Furthermore, the C<sup>5</sup> and C<sup>6</sup> hydroxyl groups should be cis in view of the ease of formation of the various isopropylidene derivatives of type 3; molecular models show that the two hydroxyls are rigidly fixed in an anti-trans arrangement were they of the trans  $\alpha$ -glycol type.



Thus, the stereochemistry of grayanotoxin-I and -II can be represented by 19 (R=Ac) and 19 (R=H), respectively, and that of grayanotoxin-II by 20. The remaining points are being studied.

The authors are grateful to Professor K. Tsuda, University of Tokyo, for his continued encouragement.



<sup>7</sup> C. Djerassi, J. Osiecki and W. Herz, *J. Org. Chem.* **22**, 13161 (1957).

<sup>8</sup> C. Djerassi, R. Riniker and B. Riniker, *J. Amer. Chem. Soc.* **78**, 6362 (1956)