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THE FULL STEREOCHEMISTRY OF THE GRAYANOTOXINS AND A NOVEL REARRANGEMENT

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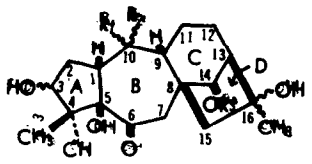
In a previous communication[1] the partial stereochemistry of grayanotoxin-I, -II and -III[2,3,4] (abbreviated to G-I, -II and -III) had been deduced as shown in 1, 2 and 3. Alpha



1; R_1=CH_3, R_2=OH, R_3=Ac

2; R_1, R_2 = CH_2, R_3=H

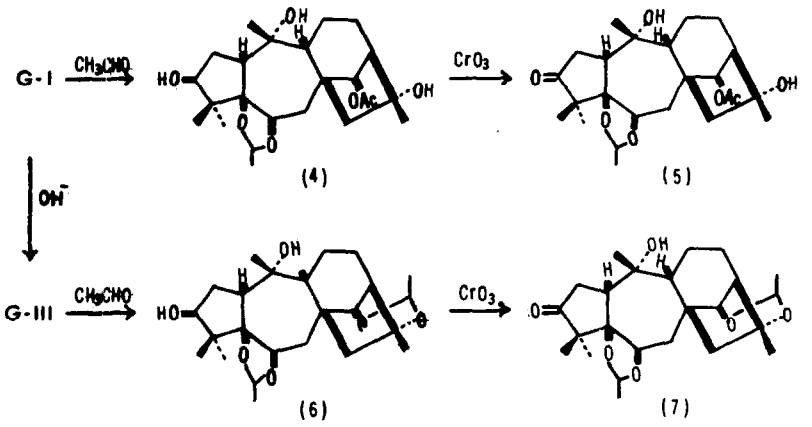
3; R_1=CH_3, R_2=OH, R_3=H

configurations have subsequently been assigned to both C_{10}-OH and C_{16}-OH on spectroscopic grounds.[4]

The present communication describes a tosylation reaction that unequivocally settles the stereochemistry at C-10, 9, 8, 14, 13 and 16, and also provides evidence for elucidation of the entire stereochemistry.

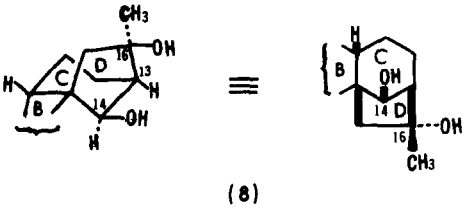
G-I reacts with acetaldehyde and zinc chloride to yield the ethylidene derivative 4, $C_{24}H_{38}O_7$, m.p. 154-6° that could be oxidized to a five-membered ketone 5, $C_{24}H_{36}O_7$, m.p. 244°

(dec.), ν^{KBr} 1739, 1724 cm^{-1}; thus the ethylidene group is



(4) (5) (6) (7)

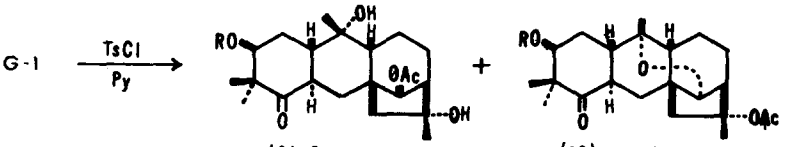
evidently attached to the α-glycol moiety. Similar treatment of G-III afforded an amorphous diethylidene derivative 6 that could also be oxidized to a crystalline five-membered ketone 7, $C_{24}H_{36}O_6$, m.p. 240-5°, ν^{KBr} 3446, 1747 cm^{-1}. The elementary analysis and N.M.R. spectrum showed this compound to be a diethylidene derivative. Since one molecule of acetaldehyde forms an acetal ring between C_5-OH and C_6-OH, it is only between C_{14}-OH and C_{16}-OH that another molecule of acetaldehyde can be attached, and this establishes the cis-relation of C_{14}-OH and C_{16}-OH with respect to ring D (8). The C_{13}-H/C_{14}-H dihedral angle is approximately 85° and this is in agreement



(8)

with the singlet nature of the C_{14}-H N.M.R. signal* in grayanotoxin derivatives having rings C and D intact.

Treatment of G-I with one mole of p-toluenesulfonyl chloride and pyridine for 2-3 weeks at room temperature or 1 hour at 100° gives the products 9, $C_{22}H_{34}O_6$, m.p. 126-7° and 10, $C_{22}H_{32}O_5$, m.p. 180-1°. Since their I.R. spectra indicate the formation of a six-membered ketone, the five-seven-membered A/B ring system has evidently changed into a six-six-membered ring by a pinacol type rearrangement of the



(9) R = H (10) R = H
(11) R = Ts (12) R = Ts

α-glycol group. The N.M.R. spectrum of 9 shows five singlets at δ 1.10, 1.17, 1.30, 1.37 and 2.17 corresponding to five methyl groups; appearance of the C_{14}-H signal as a singlet at δ 6.22 proves that the environments of C_{14} remain unchanged although the ca. 0.5 ppm down-field shift is to be noted.** On the other hand, in the product 10 there is a one-proton doublet (J 5 cps) at δ 4.42, and this indicates a structural change around C_{14}. With two moles of p-toluenesulfonyl chloride and pyridine G-I gives the ketones 11, $C_{29}H_{40}O_8S$, m.p. 146-8° and 12, $C_{29}H_{38}O_7S$, m.p. 138-9°, which in turn can also be prepared

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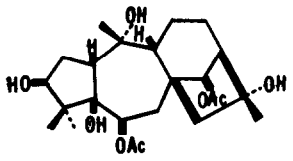
* N.M.R. data in ppm, TMS internal reference, in $CDCl_3$, unless otherwise stated.

** This down-field shift is attributed to the shorter distance between the C_{14}-H and C_{10}-OH in 9.

by tosylating 9 and 10, respectively. The fact that the α-glycol group is responsible for these rearrangements and that the tosylate group in 11 and 12 are introduced after the rearrangement is supported by the recovery of diacetyl G-III (13) without even being tosylated at C-3 under more vigorous conditions. Elementary compositions of 10 and 12 indicated that they contained one molecule of water less as compared to 9 and 11, respectively. Neither olefinic proton nor olefinic methyl signals were present in the N.M.R. spectra of 10 and 12, and furthermore, it is a secondary hydroxyl in 10 that gets tosylated to give 12 (H-C-OH at δ 3.58 is shifted to H-C-OTs at δ 4.44). Also, 10 and 12 still retain the acetyl group (I.R. and N.M.R.). Thus an ether linkage has been formed in these compounds, and the only structure for such an ether that is compatible with the mentioned findings is that involving formation of a C_{10} to C_{14} oxygen bridge and a con-



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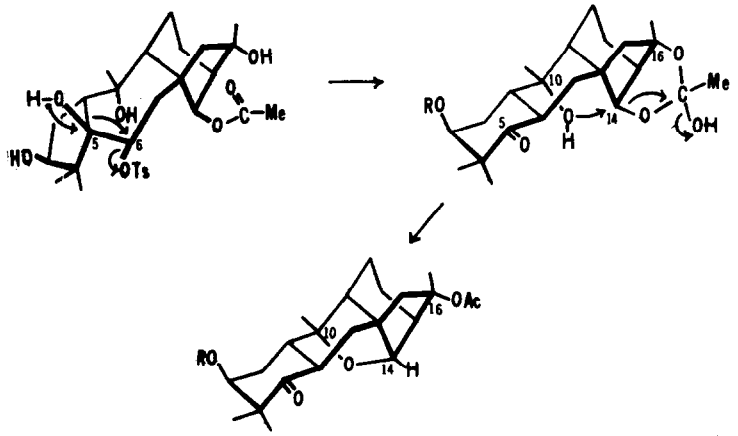
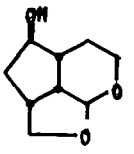


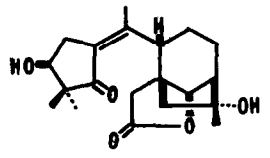
certed 1,3-acyl migration. The rearrangement of G-I to the ether 10 is shown in the scheme. The configuration of C_{10}-OH is thus alpha. This single tosylation also establishes the stereochemistry of all optical centers on rings C and D. The C_{14}-H and C_{13}-H dihedral angle in the ethers 10 and 12 is 40°, and in agreement, the C_{14}-H N.M.R. signal now appears as a doublet, e.g., δ 4.43 (J 4.7 cps) in 12. Mechanistic considerations of this rearrangement, as depicted in the scheme, suggest an A/B trans arrangement for the six-membered ketones; although it is possible that a further epimerization at C-6 might have occurred after the rearrangement, this is improbable in view of the stable trans ring arrangements. Octant diagrams of ketones 9 to 12 predict O.R.D. curves with a negative Cotton effect, which is in fact what is found (only the amplitudes[5] are given): 9, a - 7.38; 10, a - 23.7; 11, a - 62.1; 12, a - 70.8.

It was then attempted to determine the C_3-OH configuration by applying Prelog's asymmetric synthesis[6] to the phenylglyoxyl ester of G-I (esterified at C-3, amorphous). However, the atrolactic acid obtained in 40% yield was found to have no optical rotation.* Accordingly, the recently developed method of A. Horeau[7] was applied after successful trials with (-)-menthol and methyl betulinate. Compounds 14 and 15 were employed for determination of the C_3-OH configuration, whereas

* A similar failure has been encountered in tetrahydroanhydro aucubigenin (A. Karube, M. Sc. Thesis, Tohoku University, 1961).



compounds 16 and 17 were employed for determination of the C_6-OH configuration. Although 15 and 17 contain two secondary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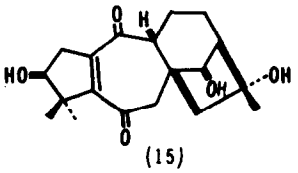
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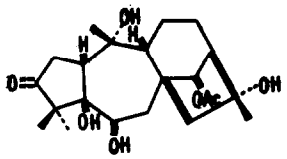
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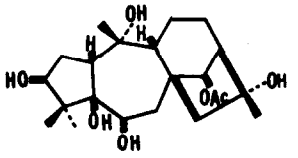
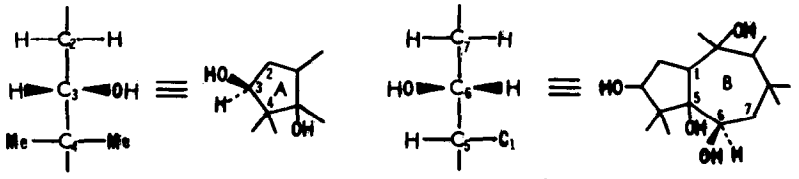

(17)

hydroxyls, the C_{14}-OH in 15 and C_3-OH in 17 are not acetylated by usual treatment with acetic anhydride and pyridine, and accordingly they can be safely used for determining the C_3- and C_6-OH configurations, respectively. The results are summarized in the Table.

TABLE

Compound	Esterification yield	Observed rotation of liberated α-phenylbutyric acid ($\alpha_D^{0.5\ dm}$)	Optical yield
14	55 %	- 0.40°	92 %
15	55	- 0.29	67
16	40	+ 0.06	19
17	61	+ 0.11	23

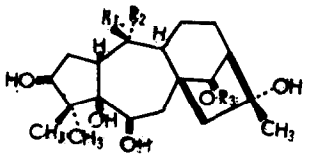
The negative rotation of the α-phenylbutyric acid liberated by esterifications of 14 and 15 shows that the configuration of C_3-OH is as in 18. This result has been further substantiated



(18) (19)

by application of the "benzoate rule"[8] to the 3-benzoate derivative of G-I, $C_{29}H_{40}O_8$, m.p. 219-223°, $\Delta_{benzoate}$ + 13.5°. The rotation of the α-phenylbutyric acid liberated by esterifications of 16 and 17, on the other hand, is positive, and this also suggests a β C_6-OH configuration as shown in 19. Although C_6-OH had previously been deduced as being β on grounds that it was cis with respect to C_5-OH because of the facile cleavage by periodate and ready formation of isopropylidene and ethylidene derivatives, the conformational mobility of the seven-membered B ring was overlooked. However, the present results provide independent evidence for the configuration of C_6-OH.

Thus the grayanotoxins can be represented by the full structures 20, 21 and 22.[9]



20; R_1=CH_3, R_2=OH, R_3=Ac

21; R_1, R_2 = $=CH_2$, R_3=H

22; R_1=CH_3, R_2=OH, R_3=H

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(9) Note: Although not reported in full, Professor Nakajima, Kyoto University, has assigned α-configurations to C_1-H and C_5-H in a special lecture addressed at the Chemical Society Annual Meeting, April, 1962; cf. "Chemistry of Natural Insecticides", Kagaku to Kogyo, 15 825 (1962). The stereochemistry at other centers in G-II is in agreement with results given here.